Blood and Marrow Transplant Handbook

Comprehensive Guide for Patient Care

Richard T. Maziarz
Susan Schubach Slater

Editors

Third Edition

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② Springer

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Preface

Hematopoietic cell transplantation has experienced a dramatic increase in activity over the past two decades with a continued marked escalation of procedures projected over the next 10 to 15 years. This expansion is not only a reflection of an ever-changing field with increasing demand but also the ongoing development of innovations that contribute to continued improved outcomes with less risk of adverse events or deleterious long-term consequences for the transplant patient population. The use of non-myeloablative, reduced-intensity conditioning regimens has allowed transplantation for patients who were previously deemed too old or frail to endure ablative conditioning regimens. Additionally, the expanded use of alternative donors, including both umbilical cord blood and haplo-identical family donors, has made the therapeutic option of transplantation available to patients who previously could not find a suitable donor.

Currently, we are in the midst of a seismic shift in the care of cancer patients, including those with hematologic malignancies who are the focus of this handbook. Precision medicine and immunotherapy have emerged as critical new tools that are providing new diagnostic and therapeutic options and contributing to improvements in disease control, overall survival, and quality of life of our patients. Antibody therapies (humoral immunity arm) have long been part of the care for hematologic malignancy patients, but multiple novel humoral immune options have recently emerged with the regulatory agencies' approval of bispecific antibodies, immune conjugates, and checkpoint inhibitors. In addition, we are now seeing the emergence of cellular therapies. Heralded a decade ago by the development and FDA approval of sipuleucel-T, a cellular vaccine therapy for prostate cancer, we are now witnessing the rapid emergence of multiple cellular therapeutics as options for our patients. With the FDA approvals of the chimeric antigen receptor T cell gene therapies, tisagenlecleucel and axicabtagene ciloleucel, multiple new cell therapies are anticipated to enter our armamentarium, including T cell, dendritic cell, natural killer cell, and mesenchymal stromal cell products. Of course, as anticipated, new challenges arise in parallel with the introduction of these new therapies. We must now address new logistical issues of maintaining and monitoring supply chain for these manufactured and transported drugs and, of course, be ready to address new complications linked to these treatments. Thus, "cytokine release syndrome" and "immune effector cell

associated neurotoxicity syndrome" are new language that is routinely used in the day-to-day discussions that take place on hematologic malignancy services.

Practicing in the field of cellular therapy requires multi-specialty input for the management of these complex patients. In the past, transplantation was the sole responsibility of a few academic centers and information resided within the hands of a few individuals. However, with the dissemination of technology and the ongoing proliferation of these procedures, there has been an obligatory need for the development of tools to provide to all practitioners, as well as a set of standard guidelines and algorithms for the management of patients.

Most institutions have established their own set of guidelines and recommendations designed for consensus management as patients are in constant need of shared care. As new workforce demands have emerged, there have been changes in the workplace with ongoing predictions of a marked shortage of transplant-trained physicians, advanced practice providers, nurses, and pharmacists. Efforts to recruit healthcare providers to this field are paramount for uninterrupted day-to-day care of transplant patients as well as those who will benefit from the increasingly available novel cellular and humoral immune therapeutics. In light of these changes, it becomes imperative to provide detailed and shared consensus guidelines to achieve the best outcomes for our patients.

This guide to patient management began as a product of years of evolution of patient care at our institution. For this third edition, we have incorporated the expertise of providers from across the USA for a broader perspective on the day-to-day care of our patients. However, *this guide is not meant to define the sole, exact care pathway for all patients*. We all know far too well that this field is constantly evolving, primarily through rigorous, controlled, well-designed, statistically valid clinical trials. Rather, we have provided a practical set of guidelines that can be shared across institutions. This effort is our contribution to the workforce shortage of transplant and cell therapy providers. By providing an easy-to-use manual that covers the basics of care for hematologic malignancies and particularly cell therapy patients, which can be utilized to educate junior faculty, physician assistants, nurse practitioners, residents, fellows, and other providers that may be recruited for the day-to-day care of patients, we have achieved our goal. We have also seen that previous editions of this handbook have been used by those primary hematology and medical oncology practitioners who accept their patients back from our programs. It is a source of management information that allows community providers to care more confidently for their patients across time. As this third edition demonstrates, this guide remains an evolving work in progress, and we anticipate that as time passes, even potentially quite quickly, a new set of guidelines will need to be generated for you to care for your patient's daily needs.

We recognize that this manual is incomplete. We do not discuss the laboratory aspects of graft engineering or stem cell expansion approaches to any great degree. We do not address the nuances of many therapies that remain in clinical trial development nor do we discuss regeneration medicine, its futures, and its overlap with cell therapy and hematopoietic cell transplantation. Rather, we provide information about standards of care needed to handle the day-to-day issues that may arise, and to accomplish this goal, we have assimilated knowledge gained from many others in the field.

Acknowledgments

Finally, we wish to thank the thousands of patients and their families who have walked through our door over the past 30+ years, putting their trust in us to guide them through the most challenging time in their lives. Many of them did not walk back out of our doors, while others have gone on to experience personal and family events that, were it not for these transplantation and cellular therapeutic procedures, would have occurred without them. We have learned from them all.

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                                                                                         Susan Schubach Slater

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Chapter 1
Overview of Hematopoietic Cell Transplantation and Cellular Therapy

Richard T. Maziarz

Introduction

Hematopoietic cell transplantation (HCT) is currently a standard-of-care procedure for many disorders. Frequently HCT procedures are curative in situations where no other potentially curative treatment options exist. Specifically, the key element in HCT as a therapy is the replacement of the host (recipient) marrow function by another source of hematopoietic stem cells (HSCs). These sources could include HSC collected from the patient (autologous) or from another individual (allogeneic). Allogeneic sources include family-related or unrelated products, either collected directly from healthy donors or cryopreserved stem cell products, including umbilical cord blood. A few rare patients have a syngeneic (identical twin) donor. In the setting of allogeneic HCT, products are preferentially matched at the major histocompatibility complex (MHC) HLA class I and II molecules located on chromosome 6, which guide immunologic recognition as self or nonself. Advances in immunogenetics and immunobiology, conditioning regimens, disease characterization and risk stratification, immune suppression, antimicrobials, and other types of supportive care have all contributed to improvements in disease control and overall survival. These outcomes have resulted in a marked increase in the number of procedures performed annually worldwide. However, it is critical to always recognize that HCT requires substantial resources. Thus, delivering this therapy requires large multidisciplinary teams of nursing, pharmacists, physicians, social workers, nurse practitioners, physician assistants, nutrition experts, and occupational and physical therapists, in addition to specialized facility and technical resources.

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HCT has been developed over the past 60 to 70 years since the first human clinical experimental transplants were performed in the 1950s. The first curative allogeneic bone marrow transplant was performed in a young child with immune deficiency syndrome in 1968. By the early 1980s, bone marrow transplantation was no longer considered experimental but emerged as the standard of care for a variety of disorders including acute and chronic leukemia, aplastic anemia, lymphoma, multiple myeloma, and a number of inherited disorders including severe combined immune deficiency, thalassemia, and other inborn errors of metabolism. With this recognition, the utilization of this procedure rapidly increased to the current state where over 50,000 procedures are performed worldwide each year as estimated by the Center for International Blood and Marrow Transplant Research (CIBMTR).

As these HCT procedures evolved and were refined, in parallel, but emerging at a slower pace has been the clinical development of cellular immune therapies, which has required a far more detailed analysis of the molecular immunology of the immune response to infectious organisms and malignant targets. Long after transplantation was established as a clinical tool, the dissection of the immune response occurred with identification of the crystal structure of HLA, the characterization of the complex effector:target cell adhesion interactions, and the appreciation of the need for costimulatory pathways for activation and inactivation of the T cell response. All these single cell understandings were coupled with the identification of multiple cellular subsets including dendritic cells, natural killer cells, T regulatory cells, activating and suppressing macrophages, and mesenchymal stromal cells, as well as discerning the role of naïve, effector, and memory cell populations. The seminal studies of Dr. Steven Rosenberg at the National Institutes of Health (NIH) in the generation and application of various cellular therapeutics, lymphocyte active killer (LAK) cells, and tumor infiltrating lymphocytes (TILs), and the training of a generation of immune therapists cannot be overlooked. The sequencing of the human genome in the 1990s and the development of successful gene transfer and expression, as well as the exploding field of gene editing, has further opened curative opportunities for patients. All these advances merge in an intricate dance of cellular biologic cross talk and the immune response, with an evolution that dates back to invertebrate coral and sponge species and their ability to perform the most critical role of immunity: the identification of self from nonself. These parallel investigations have now led to the application and commercialization of multiple cellular pharmaceuticals recently culminating in the worldwide approvals for chimeric antigen receptor T (CAR-T) cells as well as exciting gene replacement and editing studies that are tackling worldwide disorders such as sickle cell anemia and thalassemia major.

Key Principles

1. Bone marrow stem cells are capable of repopulating all hematopoietic and lymphocytic populations while maintaining capacity for self-regeneration, assuring long-term immunologic and hematopoietic viability.
2. Allogeneic HCT achieves two goals: (a) replacement of host HSC pools after conditioning and (b) establishment of the donor immune system, either by

expansion of naïve immune progenitors or by adoptive transfer of mature donor immune cells.

3. Treatment of nonmalignant disorders is directed at stem cell or immune system replacement while the treatment of malignant disorders requires both replacement of an underlying stem cell or immune system and eradication of malignancy.

4. The decision to use high-dose myeloablative chemoradiotherapy is based upon the identification of malignancies that (a) have a therapy sensitivity threshold that can be overcome and/or (b) have a short enough doubling time to allow the greatest number of malignant cells to be impacted by the conditioning regimen.

5. Conditioning agents with hematologic dose limiting toxicities are primarily selected for myeloablative chemotherapy.

6. Organ-specific toxicities can be experienced and represent "collateral damage" of myeloablative chemoradiotherapy, thus necessitating the need for evaluation of organ function reserve prior to HCT.

7. The benefits of autologous HCT are dependent upon dose escalation of conditioning regimens.

8. Graft-versus-host disease (GvHD) after allogeneic HCT may be a consequence of the adoptive transfer of a competent donor immune system that recognizes host target antigens.

9. Prophylaxis for GvHD with immune-suppressive medications is warranted in nearly all standard allogeneic HCT settings.

10. GvHD can be eliminated by depletion of mature T cells from the donor allograft.

11. Depletion of mature T cells from an allograft is associated with increased risk of relapse of the underlying malignancy.

12. In T cell replete allografts, the occurrence of GvHD has been associated with immunologic-based graft-versus-leukemia (GvL) therapeutic benefit and can be directly linked to improved survival. As populations of T cells are selectively separated, the relationship may become less linked.

13. The emergence of reduced intensity and nonmyeloablative allogeneic HCT is the direct result of an effort to maximize the immunologic GvL effect while minimizing risk of regimen related morbidity and mortality.

14. Patient selection influences outcomes; patients with better overall functional performance status, limited comorbidities and underlying organ damage, and stronger support systems have superior outcomes.

The material included within the following chapters of this patient management handbook will provide details that substantiate these principles.

Research Efforts in HCT

The success of HCT has its origins in the research laboratories and clinical research units of many worldwide institutions. The HCT community has also had the foresight to track outcomes of recipients in center-specific databases and in registry databases which have been instrumental in providing opportunities for ongoing

research. However, it is also recognized that HCT patients still face significant morbidity and mortality substantiating the continued need for ongoing research. There have been measurable improvements in survival despite the growing number procedures performed in older patients and patients with pre-existing comorbidities. But there remains room for improvement.

Much of the material within this handbook reflects established standards of care of management in the HCT patient. However, the field demands more. There are many areas of active research including new conditioning regimens, new immune suppressive approaches, vaccines (both prior to and after HCT) focused at infectious pathogens as well as the primary malignancy, T regulatory cells, new indications for HCT such as autoimmune disease or sickle cell disease, applications of natural killer cells, novel stem cell mobilization agents, and continued improvement in supportive care. In 2011, the American Society for Transplantation and Cellular Therapy (ASTCT) published a set of amended research priorities to assist in the focus of attention to those fields that are most likely to lead to continued development of hematopoietic cellular therapy [1, 2]. These priorities remain central in our focus and remain visible on the ASTCT website, available to all to review and serve as a guiding light to our field.

These include the following:

1. Stem cell biology

   a. Cell manipulation
   b. Stem cell sources
   c. Inducible pluripotent stem cells
   d. Cancer stem cells

2. Tumor relapse

   a. Prevention of and therapy for post-HCT relapse
   b. Immunotherapy with T cells and dendritic cells

3. Graft-versus-host disease

   a. Separation of GvHD and graft-versus-tumor effects
   b. Immune reconstitution and GvHD
   c. Biomarkers predicting GvHD
   d. Role of regulatory T cells

4. Applying new technology to HCT

   a. Genomics
   b. Proteomics
   c. Imaging
   d. Markers of immunologic recovery
   e. Phamacogenomics

5. Expanded indications for HCT

   a. Solid tumors
   b. Regenerative medicine
   c. Autoimmune disease
   d. Response to bioterrorism in radiation accidents

6. Survivorship

   a. Long-term complications
   b. Longevity
   c. Quality of life

7. Transplants in older patients

   a. Biology of aging
   b. Indications for transplant
   c. Outcomes and quality of life

8. Improving current use of HCT

   a. Graft sources
   b. Conditioning intensity
   c. Cost effectiveness

However, what is a glaring omission and likely will be the subject of the next ASTCT priority focus is the optimization of the cellular therapies that are rapidly emerging. The US Food and Drug Administration (FDA), European Medicines Agency (EMA), Canadian and Australian approvals of tisagenlecleucel (Kymriah®) and axicabtagene ciloleucil (Yescarta®) demonstrate the rapid acceptance of these novel T-cell therapeutics, with the expectation that multiple new drugs will follow in the very near future. We are only at the forefront of understanding the use of these agents. Additional questions remain as follows: When will they optimally be used? Will they remain as single agent therapies or will they best be served in combination with other classes of therapeutics? How can we avoid the unique associated CAR-T toxicities of cytokine release syndrome and neurotoxicity? Perhaps most importantly, how can all patients in need access these agents with their current high costs regardless of their home country?

Horizons/Challenges

As HCT remains an ever-changing field, so will be the field of cellular immuno-oncology. As described briefly above, these technologies have been applied to thousands of people within dozens of countries. The success of the varied research

initiatives will extend these applications to a greater degree. The National Marrow Donor Program (NMDP) reported 6200 unrelated donor transplants in the United States in 2018 with an approximate total of 23,000 autologous and allogeneic transplants performed in the same timeframe [3]. Worldwide, there are now approximately 37 million available donors as reported by the World Marrow Donor Association (WMDA) and over 50,000 total transplants performed annually [4]. This growth has been multifactorial and is impacted by broader indications, improved supportive care, changing age demographics with increased incidence of cancers reported, and improved survivorship of patients with cardiovascular disease.

With these predictions, one must also be aware that development of molecular therapeutics may lead to an alternate future. Much of cancer therapy research today is focused on the "personalized" medicine approach in which small molecules that target the multiple signaling pathways might convert life-threatening malignancies to truly chronic diseases. The impact of imatinib mesylate (Gleevec®) on HCT for chronic myeloid leukemia (CML) is a prime example [5]. Recognizing that the vast majority of patients with CML do not proceed to early HCT and the prevalence of CML in the general population has increased, patients who now undergo HCT are those with advanced or resistant disease. Despite this observation, HCT outcomes for patients with CML remain excellent. Additionally, data are emerging that aggressive pretreatment of Philadelphia-chromosome positive acute lymphoblastic leukemia (ALL) with tyrosine kinase inhibitors (TKI) has actually led to improved outcomes after allogeneic HCT. Similar observations with autologous HCT for multiple myeloma have been made. The use of imides and proteosome inhibitors pre-HCT and as maintenance therapy post-HCT has led to marked improvements in progression-free survival and improved overall survival in myeloma patients. Active studies addressing the role of TKI oral therapy as adjuncts to HCT for treatment of FLT3-ITD+ acute myeloid leukemia (AML) are underway. Phase II studies have demonstrated that the use of post-HCT midostaurin (Rydapt®) or sorafanib (Nexavar®) has enhanced the likelihood of survival; an international multicenter, placebo-controlled randomized trial assessing gilteritinib vs placebo is ongoing and will provide definitive answers.

Another critical advancement is in the development of highly sensitive tools and devices to detect disease-specific molecular fingerprints and residual molecular signals after transplantation. These tools are defining new levels of molecular detection and guiding therapeutic interventions. These assays often can detect residual disease to a level of less than one in a million cells or lower (see also Chap. 57).

As a result, comparative effectiveness and outcomes research will remain essential as we compare HCT therapies to these new options. The availability of registry databases has been vital for these analyses and will remain critical for the future [6].

It is not just small molecule therapy that has driven the personalized medicine efforts. One cannot underestimate the potential impact that will emerge from graft engineering efforts in immune mediated therapies. Both humoral and cellular immune systems are being exploited. Bi-specific antibodies and genetically modified T cells are actively being studied as a bridge to HCT, for relapse after HCT, and as stand-alone therapeutics. The resounding success of small institutional investigator-initiated

studies of chimeric antigen receptor-modified T cells (CAR-T) used for relapsed/refractory ALL and chronic lymphocytic leukemia (CLL) has launched large multicenter, industry-sponsored, and NIH-sponsored clinical trials to further explore these treatments in hematologic malignancies and multiple other disease settings, and as stated above has led to the regulatory approval of the first generation agents.

However, we must be aware that the increased numbers of patients undergoing HCT, as well as the observed improvement in survival, will lead to a greater demand for specialists in the field of HCT and cellular immuno-oncology [7–9]. Not only are the patients who undergo HCT or receive cellular therapeutics in need of specialized providers, the rapidly expanding population of survivors, particularly those with chronic GvHD, have difficulty in finding a medical home with their primary care providers or referring medical oncologists [10]. One potential future is that the comprehensive care delivery systems developed for HCT patients that resemble a medical home may become a model for other specialties. These care delivery systems have evolved from capitated-risk contracts for HCT patients and reflect the need for a mixed team of providers including HCT physicians, advanced practice providers, nurses, social workers, and cell processing laboratory technologists along with medical specialty assistance from infectious diseases, critical care, gastroenterology, etc. This evolution of care may become the model for survivor management.

A previous analysis suggested that within the very near future, there will be a significant shortfall in physicians trained and focused on the care of HCT patients and the potential large number of patients that may receive T cell, natural killer cell, or other cellular therapies [8]. Thus, new paradigms must be developed for the delivery of care to the HCT survivor, including expansion of the advanced practice provider workforce of physician assistants and nurse practitioners, as well as active recruitment of new trainees in the field of hematology and medical oncology. Most importantly, training programs and generation of training tools must be established for a new specialty of primary care providers focused on delivery of chronic care to the cancer survivor. Such a training curriculum for HCT providers has been developed by The American Society of Transplantation & Cellular Therapy (ASTCT) and is available through the ASTCT website (ASTCT.org). Similar training programs have been developed by the ASTCT Pharmacology Interest Group for pharmacists in the field as well as multiple training programs developed by the European Group for Blood and Marrow Transplantation (EBMT).

This handbook will provide the background for all medical professionals involved in the management of the HCT recipient, including physicians, advanced practice providers, pharmacists, nurses, etc.; however, its main focus will be those providers who provide daily bedside care. Guidelines are provided for evaluating and selecting the appropriate transplant candidate, recognizing that not only medical but also socioeconomic factors influence outcomes. Detailed descriptions of appropriate pre-HCT conditioning and identification of key prophylaxis strategies to avoid complications are provided. Supportive care efforts are critical, including appropriate selection of blood products, maintaining nutritional and functional abilities, as well as identifying the appropriate follow-up care for the recipient to minimize complications. However, consequences of the immunologic and

chemoradiotherapeutic interventions are expected, and we have provided immediate hands-on, what to do, treatment recommendations for the provider. Information on management of the long-term survivor as well as those that experienced post-HCT relapse is included. Finally, multiple contributions regarding the application of and consequences associated with varying immune effector cell therapies are provided.

Management of the HCT patient has never been accomplished as the effort of a sole individual. There is a saying that "It takes a village to raise a child," allegedly attributed to an old African proverb. Similarly, there is a very large and extensive professional community that has developed to care for the individual patients. The ASTCT and the EBMT are two large societies focused at providing the research and educational forums to further the field and have sponsored the two principal professional journals of our field, *Biology of Blood and Marrow Transplantation* and *Bone Marrow Transplantation*, respectively. But they are not alone. The American Society of Hematology (ASH), the NMDP ("Be the Match"), and the Foundation for Accreditation of Cell Therapy (FACT) all have instructional websites and literature that support the efforts. The National Heart, Lung and Blood Institute (NHLBI) and National Cancer Institute-funded Blood & Marrow Transplant Clinical Trial Network (BMT CTN) [11] were created to facilitate the generation of multicenter, transplant-focused trials for the advancement of the field. As our field rapidly expands to incorporate the advances of cellular therapy, the International Society of Cell Therapy (ISCT), the American Society of Gene & Cell Therapy (ASGCT), and the rapidly growing Society of the Immunotherapy in Cancer (SITC) are welcome new partners. These professional societies and groups represent our village.

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Chapter 2
The Business of Cellular Therapy and Hematopoietic Cell Transplantation

Peggy L. Appel and Gary Goldstein

Introduction

Hematopoietic cell transplantation (HCT) and immune effector cell (IEC) therapy are extremely complex and expensive procedures, requiring significant personnel, pharmaceutical, supportive, and patient/family resources.

Classically, after achieving primary disease control, the first step in HCT involves high doses of chemotherapy and/or radiation in an attempt to eradicate residual disease. The subsequent infusion of the stem cell product leads to hematopoietic and immunologic recovery, of which the latter may often require months to years to achieve.

The first transplant procedures were successfully performed over 50 years ago. As indications multiplied and transplant-related mortality declined, HCT utilization expanded with a dramatic increase in the number of both autologous and allogeneic procedures performed over the past decade (Fig. 2.1).

HCT has demonstrated efficacy for treatment of selected malignancies (e.g., multiple myeloma, acute and chronic leukemia, and lymphoma), as well as for immunodeficiency, bone marrow failure, and infiltrative disorders such as amyloidosis. Development of reduced intensity conditioning regimens has allowed successful treatment of older patients and those with comorbidities that would deem them ineligible for myeloablative therapy (Figs. 2.2 and 2.3).

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Fig. 2.1 Annual number of HCT recipients in the US by transplant type

Fig. 2.2 Trends in autologuous HCT in the US by recipient age (Transplants for NHL, Hodgkin Disease and Multiple Myeloma)
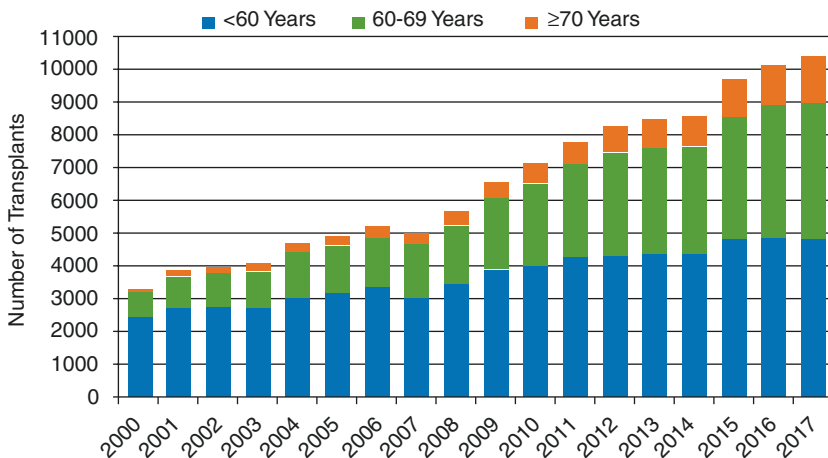
Trends in Allogeneic HCT in the US
by Recipient Age^
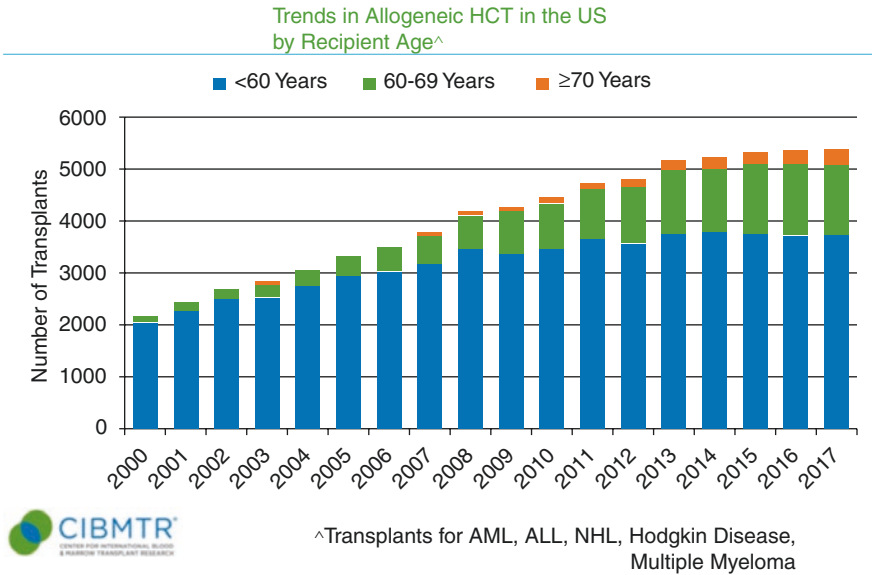
Fig. 2.3 Trends in allogeneic HCT in the US by recipient age (Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma)

The expansion beyond HLA identical sibling allogeneic HCT to unrelated donor transplants as well as alternative donors, including unrelated cord blood transplants and related haploidentical donors, has resulted in donor availability for nearly all patients in need (Figs. 2.4 and 2.5).

Recent research shows that patients 70 years and older can have comparable HCT outcomes to those of younger patients [1]. Between 2011 and 2017, there was an 80% increase in transplants performed in the patients 65 years of age and older [2].

The most common diagnosis for autologous transplant is multiple myeloma (57%), with the second most common diagnosis being non-Hodgkin lymphoma (27%) [3] (Fig. 2.6).

IEC therapy has made recent significant advancements. Following successful clinical trials, two chimeric antigen receptor T-cell (CAR-T) therapy products were approved by the United States Food and Drug Administration (FDA) for commercial use. Tisagenlecleucel (Kymriah®) was approved for use for the treatment of acute lymphoblastic leukemia (ALL) in the 0–26 age population in August 2017, and for the treatment of diffuse large B-cell lymphoma (DLBCL) in May 2018. Axicabtagene ciloleucil (Yescarta®) was approved for use in the treatment of DLBCL in October 2017. Brexucabtagene autoleucel (Tecartus®) was approved for use in the treatment of mantle cell lymphoma in July 2020. At the time of publication, a commercial CAR-T product for multiple myeloma is proceeding toward FDA approval possibly in the spring of 2021. These commercial CAR-T products have the potential to impact a center's autologous transplant program.

Allogeneic HCT Recipients in the US,
by Donor Type

Fig. 2.4 Allogeneic HCT recipients in the US, by donor type
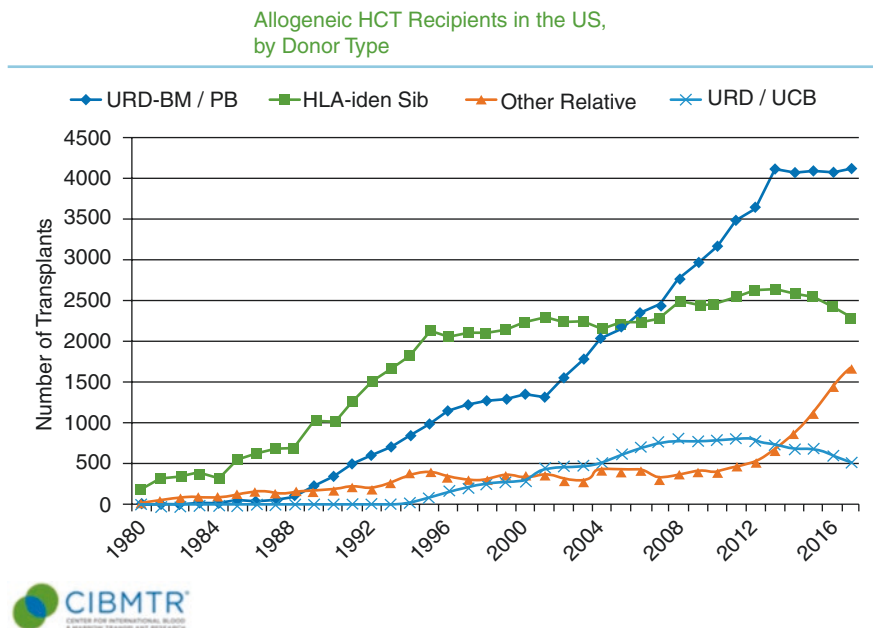
Allogeneic HCT Recipients in the US,
by Donor Type
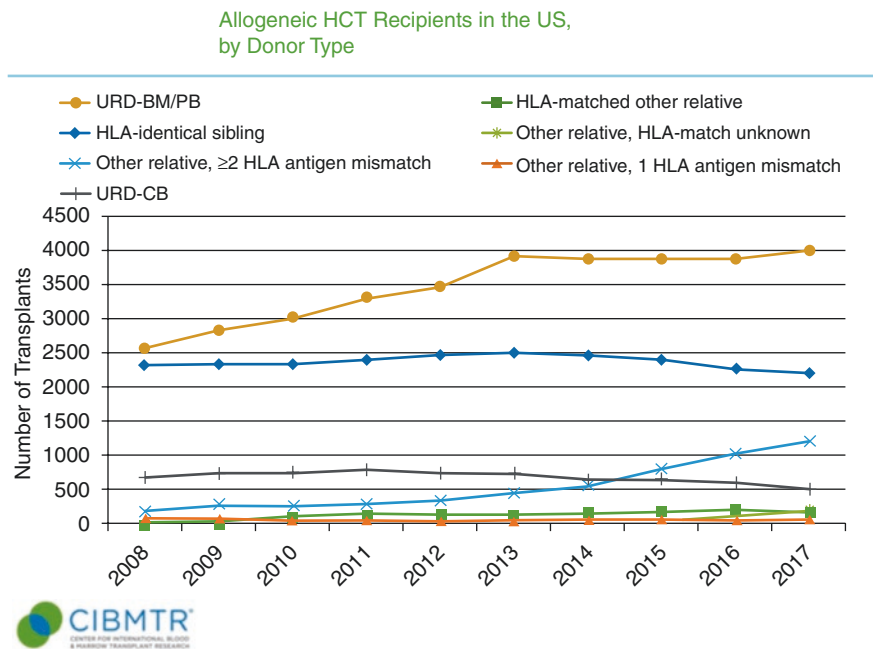
Fig. 2.5 Allogeneic HCT recipients in the US, by donor type
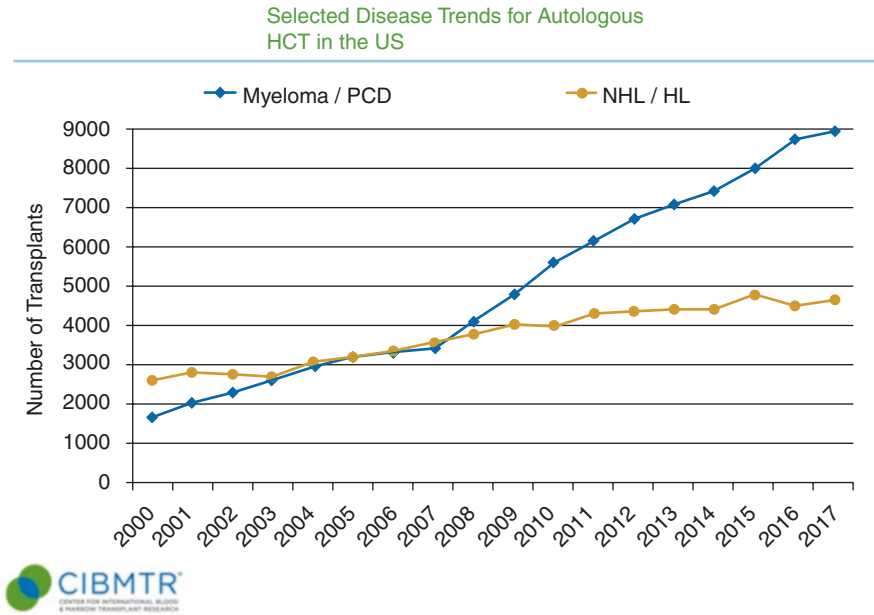
Fig. 2.6 Selected disease trends for autologous HCT in the US

Increase in Utilization and Impact of HCT on National Health-Care Costs

The amplification in numbers of HCT procedures has been associated with a dramatic increase in overall costs. Utilization of unrelated cord blood products has further impacted expenditure given the cost of a cord blood unit or, as frequently required in adult recipients, two cord blood units to meet the cell dose requirement. Cord blood recipients generally experience slower hematopoietic and immunologic recovery, adding further to the increased resource utilization.

Annual expenditures on cancer have also increased in the United States with cancer care costs estimated at $174 billion in 2020 of which the transplantable malignancy of lymphoma was #4 and leukemia was #6 in expenditure by disease sites [4]. (Fig. 2.7).

Based on population demographics and Surveillance, Epidemiology, and End Results (SEER) data for the incidence and prevalence of diseases for which transplant may be indicated and current treatment guidelines, the National Marrow Donor Program (NMDP) estimates that the need for allogeneic transplant in 2019 is approximately 17,500 annually, of which 12,500 will require an unrelated donor. The number of allogeneic transplants using related and unrelated donor sources for US patients has seen continual growth over the past decade. The number of

**Estimates of the proportion of national expenditures
for cancer care in 2017 by cancer site and phase of care**
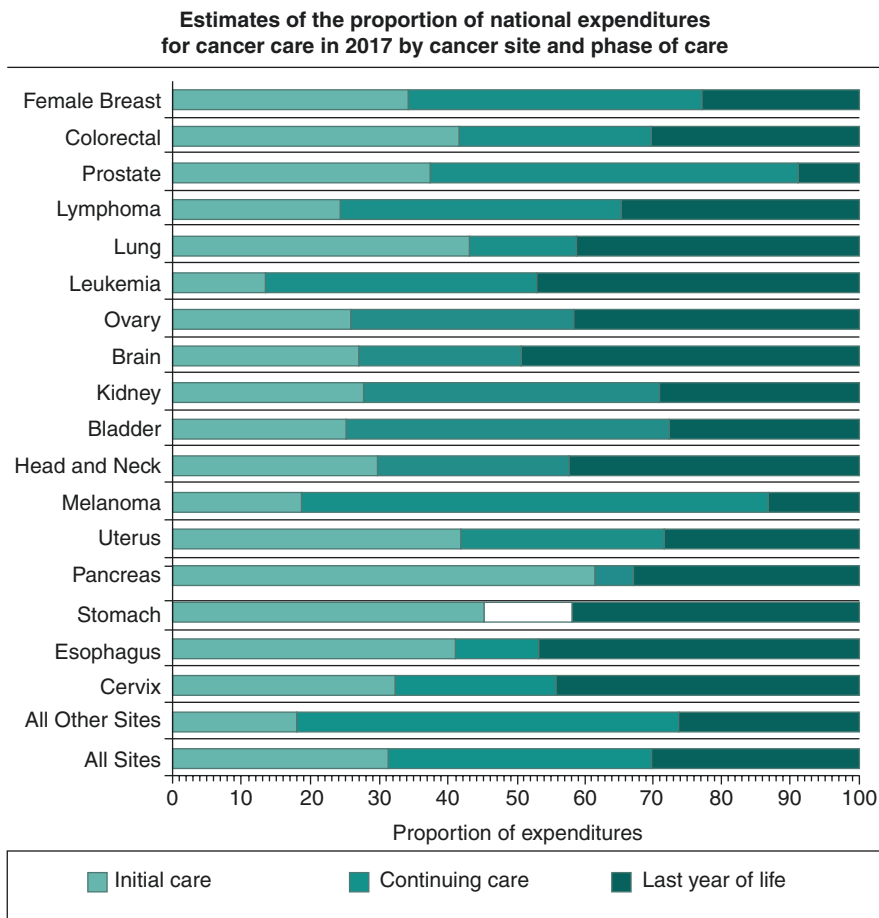
Fig. 2.7 Estimates of the proportion of national expenditures for cancer care in 2017 by cancer site and phase of care. (Source: Mariotto et al. [37]. Cancer Prevalence and Cost of Care Projections: http://costprojections.canncer.gov/ cost estimates expressed in 2010 dollars using CMS cost adjusters and adjusted for out-of-pocket expenditures, including co-payments and deductibles. Estimates for the population younger than 65 were developed using ratios of cost in the younger than 65 and older 65 populations from studies conducted in managed care populations)

unrelated donor sources leveled off in 2014 after years of double-digit growth [5] (Table 2.1).

These projections are supported by the Milliman 2017 U.S. Organ and Tissue Transplant Cost Estimates and Discussion report [3]. This analysis suggests that there was a 28% increase in billed charges for HCT procedures between 2011 and

Table 2.1 Allogeneic transplant growth

	Base Year 2011	2014	2015	2016	2017	2018
Allogeneic transplants (CIBMTR)	6400	7200	7500	7600	7800	NA
Unrelated allogeneic transplants in the United States (NMDP)	4250	4900	5100	4900	4900	5000
Unrelated allogeneic transplants worldwide (NMDP)	5600	6200	6400	6200	6000	6200

Table provided by NMDP in personal communication to Gary Goldstein; March 2019

2017. The estimates were based on billed charges (recognizing that charges do not equate to cost of procedures nor do charges indicate what percent of charges are paid by the governmental or private payor). Autologous transplant charges increased from approximately $363,800 to $409,600 (13% increase), and allogeneic transplant charges increased from approximately $805,400 to $892,700 (11% increase) in this short period of time. Also, recognizing that approximately 21,000 procedures were performed, these individual numbers suggest that transplantation has become a $13 billion industry.

Recognition of the above-described increase in HCT procedures and the ever-increasing expenditure associated with those procedures should provide motivation to program administrative leadership to be diligent in assessing opportunities to control costs and increase efficiency in order to avoid a pricing structure for these services that results in exclusion from the payor contracting arena.

Complexity of Care Increases Costs

In the setting of increasing demand for HCT, increasing cost of health care, and novel technologies (e.g., CAR-T therapy), it remains critical for providers and health systems to assure that adequate reimbursement is obtained to cover the costs of the individual procedures, costs associated with the defined incident of care, and the potential associated medical complications and sequelae.

Reimbursement based on a fee-for-service, indemnity approach no longer exists for the vast majority of patients. Insurance carriers have developed case rate contracts for HCT with negotiated payments for pretransplant evaluation, HLA typing, transplant product acquisition, and patient care. In contrast, government payors (Medicaid and Medicare) have set reimbursement schedules.

1. Medicare coverage provides funding for a period of time surrounding the actual transplant procedure, typically in a Diagnosis-Related Group (DRG)-based reimbursement structure.
2. It is important to recognize that DRG payments are provided with the presumption of a predictable resource consumption encountered by the recipient.
3. In some instances, the payor does not differentiate between autologous, allogeneic related, and allogeneic unrelated transplant in their rate-setting process. This approach ignores the greater complexity of workup, cell source selection, and post treatment risk of complications for the allogeneic recipient.
4. Preexisting comorbidities as well as the disease state and donor type drive resource consumption. These variables, seen across the spectrum of patients for whom transplant services are provided, are not accounted for by the limited DRG codes.
5. Contractual arrangements with private/commercial payors will often carve out HCT services from general medical services contracts. Strategies to carve out the unrelated donor search and acquisition components from the methodology for payment of the transplant-related care may also be employed.

Contracts and Reimbursement Strategies

If structured appropriately, contracts should reflect mutual exposure to financial risk. Reimbursement methodologies vary in the degree in which financial risk is shared.

One of the confounding issues that face those involved in the care of the transplant patient is that the actual transplant procedure is generally an infusion that occurs at a precise moment in the midst of a complicated medical treatment course. The infusion defines the actual transplant. However, reimbursement usually is focused on providing coverage for that event and for a series of surrounding days, which defines an episode of care. Various reimbursement methodologies have been undertaken, including reimbursement of the following:

1. All charges generated by providers and facilities in care of an HCT patient.
2. A discount off charges which represents a fixed rate percent discounting of total billed charges.
3. A case rate, which incorporates a fixed fee that covers all transplant-related facility services (inpatient and outpatient) within a boundary of time around the transplant, predating and following the actual infusion event. The post-infusion time period typically covers the first 30 days for an autologous HCT procedure and 100 days for an allogeneic HCT procedure.
4. A global case rate which represents a fixed fee that covers all hospital and physician charges for a specified period of time, typically involving posttransplant care. These contracts should be designed to address:

a. Recipient evaluation and assessment of transplant eligibility.
b. Donor search.
c. Harvest and acquisition of the stem cell product.
d. The immediate peri-transplant period and the posttransplant phase.
e. Special circumstances (pre-planned second transplant procedure, donor leukocyte infusion, re-transplants, high-cost pharmaceuticals (e.g., plerixafor [Mozobil®]).
f. The manner in which services covered by the global case rate will be reimbursed in the case where a recipient does not move forward to transplant.

Recognizing the unique needs of individual patients, many of the case rate and global case rate methodologies will include provisions that protect the transplant center as well as the payor from financial risk. These provisions vary in the degree of financial protection they provide. Examples include the following:

1. Outlier days: provide a per diem reimbursement for each inpatient day beyond a well-defined post-infusion time period.
2. Outlier threshold: reimburses the provider and institutions a defined percentage of billed charges after a specified threshold beyond the case rate has been reached.
3. Floor provision: assures that at no time will a hospital be reimbursed less than a specific percent of billed charges.

The setting in which the HCT procedure is performed, that is, inpatient or outpatient, may influence reimbursement. Pharmaceuticals may be reimbursed at a higher level per dollar of charge in the outpatient setting (e.g., 340B pricing for qualified institutions). The differences in reimbursement based on the setting can have a significant impact on the financial performance of the HCT program.[1]

Integrated Structure for Contract Management

The complexity of contracting for HCT services is reinforced by the implementation of separate transplant specialty contracting personnel by hospitals and payors. Development of rate structures that support the center's strategic initiatives, monitoring of the center's performance on each contract, and providing assistance to patients in understanding their benefits as they relate to the contract require an integrated team approach.

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[1] The intent of the 340B Program is to permit qualified institutions to stretch scarce Federal resources as far as possible, reaching more eligible patients, and providing more comprehensive services. Qualified institutions are allowed to purchase 340B drugs from the manufacturer at the reduced 340B contracted price. Drugs purchased with 340B pricing can only be used in the outpatient setting. The same drugs, for use in the inpatient setting, are purchased at a different contracted price.

1. A typical team for contract management would include the following:

    a. Managed care contracting
    b. HCT program medical director
    c. HCT program administrator
    d. Patient billing services
    e. Financial counseling personnel
    f. Program's managed care clinical liaison/financial coordinator

        i. Review of patient referral insurance information
        ii. Review of patients' benefits
        iii. Donor search and procurement
        iv. Lifetime maximum
        v. Transplant maximum
        vi. Prescription coverage
        vii. Travel and lodging
        viii. Clinical trial coverage
        ix. Communication with patient regarding benefits
        x. Liaison with insurance company in communication of patients' status in the process

    g. Medical social worker

Payor Types

Understanding reimbursement variability between governmental and private payors is a necessity. Traditionally, since HCT was performed in younger patients, private payors dominated the health coverage. However, over the last decade, there has been a significant change in the payor mix with an increase in patients with governmental insurance support (Medicare or Medicaid).

This shift in payor mix can have a dramatic impact on transplant program financial viability, given the low average rates of reimbursement by Medicare and state Medicaid programs.

Legislative changes, such as the Affordable Care Act (ACA), also affect a transplant program's financial viability given their impact on coverage rules and regulations.

1. Affordable Care Act

    a. The ACA was signed into law in the USA on March 23, 2010 with the potential to add over 30 million Americans to the insured ranks by 2019.
    b. The intent of the law was to increase access while reducing the overall cost of health care.
    c. Prior to the enactment and implementation of the ACA, HCT patients seeking new insurance coverage faced the potential of a lack of insurers willing to

insure them, limited benefit insurance plans with high premiums, and/or pre-existing condition exclusions of HCT-related costs [6].

d. The ACA assured access to health insurance for HCT patients in the following ways:

i. A requirement that anyone eligible for insurance could not be denied coverage.

ii. Prevented insurers from rescinding coverage when diagnosed with an illness or condition.

iii. Eliminated lifetime dollar limits on total paid benefits.

iv. Annual dollar limits were allowed only in a more restricted manner for services not covered by the definition of the Essential Health Benefits (EHB).

v. Removal of preexisting condition exclusions.

vi. Of note, some commercial payor plans may have eligibility in a "grandfathered" status that allows them to not be held to the requirement of coverage for all services required by the ACA.

e. In addition to access, the other significant principle of the ACA is an overall reduction in health-care spending, particularly in the Medicare program.

i. The impact on transplant centers has been significant given that Medicare eligible patients are the fastest growing segment of allogeneic HCTs.

ii. The elimination of lifetime, annual, and procedural financial caps and removal of preexisting condition exclusions has significantly eliminated outlier risk for patients.

f. Actions and decisions by the current and future administrations in Washington DC will continue to affect the ACA marketplaces and reshape American's access to health-care benefits [7]. This uncertainty related to the permanency of the ACA continues to influence the insurance marketplace.

2. Coordinated Care Organizations (CCOs)

a. The delivery of patient care by CCOs and Accountable Care Organizations (ACOs) is focused on managing populations and efficient delivery of primary care. Hematology and oncology patients could be viewed differently by hospital systems as the resource consumption by these patients would be significant, based on current pricing of many cancer therapeutics and procedures.

b. Transplant centers should consider how to prepare for new models of payment bundling, pay-for-quality programs, and an increased focus on cost-effectiveness and value from all payor types.

c. Transplant centers will be under pressure to document quality of care to avoid penalties and/or earn incentives.

3. Medicare Coverage for Stem Cell Transplantation

    The Centers for Medicare & Medicaid services (CMS) issued a National Coverage Determination (NCD) for stem cell transplantation. NCD 110.23 provides a list of covered and non-covered diagnoses for autologous and allogeneic HCT [8]. These coverage indications are also used by other government payors.

    The Medicare NCD also contains coverage guidelines for some indications where CMS feels that additional evidence needs to be gathered to confirm or rule out efficacy. Patients with a diagnosis addressed by a Coverage with Evidence Development (CED) determination are required to participate in a Medicare-approved clinical trial designed to determine efficacy for the Medicare population. At the time of publication, CED trials are open to evaluate allogeneic transplantation for myelodysplastic syndromes (MDS), myelofibrosis, sickle cell disease, and multiple myeloma.

    There are several diagnoses for which HCT may be considered, but which are not addressed in the NCD. In these cases, CMS delegates authority for coverage determinations to Medicare Administrative Contractors (MACs) [9]. A MAC may publish a Local Coverage Decision (LCD) to address stem cell transplant coverage in an area where CMS is silent, and this decision then applies to their geographic jurisdiction. If there is no NCD or LCD to address HCT for a specific diagnosis, then coverage is determined at the time of claims processing. This after-the-fact coverage determination can put patients and/or providers at financial risk, so the transplant community continues to work with CMS to expand the CED program or otherwise determine a way for patients with diseases commonly treated with HCT to receive coverage. Allogeneic HCT for certain types of NHL is the most common indication not addressed in the NCD [10].

    As of October 1, 2013, CMS finalized a new way to identify/determine appropriate inpatient admissions: a patient admission is presumed to be an appropriate inpatient admission for purposes of an MS-DRG (Medicare Severity – Diagnosis-Related Group) payment when there is the expectation that the patient will require a stay for more than 2 midnights. If the stay is expected to last fewer than 2 midnights, it generally would not be appropriate for an inpatient hospital admission. Since payment rates may differ significantly between inpatient and outpatient settings, the movement of patients from the inpatient to outpatient care setting can have a major impact on program revenue [11].

a. Inpatient Reimbursement Rates

    i. CMS pays for inpatient hospital stays under the Medicare fee for service Part A Inpatient Prospective Payment System (IPPS). Under the IPPS, an admission claim is categorized into a Medicare Severity Diagnosis-Related Group (MS-DRG, abbreviated to DRG). Each DRG has a payment weight assigned to it, based on the average resources used to treat Medicare patients in that DRG [12].

    ii. The DRG for autologous HCT covers the facility's technical charges for the admission in which the HCT takes place. Currently, autologous blood

      or marrow collection, including cell cryopreservation, is reimbursed separately from the admission.

   iii. The DRG for allogeneic HCT covers the inpatient transplant stay, and includes all donor search and procurement charges, whether the donor is related or unrelated to the Medicare beneficiary. Medicare requires that all donor charges to be held, until they can be billed on the recipient's inpatient facility claim for the transplant. These donor-related services are billed under Revenue code 0815; they are not separately reimbursable. It is important to include all services, including search and typing of potential donors that are not utilized, as well as for the actual allogeneic donor. All of these expenses are considered by Medicare when they calculate DRG payment rates in the future [13].

  b. Outpatient Reimbursement Rates

    i. CMS reimburses a facility's outpatient technical charges for Medicare fee for service patients under the Hospital Outpatient Prospective Payment System (OPPS). Whereas the inpatient DRG system provides an overall payment rate to the hospital (adjusted for complexity, cost outliers, and other factors), the OPPS uses a fee schedule to determine a reimbursement amount for each billable item on an outpatient claim. Reimbursement for services under the OPPS can vary significantly from IPPS rates.

4. Medicaid Services

  a. At the state level, there is wide variation in Medicaid reimbursement and coverage for HCT [14].

    i. There may be limitations based on indications for HCT, maximal allowable inpatient stays, and medication support, as well as variation in inpatient or outpatient service provision.

    ii. Clinical trial coverage variability also can be dramatically different.

      • HCT is not a mandatory covered benefit for adults, and all states have the discretion to choose whether to provide coverage or to determine the extent of coverage.

      • In austere times, states may identify control of Medicaid costs as a means to reduce their deficits and balance their budgets. An analysis of the Medicaid programs in 47 states by the NMDP assessing the degree of recommended benefit support which included transplant procedure and disease indications, donor search, medications, clinical trial support, and transportation and lodging, was unable to identify any state that provided minimal coverage benefits in all five categories and identified only three states met minimum supports level in four of the five categories. Eight states had perceived adequate Medicaid support coverage in only one of the five categories [15].

iii. The ACA mandated that all states must expand coverage under Medicaid to individuals up to 133% of the Federal Poverty Level (FPL) and provided federal funding to cover the cost of increased coverage. The United States Supreme Court declared that this requirement was unconstitutional and that each state had the right to decide whether or not to implement this provision. Thirty-seven states including the District of Columbia have adopted the ACA's Medicaid expansion [7].

b. Expanded Medicaid has both positive and negative repercussions for patients and HCT programs.

i. Increased access to coverage means more patients have HCT as a treatment option, but this expansion does not improve the quality of benefits or the reimbursement rates associated with state Medicaid plans.

ii. An increase in Medicaid patients with these less-than-ideal coverage provisions may increase burden on already limited transplant center resources.

5. Private Payors

a. There is significant variability in the aspects of HCT coverage through private payors.

b. Private payors often follow Medicare guidelines for coverage determinations for HCT indications. However, significant variability within contractual agreements for reimbursement structures, donor search and acquisition, benefit packages, clinical trial coverage, and financial procedural or lifetime benefits are found.

c. Coverage for the HCT patient is generally not an issue of medical necessity, but a detailed contractual agreement between the insurance beneficiary, the payor, and the site of employment from which the group insurance has been elected.

i. It is recognized that currently, for many payors, the majority of their members are in plans that are self-funded employer plans, for which benefits are individually selected by the employing company.

ii. As a means to control costs, one could envision that selection of high cost benefits for what would be perceived as orphan diseases might fail to be elected.

iii. Additionally, many small payor companies will have reinsurers that have their own set of contracted language, defining benefits for these high-cost procedures (https://payor.bethematchclinical.org/WorkArea/DownloadAsset.aspx?id=7501).

d. Detailed and specialized review of the recipient's insurance contract is necessary for comprehension of the benefit package and its potential for impact on both the potential HCT patient and the Program's financials.

6. Centers of Excellence

    a. Many of the larger private insurance and reinsurance companies have established center of excellence criteria and established national transplant networks.

    b. These programs may vary in size depending on the number of lives insured, the geographic regions covered by those insured, and the type of HCT procedure offered.

    c. For the transplant center, participation in these "Center of Excellence" programs and national transplant networks may allow access to greater numbers of patients.

        i. Participation is based on meeting selection criteria that is typically related to a center's volume and outcome data.

        ii. Selection to a network requires submission of detailed program information and disease-specific outcomes. There is typically an on-site inspection of facilities and review of program standards, as well as annual review of outcome data.

        iii. This payor requirement for transplant at a Center of Excellence can be a challenge for individual patients if the Center of Excellence is not geographically close, as they will need to relocate themselves and at least a caregiver family member to housing near the transplant center for an extended period of time. This additional financial burden may or may not be reimbursed by the insurance company.

Clinical Trials

The evolution of the HCT field over the last 30 years has been marked by advances in basic, translational, and clinical science. Clinical trials have been instrumental in determining the efficacy of HCT. Catalyzing the science of transplantation in the United States was the collaboration between the National Heart, Lung, & Blood Institute (NHLBI) and the National Cancer Institute (NCI) that led to the foundation of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Over 9600 patients have now been enrolled in BMT CTN trials including many who have participated in advanced phase III trials, defining new standards of care in the field [16]. Additionally, most transplant centers contribute HCT patient outcome data to the Center for International Blood and Marrow Transplant Research (CIBMTR) which has served as a central resource for retrospective analyses, answering questions that otherwise would not be answered in single-center prospective trials.

It is essential for a transplant program to verify that coverage is available for clinical trial participation. Wide variation exists with regard to coverage of clinical trial participation between governmental and nongovernmental payors.

1. CMS has a list of determined and non-determined diagnoses for coverage. There are no preauthorization pathways. If one chooses to offer a transplant procedure for a disorder in which there are no determinations, reimbursement after-the-fact will be at the discretion of the local Medicare intermediary.
2. Additionally, Medicare does not provide support for participation in phase I toxicity trials unless there are clear secondary efficacy endpoints.
3. In contrast, Medicaid programs will determine at a state level whether clinical trials are supported and to what extent.
4. With private payors, coverage of clinical trials has become even more complex.

   a. Many of the national payors have provisions that if clinical trials are supported by the National Institutes of Health (NIH), coverage is provided. Thus, funding would be provided if the recipient is receiving care at a NCI-designated cancer center or participating in a cancer intergroup or in a BMT CTN clinical trial.
   b. Participating in industry-sponsored clinical research trials or investigator-initiated research often requires strict scrutiny to verify that study-specific costs are not passed on to the payor, and that only designated standard-of-care coverage is the responsibility of the payor.
   c. The clinical trials landscape becomes even more complex as many of the group health plans are self-funded, business-selected plans.

      i. Even when HCT is considered standard care, if a portion of the care (e.g., choice of a prophylactic antifungal agent) is considered research, the entire transplant episode may be denied.
      ii. Often, clinical trials are omitted from the selection of benefits coverage for employees.
      iii. The National Business Group on Health (NBGH), in collaboration with the National Comprehensive Cancer Network, has published documents for review and implementation by employers outlining recommended benefits packages for cancer prevention and treatment among their employees.

5. Under the ACA, coverage for routine costs associated with an approved clinical trial became a requirement beginning in January 2014.

   a. Routine costs are defined as all aspects of care outside of the investigational drug, item, or procedure itself.
   b. Clinical trials must be approved or sponsored by the NIH, the Center for Disease Control and Prevention (CDC), Agency for Healthcare Research and Quality (AHRQ), and CMS.
   c. Trials may be any phase (I–IV) and must be conducted in relation to the prevention, detection, or treatment of cancer or other life-threatening disease or condition.

6. Transplant centers need to provide clear communication to payors regarding the justification for the trial, the eligibility of the patient, and the portions of the treatment plan that are routine or investigational.

Chimeric Antigen Receptor T-Cell Therapy (See Also Chapt. 52 and 58)

On August 30, 2017, the United States FDA approved the chimeric antigen receptor T-cell (CAR-T) product tisagenlecleucel (Kymriah®) for the treatment of patients up to 25 years of age with the B-cell precursor acute lymphoblastic leukemia (ALL) [17]. This approval of the first gene therapy available outside of clinical trials was met with incredible enthusiasm and eagerness by medical providers, patients, and investors, but with a mixture of excitement and trepidation by hospital administrators and insurance company leadership due to concerns regarding its cost.

The therapy involves harvesting a patient's autologous T cells, manufacturing the cells into a new construct designed to fight B-cell disease, and infusing the cells after a lymphodepleting chemotherapy regimen. The cells can expand in vivo, acting as a "living drug."

On April 17, 2012, Emily Whitehead, a 5-year-old diagnosed with ALL, became the first pediatric patient to be treated with CAR-T therapy on a phase I clinical trial at the Children's Hospital of Philadelphia (CHOP). Three weeks after receiving CAR-T treatment, Emily was in remission [18]. At the time of publication of this volume, Emily remains cancer-free [19], and she continues to provide hope and inspiration to patients and their families around the world.

The FDA's approval of tisagenlecleucel less than 6 years after the first child was treated was remarkably swift. It was only 2 months later, on October 18, 2017, that another CAR-T product, axicabtagene ciloleucel (Yescarta®), was approved by the FDA for patients with relapsed or refractory B-cell lymphoma [20]. On May 1, 2018, the FDA approved tisagenlecleucel for a second indication, that of relapsed or refractory large B-cell lymphoma [21]. This supplemental approval put these two commercial CAR-T therapies head-to-head for the same indication, giving providers a choice of treatments and allowed for market competition. Whereas tisagenlecleucel's market price was set at $475,000 for patients with ALL, using a variable pricing strategy, the market price was set at $373,000 for the NHL indication [22]. This price exactly matches the price of axicabtagene ciloleucel, also used for NHL [23].

1. Operationalizing Standard-of-Care CAR-T Therapy

   a. Bringing commercial CAR-T therapy to patients is a significant undertaking. Program administrators and medical directors need the support of medical center leadership and must build a strong case for resource allocation.
   b. In addition to staffing, inpatient and outpatient treatment space is needed.
   c. Programs must work with commercial CAR-T manufacturers for training and audits; Risk Evaluation and Mitigation Strategy (REMS) training is required for all clinical staff involved in CAR-T patient care due to the potentially significant risks of cytokine release syndrome and neurologic toxicities.
   d. Contracting and legal departments need to review and approve contracts that may cover T-cell collections and/or outcomes-based agreements.

   e. Setup and training for product ordering are required, and each manufacturer may use a different software solution.

   f. Centers will need to ensure that their charge description master (CDM) is up to date with appropriate line items, and that clinical billing screens are updated to include CAR-T billing services.

2. Coding

   a. When CAR-T therapy is performed under a clinical trial, the cost of T-cell collection and CAR-T manufacturing is typically covered by a clinical trial grant. Only standard-of-care services are billed to patients and their insurance. Once the FDA-approved CAR-T therapies, these costs must be borne by the patient, their insurance, or the medical provider. Ensuring systems are in place for charge and revenue capture is essential for a cellular therapy program to be successful.

   b. The medical billing system in the United States is extremely complex and includes different coding systems for diagnoses, procedures, and medications. When the FDA-approved CAR-T therapy, many of the necessary codes needed to bill the treatment were not in place. This created confusion in the industry, made it difficult to identify the treatment on medical claims, and made it near impossible for CMS, Medicaid, and commercial insurance companies to collect information on the cost of the therapy.

   c. Healthcare Common Procedure Coding System (HCPCS) code Q2040 (tisagenlecleucel) was added January 1, 2018 as a temporary drug code and was replaced with Q2042 on January 1, 2019 with a more accurate dose description [24]. Q2041 (axicabtagene ciloleucel) was added on April 1, 2018, but these are temporary codes and will eventually be replaced by permanent J codes. It must be noted that the Q code descriptions for these CAR-T products indicate that the item also includes "…leukapheresis and dose preparation procedures." Because of this, it is unclear whether those services can be billed separately under their own HCPCS codes.

   d. HCPCS codes for the collection of autologous T-cells for CAR-T, the preparation for transport of cells to the manufacturer (e.g., cryopreservation, shipping), the receipt and preparation for administration (e.g., thawing), and the cell administration were released to the American Medical Association (AMA) web site on July 1, 2018, and became effective January 1, 2019 [25]. These codes were issued as Category III CPT codes, which are considered temporary and used to allow data collection for emerging technologies and services. Medicare and some commercial payors may not recognize these codes as covered services.

   e. The infusion of CAR-T cells is often performed in the inpatient hospital setting, which requires the use of ICD-10 codes. On October 1, 2017, ICD-10 codes XW033C3 and XW043C3 were introduced for the administration of CAR-T cells (into peripheral vein or central vein, respectively) [26].

3. Billing

   a. Cell therapy program administrators should ensure that their hospital's charge description manual (CDM) has appropriate line items and CPT codes for the CAR-T-specific services (cell collection, processing, and infusion), and that those codes are also available when appropriate for professional fee billing. The program should also ensure that the CAR-T products themselves are available in the billing system, and that different line items are available for tisagenlecleucel based on the diagnosis being treated, due to the cost difference.

   b. The price markup for these cellular therapy products should also be carefully considered. Too low, and reimbursement from Medicare may be negatively impacted. Too high, and consumers and industry watchdogs may protest.

   c. Although the CAR-T product fall within a frame of reference for what we typically consider a "drug," many cell therapy centers house the cost and revenue for the product within the pharmacy cost center and revenue codes since the products have pharmaceutical Q codes assigned. This designation brings a unique challenge, since the pharmacy may know when a drug is ordered (through a purchase order), but they may not know when it is infused as the product is typically delivered by the manufacturer to a facility's cell therapy processing facility, and the pharmacy may not be involved in the actual infusion process. Communication to the pharmacy department is essential, if they are responsible for posting the CAR-T product charge.

4. Government Payor Reimbursement

   a. On August 7, 2019, CMS released the final decision memo for CAR-T therapy. In that decision memo, CMS stated that CAR-T therapy will be covered without the requirement of a clinical trial or coverage with evidence development (CED) when administered at health-care facilities enrolled in the FDA REMS program and used for either an FDA-approved indication, or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia [27].

   b. CMS has set coverage rates for CAR-T therapy, both in the inpatient and outpatient setting. On July 31, 2018, CMS announced that tisagenlecleucel and axicabtagene ciloleucel administered in the outpatient setting would be covered at the average sales price (ASP) +6% effective 10/1/18 [28]. This decision was significant, since prior to that there was little to no reimbursement for the high-cost cell product. However to date, most CAR-T infusions have been performed in the inpatient setting, and even an outpatient infusion would get covered as part of an inpatient claim if the patient is admitted to the hospital within 72 hours of the procedure.

   c. Inpatient coverage rates from Medicare remain far below hospital costs. Effective October 1, 2020, CMS revised the payment rates for inpatient CAR-T by creating a new diagnostic code: MS-DRG 018 Chimeric Antigen Receptor (CAR) T-cell Immunotherapy. The unadjusted payment rate is approximately 240,000. This is a considerable improvement over the previous rate of 43,127 wheh inpatient CAR-T services were part of MS-DRB 016. Yet, inpatient coverage rates still remain below hospitals' costs [29].

d. Impacting both inpatient and outpatient reimbursement is the removal of the New Technology Add-On Payment (NTAP) as of September 30, 2020. Previously an NTAP allowed centers to recover an additional 65% or a maximum of $242,450 based on total billed charges for the case and the hospital's overall cost-to-charge ratio. The increase in teh MS-DRG payment makes up some of this difference cause by the deletion of the NTAP.

e. Medicaid coverage rules and rates vary from state to state; therefore, summarization of current reimbursements for this patient population is not possible. However, Medicaid typically reimburses at rates far below commercial payors and Medicare, and frequently below the cost of providing care.

5. Commercial Insurance Contracting and Reimbursement.

a. Commercial insurance companies in the United States have typically covered HCT using some type of case rate payment structure. This structure is possible because both payors and providers have a good understanding of expected costs and outliers for those treatments. Because CAR-T therapy is still relatively new, few organizations have a clear understanding of the costs associated with delivering CAR-T treatment. A case rate is difficult to set in these instances, but could be possible as long as protections were in place (payment floors and/or stop-loss).

b. If a program is considering a case rate structure, well-defined case period start and end dates are necessary. "Evaluation" services may be considered as part of the case. However, it is often difficult to tease out CAR-T-specific services. A patient with NHL may have a PET scan to determine if they can proceed to HCT (responsive disease) or to CAR-T (nonresponsive disease); the scan is not CAR-T-specific.

c. A clinically appropriate case end date is equally important. Patients who fail to respond to CAR-T therapy may move swiftly to another salvage therapy, and patients that do well could proceed to HCT. A case period with too long of a follow-up period included could cause non-CAR-T services to be bundled into the case.

d. Although case rates are difficult to set at this point in time, general service contracts may not provide adequate reimbursement for the extremely high-cost CAR-T product. Because of that, many providers and commercial insurance companies have negotiated individual letters of agreement (LOA) to specify how the cell products and ancillary services will be paid. These agreements may include specific reimbursement for the cell product, based upon the wholesale cost. Ancillary services may be covered at the general service or other specified rates. A case rate structure is highly likely in the future, but they would need to be flexible to adjust to the various costs of cell products as more come to market.

e. Lessons learned from CAR-T therapy's commercial application will be extremely helpful as newer cellular and gene therapies come to market.

Quality

High quality outcomes for HCT patients have always been a goal of transplant providers and their teams. Determination of quality was often performed internally to

evaluate systems and elements that could influence the HCT product line and service delivery. Increasingly, there has been national attention on outcomes necessary to maintain eligibility within third-party payor' networks, and more recently, for governmental payor reimbursement. For example, CMS has implemented a reimbursement program based on "Value-Based Purchasing" in which a percentage of hospital reimbursement for CMS patients is held at risk while determining whether or not the hospital has met target goals for optimal patient experience and whether clinical measures are achieved. For HCT programs, the incidence of catheter-associated bloodstream infections, readmissions, or falls with harm can negatively influence the reimbursement of services.

The establishment of a public, national Stem Cell Therapeutic Outcomes Database (SCTOD) for patients undergoing allogeneic blood, cord, and marrow transplant procedures is a part of the US Health Resources and Services Administration (HRSA) funded C.W. Bill Young Cell Transplantation Act. This allows for assessment and comparison of interinstitutional overall 1-year survival rates.

Consistent with CIBMTR's goal to increase transparency of the Center Outcomes Report and at the urging of the HSRA, CIBMTR has made available un-blinded center-specific outcomes reports [30–32]. In this way, centers' survival outcomes are available to patients, insurers, government agencies, and the Foundation for the Accreditation of Cellular Therapy (FACT).

Comparative risk assessment based on patient pretransplant comorbidities and standardized determinations of severity of illness for the transplant stay, generated by evaluating the discharge diagnostic codes, are being utilized by groups such as Vizient (www.vizientinc.com). Member organization can use available data to compare metrics such as length of stay, percent of intensive care unit transfers, and observed-to-expected in-hospital mortality. It is anticipated that quality initiatives will be increasingly scrutinized with a major focus on survival, quality of life, and presence or absence of clinical comorbidities. Efficient health-care delivery via care pathways will also be examined, and their utilization will increasingly influence reimbursement, as well as maintaining Center of Excellence designation.

1. Foundation for the Accreditation of Cellular Therapies (FACT)

   a. FACT is a nonprofit corporation co-founded in 1996 by the International Society for Cellular Therapy (ISCT) and the American Society of Blood and Marrow Transplantation (ASBMT, currently American Society of Transplantation and Cellular Therapy [ASTCT]) to provide a peer network of experts committed to improving stem cell transplantation and cellular therapy practices by formulating and disseminating evidence-based guidelines [33].

   b. The primary objective of the FACT standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration is to promote quality medical and laboratory practice in hematopoietic progenitor cell transplantation and related therapies using hematopoietic-derived cellular products [34].

   c. FACT accreditation, which addresses clinical care, donor management, cell collection, cell processing, and cell administration, is voluntary. However, it

has become an almost necessary qualification for a program to be acknowledged and remain competitive.

d. Many insurers, Centers of Excellence programs, and National Transplant Networks include FACT accreditation as a requirement for selection/inclusion.

e. Accreditation is awarded after successful documentation of compliance with FACT standards. Compliance is judged by evaluation of written documentation and through on-site inspections.

f. The FACT standards require that clinical programs achieve 1-year survival outcomes within or above the expected range when compared to national or international outcome data for allogeneic transplant outcomes. The CIBMTR Stem Cell Therapeutic Outcomes Database (SCTOD) can be used as a source for comparison data and to demonstrate patient outcomes within the expected minimum range.

g. Improving 1-year survival when outcomes are not within the expected range requires a detailed process of analysis and performance improvement. Programs should continually study and monitor their outcome data. Routine (monthly or quarterly) review of outcome data, rather than review at only annual intervals, positions the Program to take incremental steps in outcomes improvement if appropriate.

h. If a Program's 1-year survival rate does not meet the expected survival rate in the SCTOD, FACT requires the submission of a corrective action plan (CAP). FACT provides the following guidelines for elements that must be included in a CAP: specific causes of death; quantitative data; potential causes of 1-year mortality rate; actions to be taken to address the identified causes; and measurable elements to monitor outcome improvement [34].

i. FACT has established new standards specific to the use of IEC. These standards specify the clinical and quality infrastructure to facilitate safe administration of IECs and formalize subsequent monitoring and reporting of patient outcomes to enable continual process improvement.

j. In addition to IEC standards for donor workup, apheresis collection, labeling, storage, documentation, and product administration, FACT created standards and guidance in these additional areas [35].

   i. Location of Cell Manufacturing: The level of involvement in manufacturing by a clinical site for a given IEC product may vary. Under FACT standards, programs are responsible only for the steps in which they are involved, for example, donor workup, collection, and administration but not the manufacturing of the cellular product if it occurs at a third party or commercial laboratory. Documentation to ensure and verify chain of custody through multiple handoffs from collection until infusion is required.

   ii. Identification and Management of Cytokine Release Syndrome: Specific medications and algorithms to manage this are evolving; therefore, the FACT standards do not suggest a specific management strategy, but instead suggest that physicians, nurses, and other providers have training to detect these complications and demonstrate competency in responding to them;

pharmacy formularies are adequate to treat anticipated toxicities; and an institution has guidance for management considerations that the entire health-care team can access.

iii. Communication: Given the multiple teams involved with a patient's product and care, a cell therapy program should demonstrate appropriate communication pathways between the many providers involved and procedures for rapid escalation of care when needed.

iv. Data Management and Oversight: Data on product safety, efficacy, and clinical outcomes are to be collected and reviewed by the program director at least annually. FACT encourages the use of the CIBMTR Cellular Therapy forms for IEC therapy to support the availability of data to the entire field [35].

2. Data Management

a. An HCT program's data management enterprise supports compliance with regulatory standards, internal assessment of quality and quality improvement initiatives, and research development.

b. HCT programs are expected to contribute data regarding transplant procedures to the NMDP, CIBMTR, SCTOD, or similar data repositories. These data are then available for research purposes on outcomes.

3. The Food and Drug Administration (FDA)

a. The FDA's mission is to protect the public health.

b. In May of 2005, the FDA created a registration system for establishments that collect, manipulate, and manufacture cellular therapy products.

i. The registration system was created to establish procedures to prevent the introduction, transmission, and spread of communicable disease by cellular therapy products.

ii. HCT programs are required to register and submit a list of all types of cellular therapy products collected or infused in their institution. The registration must be updated annually.

c. The FDA requires documentation of complaints involving the distribution of cellular therapy products that allege transmission of a communicable disease to the recipient of the product.

d. Enforcement of the registration and reporting requirements is accomplished by FDA inspections.

Future Considerations

HCT procedures will continue to grow in demand as outcomes improve, novel therapeutic indications are identified, and the population ages. New technologic advances in cellular therapy will continue to emerge. It is likely that continued

development of the investigational cellular products, including dendritic cells, regulatory T cells, natural killer cells, mesenchymal stromal cells, CAR-T, and viral-specific cloned T cells will prove to be beneficial in the clinical course of the transplant patient.

The FDA is witnessing a surge in cell and gene therapy products entering early development, evidenced by a large upswing in the number of investigational new drug (IND) applications. By 2025, the FDA predicts the agency will be approving between 10 and 20 cell and gene therapy products annually [36].

The advances in small molecules and targeted therapies could diminish the demand for HCT or alternatively, could enhance the likelihood of improved outcomes, thus furthering the demand for procedures. Reexamination of reimbursement strategies, particularly regarding the contractual arrangements around an "incident of care," will be necessary to assure that the cost of goods and manufacturing of these novel therapies are included within the transplant/cellular therapy patient's benefit package.

Similarly, the demand for HCT procedures may further expand if new indications emerge, such as autoimmune disorders or co-transplantation with solid organs.

Summary

1. Well-designed prospective clinical trials and retrospective data analyses have provided the critical data that led to designation of HCT as standard-of-care for a variety of malignant and nonmalignant disorders.
2. The demand for evidence-based medicine will continue as will the demand for quality outcomes with efficiency in delivery. Coverage decisions will depend on whether evidence exists to justify the support. Ongoing attention to detail for services rendered is necessary to identify whether or not payment is adequate and justified.
3. Multi-institutional comparison of outcomes will continue and will be expanded to determine if the services supported by private or governmental payors were delivered with high quality.
4. One can anticipate that assuring that both patients and providers have all the information needed to make accurate decisions will be demanded as transparency has become central.
5. The need for more flexible models of reimbursement is required, as the current approach where contractual rules supersede medical necessity generally does not keep up with the technologic advances driving the field.
6. Recognition of these issues and the critical need for collaborative interactions between providers and health-care systems will be needed to continue to manage the HCT/cellular therapy patient population, going forward.
   The ability to maintain and expand an HCT/cellular therapy program requires the efforts of a specialized business team to develop, implement, and manage contracts; personnel knowledgeable of the most current regulatory standards and

data reporting requirements; and a clinical team dedicated to the critical ongoing communication with the referring physician. This partnership is critical to the promotion of long-term survivorship for the HCT/cellular therapy patient.

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Chapter 3
Hematopoietic Stem Cell Sources and Donor Selection

Jose F. Leis, Richard T. Maziarz, and Susan Schubach Slater

Introduction

1. Human hematopoietic stem cells (HSCs) express CD34 and Thy-1 (lo) on their surface and are capable of multi-lineage growth and supporting long-term hematopoiesis.
2. HSCs can be isolated from bone marrow (BM), peripheral blood after mobilization (PBSC), and umbilical cord blood (UCB).
3. HSCs may be obtained from autologous (BM or PBSC) or allogeneic (HLA-matched related (MRD), HLA-matched unrelated (URD), or mismatched related or unrelated donors, and UCB) sources.
4. The World Marrow Donor Association (www.wmda.info) maintains an international inventory of the majority of available adult unrelated donors and cord blood units. As of 2019, multiple donor registries and cord blood banks across the world offer access to an estimated 36 million stem cell donors and products.

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Stem Cell Sources

1. Bone Marrow (BM)

    a. Gold standard for more than three decades.
    b. Aspirated from posterior iliac crest under general or regional anesthesia.
    c. Generally requires 10–20 mL/kg of marrow for adult recipients.
    d. Donors can be primed with filgrastim (e.g., Neupogen®) prior to harvest which may improve HSC recovery in heavily pretreated patients.
    e. Advantages

        i. Fewer T cells in graft compared with peripheral blood source

            • Decreased risk chronic graft-versus-host disease (GvHD)

        ii. Decreased mortality in children and adolescents

    f. Disadvantages

        i. Often requires operating room access with spinal or general anesthesia
        ii. Increased morbidity to donors

            • Potential risks include pain, infection, blood loss, nerve damage, and skeletal complications.
            • May require blood transfusions for volume replacement post-harvest, particularly in younger pediatric donors.

        iii. Later engraftment of neutrophils and platelets
        iv. Increased risk of relapse in some studies [1]

    g. Target cell dose

        i. Target cell dose 2×10^8 total mononuclear cells (TMNC)/kg recipient body weight.
        ii. Minimum 1×10^8 TMNC/kg recipient body weight.
        iii. Retrospective studies show better hematopoietic recovery, decreased treatment related mortality, and improved overall survival when CD34 cell dose $>3 \times 10^6$/kg [2].

2. Peripheral Blood (PBSC)

    a. Under normal circumstances, HSCs are found in very low levels in peripheral blood.

        i. Thousand-fold or more increase in circulating HSC seen after filgrastim (e.g., Neupogen®) stimulation or recovery from cytotoxic chemotherapy.
        ii. PBSCs have largely replaced BM as primary source of HSCs.

    b. Advantages

        i. Rapid recovery of hematopoiesis compared to BM.
        ii. Decreased morbidity to donors.

    iii. Increased disease-free (DFS) and overall survival (OS) with MRDs in high-risk hematologic malignancies [1]; however, this advantage was not demonstrated in the BMT CTN 0201 clinical trial comparing PBSC and BM in the URD setting [3].

c. Disadvantages

    i. Must mobilize stem cells into circulation

- Use of chemotherapy in autologous setting
- High-dose filgrastim (e.g., Neupogen®), sargramostim (e.g., Leukine®), +/− plerixafor (Mozobil®, currently autologous setting only)

    ii. More T cells in circulation compared with BM

- Increased risk chronic GvHD in the allogeneic setting [3–5]

d. Target cell dose

    i. Minimum 2×10^6 CD34+ stem cells/kg recipient body weight
    ii. Target $3–5 \times 10^6$ CD34+ stem cells/kg recipient body weight although this varies by institution
    iii. Doses $>8 \times 10^6$ CD34+ stem cells/kg associated with increased risk of GvHD and decreased overall survival in some allogeneic transplant studies

e. Mobilization

    i. Autologous transplant

- Disease-specific chemotherapy followed by filgrastim 10 μg/kg/day SQ until peripheral blood CD34 count meets or exceeds institutional target levels, for example, >10 cells/μl before onset of leukapheresis
- Filgrastim 10 μg/kg/day SC for 4 days followed by leukapheresis on day 5
- Filgrastim 10 μg/kg/day SC for 4 days in the morning + plerixafor 0.24 mg/kg SC (maximum dose 40 mg) on evening day 4
- Plerixafor (Mozobil®)

  – Reversibly inhibits binding of SDF-1α, expressed on bone marrow stromal cells, to the CXC chemokine receptor 4 (CXCR4), resulting in mobilization of hematopoietic stem and progenitor cells from BM to the peripheral blood.
  – Reduce dose to 0.16 mg/kg (max 27 mg) if estimated glomerular filtration rate (GFR) <50 ml/min using Cockroft–Gault equation.
  – United States Food and Drug Administration (FDA) approval in the autologous setting for patients with multiple myeloma and non-Hodgkin lymphoma. Currently not approved for use in allogeneic donors.

ii. Factors associated with poor mobilization

- Prior chemotherapy: Increased cycles and duration of treatment
- Prior radiation to BM
- Low pre-mobilization platelet count
- Female gender
- Exposure to purine analogs, for example, fludarabine
- Exposure to alkylating agents, for example, prior melphalan in myeloma
- Exposure to lenalidomide (Revlimid®)
- BM involvement by lymphoma
- Low peripheral blood CD34 count during mobilization

  - Peripheral blood CD34 count is proportional to CD34 apheresis yield.
  - Peripheral blood CD34 < 10 cells/μl associated with mobilization failure.

iii. Strategies for the hard to mobilize patient

- BID dosing of filgrastim 5–10 μg/kg/day SC for 4 days then leukapheresis
- Double growth factor: BID dosing of filgrastim 5–10 μg/kg SC plus sargramostim 250 mg/m²/once daily for 4 days then leukapheresis
- High-dose filgrastim + plerixafor
- Bone marrow harvest

iv. Risk-adapted approach from the Mayo Clinic [6]

- Start filgrastim alone 10 μg/kg/day.
- If day 4 or day 5 peripheral blood CD34 ≥ 10/μl, initiate leukapheresis the following day (if tandem transplants planned, for example, myeloma patients initiate leukapheresis if CD34 ≥ 20/μl).
- If day 5 peripheral blood CD34 < 10/μl, add plerixafor 0.24 mg/kg evening dose (dose adjusted for renal function), initiate leukapheresis the following morning.
- If daily leukapheresis yield <0.5 × 106 CD34/kg, repeat plerixafor and continue leukapheresis the following day.
- Continue daily filgrastim and plerixafor until goal is reached or ABORT collection if <0.5 × 106 CD34/kg collected despite use of plerixafor.

3. Umbilical Cord Blood (UCB)

a. High numbers of fetal HSCs are present in UCB collected after delivery.
b. Each year no suitable 7/8 or 8/8 MRD or URD can be identified for 6–10,000 patients who could potentially benefit from HCT. This deficiency is particularly true for minority patients [7].
c. Cryopreserved cord blood units are generally HLA typed only at intermediate resolution for HLA-A and HLA-B and at high resolution for HLA-DR. [8].
d. Advantages

      i. Criteria for a "match" less stringent.

- 4/6 match acceptable
- Increases the chance of finding a suitable donor

      ii. UCB lymphocytes are less alloreactive as they are immunologically naïve.

- Allows for greater HLA disparity, can engraft with 4/6 match
- Decreased GvHD for degree of mismatch

      iii. Rapid access: Suitable cord unit can be identified in a few days and shipped overnight.

e. Disadvantages

      i. Cell dose.

- Need a minimum of $3–4 \times 10^7$ total nucleated cells (TNC)/kg to ensure durable engraftment.
- Only 10% of UCB units have sufficient stem cells to transplant a patient >50 kg in weight.
- Increased non-relapse mortality to 70% with cell doses $<1.7 \times 10^7$ TNC/kg.

      ii. Slow engraftment relative to related or unrelated donor BM or PBSC transplants.
      iii. Increased infectious complications from delayed neutrophil engraftment.
      iv. No donor leukocyte infusion (DLI) available for treatment of relapse or graft failure.
      v. Currently limited inventory is available due to inadequate cell counts.

f. Impact of cell dose

      i. Slower rate of hematopoietic recovery compared with PBSC and BM.
      ii. High risk of graft rejection.
      iii. High treatment-related mortality (TRM).
      iv. Low CD34 dose is associated with poor OS.
      v. Magnified effect of HLA-mismatch.

g. Guidelines for cord blood unit selection continue to be refined.

      i. EuroCord recommendations have been standard [9, 10].

- 6/6 match $>3 \times 10^7$ TNC/kg.
- 5/6 match $>4 \times 10^7$ TNC/kg.
- 4/6 match $>5 \times 10^7$ TNC/kg.
- Single-unit UCB transplant should not be performed with <4/6 match or $<3 \times 10^7$ TNC/kg.

      ii. Updated guidelines from the National Marrow Donor Program (NMDP) and Center for International Blood and Marrow Transplant Research (CIBMTR) have expanded the selection process [10].

h. Strategies to improve UCB transplant in adults.

   i. Double UCB unit grafts to augment cell dose.

- Most patients have more than one 4 to 6/6 HLA-matched UCB unit available.
- Adult studies suggest improved engraftment and reduced TRM compared with single-unit transplants.
- Sustained engraftment seen from only one of the two units, not both.

  ii. Experimental approaches for ex vivo expansion are currently under investigation [11].

Donor Selection (See Fig. 3.1)

1. HLA typing [12]
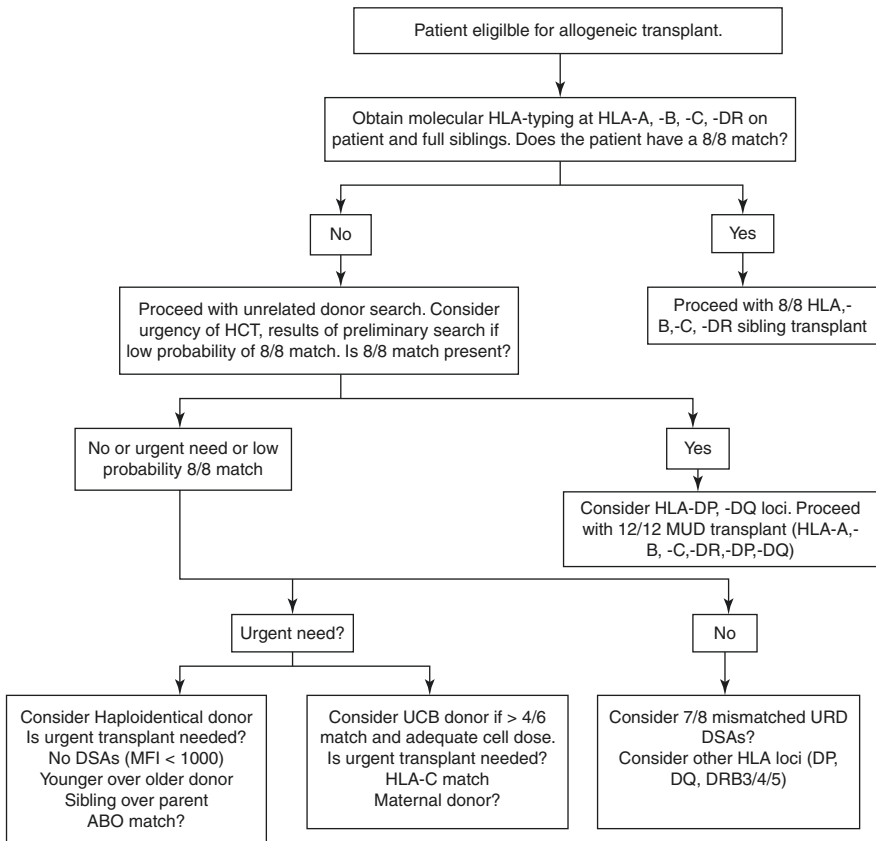
Fig. 3.1 Donor selection for allogeneic hematopoietic cell transplantation. *HLA* human lymphocyte antigen, *URD* matched unrelated donor, *UCB* umbilical cord blood, *URD* unrelated donor, *DSA* donor-specific antibodies

   a. Human leukocyte antigen (HLA) is the name of the set of genes on chromosome 6 that encode the human major histocompatibility complex (MHC).

   b. HLA genes are highly polymorphic.

   c. Each HLA allele is designated by the name of the gene/locus followed by an asterisk and a 4–8-digit number indicating the allele. The first two numbers are based on the serologic type of the resultant protein "antigen", and the next two numbers on the specific allele designation are based on the order in which the gene was discovered, for example, A*0201 is an allele of the HLA-A2 gene.

   d. HLA antigens are key components of immune function and are involved in recognizing self versus non-self, in organ or graft rejection, GvHD, infection control, autoimmunity, etc.

   e. HLA class I molecules (HLA-A, HLA-B, HLA-C) are found on the surface of all nucleated cells.

   f. HLA class II molecules (HLA-DR, HLA-DQ, HLA-DP) are found on the surface of immune system cells (i.e., B lymphocytes, dendritic/antigen presenting cells) and are inducible in most tissues.

   g. Matching donor and recipient for HLA haplotypes is the most important factor of a successful allogeneic hematopoietic cell transplant.

2. Matched related donors (MRDs)

   a. 25% chance a given sibling will be HLA-matched at A, B, and DR loci

   b. Preferred donor over other donor options.

   c. Associated with lower rates of acute and chronic GvHD.

   d. More rapid and less expensive donor workup and stem cell procurement compared with URD or CBD options.

   e. Improved clinical outcomes.

   f. Despite improvements in outcomes (TRM, relapse-free survival [RFS], and OS) of unrelated donor transplants, MRD are still favored in patients >50 years of age.

      i. Risks of acute GvHD grade 2–4 (hazard ratio [HR], 1.63; $P < 0.001$), acute GvHD grade 3–4 (HR 1.85; $P < 0.001$), and chronic GvHD (HR 1.48; $P < 0.0001$) were all higher after URD compared with MRD transplants in these older patients [13].

   g. Higher risk of relapse of malignancy if donor is an identical twin (syngeneic) [14].

3. Matched unrelated donors (URDs)

   a. Only 30% of patients who require an allogeneic HCT will have an HLA-MRD.

   b. A large number of donors are needed in registries due to the large diversity in the HLA system (>18,000 class I alleles and >7500 class II alleles have been identified resulting in millions of HLA combinations) [11].

   c. Certain racial and ethnic groups have a larger number of specific haplotyes resulting in increased difficulty in finding suitable donors (e.g. African

       Americans have a greater number of polymorphisms than Caucasians at HLA loci).

d. Identification of a suitable URD may take 2–6 months although new efforts to expedite the process are ongoing including BMT CTN 1702 which utilizes a novel computer algorithm to rapidly screen the registry to guide donor decision-making. (https://web.emmes.com/study/bmt2/protocol/1702_protocol/1702_protocol.html).

e. Longer search times make URD HCT less feasible for patients with high-risk leukemia. Donor searches should be started early in the treatment course for these patients.

f. Each HLA antigen or allele mismatch is associated with an approximate 10% decrease in 5-year post-transplant survival. In a large retrospective study of 3857 myeloablative bone marrow transplants done between 1988 and 2003 in the USA, a single mismatch detected by low- or high-resolution DNA testing at HLA-A, -B, -C, or DRB1 (7/8 match) was associated with higher mortality, lower 1-year OS (43% vs. 52%), lower DFS, and increased TRM and acute GvHD. Single mismatches at HLA-B, -C were better tolerated than mismatches at HLA-A or -DRB1. Mismatching at 2 or more loci increased the risks while mismatches at HLA-DP or DQ and other donor characteristics did not affect survival [15].

g. Retrospective analysis of 1933 unrelated donor-recipient pairs who received PBSC HCT between 1999 and 2006 showed that an 8/8 match was associated with better 1-year survival than a 7/8 match (56% vs. 47%). Mismatch at HLA-C antigen correlated with decreased leukemia-free survival (LFS) and increased risk of mortality, TRM, and grade 3–4 acute GvHD [16].

h. Other donor factors such as age, sex, parity, cytomegalovirus (CMV) status, and ABO matching may also affect outcome.

i. An updated algorithm guiding unrelated donor selection is shown in Table 3.1.

Table 3.1 Selection of a haploidentical donor

T-cell ex vivo depleted graft	Non-T-cell-depleted grafts
No DSAs (MFI < 1000)	No DSAs (MFI < 1000)
NK cell alloreactive donor (for malignancies)	Younger donor over older donor
Younger donor over older donor	Male donor for a male recipient
Male donor for a male recipient	Sibling or offspring donor over parent donor
First-degree relative over second-degree	Between parent donors, father is preferred over mother donor
HLA half-matched donor	ABO-matched is preferred to minor ABO-mismatched to major ABO-mismatched donor
Between parent donors, mother is preferred over father	First-degree relative over second-degree HLA half-matched donor
ABO-matched donor	
CMV seropositive donor for CMV seropositive recipients	

DSA donor-specific antigen, *MFI* mean fluorescent intensity, *NK* natural killer, *HLA* human leukocyte antigen, *CMV* cytomegalovirus

4. Alternative Donors

Alternative donor sources (UCB or haploidentical donors) allow for shorter time to transplant but are associated with increased risk of transplant-related complications.

a. Haploidentical donors [17, 18]

   i. Related haploidentical donors are matched at 3–5 of 6 loci (HLA-A, -B, −DR) sharing one chromosome 6 with the recipient.

   ii. Multiple individuals in a family including parents, siblings, and even children can potentially serve as the donor. See Table 3.1 and Appendix 10 for selection guidelines.

   iii. Allows for increased donor availability in racial and ethnic groups.

   iv. Historically, intensive GvHD prophylaxis was used. In one international study, antithymocyte globulin (ATG), cyclosporin, methotrexate, mycophenolate (Cellcept®), and anti-CD25 antibody were utilized. Cumulative incidence of grade 2–4 acute GvHD was 11% in the CD25 group vs 33% in the control group. DFS was estimated at 53% at 2 years [19].

   v. Immunosuppression with post-transplant cyclophosphamide is now accepted as a standard haploidentical GvHD prophylaxis in many institutions [17, 18].

   vi. The BMT CTN conducted two parallel phase II trials for patients without HLA-matched donors. Reduced intensity conditioning (RIC) with post-transplant cyclophosphamide was used followed by either double UCB (BMT-CTN 0602); or haploidentical BM (BMT-CTN 0603). The 1-year OS and progression-free survival (PFS) were 62% and 48%, respectively. The 100-day incidence of acute grade 2–4 GvHD was 32%, 1-year incidence of NRM 7%, and relapse 45% after haploidentical-transplant [20].

   vii. A prospective phase III trial comparing double UCB and haploidentical transplantation (BMT-CTN 1101) has been accrued and the data will be forthcoming [21].

   viii. Mismatch of maternal antigens are better tolerated than mismatch of paternal antigens.

     • Leukemia patients who received myeloablative conditioning followed by T-cell-depleted haploidentical maternal grafts had superior 5-year event-free survival (EFS) than those who received paternal grafts (50.6% vs 11.1%; $P < 0.001$). Improved survival was the result of lower relapse rates and TRM. The protective effect was seen in both female and male recipients [22].

5. Umbilical cord blood

a. Demand for UCB HCT has increased rapidly due to lack of suitable HLA-matched donors, particularly in ethnic groups, time limitations due to aggressive disease, and the potential lower incidence of GvHD.

b. Advantages include expanded donor pool, ease of product procurement, lack of donor attrition, donor safety, and decreased incidence of GvHD.

c. Major disadvantages include delayed engraftment, prolonged defects in immune reconstitution leading to increased risk of infection, increased risk of graft failure, and no opportunity for additional donations in the setting of graft failure/rejection or relapse.

d. In children with malignancies, HCT with UCB units matched for 4, 5, or 6 of 6 HLA haplotypes produces results that are equal to an 8 of 8 HLA-matched BM HCT.

e. Potential UCB units should be selected on the basis of greatest HLA match that contain an adequate TNC count.

   i. Acceptable UCB units should contain $\geq 3 \times 10^7$ nucleated cells/kg and also, preferentially $\geq 2 \times 10^5$ CD34+ cells/kg.

   ii. In patients transplanted for non-malignant disease, the risk of rejection is higher and a cutoff of $\geq 3.5 \times 10^7$ TNC/kg is recommended.

f. In a large retrospective study of adults transplanted for acute lymphocytic leukemia (ALL), LFS after UCB HCT was comparable to 7/8 and 8/8 allele-matched URD PBSC or BM HCT [23].

   i. TRM was higher after UCB HCT than after 8/8 allele-matched PBSC or BM HCT.

   ii. Grades 2–4 acute and chronic GvHD were lower in UCB recipients compared with allele-matched PBSC.

   iii. The incidence of extensive chronic GvHD was lower after UCB HCT compared to 8/8 allele-matched BM HCT.

g. Among patients with myelodysplastic syndrome (MDS) or minimal residual disease acute myeloid leukemia (AML) prior to transplant, OS was as favorable with a matched URD and improved compared to a mismatched URD; relapse rates were lower in the cord blood group than either of the other groups [24].

h. HLA-C matching appears to improve outcomes. In a retrospective analysis of 803 patients with leukemia or MDS who underwent an unrelated UCB HCT, patients matched for HLA-A, -B, and -DRB1 but mismatched for HLA-C had higher TRM than those matched for HLA-C (HR 3.97) [25].

i. Priority should be given to unidirectional mismatches in the GvHD direction; avoid mismatches in the host-versus-graft direction.

   i. Unidirectional mismatches in the GvHD direction are associated with significantly earlier time to engraftment.

   ii. Unidirectional mismatches in the host-versus-graft direction have delayed time to engraftment, higher rates of graft failure, and higher relapse rates.

    j. Increased incidence of infection may account for up to half of the TRM associated with UCB HCT.

        i. Both delayed neutrophil recovery and intrinsic defects in immune reconstitution contribute to increased rates of infection.

        ii. UCB HCT after non-myeloablative conditioning is associated with more rapid neutrophil recovery and immune reconstitution.

    k. Use of two UCB units (double UCB HCT [dUCB]) is acceptable for patients who do not have a single unit with adequate cell count.

        i. After myeloablative conditioning, transient-mixed chimerism may be identified early but is typically followed by sustained engraftment of only one unit by day +100.

        ii. Most studies suggest improved disease control with decreased relapse rate after dUCB HCT compared to a single-unit UCB HCT [9, 10].

- Some studies suggest that UCB units should be at least 3 of 6 HLA matched to each other in the setting of dUCB HCT.
- BMT CTN 0604 [20].
    - Demonstrated 1-year probability of OS of 54% and PFS of 46% after a cyclophosphamide/fludarabine/TBI-conditioned dUCB HCT with a day +100 cumulative incidence of grade II–IV acute GvHD of 40%.
    - This study has laid the groundwork for BMT CTN 1101 [A Multicenter, Phase III, Randomized Trial of Reduced-Intensity Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood vs HLA Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies]. At the time of publication, this study has met accrual and data are forthcoming.

6. Single-antigen mismatched related donors

    a. Early studies suggest that single HLA-antigen mismatched, related donor HCT may lead to increased rates of GvHD if the mismatch is in the GvHD vector or increased incidence of graft failure if the mismatch is in the host-versus-graft vector. There was no significant impact on OS.

    b. A retrospective registry study from Japan compared outcomes in 779 patients with acute leukemia, chronic myeloid leukemia (CML), or MDS who received a 1 antigen MRD vs 8/8 allele URD HCT [26].

        i. Higher overall mortality was observed in patients who received the mismatched related donor graft, particularly in those patients with standard risk disease.

        ii. HLA-B antigen mismatch was associated with lower OS due to increased TRM.

Other Considerations

1. Donor-specific HLA antibodies [27]

    a. HLA mismatch should mandate screening for donor-specific HLA antibodies. Flow cytometric analysis is used to define a mean fluorescent intensity (MFI) cutoff where MFI < 1000 will determine acceptable cell product, although some centers will use somewhat higher MFI as their institutional guideline.
    b. Recipient anti-HLA antibodies directed at donor HLA antigens are associated with high graft rejection rates.
    c. Other donors should be pursued in this setting.

2. Donor age

    a. Initial studies in HCT performed in the 1990s suggested that younger donors (age < 30 years) were associated with improved DFS and OS and decreased acute and chronic GvHD [28].
    b. Older matched sibling donors (> age 50) are preferred over 8/8 HLA-matched younger URDs for leukemia/lymphoma patients who are over the age of 50 years. Risks of acute GvHD grade 2–4 (HR, 1.63; $P < 0.001$), 3–4 (HR, 1.85; $P < 0.001$), and chronic GvHD (HR, 1.48; $P < 0.0001$) were higher after HCT performed with younger URDs compared with older MRD HCT [13].

3. Donor parity

    a. In a 2001 NMDP study, nulliparous female donors were associated with lower risks for chronic GvHD; however, this was not supported by the most recent CIBMTR data [29].
    b. Male donor < nulliparous female donor < female donor with one prior pregnancy < female donor with 2+ prior pregnancies.
    c. No effect of parity was seen in acute GvHD.
    d. Parity has not been an independent risk factor for OS and DFS in recent studies.

4. Cytomegalovirus (CMV) status [30]

    a. CMV seropositive recipients have a lower OS than seronegative recipients.
    b. A study from the European Society for Blood and Marrow Tranpslant (EBMT) suggested that CMV seropositive recipients should receive cells from CMV seropositive donors, as the adoptive transfer of mature lymphoid cell populations was associated with more rapid development of recipient CMV immunity [31].

5. ABO status

    a. ABO compatibility between donor and recipient is generally not considered necessary for HCT; however, one recent retrospective institutional and subsequent registry study reported increased NRM after allogeneic HCT in the setting of ABO mismatch [32].
    b. A previous meta-analysis demonstrated no adverse association between ABO mismatching and graft failure, GvHD or survival [33].

6. Killer immuoglobulin-like receptor (KIR) gene haplotype

   a. NK cells are lymphocytes with the ability to kill malignant cells without prior antigen recognition. Human NK cells express multiple receptors that interact with HLA class I molecules. KIR gene complex on chromosome 19 encodes up to 15 genes for receptors that are key regulators of NK cell activity and predominantly recognize classical HLA class I molecules [37].

   b. A balance of surface activating and inhibitory KIR receptor signals enables NK cells to kill appropriate targets and avoid healthy cells. Bound inhibitory KIR signals override activating signals and facilitate self-tolerance. KIR haplotypes can be inhibitory or activating. KIR haplotype A mainly encodes inhibitory receptors and KIR haplotype B encodes activating receptors (KIR2DS1, KIR3DS1).

   c. In a study of 1409 patients with acute leukemia by Cooley et al., donor KIR genotype influenced transplant outcome for AML but not ALL. Compared to A haplotype motifs, B haplotype motifs contributed to protection from relapse and improved survival. With B/B homozygous donors, the cumulative incidence of relapse was 15.4% compared with 36.5% for A/A donors (relative risk of relapse 0.34; $P < 0.001$) [38].

   d. Activating KIR genes from donors (KIR2DS1) appear to provide protection against relapse in an HLA-C-dependent manner. In a study of 1277 patients with AML who received either a 10/10 matched unrelated or 1 antigen mismatched unrelated transplant, lower relapse rates were seen in patients who received allografts from donors positive for activating KIR2DS1 than those with allografts from donors negative for KIR2DS1 (26.5% vs. 32.5%; $P = 0.02$). This anti-leukemic effect was primarily seen in donors who were homozygous or heterozygous for HLA-C1 antigens (24.9% with homozygosity or heterozygosity for HLA-C1 vs. 37.3% with homozygosity for HLA-C2; $P = 0.002$) [39].

   e. NK-mediated alloreactivity does not appear to be associated with an increased risk of GvHD. NK cells are thought to reduce the risk of GvHD by attacking host dendritic cells resulting in decreased antigen presentation to alloreactive T cells. However, some reports have documented increased acute GvHD in patients receiving mismatched unrelated donor allografts with KIR B/x haplotypes and with the use of NK cells for adoptive immunotherapy [40].

7. COVID-19

   a. In December 2019, the first cases of pneumonia due to a novel enveloped RNA betacoronavirus subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) where described in Wuhan, China. In just over 3 months the virus had spread globally to 206 countries with more than 900,000 confirmed cases and greater than 45,000 deaths [41].

   b. In a report of 1099 patients from China, the median incubation period was 4 days with 43.8% of patients having fever on admission but 88.7% developed fever during hospitalization. Cough was present in 67.8%, nausea

and vomiting in 5%, and diarrhea in 3.8%. 86.2% had an abnormal CT scan of the chest with the most common abnormality being ground glass opacities (56.4%) and bilateral patchy shadowing (51.8%). Primary composite endpoints of ICU admission, mechanical ventilation, and death were reported in 6.1%, 5.0%, and 1.4% of patients. Older age and co-existing illness were more common among patients with severe disease (38.7% vs. 21%) [42].

c. In this setting of high community prevalence of COVID-19, severe limitations on travel, and known effects of respiratory viruses on immuno-compromised transplant patients, the American Society for Transplantation and Cellular Therapy (ASTCT), EBMT, and (NMDP) issued interim guidelines for COVID-19 management in transplant and cellular therapy patients in March 2020. Key points of the guidelines are outlined below [43, 44].

d. Diagnostic considerations [43]

   i. Perform polymerase chain reaction (PCR) testing for SARS-CoV-2 *in addition* to other respiratory virus PCR testing on any patient with upper or lower respiratory symptoms.
   ii. Consider chest imaging in patients with positive PCR and those with negative PCR but with lower track symptoms.
   iii. Use of bronchoalveolar lavage (BAL) is not recommended if a patient tests positive given risk of transmission among healthcare workers, unless a co-infection is suspected.

e. Considerations for evaluation of HCT or cellular therapy candidates [43, 44]

   i. Candidates with symptoms of an acute respiratory tract infection should be tested for respiratory viruses by multiplex PCR including SARS-CoV-2. Procedures including PBSC mobilization, BM harvest, T-cell collections, and conditioning/lymphodepletion should be deferred for a minimum of 14 days and until symptoms have resolved.
   ii. If SARS-CoV-2 is detected, HCT or cellular therapy procedures should be deferred. For patients with high-risk malignancies, defer all procedures until the patient is asymptomatic and has at least two consecutive negative PCR tests each approximately 1 week apart (deferral for 14 days minimum).
   iii. For candidates with close contact with a person infected with SARS-CoV-2, all procedures including PBSC mobilization, BM harvest, T-cell collections, and conditioning/lymphodepletion should not be performed for at least 14 days and preferably 21 days from the day of last contact.
   iv. Screen all HCT and cellular therapy candidates for SARS-COV-2 infection by PCR in respiratory specimens at the time of initial evaluation and 2 days prior to conditioning/lymphodepletion, regardless of the presence of symptoms.

f. Considerations for evaluation of potential HCT donors

    i. SARS-CoV-2 can also be detected in blood. If virus is detected in the respiratory sample, the donor is considered ineligible to donate. However, ineligible donors may be considered in certain situations. If there is an urgent medical need, consider donor eligibility if no history of severe respiratory disease, 28 days have elapsed since resolution of symptoms, and PCR has become negative.

    ii. Potential donors with close contact with a person diagnosed with COVID-19 should be excluded from donation for at least 28 days.

    iii. The NMDP strongly recommends cryopreservation of all donor products as far in advance of the initiation of patient conditioning as is feasible. To date, there have been no reported or suspected cases of transfusion-transmitted COVID-19 or the other two coronaviruses that emerged during the past two decades. An augmented donor screening questionnaire is available on the NMDP website: https://network.bethematchclinical.org/news/nmdp/be-the-match-response-to-covid-19/.

    iv. If possible, ensure that an alternative stem cell source is available. If multiple possible donors are available, choose a donor without risk.

8. Donor screening (see also Chap. 4 for additional details)

a. Must be completed to ensure safety of the donor and that the stem cell product is safe for the recipient.

b. Medical history questionnaire targets risk factors for transmission of genetic or infectious diseases.

c. Physical examination.

d. Baseline evaluation of organ function including laboratory testing, EKG, echocardiogram and pulmonary function tests.

e. Infectious disease testing.

Donor Complications

1. BM acquisition (harvest)

a. NMDP tracks complications of its donors.

b. Of the first 9245 harvests, 125 donors (1.34%) experienced a serious medical complication including mechanical injury to tissue, bone, or nerve (55%), anesthetic complications (36%), and infection (<1%) [34].

c. Pain was the most common symptom with 82% reporting back or hip pain at the collection site and 33% reporting anesthesia-related throat pain. Fatigue was reported in 59%. Site reaction, insomnia, nausea, dizziness, and anorexia were far less common (<15%).

d. Transient changes in WBC, platelets, and hemoglobin were observed with most counts returning to baseline by 1 month post-harvest. Anemia with a 3

   gm/dl decrease in hemoglobin was observed in both male and female donors
   with a mild decrease persisting at 1 month.

   e. Marrow harvest appears safe in children with the EBMT reporting no serious
   complications in 313 pediatric donors [35].

2. PBSC donors

   a. Serious adverse events were uncommon (0.6%).
   b. In a prospective trial from the NMDP, 6768 PBSC donors who underwent
   collection between 2004 and 2009 were evaluated [36].

      i. Central venous access was required in 5% of male donors and 21% of
      female donors.
      ii. Leukocytosis with a mean WBC of 40,000/ul and 20% exceeding 50,000/
      ul was reported.
      iii. Thrombocytopenia with platelets <100,000/ul was seen in 26% of donors
      after one collection and 50% of donors after two collections.
      iv. Musculoskeletal pain which peaked at day 5 of filgrastim administration
      was reported in nearly 90% with the majority having grade I/II symptoms.
      v. Other less common symptoms included fatigue (49–50%) and insom-
      nia (30%).
      vi. Female donors were more likely to require hospitalization (3% vs. 1%).

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Chapter 4
Pretransplant Assessment for Hematopoietic Cell Transplantation Recipients and Donors

Vanessa E. Kennedy and Lori S. Muffly

Introduction

HCT is an important therapeutic modality for many malignant and nonmalignant diseases. RIC and nonmyeloablative (NMA) conditioning regimens and improvements in supportive care have broadened HCT indications to include patients with multiple comorbidities and advanced age. Over the past decade, both the utilization and success of allogeneic HCT (allo-HCT) in adults aged 70 and older have improved significantly [1]. As the population ages and the number of older adults with malignancies increases, the utilization of HCT in older adults will likely increase as well. As HCT continues to expand to older and/or less fit individuals, refining pretransplant assessment and eligibility criteria is necessary to both guide patient selection for referral and transplantation and to develop individualized supportive care plans.

Indications for Transplantation

Indications for the use of HCT are continuously evolving as new indications are identified and the role of transplant in established indications is refined. The American Society for Transplantation and Cellular Therapy (ASTCT, formerly known as the American Society for Blood and Marrow Transplantation (ASBMT))

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established a task force in 2015 to provide guidance on HCT indications, including indications in which allo-HCT or autologous HCT (auto-HCT) is considered standard of care and indications in which evidence remains insufficient (Table 4.1) [2].

Table 4.1 Disease indications for HCT per the 2015 American Society for Blood and Marrow Transplantation (ASBMT) Guidelines [2]

Disease indication	Allo-HCT	Auto-HCT	Disease indication	Allo-HCT	Auto-HCT
Acute myeloid leukemia			*Mantle cell lymphoma*		
CR1 low risk	N	C	CR1/PR1	C	S
CR1 intermediate risk; CR1 high risk; CR2	S	C	Refractory, sensitive	S	S
CR3+	C	C	Refractory, resistant; first relapse; relapse after auto-HCT	C	N
Not in remission	C	N	Second or greater relapse	C	S
Acute Promyelocytic leukemia			*T-cell lymphoma*		
CR1	N	N	CR1	C	C
CR2	C	S	Refractory or first relapse, sensitive	C	S
CR3+; not in remission; relapse post auto-HCT	C	N	Refractory or first relapse, resistant	C	N
Acute lymphoblastic leukemia			*Burkitt lymphoma*		
CR1 standard risk	S	C	First remission; relapse, sensitive	C	C
CR1 high risk	S	N	Relapse, resistant, relapse after auto-HCT	C	N
CR2	S	C	*Cutaneous T-cell lymphoma*	C	C
CR3+; not in remission	C	N	*Solid tumors*		
Chronic myeloid leukemia			Germ cell tumor, relapse or refractory	N	C
Chronic phase 1	C	N	Ewing's sarcoma, high risk	N	C
Chronic phase 2; accelerated phase; blast phase	S	N	*Nonmalignant diseases*		
Myelodysplastic syndromes			Severe aplastic anemia	S	N
Low risk; intermediate-1 risk	C	N	Fanconi anemia	R	N
Intermediate-2 risk; high risk; therapy-related	S	N	Sickle cell disease	C	N
Myeloproliferative disorders	C	N	Thalassemia	D	N
Plasma cell disorders			Wiskott-Aldrich syndrome, common variable immune deficiency	R	N

Table 4.1 (continued)

Disease indication	Allo-HCT	Auto-HCT	Disease indication	Allo-HCT	Auto-HCT
Myeloma, initial response	D	S	Systemic sclerosis	N	D
Myeloma, refractory; relapse after auto-HCT	C	C			
Hodgkin lymphoma					
CR1	N	C			
First relapse, sensitive	S	S			
Primary refractory or first relapse, resistant	C	N			
Primary refractory, sensitive; second or greater relapse	C	S			
Follicular lymphoma					
CR1	N	C			
Refractory or first relapse, sensitive; second or greater relapse	S	S			
Refractory or first relapse, resistant	S	N			
Diffuse large B-cell lymphoma					
CR1	N	C			
Refractory or first relapse, sensitive; second or greater relapse	C	S			
Refractory, resistant; first relapse, resistant	C	N			
Chronic lymphocytic leukemia					
High risk, first or greater remission	C	N			
Prolymphocytic leukemia, B or T cell	R	R			

HCT hematopoietic cell transplantation, *S* Standard of care, supported by high-quality clinical trials and observational studies, *C* Standard of care, clinical evidence available. Supported by single and multi-institutional studies, but indication requires careful consideration, *R* Rare indication, including rare diseases, *D* Developmental, pre-clinical and/or early phase data indicate HCT may be promising, *N* Not generally recommended, *CR* clinical remission/complete response

1. Acute Myeloid Leukemia (AML) (see also Chap. 15)

   a. Allo-HCT

      i. First clinical remission (CR1), except favorable-risk disease
      ii. Second or greater clinical remission (CR2+)
      iii. Refractory AML
      iv. Therapy-related AML

Table 4.2 Risk Stratification for acute myeloid leukemia per the 2017 European LeukemiaNet Schema [4]

Risk category	Cytogenetics	Molecular markers
Favorable	inv (16) or t(16;16) t(8;21) t(15;17)	Mutated *NPM1* without *FLT3*-ITD Biallelic mutated *CEBPA*
Intermediate	Normal t(9;11) Other cytogenetic abnormalities	Mutated *NPM1* with *FLT3*-ITD Wild-type *NPM1* without *FLT3*-ITD (low)
Adverse	Complex (> 3 abnormalities) inv (3) −5, del 5q −7, del 7q −17 3q21q26 t(6;9) t(9;22); *BCR-ABL1* 11q23 abnormalities (except t(9;11)) 17p abnormalities	Wild-type *NPM1* without *FLT3*-ITD (high) Mutated *RUNX1* Mutated *ASXL1* Mutated *TP53*

Allogeneic transplant for AML is well established in intermediate and high-risk disease in CR1 and second clinical remission (CR2) and is increasingly offered in third clinical remission (CR3+) or for refractory leukemia (Table 4.1). Risk stratification continues to evolve. For example, in the 2017 European LeukemiaNet guidelines (Table 4.2), mutations in *RUNX1*, *ASXL1*, and *TP53* were added to the risk stratification schema [3, 4]. In the future, use of minimal residual disease (MRD) measurement may impact formal AML risk stratification and decision to undergo HCT [5].

2. Acute Lymphoblastic Leukemia (ALL) (see also Chap. 16)

   a. Allo-HCT

      i. High-risk disease in CR1

- MRD+ after induction and/or consolidation
- Philadelphia chromosome (Ph)-positive disease; t(9;22)
- Depending on specific chemotherapy protocols, one may consider:
    - 11q23 aberrations; *MLL* rearrangements
    - Other high-risk cytogenetic or molecular ALL sub-types (e.g., hypodiploid, Ph-like ALL, early T-cell precursor ALL)

     ii. CR2+
    iii. Refractory ALL

The role and optimal use of allo-HCT in adult ALL is rapidly evolving and remains controversial. MRD by flow cytometry or next-generation sequencing is increasingly being used as a prognostic tool and to guide therapeutic

decision-making. Newly identified biological subgroups are also refining risk stratification. Highly active new agents are revolutionizing relapsed/refractory B-cell ALL and are quickly moving to the front-line and MRD+ setting [6]. Finally, pediatric-inspired regimens are safe in adults up to age 50, and patients who achieve CR1 following these regimens may not require allo-HCT, even in the presence of other risk factors [7–9].

3. Chronic Myeloid Leukemia (CML) (see also Chap. 21)

   a. Allo-HCT

      i. Chronic phase

         • Failure to achieve hematologic or cytogenetic response to tyrosine kinase inhibitors (TKIs)
         • Intolerance to at least two or three TKIs
         • T3151 mutation, especially in patients at high risk for vascular events or in young patients

      ii. Accelerated phase

         • Newly diagnosed patients who fail to achieve optimal response to TKIs
         • TKI-treated patients who progress from the chronic phase

      iii. Blast crisis

4. Myelodysplastic Syndromes (MDS)

   a. Allo-HCT

      i. Intermediate or high-risk MDS
      ii. Therapy-related MDS
      iii. May consider refractory cytopenias, transfusion dependence

   The International Prognostic Staging System for myelodysplasia (IPSS-R) (Table 4.3) remains the standard for risk stratifying MDS [10–12], although this will likely evolve as future iterations incorporate mutational data [13].

5. Myeloproliferative Neoplasms (see also Chap. 20)

   a. Allo-HCT

      i. Primary or secondary myelofibrosis with intermediate/high-risk disease [14]

6. Plasma Cell Disorders (see Chap. 18)

   a. Allo-HCT

      i. Multiple myeloma

         • Select patients with relapsed or refractory disease
         • Select patients with plasma cell leukemia

Table 4.3 Revised International Prognostic Staging System (IPSS-R) for myelodysplasia [11]

IPSS-R prognostic score values							
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
BM blast %	≤2%		2–5%		5–10%	>10%	
Hemoglobin	≥10		8–10	<8			
Platelets	≥100	50–100	<50				
ANC	≥0.8	<0.8					

IPSS-R cytogenetic risk groups	
Cytogenetic prognostic subgroups	**Cytogenetic abnormality**
Very good	−Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	−7, inv (3)/t(3q)/del(3q), double including −7/del(7q), complex (3 abnormalities)
Very poor	Complex (>3 abnormalities)

IPSS-R prognostic risk categories	
Risk score	**Risk category**
<1.5	Very low
1.5–3	Low
3–4.5	Intermediate
4.5–6	High
>6	Very high

   b. Allo-HCT

      i. Multiple myeloma

- In first response
- In second or further response
- Relapsed or refractory disease

      ii. Amyloidosis, POEMS syndrome

7. Hodgkin Lymphoma (HL) (see also Chap. 17)

   a. Allo-HCT

      i. Select patients with relapsed/refractory HL that is not chemosensitive may be considered for allo-HCT

    b. Auto-HCT

       i. First or subsequent relapse, chemosensitive disease

      ii. Primary refractory disease that demonstrates chemo-sensitivity to salvage therapy

8. Follicular Lymphoma, Low-Grade Non-Hodgkin Lymphoma (NHL) (see also Chap. 17)

    a. Allo-HCT

       i. Multiply relapsed disease and/or relapse following auto-HCT

    b. Auto-HCT

       i. Less than partial response to initial treatment, chemotherapy-sensitive disease

      ii. First or subsequent relapse, particularly in patients with response duration <12 months

     iii. Transformation to high-grade lymphoma

9. Diffuse Large B-Cell Lymphoma, high-Grade NHL (see Chap. 17)

    a. Allo-HCT

       i. Relapsed or refractory disease

    b. Auto-HCT

       i. CR1 with high–intermediate or high-risk international prognostic index (IPI)remains under study (see Table 4.6).

      ii. CR1 with dual translocations in *BCL-2* and *MYC* and/or *BCL-6* ("double hit" disease), although this is an area of ongoing controversy.

     iii. Relapsed or refractory chemo-sensitive disease.

10. Mantle Cell Lymphoma (see Chap. 17)

    a. Allo-HCT

       i. Relapse after auto-HCT

    b. Auto-HCT

       i. Following initial treatment, including CR1

      ii. Relapsed/refractory disease

Patient Evaluation

Potential HCT candidates require a thorough medical evaluation by an HCT provider. In addition to history, physical, and laboratory evaluation, several pre-HCT assessment tools exist to better characterize the impact of disease risk, patient comorbidities, psychosocial function, and, for older adult transplant candidates,

geriatric-specific function [15–18]. These standardized metrics should be integrated into pretransplant evaluation and reporting.

1. Disease Status and Risk

   Disease-specific studies are necessary in order to determine the pre-HCT disease status. These studies may include, but are not limited to, the following:

   a. Positron emission tomography/computed tomography (PET/CT)
   b. Bone marrow evaluation, hematopathology review of prior and current marrow samples
   c. Disease risk index (DRI) [19]

      i. If applicable, histology-specific risk indices, such as the Acute Myeloid Leukemia Composite Model (AML-CM) [20]

   d. Measurement of MRD when applicable

   Disease relapse remains the primary cause of post-transplant mortality, and assessing the risk of post-HCT relapse is critical in patient selection, regimen selection, and pretransplant counseling. The DRI is a validated model that captures the prognostic impact of primary diagnosis, histologic subtypes, chromosomal abnormalities, and disease status (Table 4.4) [19]. When available and applicable, assessment of MRD should be obtained prior to HCT to aid in prognostication and therapeutic decision-making.

2. Patient History

   a. Disease history

      i. Treatment history, including prior response
      ii. Complications, including therapy-related and disease-related

   b. Medications and allergies
   c. Past medical history

      i. Infectious disease history
      ii. Transfusion history

   d. Family history

      i. History of malignancies, hematologic disorders, rheumatologic disorders
      ii. Potential related donors

3. Review of Systems

   a. Dental
   b. Cardiac

      i. Electrocardiogram (ECG)
      ii. Echocardiogram with assessment of ejection fraction (EF)

   c. Respiratory

      i. Pulmonary function testing, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and diffusion capacity of carbon monoxide (DLCO)

Table 4.4 Disease Risk Index [19]

Disease	Disease risk
AML favorable cytogenetics CLL CML Indolent B cell NHL	Low
ALL AML intermediate cytogenetics MDS intermediate cytogenetics Myeloproliferative neoplasms Multiple myeloma Hodgkin lymphoma DLBCL or transformed indolent B cell NHL Mantle cell lymphoma Low risk T cell lymphoma	Intermediate
AML adverse cytogenetics MDS adverse cytogenetics High risk T cell lymphoma	High
Stage	**Stage risk**
Any CR PR (including improved but < CR MDS or MPN) Untreated Chronic phase CML	Low
Induction failure Active relapse Accelerated or blast phase CML	High

Overall assignment		
Disease risk	**Stage risk**	**DRI assignment**
Low	Low	Low
Low Intermediate	High Low	Intermediate
Intermediate High	High Low	High
High	High	Very high

AML acute myeloid leukemia, *CLL* chronic lymphocytic leukemia, *CML* chronic myeloid leuke-mia, *NHL* non-Hodgkin lymphoma, *ALL* acute lymphocytic leukemia, *MDS* myelodysplastic syn-drome, *DLBCL* diffuse large B cell lymphoma, *CR* complete response, *PR* partial response, *MPN* myeloproliferative neoplasm

   d. Renal

      i. Electrolytes
      ii. Creatinine clearance

   e. Hepatic

      i. Liver function tests.
      ii. Additional testing may be warranted if patient is at risk for cirrhosis due to underlying liver disease.

   f. Hematologic

      i. Complete blood count (CBC)
      ii. Blood type (ABO and Rh typing), red cell antibodies

    g. Reproductive

        i. Pregnancy test if applicable

4. Infectious Evaluation

    a. Required [21]

        i. HIV-1, HIV-2
       ii. Hepatitis B, Hepatitis C
      iii. Treponema pallidum (syphilis)

    b. Recommended

        i. Cytomegalovirus (CMV)
       ii. Herpes simplex virus (HSV) 1 and 2
      iii. Varicella zoster virus (VZV)
      iv. Human-T-lymphotropic virus (HTLV) 1 and 2
       v. West Nile virus
      vi. Trypansoma cruzi (Chagas disease)

    c. Recommended in select cases based on individual risk factors

        i. Tuberculosis
       ii. Fungal infections
      iii. Parasitic infections

5. Human Leukocyte Antigen (HLA) typing [22]

    a. HLA-A, HLA-B, HLA-DRB1 required for all transplant candidates
    b. HLA-C required for unrelated donors or related non-sibling donors, recommended for all other transplant candidates
    c. HLA-DQ recommended
    d. HLA-DP recommended particularly in the setting of 8/8 HLA match
    e. Assessment for anti-HLA donor-specific antibodies, particularly when considering haploidentical [23] or cord blood transplantation

6. Psychosocial Evaluation (see also Chap. 5)

    a. Available validated screening tools:

        i. Transplant Evaluation Rating Scale (TERS) [24]
       ii. Psychosocial Assessment of Candidates for Transplantation (PACT) [25]
      iii. Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) [26]

    b. Common components of psychosocial evaluation

        i. Psychiatric history, substance abuse history
       ii. Occupational history
      iii. Current living situation
      iv. Caregiver availability
       v. Financial screening and evaluation

Pretransplant psychosocial assessment is now incorporated routinely at transplant centers. Psychosocial assessments, however, remain heterogeneous, and multiple screening tools have been described and implemented successfully.

7. Comorbidity Indices

In addition to the above evaluation, the HCT-specific comorbidity index (HCT-CI) is also frequently used to capture the number and severity of individual patient comorbidities prior to allo-HCT (Table 4.5). The HCT-CI provides a comprehensive and validated assessment of pretransplant health and predicts nonrelapse mortality (NRM) [27]. A similar metric, the HCT-Age-CI, incorporates chronological age into the HCT-CI and may be useful in assessing older adult transplant candidates [28].

Table 4.5 Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) [27]

Comorbidity	Definition	Points
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, ventricular arrhythmia	1
Cardiac	Coronary artery disease[a], congestive heart failure, myocardial infarction, EF $\leq 50\%$	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemic agents, but not diet alone	1
Cerebrovascular accident	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Mild hepatic	Chronic hepatitis, bilirubin >1–1.5 times ULN, or AST/ALT >2–2.5 time ULN	1
Obesity	Body mass index >35 kg/m^2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, mixed CTD, polymyalgia rheumatic	2
Peptic ulcer	Requiring treatment	2
Renal	Serum creatinine >2 mg/dl, on dialysis, prior renal transplantation	2
Moderate pulmonary	DLCO and/or FEV1 66–80% or dyspnea with slight activity	2
Prior solid tumor	Treated at any time point in patient's past history, excluding non-melanoma skin cancer	3
Valvular heart disease	Any excluding mitral valve prolapse	3
Severe pulmonary	DLCO and/or FEV1 ≤ 65 or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin >1.5 times ULN or AST/ALT >2.5 times ULN	3

EF ejection fraction, *ULN* upper limit of normal, *SLE* systemic lupus erythematosis, *RA* rheumatoid arthritis, *CTD* connective tissue disease, *DLCO* diffusion capacity of carbon monoxide, *FEV1* forced expiratory volume in 1 second, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

[a]One or more vessel coronary artery stenosis requiring medical treatment, stent, or bypass graft

Table 4.6 Domains of geriatric assessment [29]

Domain	Metrics and tools
Comorbidity	HCT-CI [27], HCT-Age-CI [28]
Function	Patient-reported ADL and IADL Patient reported exhaustion Falls
Performance status	ECOG performance status, Karnofsky performance status Grip strength 4 and 6 minute walk, timed get-up-and-go
Cognition	Mini-mental status exam, Montreal cognitive assessment, BOMC
Nutrition	Body mass index Albumin, pre-albumin
Polypharmacy	
Psychological	Hospital anxiety and depression scale Mental health inventory-17 TERS [24], PACT [25], SIPAT [26]
Social support	

HCT-CI hematopoietic cell transplantation comorbidity index, *HCT-Age-CI* hematopoietic cell transplantation age comorbidity index, *ADL* activities of daily living, *IADL* independent activities of daily living, *BOMC* Blessed-orientation memory cognition*, TERS* transplant evaluation rating scale, *PACT* psychosocial assessment of candidates for transplantation, *SIPAT* Stanford integrated psychosocial assessment for transplantation

8. Geriatric Assessment (GA)

   a. Comprehensive GA (Table 4.6) [29]

      i. Involves multiple health domains relevant to older adults
      ii. Predicts overall survival in cancer populations

   b. Brief geriatric screening tools

      i. Vulnerable Elder Survey (VES-13)
      ii. G8 Screening tool

General Guidelines for Patient Eligibility

There are currently no standard criteria for HCT eligibility, and, in recent years, the development of RIC and NMA regimens have broadened guidelines to include older and less fit individuals. The following general guidelines are adapted from clinical trial eligibility criteria from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Importantly, there remains considerable heterogeneity even among clinical trials. There are no absolute cutoffs for HCT eligibility, and consideration for transplant must be determined carefully on an individual patient basis.

1. Disease status meets indication for transplantation
2. Patient Age

   a. Generally ≤ 65 for myeloablative conditioning
   b. No formal upper age limit for RIC, NMA, haploidentical, cord or auto-HCT

      i. HCT-Age-CI, GA, and other metrics can be used to further clarify transplant appropriateness for older adults

3. Performance Status

   a. Myeloablative regimens: Eastern Cooperative Oncology Group (ECOG) ≤ 2 or Karnofsky Performance Status (KPS) (≥ 70%)
   b. RIC and NMA regimens: ECOG ≤ 3 or KPS ≥ 50%

4. HCT-CI

   a. No absolute cut-off score, but consider RIC or NMA regimen if HCT-CI ≥ 4

5. Organ Function
   There are no universally accepted cutoff points. It is important to carefully consider organ function in light of institution-specific normal ranges and the specific agents to be used in conditioning regimens and graft vs host disease (GvHD) prophylaxis. Some example criteria are below:

   a. Cardiac

      i. Myeloablative: EF ≥ 40–45%
      ii. RIC, NMA: EF ≥ 30%
      iii. No uncontrolled arrhythmias

   b. Pulmonary

      i. Myeloablative: FVC, FEV1, and DLCO (adjusted for hemoglobin) all ≥45% predicted
      ii. RIC, NMA: DLCO (adjusted for hemoglobin) ≥ 40% predicted

   c. Renal

      i. Myeloablative, RIC: Creatinine clearance (CrCl) ≥50 mL/minute
      ii. NMA: CrCl ≥40 mL/minute
      iii. Exceptions made for amyloid and multiple myeloma

   d. Hepatic

      i. Myeloablative: AST/ALT ≤2.5 times upper limit of normal (ULN); total bilirubin ≤2 times ULN
      ii. RIC, NMA: AST/ALT ≤3 times ULN; total bilirubin ≤2.5 times ULN
      iii. Note isolated hyperbilirubinemia due to Gilbert's syndrome is acceptable

6. Active Infections

    a. No active infections requiring ongoing antimicrobials, with the following exceptions:

        i. HIV-positive patients on highly active antiretroviral therapy (HAART) with low risk of AIDS-related outcomes.

        ii. Adequately treated fungal infections on chronic suppressive therapy.

        iii. Adequately treated Hepatitis B and C.

    b. Patients with HIV, hepatitis B or C, or other chronic infections should have an infectious disease consultation prior to transplantation.

7. Malignancies

    a. Prior malignancy

        i. No current evidence of disease

        ii. Prior therapy at least 2 years before HCT

    b. Concurrent malignancy

        i. Stable and not requiring tumor-directed therapy, although hormonal therapy can be considered on an individual patient basis.

    c. In patients with prior or concurrent malignancy, the natural history and/or treatment must not be expected to interfere with the safety or efficacy of the transplant regimen and post-HCT care.

8. Psychosocial Considerations

    a. Able to provide informed consent
    b. Willing and able to comply with therapy and follow-up care
    c. Stable housing situation, caregiver availability
    d. Insurance coverage or financial resources

9. Donor Availability and Adequate Stem Cells

    a. Auto-HCT:

        i. Minimum of ≥ 2 x 10^6 CD 34+ cells/kg

    b. Allo-HCT HLA matching [22]:

        i. High-resolution, DNA-based typing
        ii. Related:

            • 5/6 or 6/6 match for HLA-A, -B, and –DRB1
            • 7/8 or 8/8 match for HLA-A, -B, -C, and –DRB1 preferable, but not required

        iii. Unrelated:

            • 8/8 match at HLA-A, -B, -C, and –DRB1

      iv. Haploidentical [23]:

- Related haploidentical donor with 2, 3, or 4 HLA-mismatches at HLA-A, HLA-B, HLA-C, and/or HLA-DRB1

      v. Cord:

- For adult HCT recipients: Two umbilical cord blood units matched at a minimum of 4/6 at HLA-A, HLA-B, and HLA-DRBI with the recipient and with each other. It is recommended two mismatches at a single HLA-locus be avoided if possible.
- Minimum total nucleated cell dose of 1×10^7/kg (or 2×10^7/kg for units that were not red-cell-depleted).
- It is strongly recommended that a cord blood specialist be consulted in choosing optimal cord blood units.

      vi. Assessment for anti-HLA donor-specific antibodies

- Exclude potential donors for whom the transplant recipient has either a positive crossmatch test of any titer or the presence of anti-donor HLA antibody to any HLA locus.

10. Absolute and Relative Contraindications

    a. Absolute contraindications

       i. Uncontrolled bacterial, viral, or fungal infection
      ii. Pregnant or currently breast feeding
    iii. Inability to tolerate preparative regimen and/or GvHD prophylaxis
    iv. Life expectancy severely limited by other illness

    b. Relative contraindications

       i. Major medical comorbidities
      ii. Major psychiatric illness, complex psychosocial circumstances, or substance abuse
    iii. Lack of stable home environment, caregiver, or insurance/financial resources

Donor Evaluation for Allo-HCT

1. History and Physical

    a. Risk factors for transmissible diseases

       i. Travel history
      ii. History of high-risk behaviors, e.g. substance use/abuse

    b. Transfusion history
    c. Prior pregnancies if applicable
    d. Inherited, hematologic, autoimmune, or malignant conditions

    e. ECOG and KPS performance status

2. Laboratory and Cardiopulmonary Evaluation

    a. CBC, electrolytes, and renal function, hepatic function, coagulation
    b. ABO and Rh typing, red cell antibody screen
    c. Serum pregnancy test
    d. Chest X-ray, EKG, and anesthesiology consultation (only required for donors undergoing bone marrow harvest)

3. HLA Typing [21, 22]

    a. HLA-A, -B, -DRB1 required for all transplant candidates.
    b. HLA-C required for unrelated donor or related nonsibling donor, recommended otherwise.
    c. HLA-DQ recommended.
    d. HLA-DP recommended.
    e. If donor is a match at low resolution, HLA typing is extended to high resolution. If donor is not a match at low resolution but is being considered a potential haploidentical donor, HLA typing is extended to high resolution.

4. Infectious Evaluation

    a. Required per Foundation for the Accreditation of Cellular Therapy-Joint Accreditation Committee ISCT Europe and EBMT (FACT-JACIE) international standards, must be tested within 30 days of stem cell collection [21]

        i. HIV1, HIV-2
        ii. Hepatitis B, Hepatitis C

    b. Recommended

        i. Treponema pallidum (syphilis)
        ii. CMV
        iii. HSV-1, HSV-2
        iv. VZV
        v. HTLV-1, HTLV-2 (required in the United States)
        vi. West Nile Virus (required in the United States)
        vii. Trypanosoma Cruzi (Chagas disease)

    c. Recommended in select cases based on individual risk factors

        i. Tuberculosis
        ii. Fungal infections
        iii. Parasitic infections

    d. Consider screening for Epstein-Barr virus (EBV) if recipient is at high risk of post-transplant lymphoproliferative disorder (diagnosis of severe aplastic anemia or receiving T-cell depletion)

5. Consent and Notification

    a. Consent to either (1) donate bone marrow or (2) receive granulocyte colony-stimulating factor (G-CSF) and mobilization of peripheral blood stem cells
    b. Adequate peripheral venous catheter access for leukapheresis or consent for central catheter
    c. Ensure that the potential donor is informed of any clinically significant findings discovered during donor evaluation

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Chapter 5
Social Work: Evaluation and Social Supports

Nancy J. Boyle and Keren McCord

Introduction

Hematopoietic cell transplant (HCT) and emerging therapies, such as chimeric antigen receptor T (CAR-T), are complex treatments that often result in high levels of psychological distress and social/financial strain for patients and their families. These procedures and the ensuing recovery can test even the most adaptive, functional patient and support system. Indeed, psychosocial issues often the most vexing for transplant teams.

HCT patients and their support teams require information, as well as physical and emotional resources, in order to maximize the benefit of the procedure. Each patient brings their past medical, emotional, financial, and personal experiences, which impact their ability to tolerate the ardors of transplant.

Five phases of the HCT process have been described:

1. The decision to undergo HCT
2. Pre-HCT preparation
3. HCT hospitalization
4. Hospital discharge and early recovery
5. Long-term recovery

This chapter will focus on the psychosocial issues along this continuum.

Each patient has a unique diagnosis, staging, and comorbidities that affect their journey through transplant. Psychologically, an individual adjusts to each transition utilizing their adaptive to maladaptive coping mechanisms. An early study on "returning to normal" revealed that patients least likely to report return to normalcy were those with unrealistic expectations. While there will be patients who will

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remain unrealistic, a majority can be assisted by providing realistic information and support [1].

A patient-centered approach is at the forefront of new accreditation standards for hospital cancer programs released by the Commission on Cancer (CoC) of the American College of Surgeons (ACS). Four national cancer patient support/advocacy organizations worked closely with the CoC to develop patient-centered standards to better enable cancer patients to work with their interdisciplinary cancer treatment team: American Cancer Society, Cancer Support Community, National Coalition for Cancer Survivorship, and LIVE**STRONG**™. The CoC includes *Distress Treatment Guidelines for Patients* as a standard to be established for accreditation [2].

Distress in pre-HCT patients was first described in 1997 as demonstrated by scores on the Profile of Mood States Scale. Study results showed that a decreased sense of control (intrapersonal mastery) and a decreased sense of optimism were related to a higher level of distress [3]. In a 2006 study, it was identified that pretransplant distress is highly predictive of posttransplant distress, and there was a statistically significant association between self-reported distress and medication noncompliance [4]. The Distress Thermometer (DT) with HCT patients, when studied for validation in comparison to the Center for Epidemiological Studies-Depression Scale (CES-D) and the State–Trait Anxiety Inventory-State Version (STAI-S), showed that the single-item DT compares well with the longer measures to assess psychological distress [4]. The DT cutoff score of 4 supports significant distress to warrant further assessment, and while the DT is being promoted as a screening tool by the National Comprehensive Cancer Network (NCCN), they suggest a cutoff of 5 or above for further assessment [5]. Additional studies are indicated in the HCST population.

Seven causes of distress in patients who undergo HCT have been identified [6] (Siegel, 2008):

1. Uncertainty regarding treatment outcome, recurrence, and mortality
2. Impact of treatment on their family
3. Changes in appearance and impact on sexuality
4. Long-term burden of treatment such as reduced functional status
5. Interaction with the medical system
6. Communication with medical personnel and obtaining information
7. Financial considerations, such as insurance coverage, the cost of treatment, and supporting self/family

Although no consensus guidelines regarding psychosocial eligibility for HCT have been developed, there are data identifying psychosocial factors associated with pre-HCT vulnerability that influence outcomes. In a study of HCT clinicians deciding whether to proceed with transplant given specific psychosocial risk factors, 75% of responding physicians recommended not to proceed in cases of suicidal ideation, use of illicit drugs, and history of noncompliance while 69% recommended not to proceed in cases where no caregiver support was identified [7].

Psychosocial issues have been studied in the solid organ transplant population, as these patients require psychosocial evaluation prior to being added to the transplant

waiting list. In HCT, psychosocial evaluation is required for all donors and recipients. Pretransplant screening for HCT has borrowed from solid organ transplant in the format of the Psychosocial Assessment of Candidates for Transplant (*PACT*) and Transplant Evaluation Rating Scale (*TERS*) [8–11].

While transplant programs vary in size and funding, there is value in having a mental health professional assess a patient's ability to withstand the psychological stresses of HCT, including assessment of preexisting psychiatric morbidities [12]. Individuals with anxiety and depression are at risk for poor health outcomes [13]. Patients who experience overall mood, anxiety, or adjustment disorders have 8% longer length of stays [14]. Pre-HCT screening can identify patients who are at higher risk of readmission and would benefit from additional services, including psychiatry, counseling, and increased navigation [15, 16].

Psychosocial Evaluation and Assessment

The key aspects for assessment are the characteristics and needs of the patient, family, and caregiver(s) including financial status, employment/disability, insurance, past/current mental health, and/or substance abuse history, and details about their care plan: who, what, and where.

1. Demographics

   a. Marital status
   b. Family composition
   c. Current living situation
   d. Developmental stage
   e. Formal education
   f. Legal issues
   g. Children's issues/preparation

2. Employment and financial information

   a. Employment and/or disability status
   b. Source of income
   c. Primary wage earner
   d. Insurance status
   e. Out-of-pocket obligation
   f. Prescription coverage
   g. Ability to maintain insurance and income
   h. Other (alimony, outstanding debts, financial planning, Power of Attorney, etc.)

3. Cognitive/mental health/substance abuse

   a. Cognitive deficits
   b. Literacy
   c. Learning ability

d. Mental health history, including trauma history, hospitalizations, need for medications.
e. Psychiatric medications
f. Counseling or hospitalization history
g. Significant recent stressors (marriage, divorce, death, job loss, moves, etc.)
h. Substance abuse history

4. Coping Skills

a. Strengths/weaknesses
b. Coping approach
c. Avoidance mechanism
d. History of significant losses
e. Use of alternative/complementary treatments
f. Adaptation to illness

5. Relationships/support systems

a. Partner relationship (cohesion)
b. Extended family support/availability
c. Identification of caregivers
d. Familial coping patterns
e. Adaptation
f. Spiritual/faith-based support
g. Cultural traditions, informal and community support

6. Medical concerns

a. Level of understanding of the HCT process, as well as emerging therapies, including CAR-T.
b. Decision-making issues (and agreement of support persons)
c. Pain issues
d. Expectations
e. Optimism
f. Ability to make post-HCST plans
g. Advance care planning/directives

7. Related donor concerns [17]

a. Donor experience and understanding
b. Recipient's health condition and concerns of the donor
c. Decision-making ability and genuine willingness
d. Mental preparedness
e. Emotional distress
f. Family dynamics

Preparation and Planning

1. Issues

   a. Comprehension of the medical circumstance (e.g., remission vs recurrence, intensity of therapy, prognosis)
   b. Mode of learning of the patient and caregiver (i.e., written or verbal? Are they literate? Is English their primary language?) [18]
   c. Informed consent and decision-making
   d. Anxiety/fear
   e. Practical arrangements (e.g., distance from the transplant center, housing arrangements, caregiver support)

2. Interventions

   a. Education about medical status and proposed treatment, as well as duties and duration of commitment of a caregiver
   b. Maximizing information delivery (e.g., repetition, multiple formats including written information, audio-visual aids, support groups, internet sites)
   c. Institution-specific expectations and requirements
   d. Preparative counseling

3. Referrals

   a. Educational classes are a way to reinforce prior teaching and discussions with HCT staff; orient the patient to the hospital campus, the inpatient unit, and outpatient clinic; begin discharge planning; review advance directives and patient/caregiver agreement forms; and provide a forum to share anxiety and distress.
   b. Connect with community resources, such as the Leukemia & Lymphoma Society, Medicaid, counseling services, etc.
   c. HCT assistance resources available on the Internet (see Table 5.1).

Active Treatment – Inpatient and Outpatient

1. Issues [19]

   a. Patient/caregiver anxiety and uncertainty about the HCT process and outcome
   b. Disruption of patient/family roles
   c. Fears of recurrence, infection, death
   d. Interpersonal stressors (e.g., poor coping strategies, mental health issues, and so on)
   e. Uncertainty about discharge plans

Table 5.1 HCT Internet resources (see also Chap. 9 for AYA-specific resources)

Organization	URL
Transplant resources	
Be the Match	www.marrow.org
Blood & Marrow Transplant Information Network (BMT Infonet)	www.bmtinfonet.org
National Bone Marrow Transplant Link	www.nbmtlink.org
General resources	
American Cancer Society	www.cancer.org
Camp Kesem	https://campkesem.org/
Camp Koru	https://www.projectkoru.org/camp-koru
Camp Mak-A-Dream	www.campdream.org
Cancer.net	www.cancer.net
Cancers and Careers	www.cancerandcareers.org
Cancer Legal Resource Center	www.disabilityrightslegalcenter.org
Losta Helping Hands	www.lotsahelpinghands.com
LIVE**STRONG**	www.livestrong.org
Leukemia & Lymphoma Society	www.lls.org
Lymphoma Research Foundation	www.lymphoma.org
Multiple Myeloma Research Foundation	www.multiplemyeloma.org
Financial resources	
Be the Match	http://bethematch.org/For-Patients-and-Families/Getting-a-transplant/Planning-for-transplant-costs/Financial-Assistance-for-Transplant-Patients
Disability Rights Center	https://thedrlc.org
Bone Marrow Foundation	www.bonemarrow.org
CancerCare, Inc.	www.cancercare.org
Patient Advocate Foundation	www.patientadvocate.org
RX Assist	www.rxassist.org

2. Interventions

   a. Negotiate personal control

   b. Build on previous experiences/successes

   c. Ongoing self-assessment and training

   d. Educate about the outpatient process (e.g., medications, expected appointments, availability of 24-hour medical advice/support)

   e. Provide or refer for cognitive-based interventions (mindfulness-based stress reduction, cognitive-behavioral therapy, dialectical behavioral therapy)

Immediate Short Term

1. Issues [20, 21]

    a. Transition to outpatient setting post-HCT
    b. Increased stress on relationship between patient and caregiver
    c. Caregiver burden and feelings of incompetence
    d. Patient's dependency and loss of control
    e. GvHD risk in allogeneic recipients

2. Interventions

    a. Assess the meaning of uncertainty and stressors
    b. Evaluate burdensome tasks
    c. Assist patient/family to identify and mobilize available resources
    d. Assist in evaluating relationship enhancements
    e. Assure continuation of medical support/management in transitions to outpatient setting
    f. Encourage caregivers to engage in physical and emotional self-care
    g. Refer to appropriate community resources (i.e., financial, home health, counseling, and so on)

Long Term/Survivorship

1. Issues [22]

    a. Transition back to home, work and/or previous family roles
    b. Changes in patient's emotion and physical function due to complications and long-term effects of HCT
    c. Fear of recurrence
    d. Feelings of "being different"

2. Interventions

    a. Assess transitional needs and provide referrals to the Department of Vocational Rehabilitation, Social Security Disability, etc.
    b. Evaluate the effect of complications/late effects on relationships
    c. Problem-solve positive steps to build on strengths
    d. Survival techniques
    e. Support groups and reunions for survivors (NBMTlink webinars, Peer to Peer, BMTinfonet, etc.)

End-of-Life Care

1. Issues [23–25]

    a. Emotions including fear, sadness, failure
    b. Effects on the family, especially young children
    c. Physical changes, pain, comfort
    d. Spiritual needs
    e. Home vs. hospital vs. skilled facility

2. Intervention [26]

    a. Assess the source of expressed emotions
    b. Assess the impact on the family and assist with children, involve Child Life Services when appropriate
    c. Foster hope
    d. Consider home hospice as an option for patient and family
    e. Advocate with the provider team and family to meet the patient's wishes as possible
    f. Identify healthcare surrogate

3. Special considerations

    a. Patient questioning if they should have had the transplant? Did it matter?
    b. Related donor's grief and feelings about transplant outcome. Are they responsible for the outcome?

Palliative Care and Hematologic Malignancies (See Also Chap. 48)

The American Society of Clinical Oncology (ASCO) has developed recommendations regarding the delivery of palliative care to all oncology patients. They encourage the integration of palliative care into the ongoing provision of oncology treatment. ASCO has set a vision of comprehensive cancer care to include routine palliative care in the United States and several other countries by the year 2020. An interdisciplinary team is required to provide comprehensive palliative care [27].

A U.S. retrospective study showed patients with a hematologic malignancy accessed palliative care less frequently than those with solid tumors (11% vs. 89%, respectively) [28]. Research suggests that while hematology staff are aware of the needs for palliative care, the lack of access and integration to care has an adverse effect on families and caregivers. Qualitative analysis suggests family members were aware of impending death, but were reluctant to speak to staff and felt inadequately assisted in preparing for the dying experience.

Barriers to integration of palliative care in the setting of hematologic malignancies include [29, 30]:

1. The course of the illness
2. Availability of community resources including hospice support with no reimbursement for palliative care or ongoing transfusion support
3. Unpredictability of the illness
4. Unclear goals of care
5. Availability of early phase clinical trials and the patient's comprehension of the study objective
6. Availability of ongoing supportive therapies
7. Psychological dependency and the ongoing relationship between patient/family and providers

Provider skills needed for the provision of palliative care [31]:

1. Assessment
2. Information sharing
3. Decision-making capacity
4. Ability to determine the patient's capacity for decision making
5. Ability to clearly define goals of care. Discuss code status and Physician Orders for Life Sustaining Treatment (POLST). If inpatient, coordinate between providers on goals of care discussions.
6. Capacity for an objective discussion of withdrawal of therapy
7. Openness to discussion of *Death with Dignity* where state statutes allow
8. Advance care planning and delivery
9. Surrogate decision-making
10. Conflict resolution
11. Affirmation of patient/family understanding, satisfaction, concerns

Caregiving Needs and Requirements

Individuals who undergo HCT and CAR-T require caregiver support until otherwise told by their medical provider team. Autologous HCT and CAR-T recipients typically require a 24-hour caregiver for approximately 2–3 weeks after discharge from the hospital while allogeneic HCT recipients may require a caregiver anywhere from 2 to 6 months depending on complications that may arise.

Changes in healthcare delivery systems and policy highlighting reduction of costs have moved much of the HCT process from the inpatient to the outpatient setting, which may extend the caregiver's commitment by weeks to months. These changes also extend the caregiver's responsibilities, as greater involvement during the earlier phases of HCT is required. Payer contracts may not reimburse for post-HCT caregiver support. Therefore, the responsibility lies with the patient's natural supports, that is, family members or friends. This incredible commitment requires even further time away from work and other personal responsibilities.

Psychosocial Impact of Caregiving and Protective Factors

While there has been a breadth of research that explores the psychosocial implications for the HCT recipient, less is known about the experience of the caregiver. Research has shown that the psychosocial health of the caregiver has a direct impact on the health and well-being of the patient [32]. Caregivers suffer from anxiety and depression, sleep deprivation and fatigue, sexual dysfunction, and greater vulnerability to illness, and may experience fear, frustration, and isolation. Adaptation of the caregiver is important not only for his/her own well-being but also in achieving optimal patient outcomes. It has also been shown that caregivers will avoid reporting their own distress for fear that this will distract from the care of the transplant recipient [33, 34].

Studies have shown female caregivers tend to report higher levels of distress than male caregivers because they are more likely to assume the role of primary caregiver while maintaining responsibility for the care of the rest of the family. Additionally, small studies suggest females to be more empathetic.

Control refers to the caregiver's ability to maintain a sense of predictability and manageability within their life and the lives of their loved ones. Adaptation to the caregiving role, as indicated by lower levels of distress, was noted in caregivers who reported a higher sense of personal control and spiritual well-being. Providing caregivers with detailed information about a patient's treatment course may offer more predictability. Caregivers who identified with a form of spiritual practice also showed increased adaptation to distress. Their faith allowed them to navigate the burdens of caregiving by applying meaning to their role and the role of illness in the life of their loved one [35].

Developing strategies and interventions to support caregivers can prove to be an important part of a patient's care. It has been shown in studies that caregivers tend to delay self-care activities in order to care for their loved one. This can have a dramatic impact on the health of the HCT patient, which can result in increased length of inpatient hospital stays. Support groups, online resources, and web-based tools to assist caregivers in managing their role are emerging. Additionally, cognitive-behavioral therapy has proven to be an effective modality for HCT patients and their caregivers. These resources are likely to be more beneficial when provided early in the planning process, as coping patterns established early can prove to be an essential part of the overall effectiveness of stress management.

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Chapter 6
Conditioning Regimens

Joseph Bubalo

Introduction

The preferred conditioning regimen for hematopoietic cell transplantation (HCT) should be capable of reducing the tumor load in the setting of a malignant disorder, provide adequate immunosuppression to prevent graft rejection, and have manageable side effects or regimen-related toxicities [1]. Traditionally, allogeneic conditioning regimens were ablative (see Table 6.1), meaning that stem cell support was required in order to attain hematopoietic recovery of the bone marrow [1]. Beginning in the early twenty-first century, there has been a trend in multiple patient populations to move toward nonmyeloablative (NMA) and reduced-intensity conditioning regimens (RIC) (see Table 6.2). The NMA and many of the RIC regimens do not require additional stem cell support for hematopoietic recovery in the event of donor graft failure, have lower rates of regimen-related organ and tissue toxicity, and result in mixed donor-recipient chimerism in a substantial proportion of patients in the early posttransplantation period. Reduced intensity regimens have a range of associated toxicities higher than that of NMA regimens but achieve the same therapeutic goals and are less toxic than traditional myeloablative regimens. Some, however, may approach ablation in their effects upon the bone marrow [2]. Most transplantation experts agree that any regimen that includes (i) total body irradiation (TBI) of <500 cGy as a single fraction or <800 cGy if fractionated, (ii) <9 mg/kg of oral busulfan, (iii) <140 mg/m^2 of melphalan, or <10 mg/kg of thiotepa is an RIC regimen [3, 4].

The selection of stem cell source for those individuals who lack a matched related or unrelated donor continues to evolve. Cord blood units to provide progenitor cells are seeing increased utilization in adults (see Table 6.3). This includes the use of both single and double cord units to enhance the clinical benefit [5, 7]. The development of posttransplant cyclophosphamide for selective depletion of

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Table 6.1 Common ablative conditioning regimens [14–17] (see sect. "Chemotherapy Dosing in Conditioning Regimens" for dosing recommendations)

Regimen	Disease states treated	Comments
Cy + ATGe +/− TBI	Aplastic anemia	TBI added for unrelated donors (URD)
tBu-Cy	AML, ALL, CLL, CML, NHL, MM, MDS	The busulfan exposure target varies by disease state and is managed with pharmacokinetic assessment
Cy-TBI	AML, ALL, CLL, NHL, MDS	
BEAM	NHL, HD, MM	

Cy cyclophosphamide, *ATGe* antithymocyte globulin (equine), *TBI* total body irradiation, *tBu* targeted busulfan, *AML* acute myelogenous leukemia, *ALL* acute lymphocytic leukemia, *CML* chronic myelogenous leukemia, *CLL* chronic lymphocytic leukemia, *NHL* non-Hodgkin lymphoma, *HD* Hodgkin disease, *MM* multiple myeloma, *MDS* myelodysplasia, *BEAM* carmustine, etoposide, cytarabine, melphalan

Table 6.2 Common reduced intensity conditioning (RIC) regimens [9, 18–21]

Regimen	Disease states treated	Comments
Bu-Flu	AML, MDS, ALL, CLL	
Bu-Flu-TBI	AML, ALL, CLL	
Flu-Mel	AML, MDS, NHL, MM	
Flu-TBI	AML, ALL, CLL	
TBI-200 cGY	AML, ALL, CLL	Rapidly growing disease may require more aggressive therapy. This is considered to be a non-myeloablative regimen which is the least intense of all RIC regimens

Bu busulfan, *cGY* centigray, *Cy* cyclophosphamide, *Flu* fludarabine, *Mel* melphalan, *TBI* total body irradiation

Table 6.3 Common conditioning regimens for cord blood transplants [5–7, 10, 21–23]

Regimens	Disease states treated	Comments
Flu-TBI (ablative)	AML, ALL, CML, MDS, NHL	Engraftment occurs approximately 2–3 weeks later than with other stem cell sources. Dual cord blood units often used for adults
Cy-Flu-TT-TBI	AML, ALL MDS	Dual cord blood units often used for adults
Cy-Flu-TBI	AML	
TT-Bu-Flu-rATG	AML, ALL, NHL, CML, MDS	Single cord blood unit used for adults and children

TT thiotepa, *rATG* antithymocyte globulin (rabbit)

Table 6.4 Haploidentical conditioning regimens [8, 9, 29]

Regimen	Disease states treated	Comments
Flu-TBI (ablative)	AML, ALL, CML, MDS, NHL	Post-HCT Cy +3 & +4
Flu-Cy-TBI (RIC)	AML, ALL, HL, MDS, NHL, MM	Post-HCT Cy +3 & +4
TT-Cy-Flu-TBI (ablative)	HL	Post-HCT Cy +3 & +4

Table 6.5 Common autologous conditioning regimens [11, 12, 14, 15, 24–28]

Regimen	Disease states treated	Comments
Bu16-Etoposide	AML	
BEAM	NHL, HD	
BuMelTT	NHL, HD	
Carbo-Etoposide	Germ cell	May be done in tandem
Carbo-Etoposide-Cy	Germ cell	May be done in tandem
CBV	NHL, HD	
Melphalan	MM, amyloid	May be done in tandem

Carbo carboplatin, *CBV* cyclophosphamide, carmustine, etoposide

alloreactive T-cells as immune suppression has broadened the use of haploidentical donors (see Table 6.4) [8, 9]. Either of these approaches lends itself to variations in conditioning regimens with a trend toward nonmyeloablative conditioning and may require changes in associated supportive care and immune suppression [8–10].

In the autologous HCT setting, high-dose therapy with stem cell support is frequently used to salvage relapsed or persistent disease as well as to consolidate or prolong cancer remission. Sequential, also known as tandem, stem cell transplants are used in some disease states to further deepen a remission, increase the chance for cure, or facilitate a period where the patient can take a break from antineoplastic therapy or be maintained on a less intense maintenance therapy (see Table 6.5) [11–13]. With regard to dose intensity, autologous regimens are typically ablative, and the rescue is derived from the individual's own cells as opposed to an allogeneic donor. Therefore, these individuals may experience a higher rate of regimen-related toxicities compared to patients receiving a reduced intensity allogeneic HCT conditioning regimen.

Conditioning Agents

Most conditioning agents are associated with pancytopenia, sterility, and alopecia in the doses used in myeloablative regimens. Mucositis may encompass the entire GI tract and result in stomatitis, esophagitis, nausea, vomiting, and diarrhea (see Chap. 32). Selected toxicities and important aspects of care are presented, which are unique or more prevalent in the high-dose therapy setting. On a day-to-day basis, these effects may require additional therapy or attention to specific patient-care techniques to support the patient and minimize morbidity.

1. Antithymocytic Immune Globulin (ATG) Equine (ATGAM®)

   a. Type: immune modulator, polyclonal antibody mixture
   b. Dose: varies by protocol; one example is 30 mg/kg IV daily for 3 days
   c. Toxicities:

      i. Fatal allergic reactions; require test dose prior to initiation of treatment
      ii. Serum sickness (or maturation syndrome) symptoms including fever, chills, hypotension, rash, arthralgias, joint pain, and renal insufficiency

   d. Patient Care Points:

      i. Intradermal test dose prior to the first dose with contralateral saline dose
      ii. Premedicate with diphenhydramine, acetaminophen, and steroids
      iii. Infuse slowly initially, then may accelerate rate as tolerated
      iv. Have emergency medications at bedside (epinephrine, hydrocortisone, diphenhydramine)

   e. Rabbit ATG (Thymoglobulin®) can be substituted in some circumstances, often based on institutional guidelines. 1.5 mg/kg rabbit ATG is considered approximately clinically equivalent to 15 mg/kg equine ATG. This interchange should only be performed with oversight by an experienced HCT transplant physician and pharmacist as the different products have different potencies, and substitution may be inappropriate in some underlying disease states [30].

2. Antithymocyte Immune Globulin (ATG) – Rabbit (Thymoglobulin®)

   a. Immune modulator, polyclonal antibody mixture
   b. Dose: varies by protocol; one example is 2–2.5 mg/kg IV daily for 2–4 days
   c. Toxicities:

      i. Fatal allergic reactions are very rare; no test dose required.
      ii. Serum Sickness symptoms: fever, chills, rash, arthralgias, joint pain, and urticarial.

   d. Patient Care Points:

      i. Premedicate with diphenhydramine, acetaminophen, and famotidine
      ii. Infuse over 6 hours on the first day, infuse over 4 hours on subsequent days if tolerated well on the prior day
      iii. Have emergency medications at bedside (epinephrine, hydrocortisone, diphenhydramine)

   e. Product note: ATG-Thymoglobulin® and ATG-Fresenius® have different potencies and cannot be directly interchanged.

3. Busulfan (Myleran®, Busulfex®) [31]

   a. Type: Alkylating agent
   b. Dose: See 6.6 for dosing weights for different patient populations

      i. Myeloablative = 1 mg/kg/dose PO for total of 12–16 mg/kg or 0.8 mg/kg/dose IV every 6 hours or 3.2 mg/kg/day × 3–4 days for a total of 9.6–12.8 mg/kg.

      ii. Reduced intensity = 3.2–6.4 mg/kg IV total per regimen in 1–2 doses.

      iii. 0.8 mg IV is equivalent to 1 mg PO.

  c. Toxicities:

      i. Lowers seizure threshold

      ii. Nausea, vomiting

      iii. Pulmonary fibrosis (busulfan lung): symptoms of cough, dyspnea, low-grade fever

      iv. Hepatitis/sinusoidal obstructive syndrome (SOS): may have late onset

      v. Mucositis

      vi. Hyperpigmentation/skin blistering

  d. Patient Care Points:

      i. Anticonvulsants required to prevent seizures. A loading dose of phenytoin, levetiracetam +/− clonazepam, lorazepam, or equivalent given the evening prior to first dose of busulfan with maintenance dosing daily, continuing through the morning after the administration of the last dose [32, 33].

      ii. Pharmacokinetic targeting is necessary for ablative IV or oral regimens. Target levels of busulfan with cyclophosphamide or other regimens as directed in the original literature. Others such as BuMelTT (busulfan, melphalan, thiotepa) and other busulfan conditioning schedules do not require pharmacokinetic monitoring unless the original reference provides a dosing target [17].

- Daily AUC 4400–5400 for AML, ALL, NHL, and MDS
- Daily AUC 5300–6000 micromole minutes for CML
- Divide daily AUC by 4 for per dose AUC if targeting every 6-hour dosing

      iii. Give oral drug on an empty stomach.

      iv. If patient vomits within 0–30 minutes of oral drug administration and tablets are visible, count tablets and repeat that number of pills. If unsure, repeat entire dose.

      v. If patient vomits within 30–60 minutes of drug administration and tablets are visible, count tablets and repeat that number of pills. If unsure, repeat one-half the dose.

      vi. Tablets should be placed in gelatin capsules for ease of consumption.

      vii. If there is more than one episode of emesis requiring re-dosing, consider changing to IV busulfan.

4. Carboplatin (Paraplatin®)

  a. Type: Platinum alkylating agent

  b. Dose: 600–700 mg/m^2/day IV for 3 days

   c. Toxicities:

      i. Irreversible ototoxicity
     ii. Delayed nausea/vomiting
    iii. Renal insufficiency
    iv. Electrolyte disturbances: acidosis, hyponatremia
     v. Neurotoxicity

   d. Patient Care Points:

      i. Maintain adequate hydration

5. Carmustine (BCNU, BiCNU®)

   a. Type: Nitrosourea alkylating agent.
   b. Dose: 300 mg/m^2 IV for 1 day or 150 mg/m^2 daily for 3 days are common dose schedules.
   c. Toxicities:

      i. Infusional hypotension related to rate of administration. See maximum infusion rate.
     ii. Nausea/vomiting.
    iii. Progressive pulmonary fibrosis; acute onset usually responds to steroids but if unresponsive may be fatal. Symptoms include cough, dyspnea, or restrictive pattern on pulmonary function tests (PFTs).
    iv. Mucositis.

   d. Patient Care Points:

      i. Pre-administration baseline PFTs with diffusion capacity for carbon monoxide (DLCO)
     ii. Administer at a maximum rate of 3 mg/m^2 per minute
    iii. Requires pre- and post-hydration

6. Cyclophosphamide (Cytoxan®)

   a. Type: Alkylating agent
   b. Dose: 60 mg/kg/day IV daily for 2 days (based on IBW) incorporated into conventional hematologic malignancy conditioning regimens

      i. Aplastic anemia: 50 mg/kg IV daily for 2–4 days (based on IBW) is commonly used [34, 35].

   c. Toxicities:

      i. Hemorrhagic cystitis
     ii. Cardiomyopathy
    iii. Nausea/vomiting
    iv. Mucositis
     v. Syndrome of inappropriate antidiuretic hormone (SIADH)
    vi. Histamine reaction characterized by sinus burning, cough, itchy/watery eyes, chest discomfort/tightness
   vii. Gonadal failure

    d. Patient Care Points:

        i. Multigated radionuclide angiography (MUGA) or transthoracic echo-cardiogram (TTE) pretreatment with baseline left ventricular ejection fraction (LVEF) >45%.

       ii. Adequately hydrate the patient for 12 hours prior to cyclophosphamide dose with normal saline (NS). The cyclophosphamide should run concurrently with 2-mercaptoethane sulfonate (MESNA) to protect the bladder. The patient is asked to void every 1–2 hours during cyclophosphamide administration. Check for hematuria with each void. If the patient should develop hemorrhagic cystitis, continuous bladder irrigation is indicated.

      iii. Diurese to maintain euvolemia.

      iv. Monitor daily intake/output and weights.

       v. Daily chemistries (sodium, potassium) during infusion days.

      vi. Infuse slowly if histamine reaction occurs and consider pseudoephedrine PRN or nasal ipratropium.

7. Cytosine Arabinoside (ARA-C, Cytosar-U®)

    a. Type: Antimetabolite

    b. Dose: 400 mg/m^2 IV daily for 4 days as part of the BEAM regimen

    c. Toxicities:

        i. Mucositis.

       ii. Cerebellar dysfunction: ataxia, nystagmus, slurred speech.

      iii. Chemical conjunctivitis: prophylactic eye drops are not required at this dose.

      iv. Acral erythema.

       v. Biliary stasis and elevated liver function tests (LFTs).

      vi. Fevers, myalgia, bone pain, chest pain.

     vii. Capillary leak syndrome.

8. Etoposide (VP-16, Vepesid®)

    a. Type: Plant alkaloid, inhibits topoisomerase II

    b. Dose:

        i. With carboplatin: 750 mg/m^2 IV daily for 3 days

       ii. With TBI or busulfan: 30–60 mg/kg IV for 1 day

      iii. With BEAM 200–400 mg/m^2/day IV for 4 days

    c. Selected toxicities:

        i. Hypersensitivity, anaphylactic type reaction

       ii. Hypotension, usually during or shortly after infusion

      iii. Mucositis

      iv. Large volume diarrhea

       v. Elevated LFTs. Consider dose adjustment for bilirubin >5 mg/dL

      vi. Erythema multiforme, plantar/palmer erythema

       vii. Fever

     viii. Peripheral neuropathy

       ix. Cystitis

  d. Patient Care Points:

        i. If using "undiluted" etoposide (20 mg/mL), premedicate for infusion with steroids and diphenhydramine and repeat 2 hours into the infusion.

       ii. Fluid bolus with 500–1000 mL NS for hypotension (SBP <85 mmHg or blood pressure decrease >20 mmHg from baseline) during infusion.

     iii. If unresponsive to fluid bolus, stop the infusion. May consider restarting at a lower dose after blood pressure stabilizes with additional steroids, antihistamines, and blood pressure support including dopamine 2–5 mcg/kg/min.

     iv. Maintain adequate hydration pre- and post-infusion.

      v. Consider not giving diuretics or antihypertensive medications on days of etoposide administration.

     vi. Skin rash may require topical steroid treatment.

9. Fludarabine (Fludara®) [36]

  a. Type: Antimetabolite, purine analogue

  b. Dose: 30–40 mg/m^2/day for 3–5 days

  c. Selected toxicities:

        i. Rare, severe neurologic toxicity (cortical blindness, coma, death). Risk increases above doses of 140 mg/m^2/regimen [37].

       ii. Rare hemolytic anemia.

     iii. Combination use with pentostatin has resulted in severe pulmonary toxicity.

  d. Patient Care Points:

        i. Causes profound lymphopenia, therefore prophylaxis and surveillance for opportunistic infections are important.

10. Melphalan (Alkeran®)

  a. Type: Alkylating agent

  b. Dose:

        i. Single agent: 100 mg/m^2 IV daily for 2 days or 200 mg/m^2 × 1 day; may be dose reduced to a total dose of 100 mg/m^2 or 140 mg/m^2 in patients with AL amyloidosis or multiple myeloma

       ii. BEAM, FluMel: 140 mg/m^2 IV for 1 day

     iii. Creatinine clearance <10 or dialysis: 70 mg/m^2 IV daily for 2 days (MM or amyloid)

     iv. Age >75:70 mg/m^2 IV daily for 2 days (MM or amyloid)

  c. Selected toxicities:

   i. Mucositis
   ii. Hyperpigmentation
   iii. N/V
   iv. Arrhythmias

  d. Patient Care Points:

   i. Give immediately after mixing as stability in solution is limited.
   ii. Ask the patient to suck on ice chips before, during, and after infusion (at least 30 minutes) to decrease blood flow to oral mucosa to help prevent mucositis. Cryotherapy has been shown to decrease stomatitis.

  e. Product Note: Propylene glycol-free melphalan (Evomela®) has longer stability and is currently considered equivalent mg:mg with conventional melphalan formulations with similar adverse event profile [38].

11. Thiotepa (Thioplex®)

  a. Type: Alkylating agent
  b. Dose: 250 mg/m² IV daily × 2–3 days
  c. Selected toxicities:

   i. Nausea/vomiting.
   ii. Central nervous system (CNS) changes including decline in mental status.
   iii. Hepatic changes including late SOS and elevated LFTs.
   iv. Pulmonary toxicity.
   v. Headache.
   vi. Skin desquamation, especially in intertriginous areas as thiotepa, is excreted in sweat.
   vii. Mucositis.

  d. Patient Care Points:

   i. Consider having patient shower 2–3 times daily during and for 24 hours post high-dose thiotepa administration. Use hydrocortisone cream 1% underarms, in groin area or face or triamcinolone cream 0.1% for other areas of desquamation.
   ii. Round dose to nearest 15 mg due to vial size.

12. Total body irradiation (TBI) [16, 21]

  a. Dose:

   i. Non-ablative transplants: 200–500 cGy in a single fraction

    ii. Conventional transplantation: 1200–1400 cGy given in divided fractions; dose, number, and delivery per institutional guidelines

    iii. Examples of conventional TBI

- Low-risk disease: 1200 cGy divided into 8 doses delivered BID over 4 days
- High-risk disease: 1400 cGy divided into 8 doses delivered BID over 4 days

b. Selected toxicities:

    i. Sunburn-like rash, diffuse erythema

    ii. Parotitis

    iii. Cataracts

    iv. Thyroid dysfunction, usually seen late

    v. Nausea/vomiting

    vi. CNS toxicity, leukoencephalopathy

    vii. Acute pneumonitis/alveolar hemorrhage

    viii. Fatigue

    ix. Growth failure

    x. Gonadal failure

    xi. Diarrhea

c. Patient Care Points:

    i. Antiemetics prior to each treatment fraction

    ii. Shield lungs as per protocol

    iii. Pretreatment thyroid-stimulating hormone (TSH)

Antiemetic dosing

Agent	Risk	Antiemetic regimen	Comments
Antithymocyte globulin	Low	None needed	Other premedications required
Busulfan	Moderate to high	Ondansetron 8 mg PO Q 6 hours or 16–24 mg PO daily for single daily dose IV	Dexamethasone 20 mg daily with once daily ondansetron
Carboplatin	High	Ondansetron 24 mg PO or 8 mg IV prior to each daily chemotherapy dose	Dexamethasone 20 mg daily with each daily ondansetron
Carmustine	High	Ondansetron 24 mg PO or 8 mg IV prior to each daily chemotherapy dose	Dexamethasone 20 mg daily with each daily ondansetron

Agent	Risk	Antiemetic regimen	Comments
Clofarabine	Low	Ondansetron 8 mg PO daily (single agent); 16 mg (8 mg IV) if other chemotherapy agents given	Dexamethasone 8–12 mg daily with each daily ondansetron
Cyclophosphamide	High	Ondansetron 24 mg PO daily or 8 mg IV Q 12 hours start prior to first chemotherapy dose; consider adding PO aprepitant each day cyclophosphamide is given plus 1 additional day after or single dose IV dose with first daily cyclophosphamide dose, give second IV dose on day 3 if 4 day regimen	Dexamethasone 20 mg daily with each daily ondansetron Dose adjust dexamethasone if aprepitant used
Cytarabine	Low (<1000 mg/m²/day)	Ondansetron 16 mg PO daily (single agent); 24 mg (8 mg IV) if other chemotherapy agents given	Dexamethasone 12–20 mg daily with each daily ondansetron
Etoposide	Moderate to high	Ondansetron 24 mg PO or 8 mg IV prior to daily chemotherapy dose	Dexamethasone 20 mg daily with each daily ondansetron
Fludarabine	Low	Ondansetron 8 mg PO daily (single agent); 16–24 mg (8 mg IV) if other chemotherapy agents given; If only agent used that day may substitute 10 mg prochlorperazine for the ondansetron	Dexamethasone 8–12 mg daily with each daily ondansetron
Melphalan	High	Ondansetron 24 mg PO daily (or 8 mg IV) start prior to chemotherapy dose; consider adding PO aprepitant each day melphalan is given plus 1 additional day after or single dose IV dose with first daily melphalan dose	Dexamethasone 20 mg daily with each daily ondansetron Dose adjust dexamethasone if aprepitant used
Total body irradiation	High	Ondansetron 8 mg PO prior to each radiation fraction	Dexamethasone 20 mg once per 24 hours with the first daily ondansetron
Thiotepa	High	Ondansetron 24 mg PO or 8 mg IV prior to first daily chemotherapy dose	Dexamethasone 20 mg daily with each daily ondansetron

Notes: (1) Ondansetron (Zofran®) is interchangeable with granisetron (Kytril®) at equivalent doses. Palonosetron (Aloxi®) dosing for optimal effect is unclear. (2) Lorazepam 0.5 mg PO/IV may be offered if needed prior to each day's first chemotherapy dose for management of anticipatory or anxiety-related nausea/vomiting

Chemotherapy Dosing in Conditioning Regimens [15, 22, 23, 35, 39–52]

Agent	Dosing	Dose adjustment for renal insufficiency	Dose adjustment for hepatic insufficiency	Additional information
Alemtuzumab	Flat dosing in adults based upon regimen selected	No dose adjustment required for renal dysfunction	No dose adjustment in hepatic impairment	No dose adjustments for obese individuals
Busulfan	Dose on ABW25 in adults (obese and nonobese) receiving per kg dosing or BSA based on TBW for m2 dosing. All regimens >12 mg/kg PO equivalent are recommended to have PK targeting as appropriate for the disease state. Regimens using doses ≤12 mg/kg PO equivalent do not have sufficient information to recommend routine PK monitoring at this time　Pediatrics should be dosed upon TBW with similar monitoring guidelines	No dose adjustment required for renal dysfunction	Treosulfan may be a less toxic alternative if available Consider maximum Css of 600 with targeting	PK monitoring has reduced rate of SOS from ~20% to <5% AUC/Css targeting varies by regimen For BuCy regimens the MTD is 16 mg/kg PO equivalent over 4 days for adults
Carboplatin	Dose adults on BSA based on TBW; calculate CrCl based on ABW40 if BMI>30	If CrCl <50 dose based on an AUC of 7 per day using 24 hour or calculated CrCl	Transaminitis common post auto-HCT for germ cell; no suggested adjustments at this time	No dose adjustment required for BSA dosed obese individuals; if using Calvert formula dose based on 24 hours urine collection derived CrCl; optional to use calculated CrCl per institutional standard
Carmustine	Dose adults on BSA based on TBW unless >120% IBW or BMI >30. Then dose on BSA based on ABW25	CrCl 46 to 60 = give 80% of usual dose CrCl 31–45 = give 75% of usual dose, CrCl < 30: Do not use	In HCT 25% empiric reduction suggested in moderate dysfunction	Pulmonary toxicity > 50% at 600 mg/m2 with multiple agent regimens; MTD of 1200 mg/m2 as single agent with 9.5% pulmonary toxicity

Agent	Dosing	Dose adjustment for renal insufficiency	Dose adjustment for hepatic insufficiency	Additional information
Clofarabine	Dose on BSA based on TBW	CrCl 30–60 50% dose CrCl <30 do not use	No dose adjustment in literature but minimally investigated; consider 20% dose decrease in moderate dysfunction	No dose adjustments for obese individuals
Cyclophosphamide	Dose on IBW for Cy 120 or 200 Exception: Aplastic anemia for Cy 120 dose on TBW unless >120% IBW then ABW25	For CrCl <30, dose at 75% of protocol dose	Total dose not to exceed 90–110 mg/kg; give Cy before Bu or wait 1–2 days after Bu to give Cy; give TBI prior to Cy to minimize hepatic injury; decrease Cy dose 10–20%	For obese patients see dosing column
Cytarabine	Dose on BSA based on TBW	No dose adjustment required if <500 mg/m^2	No dose adjustment required	No dose adjustment for obese patients
Etoposide	Dose on ABW25 for mg/kg dosing; used BSA based on TBW for BSA based dosing	Dose at 50% for CrCl <30; do not exceed 30 mg/kg	Full dose if normal renal function, if CrCl <30–50 *with mild–moderate* hepatic dysfunction or albumin <3, decrease dose by 25%	DLT of mucositis
Fludarabine	Dose on BSA based on TBW	CrCl 17–40 ml/min dose at 80% CrCl<17 ml/min dose at 60%	Increased transaminitis risk, consider dose decrease of 20% if dosing with Busulfan	Posttreatment leukoencephalopathy still being studied for conditioning regimen doses above 125 mg/m^2 No dose adjustment for obesity
Melphalan	Dose on BSA based on TBW	For CrCl <40 dose at 70 mg/m^2/day × 2 or 140 mg/m^2 on 1 day for goal dose 200 mg/m^2	No dose adjustment as single agent; may be added hepatic toxin in combination regimens	DLT of mucositis No dose adjustment for obesity as long as dose is < 3.6 mg/kg of TBW

(continued)

Agent	Dosing	Dose adjustment for renal insufficiency	Dose adjustment for hepatic insufficiency	Additional information
Pentostatin	Dose on BSA based on TBW	CrCl <60, 75% dose CrCl <30, 40% dose	No dose adjustment required	No dose adjustment for obesity.
Thiotepa	Dose adults on BSA based on TBW unless >120% above IBW then dose on BSA based on ABW40	No dose adjustment required for renal dysfunction	No dose adjustment required; hepatic metabolism unclear; if moderate dysfunction, consider empiric 25% dose decrease	Multi-agent MTD is 500–750 mg/m², single agent MTD is 900 mg/m²
Antithymocyte globulin – Equine	Dose on mg/kg based on TBW	No dose adjustments for renal dysfunction	No dose adjustments in hepatic dysfunction	No dose adjustments for obese individuals
Antithymocyte globulin – Rabbit	Dose on mg/kg based on TBW	No dose adjustments for renal dysfunction	No dose adjustments in hepatic dysfunction	No dose adjustments for obese individuals

Patients with a CrCl <10 ml/min or requiring dialysis at the time of transplant should have their doses reviewed by a pharmacist trained in the care of HCT patients

Moderate renal dysfunction = 30–50 mL/min CrCl

Patients with a history of cirrhosis, viral hepatitis, bilirubin >2, AST/ALT >3× ULN should have all of their doses reviewed by a pharmacist trained in the care of HCT patients. Individuals with severe dysfunction (Childs-Pugh C) should not undergo HCT

Patients with TBW < IBW should be dosed on TBW for per kg or BSA based dosing

TBW total (e.g. actual) body weight, *ABW25* adjusted body weight [IBW + 0.25(TBW − IBW)], *ABW40* adjusted body weight [IBW + 0.4(TBW − IBW)], *AUC* area under curve, *BSA* body surface area, *CrCl* creatinine clearance, *Css* concentration at steady state, *DLT* dose limiting toxicity, *IBW* ideal body weight, *MTD* maximally tolerated dose, *PK* pharmacokinetics

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Chapter 7
Nutrition

Stacey Evert

Introduction

Hematopoietic cell transplant (HCT) patients have huge metabolic demands related to wound healing after conditioning regimens, infectious events with associated febrile states, and in allogeneic HCT recipients, the systemic inflammatory state and local tissue damage imposed by acute graft versus host disease (GvHD). In the long term, ongoing inflammatory conditions and maldigestion/malabsorption can contribute to a chronic wasting syndrome. The central and critical importance of maintaining adequate nutritional balance throughout the transplant process cannot be understated. Understanding the anabolic and catabolic states seen in the HCT population, as well as issues related to the restriction of diet for these patients, is essential.

While we seek to optimize the nutritional state of the patient, it is also important to recognize that the gastrointestinal (GI) tract can be a portal of entry for systemic infection. As such, the identification of an appropriate diet that limits further infectious risk in this immunocompromised patient population is essential.

Within this section, the rationale for a controlled low bacteria diet, GvHD diet restrictions, and general diet guidelines are provided. Additionally, details regarding the goals for nutrition during HCT and guidelines for initiation of total parenteral nutrition (TPN) and enteral nutrition (EN) are given, with additional recommendations including a discussion of the ongoing debate regarding L-glutamine. Also included is a discussion on gut microbiome with pre- and probiotics.

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Low Bacteria Diet

Patients undergoing intensive conditioning regimens for HCT who develop a period of neutropenia have an increased risk for developing a food-related infection from bacteria, yeasts, molds, viruses, and parasites. The low bacteria diet is thought to help prevent food-related infections, but studies have been unable to show significant difference between placebo and intervention groups [1, 2]. One study showed that during the neutropenic phase, there was no significant difference in infections, but after the resolution of neutropenia the patients on low bacteria diet had higher rate of *Clostridium difficile* (*C. diff*) and vancomycin-resistant *Enterococcus* [3]. The most common bacteria that can cause harm to the immunocompromised patient are *Campylobacter jejuni*, *Salmonella*, *Escherichia coli* (*E. coli*), and *Clostridium*; these bacteria rarely cause blood-borne infection except for *E coli*. Safe food handling is the primary cause of food-borne illness in immunocompromised patients [4]. Other institutional variations include sterile diet, well-cooked foods only, or a modified house diet that omits fresh fruits and vegetables from an otherwise regular diet [4]. While the effect of a low bacteria diet on preventing infection is unknown, HCT patients who are neutropenic and immunosuppressed should avoid foods associated with increased infection risk. More studies are needed to determine the safety, efficacy, and necessity of a low bacteria in this setting [2, 4].

The Centers for Disease Control (CDC) has developed a list of foods that a HCT patient should avoid, as well as food safety guidelines. These guidelines should be the building blocks that individual institutions can utilize to develop their own version of a low bacteria diet. These guidelines include the use of separate cutting boards for raw meats and vegetables, meticulous hand hygiene after handling of raw meats, and cooking meats to the appropriate internal temperature for that product [5].

Foods patients should avoid include [5, 6]:

1. Foods containing raw and undercooked eggs
2. Unpasteurized dairy products
3. Unpasteurized fruit and vegetable juices
4. Unpasteurized cheeses or cheeses containing molds
5. Undercooked or raw poultry, meats, fish and seafood
6. Vegetable sprouts (e.g., alfalfa, bean and other seed sprouts)
7. Raw fruits with a rough texture (e.g., raspberries)
8. Smooth raw fruits (unless washed under running water, peeled or cooked)
9. Unwashed raw vegetables (unless washed under running water, peeled or cooked)
10. Undercooked or raw tofu
11. Raw or unpasteurized honey
12. Deli meats, hot dogs and processed meats
13. Raw, uncooked grain products
14. Mate tea
15. All moldy and outdated food products
16. Unpasteurized beer

17. Raw, uncooked brewer's yeast
18. Unroasted raw nuts
19. Roasted nuts in the shell

In general, some version of a low bacteria diet should be followed until day +100 for allogeneic transplant recipients. Autologous recipients should be reminded of food safety practice (cooking meat to appropriate temps, proper cleaning and cooking techniques, etc.) and avoidance of high-risk foods (sprouts, undercooked proteins, unpasteurized products, etc.). If patients follow a low bacteria diet, they should do so for 1–2 months post-transplant. In the end, it is up to each institution to determine which dietary restrictions should be implemented and when they can be discontinued.

Probiotics are under study for the management of a variety of medical conditions. Their use is gaining popularity by both the medical community and general population. Probiotics can be found in over-the-counter capsules or in foods such as yogurt, kefir, and fortified milk. Strong evidence has been found for probiotic use for the treatment of infectious diarrhea and prevention/treatment of antibiotic-induced diarrhea. Theoretically, probiotic use in the HCT population could be viewed as a way to treat antibiotic-induced or radiation-induced diarrhea; however, this could promote infectious complications in this immunocompromised population.

While probiotics are being utilized to treat medical conditions in the immune-competent population, there have been minimal studies done to evaluate their efficacy in patients undergoing HCT. Without those data, the safety of probiotics in HCT recipients is unknown and use should be avoided, recognizing the risk of bacterial translocation through the GI tract wall potentially resulting in systemic infection.

Water safety is also a concern for these patients. HCT recipients should avoid using well water as water testing is performed too infrequently. If patients choose to use tap water they should heed public health advisories on water safety. Use of a water filtering system or home distiller may reduce the risk for waterborne pathogens found in tap water. The filter "should be capable of removing particles ≥1 μm in diameter or filter by reverse osmosis." Bottled water should be used with caution and checked to be sure that reverse osmosis, distillation, or 1 μm particulate absolute filtration is used to remove *Cryptosporidium* (patients may need to check with bottler to see if this has been done). Also patients should be aware that the water used to make ice, tea, coffee, etc., must be free of *Cryptosporidium* (especially important if patients are not residing in their own homes) [5, 7].

Graft-Versus-Host Disease Diet

GvHD is a T-cell-mediated immunologic reaction of engrafted lymphoid cells against the host tissue that may involve major organs, most commonly the skin, GI tract, and liver typically occurring within the first 100 days (acute GvHD). Chronic GvHD can evolve directly from acute GvHD, can occur after a period of recovery

from previous GvHD, or can develop *de novo*. Prognosis for these presentations of chronic GvHD varies from poor to good, respectively [8]. Clinical symptoms seen in patients with acute GvHD of GI tract may include abdominal pain/cramping, diarrhea, dysphagia, nausea, and vomiting [8]. Chronic GvHD may be seen in some patients with symptoms of weight fluctuation, xerostomia, stomatitis, anorexia, reflux symptom, and diarrhea. All of these clinical findings can lead to malabsorption, bacterial translocation across the GI mucosa, dehydration and weight loss in a patient population already at risk for these complications.

Management of GvHD of the GI tract is especially challenging. Nutritional assessment and support of these patients may be difficult due to severe GI symptoms with inaccurate output measurement (large volume diarrhea, incontinence, or mix of stool/urine), as well as fluid retention that could mask weight loss. Determination of precise nutrient (macro and micro) requirements is inexact but should provide adequate calories (30–35 kcal/kg) [9] and a minimum of 1.5 gm protein/kg or higher for protein-losing enteropathy [10].

Nutrition therapy can range from bowel rest and TPN to a diet that is low in GI stimulants/irritants (i.e., caffeine, lactose, acid, fat, and fiber) based on the severity of the patient's symptoms [6, 11]. For patients with acute GvHD who present with large volume watery diarrhea and GI cramping, bowel rest and TPN should be the initial steps of nutrition therapy. Once signs and symptoms have begun to improve (decreased abdominal cramping and decreased stool output, typically <500 ml per day), patients may start a limited isotonic clear liquid diet as tolerated.

Once stools start to become formed and the patient reports minimal cramping, one could expand to a diet that is low fat, low fiber, and lactose restricted with a gradual advancement to regular diet as tolerated. Regular monitoring for patient tolerance of diet advancement is important; increased diarrhea, emesis, or abdominal cramping should warrant a return to the previous diet restrictions. Patients should remain on TPN until tolerating adequate calories and protein. The addition of new foods and diet advancement will vary by patient based on symptoms and tolerance.

In patients with long-term chronic GvHD of GI tract, low-fat diet education, pancreatic enzymes, and monitoring and repleting fat-soluble vitamins may be beneficial [7, 10–12].

Goals of Nutrition During HCT

Because HCT patients are predisposed to treatment-related malnutrition, they should receive ongoing nutrition assessment throughout the HCT process including nutritional and medical histories, anthropometry, chemistry review, and assessment of additional factors that may interfere with the patient taking adequate nutrition (pain control, activity level, etc.). This information will assist in determining the nutrient requirement for individual patients.

In general, patients who are in the immediate post-HCT phase have the following energy and protein requirements [6, 7, 13]:

1. Energy needs (BEE = Basal Energy Expenditure)

    a. Calculated by Harris Benedict Equations

        i. For men, the BEE = 66.5 + (13.75 × kg) + (5.0 × cm) – (6.78 × age)
        ii. For women, the BEE = 655.1 × (9.56 × kg) + (1.85 × cm) – (4.68 × age)

    b. Baseline needs: BEE × 1.3–1.5 (30–35 kcal/kg) [14]

        i. Typically used with patients with evidence of engraftment and no metabolic stressors

    c. Stressed needs: BEE × 1.5–1.6

        i. Typically used in the immediate post-HCT period

    d. Can also use [14]

        i. Critically ill: 30–35 kcal/kg
        ii. Non malnourished: 25–30 kcal/kg

2. Protein needs

    a. Estimated as approximately two times the Recommended Dietary Allowance (RDA).
    b. 1.5–2 gm/kg – use adjusted weight for obesity: [ideal weight +0.025(actual weight – ideal weight)]. Increased in the immediate post-HCT period or with corticosteroid treatment (first 1–3 months) [14].
    c. Protein requirements may need to be adjusted due to other medical conditions.

        i. Increase requirements due to muscle wasting, steroid myopathy, GvHD, etc.
        ii. Decrease requirements in the setting of renal insufficiency, hepatic encephalopathy, etc.

3. Fluid requirements [14]

    a. Individualized based on the patient's clinical status (i.e., increased in the setting of excessive GI loss, nephrotoxic medications, etc. and decreased in the setting of compromised organ function and iatrogenic fluid overload).
    b. Maintenance fluid needs for adults is 1500 mL/m^2 body surface area.

Oral nutrition should be consistently encouraged throughout the transplant process to help maintain muscle mass and weight, avoid sarcopenia, and potentially decrease the risk of developing GvHD [15]. Autologous and some allogeneic HCT recipients may be able to maintain adequate oral intake and avoid TPN during the transplant period with attention to symptom management. Symptom control via medication or dietary adjustments may allow the patient to avoid TPN and maintain adequate oral intake. However, the majority of allogeneic HCT recipients and all patients with severe mucositis are likely to require TPN to maintain positive nitrogen balance and prevent significant weight loss.

Use of Total Parenteral Nutrition

Patients who are undergoing myeloablative HCT have a higher incidence of various oral and GI complications. Examples of these complications can include but are not limited to oral/esophageal mucositis, anorexia, and nausea/vomiting/diarrhea (see Chaps. 31 & 32). These complications can impair nutritional status by limiting oral intake immediately post-HCT. It is common practice to utilize TPN during this period for those patients unable to tolerate oral intake.

1. TPN initiation guidelines

   a. TPN should be considered if the following conditions exist [11]:

      i. Weight loss of ≤10% of usual body weight
      ii. Malnourished on admit
      iii. Patient unable to consume at least 50% of BEE for ≥3 days (see sect. 7.3)
      iv. Negligible oral intake (or >50% of BEE) is anticipated for at least 7 consecutive days
      v. Severe GI toxicity lasting >5 days expected with the conditioning regimen (e.g., busulfan, etoposide, melphalan, and/or total body irradiation combinations)

   b. Recommend a baseline of 25–30 kcal/kg/day, 1.5 gm protein/kg/day, and 20–30% of kcal from lipids [16]

      i. Adjusted body weight should be used for patients ≥125% ideal weight.
      ii. Calories and protein provided should be adjusted based on patient's medical condition (i.e., acute kidney injury, fluid status, etc.).
      iii. Lipids are not contraindicated in HCT patients unless the patient has excessive hypertriglyceridemia. Recommendations in the setting of hypertriglyceridemia:

         • For fasting triglycerides >500, consider holding lipids until triglycerides decrease but for no longer than 2 weeks. Then reintroduce at 4–8% and monitor triglycerides. As triglyceride levels stabilize, increase back to 20–30%.
         • Consider other causes of hypertriglyceridemia if this remains an ongoing issue.
         • Minimum amount of lipid necessary to prevent essential fatty acid deficiency is 4–8% of total energy intake.
         • Evidence of essential fatty acid deficiency will appear in 1–2 weeks in HCT patients not receiving lipids.
         • SMOFlipid® (a blend of soybean oil, medium-chain triglycerides, olive oil, and fish oil) have not been studied in this population and should be used with caution due to amount of fish oil and patient's platelet status. Intralipid® (soybean oil) is currently being utilized.

   c. Vitamin C at a dose of 500 mg/day should be provided to promote tissue recovery via collagen biosynthesis.

    d. Additional zinc should be added to TPN for patients with diarrhea at a dose of 1 mg/100 mL.

    e. For patients with persistent hyperbilirubinemia (serum bilirubin >10 mg/dL) the trace elements of copper and manganese should be removed from TPN. If remains elevated may need to consider adjusting macronutrients (carbohydrate and fat).

2. TPN discontinuation recommendations

    a. Taper TPN to 50% of caloric needs as soon as possible when oral intake resumes to stimulate appetite (minimum Kcal in TPN will be 1000/day).

    b. When oral caloric intake is >50% of caloric needs ×2 consecutive days, discontinue TPN.

    c. Discontinue TPN at least one day prior to anticipated discharge to ensure adequate oral intake.

    d. If prolonged nutritional support is anticipated, EN should be considered in patients who have resolution of severe mucositis, esophagitis, and/or diarrhea.

Use of Enteral Nutrition

EN is the preferred method of feeding patients to maintain the integrity of the GI tract and prevent bacterial translocation through the GI mucosa; this is suggested to be a trophic effect of nutrients directly to the epithelial surfaces of the GI tract [11]. However, TPN has long been the commonly utilized method of nutritional support due to the availability of central access and consistent delivery of calories and protein. Initiating and maintaining EN in patients after an HCT can be difficult due to risk of bleeding during tube placement and dislodgement of tube or aspiration during vomiting related to regimen-related toxicity [11].

Strategies to improve patient tolerance of enteral feedings include placing the feeding tube after completion of the conditioning regimen but prior to the onset of mucositis, using a nasogastric tube instead of nasojejunal tube due to the ease of placement, and/or gradual increase in volume to overcome the gastroparesis effect [17, 18].

The benefits of EN over TPN include reduction of risk of venous access device infection, venous thrombosis, and metabolic disturbances, as well as decreased risk of bacterial translocation across the GI tract. Some studies have shown that patients who received EN when unable to consume oral intake were less likely to develop acute GvHD of GI tract [17]. EN after HCT may provide a direct trophic effect on the GI mucosa, thus maintaining the integrity of the GI wall and limiting excess cytokine production, which may ultimately influence the development of acute GvHD of the GI tract [15].

Typically when beginning an EN regimen, one would start with a low infusion of continuous feeds and slowly advance to goal based on tolerance and risk for refeeding syndrome. Formulas selected for HCT patients would be individualized based on their current condition. If starting EN due to poor intake, one would evaluate

caloric and protein goals and select between a standard formula with fiber or a high-protein formula with fiber. One can adjust feedings based on tolerance to a concentrated formula (to decrease total volume provided if a need for fluid restriction, renal conditions) or elemental type (if the patient is having trouble with tolerance). Caloric goals for the patient would be individualized based on their actual needs (see 7.4) and based on the calories/protein ingested orally, with ongoing evaluation for necessary adjustments. Once the patient is tolerating their goal rate, feedings can then be reevaluated and adjust to cyclic EN or bolus EN based on the clinical situation, discharge goals, and insurance coverage.

Catabolic/Anabolic States

An anabolic state is part of the metabolic process where an individual builds muscle mass and loses fat mass; this is achieved through adequate nutrition and exercise. Multiple factors may prevent achieving anabolic status by cancer patients including a general systemic inflammatory effect, a local effect (depending on tumor location), and the type of therapy used to treat the cancer. Despite consuming what appears to be an adequate amount of nutrients, a patient still may not be able to maintain a state of anabolism due to alterations in host metabolism, inefficiency of nutrient use, and/or competition for nutrients between the malignancy and normal host elements [19].

The catabolic process occurs when the body needs to break down its own tissue for energy use because there is not enough energy available in the form of food. During times of illness and stress, as in the settings of active disease processes such as cancer, the body's response is both hypermetabolic and hypercatabolic. The tissue catabolism that happens during this time is mediated through cytokine and counter-regulatory hormone release (cortisol, glucagon, epinephrine, and growth hormone). If left uncorrected, the process of catabolism can lead to loss of lean body mass and total protein body deficiency, impairing the ability to recover from illness [14].

Tissue catabolism in cancer patients is likely a factor of inadequate energy intake due to nutritional deficiency, hypermetabolism or both. While hypermetabolism is not present in all patients with cancer, a significant correlation between the disease duration and hypermetabolism has been shown. Recently, data have suggested that hypermetabolism in cancer patients can be related to tumor-induced changes in host hormones, neuropeptides, cytokines, and neurotransmitters, which can have negative effects on appetite and increase protein breakdown [20].

Discussion of Glutamine Controversy

Glutamine, normally a nonessential amino acid, is important in many metabolic processes including proliferation of lymphocytes, macrophages, and fuel for enterocytes, as well as preserving the integrity of the GI mucosa and function of the

intestines. The body may not be able to synthesize adequate amounts of glutamine in times of severe physiological stress causing a deficiency and thus may require either oral or IV glutamine supplementation [21].

In regards to IV glutamine, the American Society for Parenteral and Enteral Nutrition clinical guidelines [22] concluded, "pharmacologic doses of parenteral glutamine may benefit patients undergoing hematopoietic cell transplantation." It should be noted that parenteral glutamine is not readily available by US Food and Drug Administration-approved manufacturer but instead as a prescription prepared by a compounding pharmacy. In three separate meta-analyses of using IV gluta-mine, the conclusion was the same; IV glutamine could possibly decrease the num-ber of blood stream infections [23]. There was no benefit with regards to length of stay, duration of TPN use, or improvement in morbidity/mortality [14]. Oral gluta-mine has been shown to decrease the incidence or severity of mucositis developed by patients undergoing HCT especially if started before day 0, which may be due to glutamine acting as an antioxidant via glutathione pathway [21]. Despite these posi-tive reports, these particular studies were small, and drug dosing and administration schedules were inconsistent. More studies of glutamine supplementation, either IV or oral, are needed to determine the benefit in the HCT population [23].

Microbiome

The gut microbiome can be defined as the totality of microorganisms and collective genetic material found in the intestine, including commensal, symbiotic, and patho-genic organisms. The majority of the bacteria in the human body is found in the GI tract, which may consist of at least 800 different species, more than 7000 strains, and about 100 trillion total bacteria [22]. The four main types of phyla that can be found are *Firmicutes*, *Bacteroidetes*, *Actinobacteria,* and *Proteobacteria*. Immune regulation, nutrition, and maintenance of host barriers against pathogens are roles for commensal microbes. The loss of these commensal flora and microbial diversity can lead to an overgrowth of pathogenic organisms and increase the risk for sepsis by antibiotic-resistant organisms [24].

Antibiotics have commonly been used as microbiota-based preventative and therapeutic interventions to help improve the outcomes in the transplant population but not without some cost to the patient. Regular use of antibiotics can lead to anti-biotic resistance and possible eradication of commensal organisms. In transplant patients, the use of antibiotics can cause dysbiosis (imbalance of microbial ecosys-tem) and has been linked to various complications including diarrhea, GvHD, and systemic infections due to the promotion of pathological conditions that involve bowel inflammation and immune reactions (i.e., acute GvHD) [24, 25]. This loss of microbial diversity can increase the risk of sepsis by causing an overgrowth in pathogenic organisms and increased GI inflammation.

Strategies under investigation other than antibiotics for microbiota-based preventa-tive and therapeutic interventions include a more narrowly focused antibiotic regimen

for prophylaxis and treatment, dietary changes to include pre- and probiotics, as well as fecal microbial transplants (FMT). Additional studies are required to determine the complications and infection risks utilizing some of these methods [24, 26].

Prebiotics are associated with the indigestible carbohydrates that may increase the beneficial bacteria in the GI tract, reducing the risk of disease and improving the overall health of patients. Prebiotics can be found in foods high in fiber, that is, oatmeal, wheat bread, apple skins, and so on. They travel through the small intestine, fermenting in the large colon thereby feeding beneficial bacteria and increasing the number of desirable bacteria that enhance general health. The positive influence of introducing prebiotics into the GI tract in the peri-transplant period may help prevent complications such as GvHD by improving the gut flora while posing little risk to the patient.

In contrast, probiotics are live bacteria found in fermented foods (sauerkraut, kimchi, etc.) and yogurt that are considered beneficial when introduced into the GI tract. Many bacteria may be classified as probiotics but the two main groups are *Lactobacillus* and *Bifidobacterium*. While probiotics have been shown to treat various diarrheal illnesses (antibiotic associated diarrhea, irritable bowel syndrome, ulcerative colitis, etc.) by improving the microbiota diversity, it has been hypothesized that probiotics may be beneficial in treating GvHD [24]. While there have been small retrospective studies showing safety and the potential prevention of GvHD of GI tract with probiotics [27], the potential risk of adverse effects including bacteremia due to bacterial translocation, sepsis, worsening of GI symptoms, fevers, etc. remains. Without confirmatory data from prospective, randomized trials, hesitation to use probiotics in this patient population persists.

Lastly, FMT has recently been used to treat refractory *C. diff* colitis. As there are emerging studies demonstrating safe and efficacious treatment of *C. diff* with FMT, interest in its application for other disease states associated with dysbiosis of the microbiome is growing. However, like probiotics, the risk of bacterial translocation resulting in bacteremia or sepsis, worsening of symptoms, and/or fever still contribute to hesitation of its application in other populations.

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Chapter 8
Physical and Occupational Therapy

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Introduction

Cancer is one of the leading causes of death worldwide, but advancements in cancer care have led to increased survivorship and decreased morbidity and mortality. Hematopoietic cell transplantation (HCT), in combination with high-dose chemotherapy and total-body irradiation (TBI), is one of the most effective therapies for hematologic malignancies [1]. Patients are living longer; however, some patients develop physical and mental impairments resulting from both cancer and its treatments, in addition to medical comorbidities acquired over time [2]. These physical and mental sequelae can lead to functional limitations and activity restrictions in performing self-care, work, leisure, or social activities. Common side effects of cancer or its treatments include fatigue, pain, weakness, cognitive difficulties, anxiety or depression, and changes in self-esteem or self-image [3].

Effects of Cancer and HCT: Serious Adverse Events (SAEs) and Impairments Impacting Functional Ability and Rehabilitation

Physiological Effects [4–8] Nausea, mucositis, diarrhea, fatigue, cytopenia, graft-versus-host disease (GvHD), venous thromboembolus (VTE), cardiovascular system, pulmonary, endocrine and thyroid dysfunction, inflammation, loss of muscle

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mass, neuropathy, neuropsychological, arthralgia, myalgia, immune deficiency related infections, and secondary cancers

Functional Impairments/Activity Limitations [5, 6, 9–12] Decreased nutritional uptake, prolonged bedrest, decreased physical capacity, decreased physical activity, compromised balance, decreased pulmonary function, depression, cognitive dysfunction, memory impairment, and fatigue

The Role of Physical and Occupational Therapy Services

Physical Therapy (PT) and Occupational Therapy (OT) services are beneficial to the patient/client and invaluable members of the interdisciplinary team. While both services may have similar goals to improve overall QOL and function of patients, there may be different approaches taken to accomplish them.

1. *Physical Therapy*

    a. The American Physical Therapy Association defines the PT profession as "movement experts who optimize quality of life through prescribed exercise, hands-on care, and patient education."
    b. Following evaluation, "physical therapists create patient-centered treatment plans that help their patients manage pain and other chronic conditions, improve mobility, recover from injury, and prevent future injury and chronic disease" [13].

        i. In the case of HCT, the PT oncology specialty provides services within acute care and rehabilitation hospitals, skilled nursing units, outpatient and home health settings, and health/wellness centers.
        ii. Therapists are often involved during the early stages of an individual's cancer diagnosis and can be vital throughout the course of a patient's treatment by helping maintain/gain strength, flexibility, and endurance and maximizing function [13].
        iii. Additionally, the complexity and significance of the medical risks of HCT may also require patients to seek services provided by PT specialists in acute care, pelvic health, neurology, cardiovascular, and pulmonary therapies.

    c. PT evaluation assesses the physical and functional impairments to guide patient-specific goals that may include preventing and reducing weakness, optimizing pulmonary function, maintaining range of motion and bone and joint integrity, and preserving balance, coordination, and endurance. The physical therapist may address these aims in the following ways:

      i. Functional rehabilitation and exercise including, but not limited to: aerobic activity and strengthening while monitoring the medical effects of the physical activity including cardiac, pulmonary, and sexual function

      ii. Assessment and treatment of mobility deficits including fall prevention strategies through balance and gait training and incorporation of assistive devices (e.g., walkers, canes) as necessary

      iii. Management of edema

      iv. Pulmonary and cardiovascular conditioning

      v. Pacing and energy conservation

  d. PT may provide the greatest benefit if initiated in the pre-HCT time frame to assist with prevention rather than remediation [14].

  e. If PT begins during the hospitalization, it is best to begin immediately after hospital admission and before the onset of treatment side effects [14].

2. *Occupational Therapy*

  a. While PT tends to focus on addressing impairments that result in functional limitations and activity restrictions, the American Occupational Therapy Association (AOTA) defines the role of OT in oncology as "[facilitating] and enabl[ing] an individual patient to achieve maximum functional performance, both physically and psychologically, in everyday living skills regardless of his or her life expectancy" [15, 16].

  b. As such, the occupational therapist focuses more on the patient/client's roles/occupations and responsibilities, from experiencing difficulty with self-care activities such as bathing or dressing to others who require specific skillsets in order to maintain or acquire full-time employment.

  c. Common side effects of cancer or its treatments include fatigue, pain, weakness, cognitive difficulties, anxiety or depression, and changes in self-esteem or self-image, which are addressed by interventions aimed at restoring function, modifying activities to conserve energy during important everyday activities, or modifying environments to suit the individual's needs.

  d. The domains of the Scope of Practice for Occupational Therapy include the following [17]:

      i. Activities of daily living (ADLs): self-care activities

      ii. Education: activities to participate as a learner in a learning environment

      iii. Instrumental activities of daily living (IADLs): multistep activities to care for self and others, such as household management, financial management, and childcare

      iv. Leisure activities: non-obligatory, discretionary, and intrinsically rewarding activities

      v. Play: spontaneous and organized activities that promote pleasure, amusement, and diversion

      vi. Social participation: activities expected of individuals or individuals interacting with others

      vii. Work: employment-related and volunteer activities

e. OT services are provided for "habilitation, rehabilitation, and the promotion of health and wellness to those who have or are at risk for developing an illness, injury, disease, disorder, condition, impairment, disability, activity limitation, or participation restriction" [18].

f. These services address the "physical, cognitive, psychosocial, sensory-perceptual, and other aspects of performance to support engagement in occupations that affect physical and mental health, well-being, and quality of life" [18].

g. The individual undergoing treatment faces many burdens including fatigue, loss of strength, loss of independence, cognitive deficits, and anxiety. These areas may be addressed by utilization of the following methods [19]:

   i. Adaptation and management of ADLs including but not limited to the use of adaptive techniques to both task and environment, adaptive equipment, and caregiver training to promote independence

   ii. Utilization of energy conservation techniques via a variety of techniques including pacing, planning, delegation, and priority setting

   iii. Addressing psychosocial concerns by engaging in lifestyle changes, relaxation techniques, coping strategies, and exploration of new valuable occupations

   iv. Implementation of cognitive strategies to address chemotherapy-induced cognitive impairment (CICI—sometimes referred to as "chemo brain" [see also Chap. 49]) via compensatory techniques and the use of a variety of aids and adaptations

   v. Use of physical activity including exercise, range of motion, stretching, and strengthening

   vi. Utilization of a collaborative and client-centered approach to address the side effects of cancer, bringing a holistic approach to the individual's needs beyond the cancer treatment

Physical and Occupational Therapy Interventions

Prior to HCT, many patients are at or near their functional baselines; however, many others may be poorly conditioned. The side effects of the HCT process may result in significant loss of their baseline function. Nausea, mucositis, diarrhea, fatigue, cytopenia, GvHD, and compromised nutritional intake may result in prolonged bed rest and inactivity, which may decrease the patient's ability to engage in physical activity [10]. It has been well studied that inactivity can have detrimental outcomes including diminished cardiovascular function, significant loss of muscle mass (sarcopenia), pneumonia, orthostatic hypotension, and VTE, with the greatest loss of physical function from muscle wasting occurring within the first 10 days of inactivity, particularly in the critically ill that require prolonged stays in intensive care units [20]. It has also been shown that the use of long-term corticosteroids, such as those used to treat GvHD, causes muscle fiber atrophy which contributes to

clinically significant steroid myopathy [21, 22]. A wealth of research supports the implementation of exercise programs to address patients' functional impairments that include decreased physical capacity, cancer-related fatigue, decline in QOL, and cognitive dysfunction.

1. *Physical Capacity* [23, 24]

   a. Multiple studies have demonstrated that engagement in a physical exercise routine can improve physical capacity. Exercise participation has been correlated with increased walking speed, increased strength, and decreased potential loss of endurance.
   b. Higher gait velocity and improved power have in turn been correlated to decreased likelihood of falls and improved overall QOL.
   c. Additional studies have demonstrated that skeletal muscle mass was preserved, and muscle strength was improved in patients with cancer diagnoses who participated in a supervised aerobic and resistive exercise routine. Improved physical capacity can minimize functional loss and restore or maintain independence in ADLs.

2. *Cancer-Related Fatigue (CRF)*

   a. The use of physical exercise has been shown to be effective as an adjuvant therapy for cancer-related fatigue [9–11, 14, 25–27].
   b. The National Comprehensive Cancer Network (NCCN) describes cancer-related fatigue as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [25].
   c. HCT may result in incapacitating fatigue, more common in allogeneic than autologous recipients [26].
   d. Additionally, mean fatigue scores decreased after completion of a physical exercise program. The use of exercise has been proposed to be effective in management of both acute and chronic fatigue [11, 27, 28].

3. *Quality of Life*

   a. Many studies have shown a positive correlation between betterment in physical function and improvement in overall QOL [29, 30].
   b. Additionally, positive changes in physical, emotional, and social well-being were integrally connected to improved muscle strength and improved aerobic capacity [11, 28]. These improvements correlated with decreased depression in the individuals studied [30].
   c. Studies have also explored the role of sexual dysfunction on QOL concerns. Early diagnosis and management can include psychosocial support and pelvic health PT [31].

4. *Cancer-Induced Cognitive Impairment (CICI)*

   a. While research examining the impact of exercise for treatment of cancer-induced cognitive impairment in the HCT population is relatively new, multiple studies have previously established that exercise produces cognitive benefits in both children and the elderly [32–35].

   b. Comprehensive reviews of the current literature suggest physical rehabilitation approaches to alleviate symptoms related to cognitive dysfunction are augmented by mindfulness-based stress reduction, medicinal Qigong, Tai chi, physical activity, and breathing/progressive relaxation exercises [30, 36].

   c. Regardless of the techniques implemented, the interventions focus on adaptation to compensate for memory or attention deficits during task performance and/or restorative cognitive strategies to ameliorate cognitive dysfunction [37].

1. Areas of consideration

   a. General observations from studies

      i. All studies included some form of aerobic activity +/− strengthening exercises.

      ii. Many of the studies were retrospective.

      iii. Regardless of patient setting (inpatient vs. outpatient), similar treatment effects were observed in study participants.

      iv. There is no standardized, validated exercise protocol to emerge from these studies, with consistent lack of validated measures of exercise intensity, frequency, and duration.

   b. Contraindications/indications for therapeutic interventions

      i. Sequelae from thrombocytopenia and anemia may limit participation in a structured physical exercise program.

         • A study completed in 1986 suggested that physical exercise should be discontinued when a patient experienced severe thrombocytopenia (platelets <50,000/mL) and anemia (hemoglobin <8 g/dL) [24].

         • In 1989, another study recommended that those with acute leukemia receiving chemotherapy should not complete any form of physical activity until complete remission was obtained [38].

         • It has since been shown, however, that it is possible for physical exercise to be safely performed in the setting of severe cytopenia [39, 40].

         • Elter et al. demonstrated that no patients suffered bleeding complications with a platelet count <10,000 mL or critical tachycardias with hemoglobin <8 g/dL [39].

         • Rather than blood counts, the criteria used for terminating physical exercise were based on either bleeding, cardiac complications, or physiological presentation of the patient. The Academy of Acute Care Physical Therapy recommends the following [40].

- Hemoglobin (Hgb) <8 gm/dL: essential daily activities
- Hgb <8–10 gm/dL: essential ADLs, assistance as needed for safety, light aerobics, light weights (1–2 lb)
- Hgb>10: ambulation and self-care as tolerated, resistance exercises
- Platelets (PLT) <10,000 and/or temperature>100.5F: no therapeutic exercise/hold therapy
- PLT 10,000–20,000: therapeutic exercises/bike without resistance
- PLT >20,000: therapeutic exercises, bike with or without resistance

- General guidelines contraindicate physical exercise in the setting of active infections and/or fever [39].

ii. Patients' medical conditions and comorbidities may dictate program intensity, duration, and frequency.
iii. Aerobic and strengthening programs.

- Aerobic exercise consisted of ergometry via a stationary bicycle or bed ergometer and/or walking either around the hospital ward or on a treadmill.
- The average time spent on aerobic activity was between 15 and 30 minutes, either consecutively or in intervals.
- The frequency over the period of one week varied between daily, three times/week, and five times/week.
- The definition of moderate intensity varied greatly, ranging from 40% to 80% of the maximum heart rate or the use of the Borg Rate of Perceived Exertion Scale (see Table 8.1).
- Studies also suggested the inclusion of strength training, using exercise bands and/or body weight for resistance.
- A proposed physical exercise program is outlined in Table 8.2. The American College of Sports Medicine (ACSM) concluded that aerobic

Table 8.1 Borg Rating of Perceived Exertion scale

6		How you feel when lying in bed or sitting in a chair, relaxed. Little or no effort
7	Very, very light	
8		
9	Very light	
10		
11	Fairly light	
12		Target range: How you should feel with exercise or activity
13	Somewhat hard	
14		
15	Hard	
16		
17	Very hard Fairly light1	How you felt with the hardest work you have ever done
18		
19	Very, very hard	
20	Maximum exertion	

Table 8.2 Recommendations for physical exercise

Phase of therapy	Type of exercise
Before HCT	Mixed exercise (3–5×/week) Duration (session): up to 30 min Intensity: moderate (12–14 Borg scale, 70–80% maximum HR)
During HCT	Starting with endurance training (5×/week up to daily), adding resistance training with increasing platelet counts in the last third of hospitalization (2–3×/week) Duration (session): 10–15 min at the beginning (if helpful use the interval method), up to 30 min in the end Intensity: moderate (12–14 Borg scale, 70–80% maximum HR)
After HCT	Mixed exercise (3–5×/week) Duration (session): up to 30 min and more Intensity: moderate (12–14 Borg scale, 70–80% maximum HR)

HR heart rate

Reprinted by permission from Macmillan Publishers Ltd: [BONE MARROW TRANSPLANTATION] Wiskemann and Huber [46]

activity should follow the Physical Activity Guidelines for Americans, which "suggests at least 150 minutes/week of moderate-intensity activity or 75 minutes/week of vigorous-intensity activity (or an equivalent combination)" with a lighter intensity and slower progression for those who have undergone HCT.

- As for strength training, the ACSM recommends "muscle-strengthening activities of at least moderate intensity at least 2 days/week for each major muscle group."

  - It is important to note that these guidelines are for "survivors" or those who have completed treatment.
  - It has been shown that flexibility in the regimen may empower patients to continue to participate in a program by allowing them to regulate their own behavior.
  - This approach may also increase the patient's self-reliance and result in behavior change, especially for those who were sedentary prior to HCT.

2. Referral to interdisciplinary team

   a. It is essential that patients determine the healthcare providers in the local area that can treat the pathologies and impairments resulting from cancer and its treatments. Neurologists, psychologists, neuropsychologists, occupational therapists, and speech language pathologists ideally work synergistically to evaluate and treat the myriad of complications that could arise. Initiation of therapy may require individual provider referrals. Regardless of systems and relationships involved, efficient communication among all the members of the interdisciplinary team is key to patients' optimal and comprehensive recoveries [42].

    b. Length of time spent with patient.

        i. Rehabilitation service professionals are sometimes able to spend longer time with patients than other members of the interdisciplinary oncology team and, as such, therapists may be in a position of fidelity/trust which might make them more amenable to suggestion or conversation.

    c. Acknowledgment of patients' concerns.

    d. Clinical specializations: pelvic health, sexual health, pulmonary/cardiac rehab, orthopedics, neuro PT, burns/wounds.

    e. Behavioral health.

        i. HCT patients report significant distress associated with the burden of treatment adherence and follow-up. Recent studies suggest early biopsychosocial support may be associated with improved survival and quality of life during and after treatment [43, 44].

    f. Speech therapy.

    g. Recreational and music therapies.

    h. Nutrition/dietician.

    i. Complementary and alternative medicine [45] (see also Chap. 46)

        i. Acupuncture

        ii. Naturopathy

        iii. Massage

        iv. Creative arts

        v. Expressive writing

        vi. Music

        vii. Guided imagery

        viii. Reflexology

        ix. Tai chi

Conclusion

Physical debilitation is commonly experienced by patients undergoing HCT. The incorporation of physical activity has been shown to minimize the loss of strength, independence, energy, and QOL. Although most of the research has been performed on limited sample sizes, it can be inferred by the multitude of studies across the spectrum of cancer diagnoses that physical activity is likely to be beneficial for the HCT population.

An optimal exercise program has not been defined; however, clinical and observational data show that moderate aerobic activity along with a strengthening routine may help prevent steroid myopathy and improve CRF and overall QOL for these patients.

Physical and occupational therapists are essential members of the HCT treatment team who provide recommendations on the implementation of physical activity, as well as assist with prevention, remediation, and compensation of the complications associated with treatment.

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Chapter 9
Adolescent and Young Adult Concerns

Van T. Huynh, William A. Wood, and Brandon Hayes-Lattin

Introduction

Since the publication of the National Cancer Institute Progress Review Group report, Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer, there has been an increasing effort to address the unique needs of patients between the ages of 15 and 39 diagnosed with cancer, who often feel isolated between the worlds of pediatric and adult oncology. This group of individuals is now identified in clinical trials and in clinical care as the adolescent and young adult (AYA) population.

Historically, hematopoietic cell transplant (HCT) has been applied selectively to younger, healthier patients, and hematologic malignancies are among the most common cancers of the AYA population. Therefore, attention to their age-specific needs constitutes quality care. Each domain of AYA cancer care (Table 9.1) should be approached with the patient's age and developmental status in mind. An ideal AYA team consists of medical providers, nurse specialists, social workers,

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Table 9.1 Domains of AYA cancer care

Domain	Examples
Medical	Oncology, palliation, nutrition, endocrinology, etc.
Emotional/ Psychological	Psychology, coping, distress
Physical	Exercise, activities of daily living, myopathy
Neurocognitive	Education, vocation
Social	Relationships with peers and providers; family roles (parent, child) and relationship with significant others
Reproductive	Fertility preservation, parenting options
Financial	Disability, insurance
Lifestyle issues	Environment, risky behaviors, balance with treatment
Late effects	Prevention, monitoring
Care community	Caregivers, family, friends

AYA adolescent and young adult

vocational counselors, fertility experts, physical and occupational therapists, and community-based services with peer support.

Priority concerns for these domains are listed below.

Medical

1. Leukemias, lymphomas, and germ cell tumors are common cancers among AYA-aged patients. HCT may play an important role in the therapy of these malignancies.

   a. Compared to children, the treatment-related morbidity and mortality may be increased for AYAs, but less so than for older adults. Consequently, survival often varies inversely by age group, especially in leukemias [2–4].

   b. Changes in initial treatment, such as pediatric-inspired therapies for acute lymphoblastic leukemia, have led to a reconsideration of the role of HCT in first remission in some circumstances [5]. The presence of minimal residual disease (MRD) may predict the benefit of transplant [6]. Thus, the efficacy of initial therapy, which may be higher with pediatric inspired regimens, is especially important.

   c. An increased understanding of the prognostic importance of specific molecular features, and their prevalence in the AYA population relative to other age demographics, may improve the ability to tailor the role and timing of HCT for the AYA patient.

2. Attention to issues related to growth, development, and nutrition in the AYA patient may optimize short- and long-term medical care, including screening for late effects. These issues include the impact of preparative regimens and the

HCT process upon growth hormone, thyroid hormone, gonadotropin production, adrenal function, and other aspects of nutrition and metabolism.

3. A variety of genetic syndromes may present with cancer in the AYA age range including Fanconi anemia, Li–Fraumeni syndrome, dyskeratosis congenita, and others. A careful physical examination and family history is always warranted for an AYA with cancer, especially when a cancer presents with an earlier than expected age onset.

Emotional/Psychological

HCT in the AYA patient carries a significant risk of emotional and psychological dysfunction [7]. The adverse experiences endured during and post-HCT, along with disruptions to their daily life routine, can impact the emotional well-being and development of AYA patients.

1. Adolescent HCT survivors report more somatic problems compared to controls and siblings [7].
2. An AYA patient's physical and sexual development, sense of identity, ability to have achieve independence, and social development may be delayed due to the diagnosis and treatment of cancer and undergoing HCT.
3. AYA survivors of HCT are at higher risk of mood disorders that include depression and anxiety.

    a. Depression and anxiety are associated with longer hospital admissions, higher reporting of pain symptoms, and decreased adherence to medications and other elements of medical care.

4. Social anxiety and posttraumatic stress disorders can also be seen in this population.

    a. Both diagnoses are associated with social withdrawal, low self-esteem, and poor quality of life.

5. Medical providers should recognize the potential for altered emotional and psychological outcomes. Referrals to mental health professionals should be placed early to allow patients to receive appropriate psychological counseling and help with coping mechanisms.

Physical

Many AYAs who undergo HCT also experience physical changes as a result of treatment. These alterations may include changes in appearance and sexual development and function, as well as limitations in their normal activities. It is important for

patients to be encouraged to speak with their healthcare team about these changes and learn ways to cope or to identify changes that warrant treatment or referral.

1. Changes in appearance

    a. Chemotherapy, radiation, and treatment for acute and chronic graft-versus-host disease (GvHD) such as steroids are associated with changes in appearance including alopecia, weight gain or loss, scars, and/or changes in pigmentation.
    b. AYA patient's body image and identity can be negatively affected by these physical changes, and for some patients may lead to social isolation.

2. Sexual development and function [8]

    a. Sex and intimacy are an important part of many AYAs' lives.
    b. Conditioning regimens, GvHD, medications, and psychosocial issues can contribute to physical and psychological sexual dysfunction.
    c. Consequences can include decreased libido, hormonal dysregulation, erectile dysfunction, dyspareunia, and infertility.
    d. Often, sexuality is a difficult topic for patients and their significant others to discuss. Moreover, many healthcare providers may not feel comfortable or think about addressing it with patients.
    e. Since sexual dysfunction can have a negative impact on a patient's quality of life, it is important for healthcare providers to perform assessment of sexual function to identify changes and issues that may warrant treatment or referral.

3. Activity limitations

    a. Patients can be limited in their activities due to a myriad of causes that include physical isolation recommended due to their immunocompromised status, fatigue/low energy as a consequence of therapy, and possible cardiovascular or pulmonary complications. In addition, severe chronic GvHD can restrict patient's movements.

Neurocognitive

Neurocognitive dysfunction in AYA patients undergoing HCT can be a consequence of various factors such as systemic chemotherapy, intrathecal chemotherapy, cranial radiation, total body irradiation (TBI), immunosuppressive therapies, and GvHD. Symptoms of neurocognitive dysfunction can include impaired attention/concentration, memory impairment, and problems with executive function [9]. Although it is possible to regain many of these domains, 40% of HCT survivors may have persistent deficits [10].

1. The domains of neurocognitive function include the following

    a. Attention and concentration
    b. Perceptual processing
    c. Learning and working memory
    d. Abstract thinking and working memory
    e. Language
    f. Information processing speed
    g. Motor function

2. Neurocognitive dysfunction can have a major effect on activities of daily living

    a. Return to work or school and reintegration into society may be affected.
    b. Patients have reported poor self-image, physical and social functioning.
    c. Compliance to medication and post-HCT follow-up care may be affected [11].

3. Treatment effects and risk of neurocognitive impairment

    a. Systemic chemotherapy

        i. Patients treated with chemotherapy alone have greater deficits in neuro-cognitive function than controls.

    b. Intrathecal chemotherapy

        i. Both triple intrathecal (methotrexate, hydrocortisone, and cytarabine) and single intrathecal (methotrexate) had comparable neurocognitive deficits [12].

    c. Conditioning regimen

        i. Preparative regimens may include chemotherapy, TBI, or both in addition to cranial or cranio-spinal radiation.
        ii. Chemotherapeutic agents with risk of neurocognitive dysfunction include, but are not limited to [13]:

            • Busulfan
            • Carboplatin
            • Carmustine
            • Cytarabine
            • Etoposide
            • Ifosfamide
            • Thiotepa

        iii. TBI

            • Late neurocognitive dysfunction has been reported in patients who receive high-dose chemotherapy with TBI up to 12 Gy [14].

4. Other risk factors for neurocognitive impairment [13]

    a. GvHD and immunosuppressive therapies

        i. Calcineurin inhibitors (cyclosporin and tacrolimus) can cause tremors, posterior reversible encephalopathy syndrome (PRES), and thrombotic microangiopathy (TMA).

    b. Infections

        i. Cytomegalovirus (CMV), Epstein–Barr virus (EBV), and human herpesvirus 6 (HHV6) can affect attention and speed of cognitive performance [15].

5. Neuropsychological assessments

    a. Consider neurocognitive evaluation prior to HCT for baseline assessment and during follow-up post HCT as indicated.

    b. Timely awareness of neurocognitive impairment is crucial for referral for psychosocial support and neurocognitive intervention.

6. Vocational training

    a. AYA patients may benefit from vocational training.

Social

1. Cancer treatment and HCT occur over protracted time periods, with physical and psychological complications and side effects from disease and treatment leading to repeated and prolonged hospitalizations and frequent clinic visits. Cumulatively, this leads to disruptions in school, work, and family life. Peer relationships often change, and it is critical not to neglect exploration of patient's social support systems.

2. Relationships with coworkers and employers may also change as patients experience prolonged time off work. Concerns related to disability, loss of employment, and reduced income are particularly important in this population.

3. For similar reasons, family relationships with a spouse, children, or parents often change as a result of disease and treatment.

    a. AYA patients may experience a loss of autonomy related to physical and psychological effects of disease and treatment.

    b. AYA patients may find that their roles and responsibilities within their family dynamics change over time. Understanding and discussing these concerns may alleviate psychological distress and promote resilience.

4. Many healthcare providers are also young adults and develop particularly intense relationships with AYA patients. Support for patients and providers is an important component to patient-centered care in this population.

Reproductive (see also Chaps. 39 and 40)

Reproductive health is a common concern for AYA patients undergoing HCT. AYA patients with cancer often rank having children as an important life goal. Thus, loss of fertility can have a negative impact on the reproductive and quality of life of young survivors of HCT [16]. Chemotherapy (alkylating agents) and radiation (TBI/testicular/cranial) adversely effect gonadal function and can lead to infertility. In particular, the factors that influence the risk of infertility include dose of radiation, age at treatment, and dose of chemotherapy. For example, TBI with 10–13 Gy can result in azoospermia in 85% of males undergoing HCT [17]. Cranial radiation, which is often utilized in patients with CNS leukemia and brain tumors, can also lead to secondary gonadal failure.

1. Guidelines from the American Society of Clinical Oncology (ASCO) recommend that a discussion of the possibility of infertility be part of education and informed consent for all patients of reproductive age [18]

   a. Discussion should include risks, fertility preservation options, and appropriate referrals to reproductive specialists:

      i. Every effort should be made to discuss fertility as early as possible at the time of cancer diagnosis.
      ii. Published guidelines also state that fertility preservation should be readdressed prior to HCT.
      iii. In addition to fertility preservation options, alternative parenting methods including adoption or surrogacy should be discussed.

2. Males

   a. Risk: Rates of azoospermia after high-dose conditioning regimens are as high as 90%; rates for patients treated with busulfan and cyclophosphamide are 50% and with cyclophosphamide alone 10%.
   b. Assessment: Semen analysis for quantitative analysis and motility.
   c. Fertility preservation options:

      i. Sperm banking [19]:

         • This method provides the highest likelihood of having biological children and should be discussed with postpubertal males prior to undergoing HCT.
         • Semen is generally obtained by masturbation, which can be uncomfortable or embarrassing and can lead to inability to ejaculate.
         • It is important to provide adolescent males with careful counseling with age-appropriate instructions as these patients are at risk for emotional distress from sperm banking.

- If possible, offer patients a private and relaxing environment or option to sperm bank at home. However, the specimen must remain at room temperature and return to the lab within 1 hour of collection.
- This method can be hampered by findings of decreased sperm motility or azoospermia.

   ii. Testicular tissue cryopreservation

- This is the only current method available for preserving fertility in pre-pubertal males.
- It involves surgically removing a small portion of the testicular tissue, cryopreserving, and storing the specimen.
- In postpubertal males, the tissue is later thawed and transplanted via intratesticular grafting or by infusion into seminiferous tubules.
- As this method is investigational, it should be performed only as part of a clinical trial.
- There is a theoretical risk of reseeding tumor cells after reimplantation of tissue.

3. Females

  a. Risk: Rates of ovarian failure after high-dose conditioning regimens are as high as 65–85%. However, this statistic may not be accurate as studies do not account for whether patients are trying to conceive. Younger age at the time of HCT may be associated with lower risks of infertility.

  b. Assessment: Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), estradiol level, and ovarian follicle assessment by ultrasound

  c. Fertility preservation options [20]:

    i. In vitro fertilization (IVF) and embryo cryopreservation:

- Advantages:
  - This approach is a well-established therapy that is available to most women.
  - Involves hormonal stimulation of ovaries and collection of oocytes to create embryos using IVF.
  - Success rates vary, with pregnancy rates as high as 59% and 50% live births [21].

- Disadvantages:
  - Requires two-three weeks from initiation of therapy for oocyte retrieval.
  - Requires a partner for sperm donation or willingness to accept banked sperm.
  - Females must be postpubertal.
  - This method is costly and may not be covered by insurance.

    ii. Oocyte cryopreservation:

- This method involves hormonal stimulation of ovaries and collection of oocytes for cryopreservation. The unfertilized oocytes are later fertilized to produce embryos.
- Advantages:

  – Success rates are comparable to procedures using fresh embryos [22].
  – This method does not require a sperm source.

- Disadvantages:

  – Oocytes are more susceptible than embryos to damage during freezing/thawing.
  – Requires two-three weeks from initiation of therapy for oocyte retrieval.
  – This method is costly and may not be covered by insurance.

iii. Ovarian tissue cryopreservation:

- This approach is an experimental option to preserve fertility among prepubertal females.
- An ovarian cortical biopsy or oophorectomy is done laparoscopically with the goal of preserving eggs within the primordial follicles of the ovarian cortex.
- The cortical tissues are then frozen and later thawed and transplanted back to the patient.
- Advantage:

  – This is the only current option available for prepubertal girls.

- Disadvantages:

  – This approach is not recommended for females with hematologic malignancies or ovarian cancers due to the higher risk of cancer recurrence.
  – This option is an investigational treatment and should only be done in the setting of a clinical trial.

iv. Hormonal suppression with gonadotropin-releasing hormone (GnRH) analogue:

- Available to postpubertal females to help maintain ovarian follicles in a dormant state.
- Advantages:

  – It is relatively easy to administer with no delay in therapy.

- Disadvantages:

  – The efficacy of this method is not well established, and it is not sufficient alone to preserve fertility in HCT recipients.
  – GnRH is associated with bone loss, which may cause other long-term complications.

Financial

Undergoing HCT can have a significant impact on the socioeconomic well-being of patients and their families [23]. Financial toxicity or financial distress refers to the treatment-related financial burden experienced by patients with cancer. Financial toxicity can negatively influence a patient's quality of life, adherence to treatment plan, and perception of pain and symptoms.

1. Insurance

    a. HCT may be associated with high out-of-pocket costs despite insurance coverage.
    b. It is important for AYA patients and their families to meet with a financial navigator who can help them better understand the health insurance plans and their out-of-pocket costs for treatment and payment options.
    c. Patients should evaluate and budget coverage for their living, determining which expenses can be reduced or eliminated.
    d. Patients should consider applying for financial assistance programs if they qualify.

2. Employment

    a. Patients who are employed will need to take time off from their job during pretransplant treatment, transplantation, and posttransplant recovery.
    b. During this employment break, there will be a loss of income, but the cost of living and household bills will continue to incur.
    c. Patients may need to consider whether they qualify for disability insurance or other benefits through their employer or state.

3. Housing and transportation

    a. Some patients and families many need to temporarily relocate and move closer to the transplant center.
    b. Costs may be incurred due to new living arrangements as a result of relocation.
    c. Patients and families may also need to travel long distances to transplant centers and incur costs for gas and transportation.

4. Financial loss or bankruptcy

    a. Many families suffer large financial loss or file for bankruptcy as a result of significant out-of-pocket costs for medical care, loss of wages, and ongoing housing and transportation costs.
    b. Khera et al. showed that 73% of recipients of allogeneic HCT reported financial losses in some manner with a large percentage needing to sell or mortgage their home or prematurely utilize their retirement savings [24].

Lifestyle Issues

Young adults are particularly vulnerable to engaging in risky health and lifestyle behaviors [25]. Substance use/abuse may be common in this patient population and includes alcohol, tobacco, marijuana, or illicit drugs. Cigarette smoking is widely known to be linked to many adverse healthy problems and increases the risk of developing a secondary neoplasm. Some studies show that cancer survivors who smoke are more likely to fail cessation attempts [26]. The rate of marijuana use (medical and/or recreational) is increasing with rates climbing due to legalization in many states. The risk of marijuana and illicit drug use is higher in males, patients with lower socioeconomic status, and patients who report depressive symptoms. It is important for healthcare providers to screen and ask patients about their health behaviors.

Late Effects (see also Chap. 49)

1. Prevention
2. Monitoring

Care Community

Young adults have a variety of life situations that include living at home, being employed, attending school, or caring for a family of their own. Having a cancer diagnosis and going through transplant is a heavy burden for AYAs to bear alone. Thus, it is crucial for AYA patients undergoing HCT to have a support community to rely on. This care community may consist of family, partner, peers, community groups, or professionals who can help them navigate through the complex journey of a transplant.

1. Family (parents, spouse, siblings) or significant other

   a. AYAs should enlist family and partners early in the HCT process.
   b. Can serve as support persons during important discussions with the medical team as it can be difficult to remember everything being discussed.
   c. May assist with logistics such as transportation, meals, and financial issues.

2. Peers (friends, AYA organizations)

   a. Friends can be a source of support and comfort through the HCT process.
   b. Patients can also connect with other AYAs who have been through transplant and can better relate with their experience. However, it is important for healthcare providers to remind AYAs that each patient's experience is different.

3. Professional help (case coordinator, patient/nurse navigator, social worker)

   a. These individuals can assist with medical insurance issues such as patient's out-of-pocket costs and help apply for financial assistance programs if patients qualify.
   b. For patients who are employed outside of the home, they may provide information on employer benefits and disability insurance.
   c. Professionals can also help AYAs navigate through student loans and forbearance for those who are in college and need to take a leave of absence.

4. Community

   a. Support can also be found through religious organizations, clubs, and social networks.

AYA-Specific Resources

1. National Cancer Institute (http://www.cancer.gov/cancertopics/aya)
2. NCCN Guidelines for Patients – Adolescents and Young Adults with Cancer (https://www.nccn.org/patients/guidelines/aya/files/assets/common/downloads/files/aya.pdf)
3. Livestrong: Young Adults with Cancer (https://www.livestrong.org/we-can-help/just-diagnosed/young-adults-with-cancer)
4. Stupid Cancer (https://stupidcancer.org/)

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Chapter 10
Infection Prevention and Prophylaxis

Lynne Strasfeld and Marcie Riches

Introduction

Infection remains an important cause of non-relapse mortality in hematopoietic cell transplant (HCT) recipients. Specific risk for infection is related to prior exposure history (e.g., relapse of latent infection), intensity of the conditioning regimen, immuno-suppressive agents utilized, and new exposures in the setting of altered host immune response. Prevention of infection by way of prophylactic and preemptive strategies has been associated with improvement in transplant outcomes over the past few decades.

Herpes Simplex Virus (HSV)/Varicella Zoster Virus (VZV) Prophylaxis/Prevention

1. Antiviral prophylaxis with acyclovir or a related congener is broadly used in the posttransplant period to prevent HSV and VZV infection. Duration of prophylaxis is for at least 1 year posttransplant, and until off all immune suppression. For dosing recommendations, see Table 10.1. If nausea or mucositis preclude oral intake, change to IV acyclovir until patient is able to tolerate oral intake.
2. VZV-seronegative allogeneic recipients who are <24 months posttransplant, >24 months posttransplant and on immunosuppressive therapy, or have active chronic graft-versus-host disease (GvHD), and have had close contact with a

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Table 10.1 Dosing recommendations for acyclovir and valacyclovir

			Renal impairment	
Drug and route	Transplant type	CrCl ≥ 50 mL/min	CrCl 30–49 mL/min	CrCl < 30 mL/min
Acyclovir PO	Autologous	800 mg po daily	800 mg po daily	400 mg po daily
	Allogeneic	800 mg po BID	800 mg po daily	400 mg po daily
Valacyclovir PO	Autologous	500 mg po daily	500 mg po daily	500 mg po daily
	Allogeneic	500 mg po BID	500 mg po daily	500 mg po daily
Acyclovir IV	Autologous or allogeneic	250 mg/m² IV Q12H	250 mg/m² IV Q24H	250 mg IV Q24H

person with either primary VZV infection (chickenpox) or herpes zoster (shingles) should receive VZV-specific immunoglobulin as soon as possible and for up to 10 days following the exposure [1]. VariZIG® is a purified human varicella zoster immune globulin preparation. If VariZIG® cannot be obtained in a timely manner, intravenous immunoglobulin (400 mg/kg × 1 dose) is an alternative, although the data to support efficacy are limited.

3. While HCT recipients are NOT candidates for vaccination with live attenuated varicella virus vaccines, use of Shingrix®, a recombinant vaccine, can be considered in transplant recipients. There are safety and efficacy data to support use of Shingrix® for prevention of herpes zoster in immunocompetent adults ≥50 years of age [2]. A phase III, placebo-controlled study using two doses of Shingrix® in autologous HCT recipients demonstrated a significantly reduced incidence of herpes zoster over a median follow-up of 21 months, with no excess of serious adverse events and with an incidence rate ratio of 0.32 corresponding to a vaccine efficacy of 68% [3].

4. Family members and close contacts who receive the Varivax® or Zostavax® vaccine and develop a rash within 3–6 weeks after vaccination should avoid contact with the HCT recipient to decrease risk for transmission of vaccine-strain virus.

5. Hospitalized transplant recipients with active VZV infection (either primary infection or reactivation infection, with or without dissemination) should be placed in a negative air flow room on airborne and contact isolation precautions to decrease risk for transmission in the healthcare setting. Placement in a location off the transplant ward should be considered to decrease risk for transmission in the healthcare setting.

Cytomegalovirus (CMV) Disease Prevention

1. *Autologous recipients*: With a few exceptions*, autologous recipients do not require CMV surveillance because risk for CMV disease is exceedingly low.

   a. *CMV-seropositive autologous recipients who have received major T-cell suppression prior to HCT (e.g., alemtuzumab [Campath®]), total body irra-

diation (TBI) as part of the conditioning regimen, and/or high-dose cortico-steroids for another indication are at risk for symptomatic CMV infection or disease and should have preemptive monitoring posttransplant.

2. *Allogeneic recipients*: Both prophylactic and preemptive strategies can be used to prevent CMV disease in allogeneic recipients. Owing to the toxicities of CMV antiviral agents (myelosuppression with ganciclovir [Zirgan®] and valganciclovir [Valcyte®], nephrotoxicity with foscarnet [Foscavir®]), a preemptive monitoring strategy has historically been the favored approach [4]. Prophylaxis is undertaken by some centers and in certain circumstances, particularly for high-risk patients such as recipients of cord blood or haploidentical products, and increasingly with the introduction of the novel CMV antiviral letermovir (Prevymis®).

    a. In a 2017 randomized, placebo-controlled study of a select CMV-seropositive recipient population with no detectable CMV at time of randomization, letermovir prophylaxis was associated with a significant decrease in "clinically significant CMV infection" (that requiring initiation of preemptive therapy or CMV disease) [5]. Neither myelosuppression nor nephrotoxicity was associated with letermovir. Based on these data, many centers have opted to incorporate letermovir prophylaxis for those patients at highest risk for CMV infection/disease. Patients receiving letermovir prophylaxis require ongoing CMV DNA monitoring due to a continued, albeit low, rate of breakthrough viremia. Furthermore, as letermovir does not have intrinsic HSV or VZV activity, acyclovir (or a related congener) prophylaxis should be administered with letermovir.
    b. Given the poor outcomes associated with CMV disease prior to allogeneic transplantation, patients with documented pretransplant CMV infection warrant special consideration with regard to preemptive monitoring strategies, and even consideration for prophylaxis in some settings.
    c. HCT recipients who are CMV-seronegative should receive either CMV seronegative or leukocyte-reduced blood products to decrease the risk of primary CMV infection. For a CMV-seronegative recipient, a CMV-seronegative donor is preferred if other factors (e.g., HLA match) are equal.

3. For *preemptive monitoring*, CMV DNA viral load is the standard test. Ideally, measurement of CMV DNA should be with the international reference standard to decrease inter-laboratory variability.
4. Preemptive monitoring should occur with sufficient regularity (e.g., at least weekly) and with timely turnaround so as to allow time for intervention prior to the onset of CMV end-organ disease.
5. *At our centers*, we use the following protocol for preemptive monitoring:

    a. Patients who are CMV-seropositive or who have a CMV-seropositive donor should have weekly monitoring with CMV PCR through day +100, every 2–4 weeks until at least day +180, and then at least monthly until off immune suppression.

    b. Patients who are CMV-seronegative with a CMV-seronegative donor should have monthly CMV PCRs through day +100, and when clinically indicated (e.g., if protracted fevers, GI symptoms, unexpected cytopenias).

    c. Any patient with CMV infection prior to or after day +100 should have prolonged surveillance.

    d. The frequency and duration of prolonged CMV surveillance should take into consideration the presence of GvHD and degree of immune suppression.

6. *Preemptive therapy* is typically initiated after the detection of CMV DNA. It should be recognized, however, that there are no standardized or validated thresholds to initiate treatment. Prophylactic acyclovir/valacyclovir should be discontinued if preemptive therapy with ganciclovir, valganciclovir, or foscarnet is initiated.

    a. While there is ample literature and expert guidelines to support the safety and efficacy of oral valganciclovir for preemptive therapy in select HCT recipients, parenteral ganciclovir and foscarnet are the FDA-approved drugs for this indication [4].

    b. The use of oral valganciclovir may be considered for preemptive therapy for patients meeting the following criteria:

        i. No signs/symptoms of or suspicion for CMV end-organ disease
        ii. No history of medication noncompliance
        iii. Able to tolerate adequate oral intake/medications

    c. Preemptive valganciclovir or ganciclovir (renal dose adjustment as indicated, outlined in Tables 10.2 and 10.3) consists of induction dosing until quantitative PCR assays are negative.

    d. Some centers transition to maintenance (or prophylactic) dosing of oral valganciclovir or IV ganciclovir after completion of induction dosing, particularly for heavily immune-suppressed patients. At this writing, maintenance dosing following induction dosing is often utilized; however, there are emerging data to suggest this practice may be of limited value [6].

    e. If viral load continues to rise after 2 weeks of valganciclovir or ganciclovir therapy, consider the possibility of ganciclovir-resistant CMV [4]. In this set-

Table 10.2 Dosing recommendations for valganciclovir in renal impairment

	Normal renal function	Renal impairment[a]			
CrCl	≥60 mL/min	40–59 mL/min	25–39 mL/min	10–24 mL/min	<10 mL/min (hemodialysis)
Induction	900 mg po BID	450 mg po BID	450 mg po daily	450 mg po QOD	Do not use
Maintenance	900 mg po daily	450 mg po daily	450 mg po QOD	450 mg po twice weekly	Do not use

[a]Patients with renal insufficiency should receive valganciclovir 900 mg po BID × 2 doses. The dose should then be adjusted for their renal function as outlined in the table below

Table 10.3 Dosing recommendations for ganciclovir in renal impairment

	Normal renal function	Renal impairment[a]			
CrCl	≥70 mL/min	50–69 mL/min	25–49 mL/min	10–24 mL/min	<10 mL/min (hemodialysis)
Induction	5 mg/kg IV q12hr	2.5–5 mg/kg IV q12hr	2.5 mg/kg IV q24hr	1.25 mg/kg IV q24hr	1.25–2.5 mg/kg IV 3×/week (dose following dialysis)
Maintenance	5 mg/kg IV q24hr	2.5 mg/kg IVq24hr	1.25 mg/kg IV q24hr	0.625 mg/kg IV q24hr	0.625 mg/kg IV 3×/week (dose following dialysis)

[a]Patients with renal insufficiency should receive ganciclovir 5 mg/kg IV q12hr × 2 doses. The dose should then be adjusted for renal function as outlined above

ting, consultation with the Infectious Diseases service is advised. If concern for ganciclovir-resistance is sufficiently high, resistance testing (typically by genotypic analysis) should be obtained, with consideration for an empiric switch to foscarnet in patients who develop life-or sight-threatening disease (see Chap. 30).

f. If cytopenias preclude use of valganciclovir or ganciclovir for preemptive treatment, use of alternatives (e.g., foscarnet if renal function allows, or off-label use maribavir [7] or letermovir with close monitoring) can be considered. Formal consultation with the Infectious Diseases service is advised.

7. If CMV reactivation occurs after day +100, the decision to initiate preemptive treatment will depend on the height of the circulating viral load as well as host immune status.

Antibacterial Prophylaxis

1. Fluorofluoroquinolone prophylaxis should be considered for patients with expected duration of profound neutropenia (absolute neutrophil count [ANC] ≤ 100 cells/mm^3) > 7 days [8, 9]. Both levofloxacin and ciprofloxacin are reasonable options for this indication, though levofloxacin offers an advantage in situations with increased risk for mucositis-related viridans group streptococcal infection. If fluoroquinolone prophylaxis is undertaken by a center, systematic monitoring for the emergence of fluoroquinolone-resistant gram-negative bacilli, *Clostridioides difficile* infection and/or excess drug toxicity is recommended. Institutional use of fluoroquinolone prophylaxis is a decision that requires revisiting risks and benefits over time.

2. Autologous and allogeneic recipients should receive levofloxacin prophylaxis (500 mg po daily, with renal dose adjustment as indicated) during neutropenia. The optimal start time for fluoroquinolone prophylaxis is uncertain – some centers begin during the conditioning regimen or at the time of transplant whereas others start when the ANC is <500/mm^3. Prophylaxis should be continued until the ANC is >500/mm^3, or until first neutropenic fever (temperature ≥ 38.0 °C) at which time empiric broad-spectrum parenteral antibiotic therapy is begun (see Chap. 30) [8, 9].
3. In the case of a documented fluoroquinolone allergy or intolerance, alternative prophylaxis, such as with an oral third-generation cephalosporin, can be considered, though acknowledging the lack of *Pseudomonas aeruginosa* activity. Alternatively, no prophylaxis may be considered in this situation.

Encapsulated Organism Prophylaxis for Patients with Chronic GvHD

1. All patients with chronic GvHD and asplenic patients should receive prophylaxis for encapsulated organisms with oral penicillin (250–500 mg po twice daily or 500–1000 mg po once daily) [9].
2. Alternatives for patients who are penicillin-allergic include trimethoprim/sulfamethoxazole single strength 1 tablet po daily or azithromycin 250 mg po daily (in particular in patients with chronic bronchiolitis obliterans syndrome). Note, however, that prolonged use of azithromycin is controversial, with recent data suggesting an increased risk for relapse of underlying disease when used in the early posttransplant period [10].

Antifungal Prophylaxis

1. Autologous and allogeneic recipients should receive antifungal prophylaxis posttransplant, acknowledging the survival benefit associated with use of fluconazole for this indication [11]. See Table 10.4 for antifungal dosing guidelines.

   a. Autologous recipients should receive fluconazole beginning day 0 and continuing until ANC is >500/mm^3 and perhaps longer based on full recovery from transplant-associated toxicities and/or center practice.
   b. Allogeneic recipients should receive fluconazole beginning day 0 and continuing until a minimum of day +75 or longer based on clinical indication and/or center practice.

2. For allogeneic recipients who are receiving fluconazole prophylaxis, consider weekly serum *Aspergillus* galactomannan monitoring through day +100. Serum galactomannan monitoring is not advised for patients who are on mold-active

Table 10.4 Dosing recommendations for azole antifungals

Drug	Adult dose	Comments
Fluconazole	400 mg po/IV daily[a]	
Posaconazole[b]	300 mg po/IV BID (for oral administration use tablets, *not suspension*) on day 1 (loading dose), followed by 300 mg po/IV QD thereafter	To maximize absorption, dose with meals and ensure no proton-pump inhibitor/H2-blocker therapy
Voriconazole[b]	6 mg/kg po/IV q12 × 2 doses (loading dose), followed by 4 mg/kg po/IV q12 thereafter [round to nearest 50 mg for oral, with suggested initial maximum dose of 300 mg BID when used for prophylactic indication]	Oral dosing on an empty stomach to maximize absorption
Isavuconazole[b]	372 mg po/IV every 8 hours for 6 doses (loading dose), followed by 372 mg po/IV QD thereafter	

[a]Renal dose adjustment required, dose at 200 mg daily for CrCl < 50 mL/min
[b]Extended-spectrum azoles are metabolized primarily by cytochrome P450 enzymes, and as such there are numerous critical drug–drug interactions to be mindful of, including but not limited to the calcineurin inhibitors and sirolimus as well as multiple chemotherapeutic agents [25]. Consult package insert, transplant pharmacist, and/or Infectious Diseases consultation service before prescribing these medications

antifungal prophylaxis (e.g., voriconazole [VFend®] or posaconazole [Noxafil®]), given very low yield in this setting.

3. Patients who receive high-dose steroids after transplant (≥0.4 mg/kg/day of methylprednisolone equivalent, or >20 mg/day of prednisone equivalent) and those who have prolonged neutropenia related to graft failure should receive prophylaxis with an extended-spectrum azole (e.g., posaconazole or voriconazole) [12]. The oral suspension formulation of posaconazole should not be used, given poor oral bioavailability; instead, posaconazole should be given as delayed release tablets or by IV route. See Table 10.4 for antifungal dosing guidelines.

   a. Monitoring of drug trough levels for patients receiving voriconazole and posaconazole are recommended due to variability in achievable serum concentration and the suggestion that both therapeutic outcomes as well as toxicity, in the case of voriconazole are dependent on drug level [13, 14].

      i. A voriconazole trough level should be checked within 1 hour prior to dose on/about day 7 (day 5–7) after drug initiation. Target level for voriconazole prophylaxis is 1.5 to 5 mcg/mL.
      ii. A posaconazole trough level should be checked within 1 hour prior to dose on/about day 7 after drug initiation. Target level for posaconazole prophylaxis is ≥0.8 mcg/mL.
      iii. If a drug level does not fall within the suggested target range despite dose adjustment, please consult with the transplant pharmacist and/or the Infectious Diseases service for advice on dose adjustment or other maneuvers to optimize dosing.

4. Alternatives to posaconazole or voriconazole prophylaxis (if dose-limiting liver function test abnormalities, documented allergy, QT_c prolongation, or insurmountable drug–drug interactions) include isavuconazole (Cresemba®) or an echinocandin (e.g., micafungin [Mycamine®] 100 mg IV daily), though noting breakthrough mold infections have been reported with both [15–18]. Liposomal amphotericin (3 mg/kg three times weekly or daily) with close monitoring of renal function is another option.

Pneumocystis jiroveci Prophylaxis

1. All HCT recipients should receive pneumocystis prophylaxis [9].
2. All patients should receive trimethoprim/sulfamethoxazole DS (Bactrim DS®) 1 tablet po BID beginning on the first day of their conditioning regimen, continuing through day −2.
3. Both autologous and allogeneic patients should resume pneumocystis prophylaxis following engraftment, typically restarting between days +25 and +30.
4. Trimethoprim/sulfamethoxazole is first line for pneumocystis prophylaxis*. There are various dosing regimens that have been shown to be effective – for example, single strength daily, double strength thrice weekly, double strength two times daily twice weekly.
   *Barring clear contraindications, trimethoprim/sulfamethoxazole is the drug of choice given its superior efficacy for pneumocystis prophylaxis, as well as activity against *Listeria*, *Nocardia*, and *Toxoplasma*, which the alternatives lack.
5. Alternatives in sulfa-allergic or otherwise intolerant patients include:

   a. Pentamidine 300 mg aerosolized or 4 mg/kg IV every 4 weeks [19, 20]
   b. Dapsone 100 mg po daily (check G-6PD level prior to initiation of dapsone and monitor for methemoglobinemia if long-term use is required)
   c. Atovaquone 750 mg BID or 1500 mg po daily

6. Pneumocystis prophylaxis should continue until discontinuation of all immunosuppressive therapy in allogeneic recipients, and for at least 60 days in autologous recipients with ultimate duration dependent on center practice.

Toxoplasma gondii

1. Allogeneic recipients who are seropositive for *Toxoplasma gondii* at the time of transplant are at highest risk for posttransplant toxoplasmosis by reactivation [21]. Toxoplasmosis can occur in seronegative recipients, either by way of transmission through HCT or transfusion or through infection acquired posttransplant.
2. HCT recipients, particularly those who are *Toxoplasma* seronegative, should be counseled on risk avoidance strategies to decrease risk for acquisition of infec-

tion – for example, to avoid changing cat litter boxes or close contact with kittens.
3. Trimethoprim/sulfamethoxazole is first line for *Toxoplasma* prophylaxis [21].
4. For high-risk (*Toxoplasma* seropositive) HCT recipients who are sulfa-allergic or otherwise intolerant, the choice of an alternative regimen for prophylaxis is not well studied in this population. Alternatives include:

   a. Clindamycin with pyrimethamine and leucovorin
   b. Dapsone with pyrimethamine and leucovorin
   c. Atovaquone with or without pyrimethamine and leucovorin [22]

5. In situations where there is no acceptable regimen for prophylaxis in high-risk recipients, serial monitoring (e.g., weekly) with *Toxoplasma* PCR with preemptive treatment is a reasonable strategy [23].

Viral Hepatitis

1. Patients who are Hepatitis B virus (HBV) infected (HBV surface antigen and/or HBV DNA positive) should be evaluated by Hepatology and/or the Infectious Diseases services prior to transplant, with consideration for HBV-active antiviral therapy (e.g., lamivudine [Epivir®] or entecavir [Baraclude®]) prior to proceeding with the transplant conditioning regimen.

   a. During the course of antiviral therapy, HBV DNA should be monitored to ensure suppression, in particular in the setting of abnormal liver function tests.
   b. HBV-active antiviral therapy should be continued for at least 6 months post-transplant in autologous recipients and at least 6 months following discontinuation of immunosuppressive therapy in allogeneic recipients.

2. Patients who are Hepatitis C virus (HCV) infected (HCV RNA positive) should be evaluated by Hepatology and/or the Infectious Diseases services prior to transplant, with consideration for pretransplant (if time allows) initiation of direct-acting antiviral therapy [24].

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Chapter 11
Graft-Versus-Host Disease (GvHD) Prophylaxis

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Introduction

Immunologic signaling cascades and cellular interactions paramount to graft-versus-host disease (GvHD) pathogenesis begin promptly after allogeneic hematopoietic stem cell (HSC) infusion, but the multistep pathogenesis takes some time to manifest clinically [1, 2]. As the initiating insult, conditioning regimen-related tissue damage and resultant cytokine release stimulate major histocompatibility complex (MHC) and adhesion molecule expression on host antigen presenting cells (APCs) [3, 4]. Immunocompetent donor T cells then recognize major and minor alloantigens, generate an inflammatory cytokine milieu, and ultimately mediate both graft-versus-tumor (GvT) effects and GvHD [5]. In most hematopoietic cell transplantations (HCTs), the cytokine storm is clinically masked given that prophylaxis with calcineurin inhibitors (CNIs) is initiated before graft infusion, but its robustness is apparent in hyperacute GvHD [6, 7] and evidenced by high fevers and marked malaise in the three-day immunosuppressant-free window after T-cell replete haploidentical stem cell infusion (before post-transplant cyclophosphamide begins) [8].

Despite development of improved GvHD prophylactic strategies in the last few decades, GvHD remains the leading cause of non-relapse morbidity, mortality, and reduced quality of life after allogeneic HCT (alloHCT) [9–11]. Grade 2–4 acute GvHD (aGvHD) occurs in 20–70% of alloHCT recipients and is a key risk factor for development of subsequent chronic GvHD (cGvHD). Occurring in 30–50% of patients, cGvHD often involves multiple organs, presents distinctly from aGvHD,

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and requires prolonged use of immunosuppressive therapies (often with trials of various medications and/or other treatment modalities to obtain a response) [12–14]. In contrast to rapid pre-formed T-cell allorecognition underlying aGvHD origination, cGvHD results, in part, from loss of regulatory cells and peripheral tolerance, amplified fibroblast activation, tissue deposition of pathogenic immunoglobulins, and other factors [15]. The predominant use of peripheral blood stem cell (PBSC) allografts [16] and relative infrequency of matched-related donor (MRD) availability (~30%) [17] leave most HCT recipients with at least one stronger risk factor for GvHD [18].

Donor selection is vital for mitigation of the GvHD risk [19]. Among all donor-related factors considered, GvHD risk and survival is most predicated on high-resolution allelic matching at human leukocyte antigen (HLA) loci A, B, C, and DRB1 (8/8 match) [20]. DQB1 matching is routinely performed, but some series show no effect on morbidity or mortality outcomes. In otherwise fully HLA-matched cases, permissive DPB1 mismatches, which are common given the weak linkage disequilibrium with other class II HLA loci, have been shown to increase GvHD and decrease disease relapse. Non-permissive DPB1 mismatches may increase overall mortality (depending on the case series). Even with an optimal MRD graft, the incidence of aGvHD requiring therapy with systemic corticosteroids is approximately 40% [21], and because of increased PBSC use, cGvHD has become an ever-expanding clinical issue [12]. Therefore, manipulation of the graft continues to generate fervent research interest. *In vivo* and *ex vivo* allograft manipulations have produced significant reductions in aGvHD and cGvHD rates; however, these maneuvers may lead to higher relapse rates (e.g. CD34 selection and loss of donor effector cells) and increased risk of opportunistic infection (e.g. anti-thymocyte globulin [ATG]). Additionally, data for some strategies are limited (e.g. post-transplant cyclophosphamide after conventional alloHCT) or are still in early phases of clinical investigation (e.g. *ex vivo* allograft treatments). This chapter offers practical information for GvHD prophylaxis and summarizes both established and emerging strategies.

Risk Factors for GvHD

1. HLA antigen/allele mismatch (aGvHD > cGvHD) [20, 22, 23]
2. Unrelated donor (aGvHD > cGvHD) [22, 24]
3. Older recipient age (cutoffs vary across studies, cGvHD > aGvHD) [25–27]
4. Higher conditioning intensity [28]
5. Multiparous female donor to male host (cGvHD > aGvHD) [29, 30]
6. Total body irradiation (aGvHD only) [22, 31]
7. Cyclosporine (vs. tacrolimus, aGvHD only) [32–34]
8. Mobilized peripheral blood stem cells (cGvHD > aGvHD) [22, 35–37]
9. Higher CD34 cell dose in PBSC product (cGvHD only) [38]
10. Higher T-cell dose in T-cell-depleted allografts [39]
11. T-cell replete allografts (cGvHD > aGvHD) [40, 41]

12. aGvHD (one of the most important risk factors for cGVHD) [41–43]
13. ABO mismatch [44, 45]
14. CMV seropositivity [25]
15. Decreased intestinal microbiota diversity [46–48]

aGvHD Prophylaxis

A calcineurin inhibitor (CNI) in combination with methotrexate (MTX) on days +1, +3, +6, and +11 is the standard combination for GvHD prophylaxis for most standard allogeneic HCT recipients [49, 50]. When compared with cyclosporine (CyA), some evidence suggests tacrolimus (Tac) may increase the relapse rate in patients who have active disease at time of HCT [34]; however, Tac also may decrease the risk of grade 3–4 aGvHD [51].

Prednisone/methylprednisolone ("steroids") or mycophenolate have been used to replace the last methotrexate dose (day +11) in patients who develop prohibitive toxicities or significant organ dysfunction [52, 53], although limited data support this practice [54–56]. Steroids should not be added to a CNI/MTX regimen as a standard third agent given the heterogeneous outcomes with this regimen [51, 57, 58], potential antagonism of CNI/MTX [59], and increased infection risk [60].

Sirolimus (siro) may be substituted for MTX (most data after MRD alloHCT); however, as it still lacks a defined niche and increases risk for certain post-transplant complications (see below), most centers do not routinely use sirolimus for GvHD prophylaxis [61, 62]. Also, sirolimus offers no benefit when added to a CNI/MTX combination.

Mycophenolate (Cellcept®, MMF)reduces early toxicity and may permit faster engraftment [63], but it has not supplanted MTX as first-line prophylaxis for patients receiving T-cell replete conventional MRD, matched unrelated donor (MUD), or mismatched unrelated donor (MMUD) allografts. Study results with mycophenolate, though heterogeneous, have shown increased risk for severe aGvHD [64–66], particularly with use of unrelated donors [67], and worse overall survival compared with Tac/MTX after myeloablative condidtioned (MAC) allogeneic HCT [68].

For patients receiving non-myeloablative conditioning (a.k.a. mini-transplant, NMA), early CNI target troughs are increased and MTX is often replaced by mycophenolate to better suppress host T cells and hasten engraftment, respectively [69, 70]. For the same reason, MTX is replaced with mycophenolate in umbilical cord blood (UCB) transplant recipients [71].

Haploidentical hematopoietic cell transplant (haploHCT) recipients uniquely receive post-transplant cyclophosphamide (PTCy) followed by a CNI/MMF combination (at least 24 hours later to prevent PTCy antagonism) [72–74]. Given the success of haploHCT in cGvHD reduction, some centers have begun to use PTCy in the conventional allograft setting. *In vivo* and *ex vivo* T-cell depletion (TCD) are employed extensively at some centers and minimally at others depending on familiarity and access to required equipment.

Ursodiol (Actigall®) is commonly added to prevent liver GvHD as well as sinusoidal obstruction syndrome (SOS). Its use may also prevent intestinal GvHD and improve non-relapse mortality and overall survival [75, 76].

Common aGvHD Prophylaxis Regimens

Regimens differ depending on the practice site, but these regimens are commonly used at many centers.

1. Myeloablative (MAC)

   a. CNI (usually Tac) + MTX*$

2. Reduced intensity (RIC)

   a. CNI (usually Tac) + MTX*$

3. Non-myeloablative (NMA)

   a. CNI (usually CyA) + mycophenolate

4. Haploidentical (haplo)

   a. PTCy + CNI (usually Tac) + MMF

5. Umbilical cord blood (UCB)

   a. CNI (usually Tac) + MMF

   *Siro may be substituted for MTX, though the CNI/siro combination may increase the risk of SOS and transplant-associated microangiopathy [77]. Tac is the preferred CNI to use in combination with siro.
   $MMF may be added to CNI/MTX (to permit lower MTX doses) and steroids or MMF may replace the last short-course MTX dose if toxicity warrants its omission.

cGvHD Prophylaxis

Conventional GvHD prophylaxis with a CNI/MTX combination protects against the development of aGvHD, but exerts little influence on subsequent cGvHD incidence [78, 79]. *In vivo* TCD with ATG or alemtuzumab (Campath®), or T-cell manipulation with cyclophosphamide are attractive newer strategies to lessen the occurrence of cGvHD.

1. Antithymocyte globulin (ATG)

   a. ATG is a standard component in aplastic anemia conditioning, but can also be added in recipients of both MRD and MUD allografts with malignant conditions.

   b. Unlike in European transplant centers, use of ATG in the United States is limited given study design/outcome heterogeneity, product dissimilarity/availability [80], and toxicity concerns. For the same reasons, systematic reviews and meta-analyses also hedge on making firm recommendations regarding ATG use [81, 82].
   c. *Ex vivo* TCD using ATG is another option, but this approach is employed only by a limited number of transplant centers [49].
   d. Phase 3 randomized trials show that ATG may reduce cGvHD incidence without altering disease relapse or progression after MAC regimens in both MRD [83] and MUD recipients [84].

      i. Conversely, some investigations have shown inferior progression-free survival (PFS) and overall survival (OS) [85].
      ii. A phase 3 randomized study [84] and some non-randomized studies also support the addition of ATG to RIC regimens [86–89].
      iii. Some studies have shown a dose–response relationship for ATG efficacy [90, 91] while others have not [92].

   e. Overall, use of ATG has been primarily reserved for unrelated donor HCT given the higher GvHD risk [49].

2. Alemtuzumab (Campath®)

   a. Alemtuzumab has clearly demonstrated utility in the prevention of cGvHD (and sometimes aGvHD) when added during conditioning, but its benefits are tempered by increased risks of disease relapse and opportunistic infections [93].
   b. Alemtuzumab has been used for *ex vivo* TCD [94] or for combined *ex vivo/in vivo* TCD [95]. Still, the use of ATG and CD34 selection predominate as graft manipulation techniques.
   c. A phase II open label trial comparing alemtuzumab/CyA to Tac/siro/MTX after RIC MUD alloPBSC transplant showed markedly reduced cGvHD rates (5 vs. 31%), but higher 3-year relapse rates, higher infection rates (likely secondary to prolonged T-cell lymphopenia), and similar aGvHD rates [96].
   d. Some evidence suggests alemtuzumab may ameliorate the negative impact of HLA-mismatch on GvHD risk and graft failure [97].
   e. Doses given during conditioning range from 10 mg [98] to 100 mg [99, 100]. The optimal dose for GvHD control and T-cell reconstitution has not yet been determined [101].
   f. Given the severe and prolonged lymphopenia induced by alemtuzumab, mixed chimerisms often persist [102, 103].
   g. Overall, alemtuzumab use for GvHD prophylaxis is rare and primarily reserved as an alternative to ATG in conditioning for aplastic anemia [104] and other non-malignant conditions [102], or for patients receiving an MMUD [49].

3. Post-transplant cyclophosphamide (PTCy)

   a. PTCy became a key component of GvHD prophylaxis when used with haplo-HCT and soon thereafter ignited interest in expansion to conventional allografts [105, 106], especially in patients with mismatched donors [107, 108].

   b. Several investigations have suggested that this approach may be effective as monotherapy and obviate the need for standard immunosuppressants given after MAC HCT [109], but not after RIC HLA-matched HCT [110].

      i. After RIC alloPBSC transplant (MRD, MUD, or 7/8 MMUD), the addition of PTCy to Tac/MMF improved GvHD-free, relapse-free survival (GRFS) predominantly by reducing grade 3–4 aGvHD and cGvHD requiring immunosuppression when compared to historical controls receiving Tac/MTX [111].

      ii. A randomized, multicenter, phase 3 trial (BMT CTN 1703) to compare Tac/MTX and PTCy/Tac/mycophenolate after NMA/RIC alloPBSC transplant is underway at the time of publication [112].

4. Multipotent adult progenitor cells (MAPCs) and mesenchymal stem cells (MSCs)

   a. MAPCs and MSCs are distinct cell populations with significant immunosuppressive and self-renewal potential.

   b. MAPCs and MSCs can be obtained from a myriad of sources (bone marrow, adipose tissue, placental tissues, and other organs), expanded by orders of magnitude, and administered to facilitate tissue regeneration given their broad differentiation potential into adipocytes, osteoblasts, chondrocytes, smooth muscle cells, and hematopoietic supportive stroma [113].

   c. MAPCs are an MSC-like cell that can acquire additional properties when the *ex vivo* culture conditions are modified.

      i. These cells can also differentiate into endothelial cells and exhibit more than double the *in vitro* expansion potential of MSCs [114]. Ultimately, their ability to induce immune tolerance [115] spawned interest in clinical application for GvHD prophylaxis and treatment [116–118].

   d. Though individual trial results are quite heterogeneous, one review of completed studies suggests that MSCs may reduce risk of cGvHD but not aGvHD [119].

   e. Many trials are ongoing to further elucidate their clinical utility.

5. *Ex Vivo* Graft Manipulation

   a. *Ex vivo* TCD has been investigated since the late 1970s, whereby T cells were removed in the laboratory after agglutination with soybean lectin and E-rosetting with sheep red blood cells [120]. Later techniques included treatment of the donor graft with monoclonal antibodies (MAb) against various T-cell cluster of differentiation (CD) markers followed by complement to

eliminate MAb-bound cells; however, impaired disease control and engraftment failure diminished the utility of this technique [121, 122]. In a large registry study from the Center for International Blood and Marrow Transplant Research (CIBMTR), use of these early *ex vivo* TCD techniques (as compared to T-cell replete allografts) was associated with a markedly increased relative risk for relapse in chronic myeloid leukemia [123].

b. Further technical modifications were applied in the 1990s [124, 125] which ultimately led to the predominant contemporary *ex vivo* TCD approach by positive selection of the CD34+ cells in the graft via immunoadsorption columns, thereby excluding T cells and other accessory cells.

  i. This approach consistently resulted in reliable engraftment, a low GvHD incidence, and similar relapse/survival rates in non-randomized comparisons with conventional allografts [126–128].
  ii. CD34+ selection of PBSCs is being compared with PTCy or Tac/MTX (after unmanipulated bone marrow graft) in a large randomized trial (BMT CTN 1301) [129].
  iii. *Ex vivo* TCD with CD34+ selection and *in vivo* TCD with ATG have not been compared prospectively [130].
  iv. In 2014, the Food and Drug Administration (FDA) approved the first CD34+-positive selection system for clinical use (without additional GvHD prophylaxis) after MAC in acute myeloid leukemia (AML) patients in first complete remission (CR) [131].

c. Alternative *ex vivo* graft manipulation techniques such as alpha/beta T-cell and CD19+ B-cell depletion (with preservation of gamma/delta+ T cells and NK cells) [132] are being studied in haploHCT [133–135], but such techniques remain limited to clinical trials.

  i. T cells expressing the alpha/beta T-cell receptor (TCR) account for 95% of the circulating T-cell population and are thought to be primary mediators of aGvHD given their MHC-dependent activation.
  ii. Gamma/delta T cells demonstrate innate immune recognition abilities involved in mediation of GvL, attacking malignant cells in an MHC-independent manner [136].
  iii. Removing alpha/beta T cells, but leaving gamma/delta T cells and NK cells in the allograft is thought to reduce GvHD, preserve GvL functions, and maintain partial protection against severe infections [137].
  iv. Interest continues to grow in the post-transplant add-back of alpha/beta T cells depleted of an alloreactive compartment (to promote immune reconstitution and GvL) and transduced with inducible suicide genes (to permit termination of the cellular therapy if significant GvHD occurs) [138].

d. Rituximab (Rituxan®) can reduce the high incidence of Epstein-Barr virus (EBV) reaction seen with this strategy [139], but risk of other infections warrants concern.

Medication Mechanisms, Doses, Interactions, and Toxicities

The scope of this section is limited to discussion of the GvHD prophylactic medications only. With select exceptions, pre-medications and other supportive medications (antimicrobials, hypersensitivity medications, antiemetics, etc.) are not discussed.

1. Methotrexate

    a. Mechanism of Action

        i. Inhibits dihydrofolate reductase which diminishes tetrahydrofolate production and consequently inhibits thymidylate synthetase. As a result, proliferating lymphocytes reach the S phase of the cell cycle with a paucity of purines and thymine [140].

    b. Dosing [141]

        i. 15 mg/m^2 (IV push over 2–3 minutes) on day +1 (at least 24 hours after completion of HSC infusion), followed by 10 mg/m^2 IV push on days +3, +6, and +11

        ii. Mini-MTX (5 mg/m^2 on day +1, +3, +6, and +11) [142] or micro-MTX (2.5 mg/m^2 on day +1, +3, and +6 with MMF added to CNI/MTX backbone) [143] regimens also are reported.

    c. Dose Adjustments

        i. Hyperbilirubinemia [144]

            • Total bilirubin 3.1–6 mg/dL: reduce dose by 50%
            • Total bilirubin >6 mg/dL: omit dose

        ii. Mucositis [145] (see Table 11.1 for grading)

            • World Health Organization (WHO) grade II mucositis: Consider leucovorin rescue.

Table 11.1 World Health Organization (WHO) Mucositis Grading Scale

Grade	Description
0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
III (severe)	Oral ulcers, liquid diet only
IV (life-threatening)	Oral alimentation impossible

Reference:
WHO: http://www.who.int/en/
WHO Handbook 1979, pp.15–22
Sonis et al. Cancer 2004; 100(9 Suppl):1995–2025

- WHO grade III mucositis: Reduce dose by 50% and consider leucovorin rescue.
- WHO grade IV mucositis: Omit dose.

   iii. Acute kidney injury (AKI) [34]

- Serum creatinine >2x ULN: Reduce dose by 50%.
- Serum creatinine >2 mg/dL: Omit dose.

d. Leucovorin Rescue

   i. May give in prophylactic fashion [146, 147], but without robust data, leucovorin is often reserved for patients with progressive WHO grade II–IV mucositis (usually after day +6 and/or day +11 MTX) [148]

   ii. 10 mg IV q6h for 8 doses (starting 24 hours after day + 6 and/or day +11 MTX), though reported doses, durations, and timing vary significantly [144]

e. Toxicities

   i. Gastrointestinal mucosal toxicity
   ii. Delayed hematologic recovery
   iii. Nephrotoxicity
   iv. Hepatotoxicity

f. Drug Interactions

   i. Avoid (may initiate 24–48 hours after final methotrexate dose)

- Penicillins [149]
- Sulfonamides
- Probenecid
- Non-steroidal anti-inflammatory drugs (NSAIDs)

   ii. Use without reservation (with post-transplant MTX doses)

- Proton pump inhibitors
- Fluoroquinolones

2. Tacrolimus (Prograf®)

a. Mechanism of Action

   i. Binds to the immunophilin FK506 binding protein (FKBP) which inhibits calcineurin phosphatase (CnA), preventing dephosphorylation of nuclear factor of activated T cells (NFATc) which reduces translocation from the cytoplasm into the nucleus. Inhibits interleukin-2 gene expression, nitric oxide synthase activation, cell degranulation, and apoptosis. Potentiates glucocorticoids by binding FKBPs in the hormone receptor complex. Inhibits TCR-mediated T-cell proliferation (TH1 > TH2) which in turn suppresses B-cell antibody production and impairs cytotoxic T cells [150, 151].

b. Dosing

  i. Starting doses

- IV: 0.015 mg/kg (over 2 hours) q12h beginning on day −2 (or day +5, at least 24 hours after PTCy for haploHCT)

  - Avoid giving within 4 hours of HCT infusion on day 0 as both infusions can cause adverse hemodynamic effects.
  - IV intermittent infusion (over 2 hours) is well-tolerated and logistically preferable over continuous infusion [152].
  - Use only for patients with compromised oral medication administration and/or absorption (high-grade mucositis, frequent emesis, high-volume diarrhea, etc.).

- PO: 0.025 mg/kg q12h beginning on day −2 (or day +5, at least 24 hours after PTCy for haploHCT)
- Consider using ideal or adjusted body weight for initial dose calculation in obese patients [153].
- Lower the starting dose if interacting medications are present (see below).

  ii. IV to PO conversion

- 1:2.5 (consider 1:1–2 if switching from IV to PO during concomitant therapy with an oral moderate/strong CYP3A4 inhibitor)

  iii. Monitoring

- Check first trough level on day 0 (before the 5th dose).

  - Half-life is approximately 18 hours, so the day 0 trough level is only about 50% of anticipated steady state level.

- Check additional levels twice weekly unless changing organ function or drug interactions warrant more frequent monitoring.

  iv. Goal trough levels

- MAC/RIC alloHCT regimens: 5–10 ng/mL (until day +100), then taper by up to 10% per week (off by day +180)
- NMA alloHCT regimens: 5–15 ng/mL (until day +28), then 5–10 ng/mL (day +29 to day +56), then taper by ~6% per week (off by day +180) [154]
- Haplo/UCB: 5–15 ng/mL (until day +100), then taper by up to 10% per week (off by day +180) [72] or 5–15 ng/mL (until day +180 without taper) [155]
- Switching CNIs: <5 ng/mL at time of cyclosporine initiation

v. Dose Adjustments

- Day 0 level

  - Calculate expected steady state level (e.g. if day 0 trough level is 4 ng/mL after starting on day −2, the ultimate steady state level will probably be ~8 ng/mL since Tac is only half way to steady state at this point).
  - Apply drug interaction magnitude to expected steady state level if starting a new interacting medication (e.g. if steady state level without interacting medications is predicted to be 8 ng/mL, but voriconazole starts on day 0, the new predicted steady state trough level could be 16–24 ng/mL).
  - Reduce Tac dose appropriately based on these considerations (e.g. if aiming for the middle of the goal trough range of 5–10 ng/mL with the example levels as provided above, reduce tacrolimus dose by 50–75%).

- Beyond day 0 levels

  - Adjust dose based on assumption of linear pharmacokinetics.
  - If checking blood concentrations twice weekly, the full effect of a previous dose adjustment may not be realized at the time of the next level given the long half-life of Tac.
  - If uneven doses are required (e.g. 1 mg PO qAM & 0.5 mg PO qPM), give the higher dose in the morning since trough levels are higher after PM doses than AM doses [156].

- Supratherapeutic levels (assuming goal of 5–10 ng/mL)

  - >15 ng/mL: Hold and recheck level the following day. Evaluate for possibility of central venous catheter (CVC) contamination.
  - >10 to ≤15 ng/mL (no AKI or adverse effects): Reduce dose.
  - >10 to ≤15 ng/mL (AKI and/or adverse effects): Hold one dose, then resume at reduced dose (unless AKI worsening rapidly).

- Dose adjustment for AKI

  - Serum creatinine >2 mg/dL: Hold until SCr improves.
  - Serum creatinine 1.5–2 mg/dL: Reduce goal trough range by 50% until SCr improves.

c. Toxicities [157]

i. Hypertension
ii. Electrolyte derangements (hypomagnesemia, hyperkalemia)
iii. Nephrotoxicity
iv. Diabetes (higher risk than cyclosporine)

    v. Neurotoxicity (tremor, headache, paresthesia, insomnia, dizziness, seizure)
    vi. Infections
    vii. Hypersensitivity reaction (due to polyoxyl 60 hydrogenated castor oil)
    viii. Posterior reversible encephalopathy syndrome (PRES)
    ix. Transplant-associated thrombotic microangiopathy (TA-TMA)

d. Drug Interactions [158]

    i. Interactions may be stronger when both drugs are given PO since both intestinal and hepatic CYP3A4 enzymes contribute to drug metabolism.
    ii. CYP3A4 inhibitors.

- CYP3A4 inhibitors markedly increase Tac trough concentrations (Cmin) and area-under-the-curve (AUC).
- Empiric Tac dose reductions are warranted.

    – 33–50% dose reduction with moderate CYP3A4 inhibitors
    – imatinib (Gleevec®), nilotinib (Tasigna®), amiodarone (Cordarone®), erythromycin (Erythrocin®), fluconazole (Diflucan®), isavuconazole (Cresemba®), diltiazem (Cardiazem®), verapamil (Calan®), letermovir (Prevymis®), and cimetidine (Tagamet®)
    – 66–75% dose reduction with strong CYP3A4 inhibitors: idelalisib (Zydelig®), clarithromycin (Biaxin®), telithromycin (Ketek®), voriconazole (VFend®), posaconazole (Noxafil®), itraconazole (Sporanox®), ketoconazole (Nizoral®), protease inhibitors, and cobicistat (Tybost®)

    iii. CYP3A4 inducers

- CYP3A4 inducers markedly reduce Tac Cmin and AUC: rifampin (Rifadin®), carbamazepine (Tegretol®), oxcarbazepine (Trileptal®), phenytoin (Dilantin®), primidone (Mysoline®), St. John's wort, bosentan (Tracleer®), efavirenz (Sustiva®), nafcillin (Unipen®), and enzalutamide (Xtandi®).
- Monitor Tac levels closely and adjust dose as needed.
- Do not empirically increase Tac dose upon initiation of a CYP3A4 inducer (induction may take 1–2 weeks).

    iv. Consultation with oncology pharmacy specialists is highly recommended

e. Central venous catheter (CVC) contamination

    i. Tacrolimus readily adsorbs to venous catheter lumens.
    ii. Trough levels will be falsely elevated if drawn from a CVC lumen previously used to infuse tacrolimus (even if contamination event was remote) [159].
    iii. Draw tacrolimus levels from a peripheral vein if available CVC lumens are contaminated (until the CVC is replaced).

3. Cyclosporine modified (Gengraf®, Neoral®) and cyclosporine (SandIMMUNE®)

   a. Mechanism of Action

      i. Same as with tacrolimus except cyclosporine binds cyclophilin (CpN) instead of the immunophilin FK506 binding protein [160]. Both complexes then block calcineurin.

   b. Dosing

      i. Starting doses

         • IV: 1.5–2 mg/kg (over 2–4 hours) q12h beginning on day −2 (or day +5, at least 24 hours after PTCy for haploHCT)

            – Avoid giving within 4 hours of HCT infusion on day 0 as both infusions can cause adverse hemodynamic effects.
            – IV intermittent infusion (over 2–6 hours) is well-tolerated and logistically preferable over continuous infusion. Prolong the infusion if hemodynamic adverse effects occur.
            – Use only for patients with compromised oral medication administration and/or absorption (high-grade mucositis, frequent emesis, high-volume diarrhea, etc.).

         • PO: 3–4 mg/kg q12h beginning on day −2 (or day +5, at least 24 hours after PTCy for haploHCT)

            – Cyclosporine modified (Gengraf®, Neoral®) is preferred over cyclosporine (SandIMMUNE®) non-modified given more consistent and predictable absorption.

         • Consider using ideal or adjusted body weight for initial dose calculation in obese patients [161].
         • Lower the starting dose if interacting medications are present (see below).

      ii. IV to PO conversion

         • 1:1.8 (consider 1:1–1.5 if switching from IV to PO during concomitant therapy with an oral moderate/strong CYP3A4 inhibitor)

      iii. Monitoring

         • Check first trough level on day 0 (before the 5th dose).

            – Half-life is approximately 8–18 hours, so the day 0 trough level is between 50 and 100% of anticipated steady state level.

         • Check additional levels twice weekly unless changing organ function or drug interactions warrant more frequent monitoring.

iv. Goal trough levels
- MAC/RIC alloHCT regimens: 200–300 ng/mL (until day +100), then taper by up to 10% per week (off by day +180)
- NMA alloHCT regimens: 300–400 ng/mL (until day +28), then 250–350 ng/mL (day +29 to day +56), then taper by ~6% per week (off by day +180) [69]
- Haplo/UCB: 200–400 ng/mL (until day +100), then taper up to 10% per week (off by day +180)
- Switching CNIs: ≤125 ng/mL at time of tacrolimus initiation

v. Dose Adjustments
- Day 0 level

  – Calculate expected steady state level (e.g. if day 0 trough level is 150 ng/mL after starting on day −2, the ultimate steady state level will probably be ~150–300 ng/mL since CyA is 50–100% to steady state at this point).
  – Apply drug interaction magnitude to expected steady state level if starting a new interacting medication (e.g. if steady state level without interacting medications is predicted to be 150–300 ng/mL, but voriconazole (VFend®) starts on day 0, the new predicted steady state trough level could be 375–1000 ng/mL).
  – Reduce CyA dose appropriately based on these considerations (e.g. if aiming for the middle of the goal trough range of 200–300 ng/mL with the example levels as provided above, reduce CyA dose by 50–75%).
- Beyond day 0 levels
  – Adjust dose based on assumption of linear pharmacokinetics.
  – If uneven doses are required (ex: 150 mg PO qAM & 125 mg PO qPM), give the higher dose in the morning since trough levels are higher after PM doses than AM doses [156].
- Supratherapeutic levels (assuming goal of 200–300 ng/mL)
  – >400 ng/mL: Hold and recheck level the following day. Evaluate for possibility of central line contamination.
  – >300 to ≤400 ng/mL (no AKI or adverse effects): Reduce dose.
  – >300 to ≤400 ng/mL (AKI and/or adverse effects): Hold 1 dose, then resume at reduced dose (unless AKI worsening rapidly).
- Acute kidney injury (AKI)
  – Serum creatinine >2 mg/dL: Hold until SCr improves.
  – Serum creatinine 1.5–2 mg/dL: Reduce goal trough range by 50% until SCr improves.
c. Toxicities [157]

  i. See above as for tacrolimus
  ii. Hirsutism
  iii. Gingival hyperplasia
  iv. Infusion reaction (due to polyoxyethylated castor oil)

    d. Drug Interactions [158]

       i. Interactions may be stronger when both drugs are given PO since both intestinal and hepatic CYP3A4 enzymes contribute to drug metabolism.

      ii. CYP3A4 inhibitors (see lists of selected examples above)

- CYP3A4 inhibitors markedly increase CyA Cmin and AUC.
- Empiric CyA dose reductions are warranted.

        – 25–50% dose reduction with moderate CYP3A4 inhibitors
        – 50–75% dose reduction with strong CYP3A4 inhibitors

      iii. CYP3A4 inducers (see lists of selected examples above)

- CYP3A4 inducers markedly reduce CyA Cmin and AUC.
- Monitor CyA levels closely and adjust dose as needed.
- Do not empirically increase CyA dose upon initiation of a CYP3A4 inducer (induction may take 1–2 weeks).

      iv. OATP1B1/SLCO1B1 substrates

- CyA inhibits OATP1B1, a transporter protein important for hepatic uptake of its substrates: HMG-CoA reductase inhibitors, letermovir, glyburide, bosentan
- Reduce OATP1B1 substrate dose appropriately.

       v. P-glycoprotein (p-gp) substrates

- CyA inhibits p-gp and dose reductions of sensitive p-gp substrates may be necessary (e.g. digoxin).
- Reduce p-gp substrate dose appropriately.

    e. CVC contamination

       i. See above as for tacrolimus [159].

4. Methylprednisolone (SOLU-Medrol®) and Prednisone (Deltasone®)

    a. Mechanism of Action

       i. Binds glucocorticoid receptors (GR) which then dissociate from chaperone proteins, permitting nuclear localization and attachment to target gene promoters known as glucocorticoid response elements (GREs). GREs drive transcription of various anti-inflammatory genes. Suppression of pro-inflammatory gene expression occurs, at least in part, via inhibition of histone acetyltransferases and recruitment of histone deacetylases to target genes [162].

    b. Dosing

       i. Not routinely added to CNI/MTX [163]
      ii. If day +11 MTX is omitted for toxicity, consider adding IV methylprednisolone 0.5 mg/kg/day (converting to prednisone 0.5 mg/kg/day when mucositis is resolved) until day +28, then taper off by day +56.

      iii. Consider starting prednisone 0.5–1 mg/kg/day if the CNI is held for toxicity, especially if prolonged CNI interruption is anticipated.

      iv. Methylprednisolone to prednisone conversion is 0.8:1.

  c. Toxicities

      i. Hyperglycemia

      ii. Insomnia

      iii. Mood disturbance

      iv. Edema

      v. Hypertension

      vi. Infections

      vii. Muscle atrophy

      viii. Skin atrophy

      ix. Easy bruising

5. Sirolimus (Rapamune®)

  a. Mechanism of Action

      i. Binds to FKBPs which, instead of binding calcineurin, then bind to a key cell-cycle kinase named mammalian target of rapamycin (mTOR), resulting in G1 cell-cycle arrest and reduced cytokine-induced mitogenic response and through myriad mechanisms [164].

  b. Dosing

      i. Starting doses

        • BSA >1.5 m^2: 8–12 mg PO once, followed by 2–4 mg PO q24h beginning on day −2 (if using upfront as GvHD prophylaxis)

        • BSA ≤1.5 m^2: 4–6 mg PO once, followed by 2 mg/m2 PO q24h beginning on day −2 (if using upfront as GvHD prophylaxis)

      ii. Monitoring

        • Check first trough level after 5 days.

          – Half-life is approximately 62 hours, so the first trough level is only about 50% of anticipated steady state level.

        • Check additional levels every 5–7 days unless changing organ function or drug interactions warrant more frequent monitoring

      iii. Goal trough levels

        • 4–12 ng/mL

      iv. Dose Adjustments

        • First level (5 days after initiation)

          – Calculate expected steady state level.

          – Apply drug interaction magnitude to expected steady state level if starting a new interacting medication.

          – Reduce sirolimus dose appropriately based on these considerations.

- Beyond first level

  - Adjust dose based on assumption of linear pharmacokinetics.
  - If checking blood concentrations weekly, the full effect of a previous dose adjustment may not be realized at the time of the next level given the long half-life of siro.

- Supratherapeutic levels (assuming goal of 4–12 ng/mL)

  - >15 ng/mL: Hold at least 1 dose (depending on level and drug interactions), then resume at reduced dose.
  - >12 to ≤15 ng/mL: Reduce dose.

c. Toxicities

  i. Hypertension
  ii. Electrolyte derangements
  iii. Nephrotoxicity (rare compared to CyA and Tac)
  iv. Edema
  v. Headache
  vi. Hypercholesterolemia/hypertriglyceridemia
  vii. Arthralgia
  viii. Infections
  ix. SOS (especially after busulfan-based myeloablative conditioning) [165]
  x. Interstitial pneumonitis

d. Drug Interactions [158]

  i. CYP3A4 inhibitors (see lists of selected examples above)

    - CYP3A4 inhibitors markedly increase sirolimus Cmin and AUC.
    - Empiric dose reductions are warranted.

      - 75–90% dose reduction with strong CYP3A4 inhibitors
      - 40–60% dose reduction with moderate CYP3A4 inhibitors

  ii. CYP3A4 inducers (see lists of selected examples above)

    - CYP3A4 inducers markedly reduce sirolimus Cmin and AUC.
    - Monitor sirolimus levels closely and adjust dose as needed.
    - Do not empirically increase sirolimus dose upon initiation of a CYP3A4 inducer (induction may take 1–2 weeks).

6. Mycophenolate mofetil (Cellcept®) and mycophenolic acid (Myfortic®)

a. Mechanism of Action
  i. Mycophenolate is hydrolyzed in the liver to mycophenolic acid (MPA) which then inhibits inosine monophosphate dehydrogenase (IMPDH), a rate-limiting enzyme in *de novo* guanosine synthesis, and prevents progression through the cell-cycle S phase. MPA shows selective potency toward activated B and T lymphocytes given their dependence on *de*

novo guanine synthesis and expression of the more sensitive IMPDH iso-
form II (versus isoform I in other cell types). Consequently, activated
T-cell proliferation, lymphocyte/monocyte adhesion, and primary anti-
body responses are halted [166].

b. Dosing (common schedules)

   i. Mycophenolate mofetil (MMF, Cellcept®)

- MUD/MMUD: 15 mg/kg (capped at 1 g per dose) PO or IV q8h begin-
  ning on day 0 or day +1 (until day +28), then q12h (until day +56) [69]
- MRD: 15 mg/kg (capped at 1 g per dose) PO or IV q12h beginning on
  day 0 or day +1 (until day +28) [167, 168]
- Haplo: 15 mg/kg (capped at 1 g per dose) PO or IV q8h beginning on
  day +5 (at least 24 hours after PTCy, until day +35)
- UCBT: 15 mg/kg (capped at 1 g per dose) PO or IV q8h beginning on
  day −3 (until day +35, day +60, or beyond depending on the protocol)
- Food decreases C_{max}, but does not decrease extent of absorption.
- IV to PO conversion is 1:1.

  ii. Mycophenolic acid (MPA, Myfortic®)

- Use 72% of MMF dose (same dosing frequency)

 iii. Monitoring

- Routine monitoring is uncommon and some data suggest pharmacoki-
  netic (PK) monitoring may optimize dosing [169] and reduce engraft-
  ment failure [170]
- No standard PK parameters have been defined or validated [171]

c. Toxicities [172]

   i. Gastrointestinal disturbance (including possible colitis)
  ii. Cytopenias (neutrophil and platelet recovery are faster than with
     MTX) [63]
 iii. Opportunistic infections
 iv. Progressive multifocal leukoencephalopathy (PML)
  v. Malignancies (rare occurrence of lymphomas and skin cancers)
 vi. Teratogenicity [173]

d. Drug Interactions

   i. Gastric acid suppressants

- Proton pump inhibitors (PPIs) impair MMF absorption, but do not
  affect MPA absorption. Use MPA in patients requiring a PPI [174].

  ii. Cyclosporine

- Increases MPA clearance by 33%. No empiric dose adjustments are
  warranted [171].

    iii. Cholestyramine (bile acid sequestrants)

- Reduces AUC by 40%. Separate administration appropriately.

    iv. Rifampin

- Decreases mycophenolic acid AUC via induction of glucuronidation [175].

7. Cyclophosphamide (Cytoxan®)

  a. Mechanism of Action

    i. Metabolized via CYP450 to 4-hydroxyclophosphamide which exists in equilibrium with aldophosphamide. This metabolite then decomposes to form phosphoramide mustard which cross-links DNA at guanine N-7 positions, preventing DNA synthesis and eliciting apoptosis [176]. After cyclophosphamide administration, early proliferating alloreactive T cells are killed and regulatory T-cell numbers increase [177, 178]. Hematopoietic stem cells resist toxicity via high expression of aldehyde dehydrogenase which converts aldophosphamide to inactive carboxy-phosphamide [179].

  b. Dosing

    i. 50 mg/kg (ideal body weight) IV over 2 hours on day +3 and day +4 [180]
    ii. Mesna 50 mg/kg (ideal body weight) IV over 24 hours on day +3 and day +4 (starting with first dose of PTCy)

  c. Toxicities

    i. Nausea/vomiting (highly emetogenic)
    ii. Alopecia
    iii. Mucositis
    iv. Nasopharyngeal discomfort during infusion (a.k.a. wasabi nose)

- Slow the infusion rate.
- Decongestants, antihistamines, analgesics, and/or intranasal ipratropium may be effective.

    v. Infertility
    vi. Myelosuppression
    vii. Hemorrhagic cystitis
    viii. Myocarditis
    ix. Secondary malignancies

  d. Drug Interactions

    i. Corticosteroids

- Avoid prior to PTCy, including with stem-cell infusion premedications and antiemetic premedications, to prevent theoretical antagonism [181].

    ii. CYP450 inhibitors/inducers

- Metabolized by various CYP450 enzymes, and clinical relevance of CYP450 interactions is unknown [182].
- Avoid if possible given the effects on prodrug metabolism to active metabolites [182].

8. Antithymocyte globulin, rabbit (Thymoglobulin®), and horse (ATGAM®)

  a. Mechanism of Action

    i. Anti-T-cell IgG polyclonal antibodies purified from the serum of rabbits exposed to the Jurkat cell line (Grafalon®, ATG-Fresenius) or human thymocytes (Thymoglobulin®), or from the serum of horses exposed to human thymocytes (ATGAM®). ATG causes T-cell depletion via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [183]. Given the presence of B- and NK cells in human thymocyte preparations, ATG also reduces these lineages. Lymphocyte adhesion and cell trafficking are impacted given the presence of antibodies against these molecules in ATG preparations. Most interestingly, ATG expands regulatory T cells by unclear mechanisms [184]. Equine ATG is no longer commonly employed for GvHD prophylaxis.

  b. Dosing (common schedules)

    i. Rabbit ATG (Thymoglobulin®)

- Aplastic anemia 3 mg/kg IV on days −4, −3, and −2 [185]
- Other indications: Usual dose is 2.5 mg/kg IV on days −3, −2, and −1 [186], but other dosing schemes have been investigated

  – 0.5 mg/kg IV on day −2, 2 mg/kg on day −1, 2 mg/kg on day +1 [84]
  – 2.5 mg/kg IV on days −2 and −1 [86] or 1.5 mg/kg on days −3, −2, and −1 [92]

    ii. Equine ATG (ATGAM®)

- Aplastic anemia

  – 30 mg/kg IV on days −4, −3, and −2 [185]
  – 5 mcg intradermal test dose with monitoring q15m for 1 hour is required prior to the first dose (wheal ≥3 mm suggests increased risk for systemic allergic reaction with IV dose)

- Not indicated for GvHD prophylaxis in other hematologic diseases

    iii. Rabbit ATG-Fresenius (Grafalon®, not available in the United States)

- MRD: 10 mg/kg IV on days −3, −2, and −1 [83]
- MUD: 20 mg/kg IV on days −3, −2, and −1 [85, 187]

  c. Toxicities

    i. Anaphylaxis
    ii. Pyrexia/chills
    iii. Rash
    iv. Hepatotoxicity (usually acute and transient transaminitis)
    v. Serum sickness
    vi. Opportunistic infections
    vii. CMV reactivation
    viii. EBV reactivation [84]

9. Alemtuzumab (Campath®)

  a. Mechanism of Action

    i. Humanized monoclonal antibody against CD52 which is expressed on lymphocytes (T > B), NK cells, monocytes, macrophages, eosinophils, and some dendritic cells [188]. Cytotoxicity is mediated by both CDC and ADCC. Compared to ATG, the tumor-reactive NK cell nadir is lower and longer with alemtuzumab [189], and CD4$^+$ and CD8$^+$ T-cell reconstitution is significantly delayed [103].

  b. Dosing

    i. Aplastic anemia:

     • 20 mg/day IV or subcutaneous for 3–5 days starting on day −7 (with FluCy) [104]

    ii. Other indications:

     • 20 mg/day IV or subcutaneous for 5 days starting on day −8 or −7 (usually with FluMel)

  c. Toxicities
    i. Infusion reaction
    ii. Delayed immune reconstitution
    iii. Opportunistic infections
    iv. CMV reactivation [190]
    v. EBV reactivation [99]

10. *Ursodiol (Actigall®)*

  a. Mechanism of Action

    i. Hydrophilic bile acid called ursodeoxycholic acid (UDCA) which increases the *in vivo* proportion of hydrophilic bile acids from 5% to 40–50%. Hydrophobic bile acids are toxic to hepatic parenchymal cells which may be exposed by bile duct damage during HCT. Ancillary effects include hepatocyte cell membrane stabilization and down-regulation of inflammatory cytokines [75, 76].

  b. Dosing

     i.   12 mg/kg/day PO in 2–3 divided doses starting on day 1 of conditioning [75]

     ii. Continue through day +21 for autoHCT recipients (day +60 for known liver disease or busulfan-containing conditioning).

     iii. Continue through day +90 for alloHCT recipients.

  c. Toxicities are minimal. Ursodiol is well-tolerated.

Transplant Complications Requiring Change in GvHD Prophylaxis

This section describes only how to manage GvHD prophylaxis during these complications. Additional management of these transplant-related issues (e.g. blood pressure control during PRES, eculizumab for TMA, etc.) is described elsewhere in this text.

1. Acute Kidney Injury (AKI)

  a. AKI occurs in 15 to 73% of alloHCT recipients secondary to myriad insults including sepsis, hypovolemia, nephrotoxic medications, CNIs, GvHD, pre-transplant diabetes, hepatic SOS, cystitis (viral or cyclophosphamide-related), tumor lysis syndrome, TMA, and others [191]. AKI after alloHCT increases mortality [192], and AKI risk is higher with MAC versus RIC regimens [193].

  b. Reduce the CNI trough goal as described above. If prolonged CNI interruption is anticipated or if the CNI is held during engraftment or post-engraftment, one can replace the CNI with corticosteroids (e.g. prednisone 0.5–1 mg/kg/day) [33] until renal function improves enough to permit re-challenge with a CNI or initiation of an alternative agent such as sirolimus [194]. There is scant literature or expert opinion regarding GvHD prophylaxis strategies in the setting of post-alloHCT AKI.

2. Posterior Reversible Encephalopathy Syndrome (PRES)

  a. PRES occurs in 1.6% of alloHCT recipients and typically presents with altered mental status, cognitive deficits, seizures, lethargy, hypertension, and characteristic MRI findings [195–197].

  b. Though limited case series suggest the original CNI may be continued, a typical approach is to hold the offending CNI [198], bridge with corticosteroid (e.g. prednisone 0.5–1 mg/kg/day) and/or mycophenolate, then switch to sirolimus [199, 200]. Switching to an alternative CNI is reasonable, but may cause PRES relapse in some patients [201].

3. Transplant-Associated Microangiopathy (TMA)

  a. TMA occurs in 5.9 to 15% of alloHCT recipients and typically presents with evidence of Coombs-negative hemolytic anemia (elevated serum LDH, unconjugated hyperbilirubinemia, low serum haptoglobin, blood schistocytes), thrombocytopenia, fever, AKI (with secondary hypertension), and/or encephalopathy [202, 203]. Supratherapeutic CNI levels are not correlated with TA-TMA incidence.

  b. The CNI may be temporarily held or dose-reduced to target the low end of the therapeutic range. CNI discontinuation (followed by switching to an alternative CNI or sirolimus) is common practice and is recommended if renal dysfunction or neurologic manifestations worsen; however, it may not alter TA-TMA resolution and mortality [204, 205].

  c. Eculizumab (Soliris®): Increasing use in patients with TA-TMA who do not respond to dose reduction or withdrawal of CNIs. See also Chap. 38 for a more detailed discussion.

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Chapter 12
Transfusion Medicine

Trisha Wong

Introduction

The unique immunologic status and transfusion needs of the hematopoietic cell transplant (HCT) recipient require collaboration between the clinical transplant team and transfusion services (TS). Successful interaction is essential to the optimal management of HCT recipients in order to reduce the risk of alloimmunization, infection transmission, and avoiding potential medical errors.

Pre-HCT Considerations

1. Recipients may receive any compatible blood products (see Table 12.1).
2. All products must be irradiated to prevent TA-GvHD during ongoing conditioning.
3. In patients with aplastic anemia and sickle cell disease, increased number of transfusions is associated with increased rates of graft rejection resulting in decreased overall survival [1–3].
4. Patients with sickle cell disease and thalassemia are at high risk of RBC alloimmunization. Therefore, all RBC transfusions pre-HCT should be further matched for at least RhE, RhC, and Kell to minimize risk of alloimmunization [4].
5. Use of blood components from family members who are potential donors should be discouraged. This approach will avoid immunologically sensitizing the recipient to the potential donor's minor histocompatibility antigens and human leukocyte antigen (HLA).

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Table 12.1 Acceptable ABO and Rh compatibility during pre-HCT period

Patient's Blood Type	O	A	B	AB
Compatible RBCs	O	A, O	B, O	AB, A, B, O
Compatible platelets[a] and plasma	O, A, B, AB	A, AB	B, AB	AB
Patient's RhD Type	RhD+		RhD−	
Compatible RBCs	RhD+, RhD−		RhD−	
Compatible Platelets	RhD+, RhD−		RhD−	
Compatible Plasma	RhD+, RhD−		RhD+, RhD−	

[a]Plasma-compatible platelets

Day 0 Considerations

1. As with transfusion of blood components, infusion of the HCT graft can trigger acute reactions.
2. Refer to local policy regarding routine pre-medications prior to HCT infusion.
3. Do NOT irradiate the HCT graft; however, all blood transfusion components received on day 0 must be irradiated or pathogen reduced to mitigate risk of TA-GvHD.
4. Monitor closely for adverse reactions to infusion:

   a. Volume overload: diurese as needed.
   b. Fat and bone emboli are less common with advent of in-line filters.
   c. Allergic reaction including anaphylaxis

      i. The patient may react against an allergen in the donor's plasma or from an additive used in cell processing (i.e., DMSO).

   d. Acute hemolytic transfusion reaction

      i. HCT recipients with major donor ABO incompatibility are at risk of acute RBC hemolysis as the recipient has naturally occurring ABO antibodies against the donor. To minimize risk of AHTR:

         • RBC-deplete the graft

            – Bone marrow (BM)-derived grafts contain a large quantity of RBCs and should be RBC depleted prior to infusion.

               Recommend HSC product have hematocrit ≤2%

            – Apheresis-derived grafts typically contain <20 ml of RBCs and do not usually need to be RBC-depleted unless recipient has a small blood volume, such as a pediatric patient.
            – Umbilical-derived grafts are usually RBC-depleted prior to storage so typically do not need any further manipulation.

         • Reduce alloantibodies in the recipient

            – The recipient can undergo therapeutic plasma exchange with either albumin or plasma compatible to the graft in order to decrease the titer of the incompatible ABO antibody.

Graded as second-line therapy (Category II) for ABO-incompatible transplant as per the American Society of Apheresis [5]

ii. HCT recipients with minor donor ABO incompatibility are at risk of acute hemolysis of recipient RBCs as the graft has naturally occurring ABO antibodies against the recipient.

- To minimize risk of AHTR, remove as much plasma as possible without compromising quantity and quality of stem cells
- Occurs rarely but is more common if (a) graft contains a large quantity of plasma, (b) is from a donor with high-titer ABO antibodies, or (c) if recipients have a small blood volume, such as pediatric patients
- May consider prophylactic-automated red cell exchange prior to transplantation but evidence conflicting [6, 7]

Immunohematology Basics

1. ABO blood group

    a. Widely expressed on red blood cells (RBCs) and endothelial cells and soluble in body fluids.
    b. Individuals should have naturally occurring antibodies by ~6 months of age against any A or B antigen that are not endogenously expressed. (see Table 12.2).

2. RhD antigen

    a. Expressed only on RBCs
    b. Individuals must be exposed to RhD via pregnancy, transfusion, or transplant prior to making anti-D antibody.

3. Additional "minor" blood group antigens

    a. Rarely cause fatal hemolytic transfusion reactions
    b. Examples include Rh (C, c, E, e), Kell (K, k), Duffy (Fy^a, Fy^b), and Kidd (Jk^a, Jk^b).
    c. Most require prior exposure to make an alloantibody, but some antibodies can be naturally occurring.
    d. The "antibody screen" test is designed to detect unexpected RBC alloantibodies against common clinically significant RBC antigens.

Table 12.2 ABO antigens, antibodies, and prevalence by ABO type [8]

Blood Type	O	A	B	AB
Antigens on RBCs	None	A	B	A and B
Antibodies in plasma	Anti-A and Anti-B	Anti-B	Anti-A	None
Approximate US population prevalence	45%	40%	11%	4%

   i. Further testing must be done to identify the antibody specificity when the screen is positive.

4. Autoantibodies

  a. Antibodies that one develops against antigens expressed on their own cells
  b. Production does not require prior transfusion or pregnancy.
  c. Direct antiglobulin test (DAT or direct Coombs test) is typically positive.

5. Definitions of incompatibility [9]

  a. Minor incompatibility: Donor-derived antibodies are incompatible with recipient-derived antigens. For example, blood group A recipient receiving a graft from a group O donor.
  b. Major incompatibility: Recipient-derived antibodies are incompatible with donor-derived antigens. For example, blood group O recipient receiving a graft from a group A donor.
  c. Bidirectional incompatibility: Both major and minor incompatibilities are present in the same transplant For example, blood group A recipient receiving a graft from a group B donor.

Transfusion Reactions [10, 11]

1. May occur after transfusion of any type of blood component (RBCs, platelets, plasma, cryoprecipitate, granulocytes, and stem cells) regardless of compatibility
2. Refer to institutional policy for local definitions and practices, but in general, STOP the transfusion, assess the patient, and report reaction to TS. Institute supportive care immediately as appropriate.
3. Common transfusion reactions include (in general order of most common to least):

  a. Mild/minor allergic reaction

   i. Results from an interaction between an allergen in the donor unit and a preformed antibody (usually IgE) or mediator (histamine) in the recipient leading to a localized reaction
   ii. Possible symptoms: pruritus, rash, urticaria, localized angioedema
   iii. If patient otherwise stable, transfusion can be restarted
   iv. Consider volume reduction or platelets stored in platelet additive solution (rather than plasma) in high-risk patients
   v. Premedication with diphenhydramine is common but not based on evidence [12]

b. Febrile non-hemolytic transfusion reaction

    i. Caused by cytokines in the blood product

    ii. Defined as a fever ≥38 °C and an increase of at least 1°C from pre-transfusion temperature or the presence of chills/rigors

    iii. Risk decreased with pre-storage leukoreduction

c. Alloimmunization

    i. An immune response to foreign RBC or platelet antigens after exposure to genetically different cells or tissues. Less common in HCT recipients in the presence of pharmaceutical immunosuppression; however, patients may have been previously allosensitized from prior RBC transfusions (when immunocompetent) or pregnancy.

    ii. Anticipate delayed delivery of compatible RBCs to bedside.

d. Delayed hemolytic transfusion reaction (DHTR)

    i. Positive DAT and new alloantibody develop between 24 hours and 28 days after cessation of transfusion.

    ii. Possible symptoms: often none or subclinical, jaundice, minimal increase in hemoglobin/hematocrit (H/H) after transfusion.

e. Severe allergic/anaphylaxis

    i. Interaction between an allergen in the donor unit (such as IgA) and a preformed antibody in the recipient (such as an anti-IgA) that causes a more systemic and severe reaction

    ii. Possible symptoms: stridor, wheezing, hypotension, cardiac arrhythmias, death

    iii. Prevent with washed products to remove allergen (such as IgA) from donor unit

f. Transfusion-associated cardiac overload (TACO)

    i. Acute respiratory distress within 6 hours of cessation of transfusion

    ii. Possible signs/symptoms: elevated brain natriuretic peptide (BNP) and/or central venous pressure, fluid overload; responds to diuretics

    iii. Second leading cause of transfusion-associated death in the United States [13]

g. Transfusion-related acute lung injury (TRALI) [14] (see Table 12.3)

    i. Acute lung injury within 6 hours of cessation of transfusion without other more plausible causes

    ii. Possible signs/symptoms: respiratory distress, hypoxemia, fever, hypotension, death

    iii. Leading cause of transfusion-associated death in the United States [13]

Table 12.3 Definition of transfusion-related acute lung injury (TRALI) (Division of Healthcare Quality Promotion. National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol, v2.5.2. CDC. April 2018. Available at https://www.cdc.gov/nhsn/PDFs/Biovigilance/BV-HV-protocol-current.pdf. Last accessed 2020.02.10)

Definite TRALI
Acute onset within 6 hours of blood transfusion
Hypoxemia as defined by $PaO_2/F_iO_2 \leq 300$ mm Hg, or oxygen saturation <90% on room air, or other clinical evidence
Bilateral infiltrative changes on chest radiograph
No evidence of left atrial hypertension
No other risk factor for acute lung injury
Possible TRALI
Same as for definite TRALI but there is evidence of other causes for acute lung injury
Doubtful TRALI
Evidence is clearly in favor of a cause other than transfusion, but transfusion cannot be excluded
Not Determined
The relationship between the adverse reaction and transfusion is unknown or not stated

   h. Transfusion-transmitted infections

       i. May be caused by bacteria, viruses, protozoa, and prions.

      ii. May be acute or chronic infections.

     iii. To decrease rates of transfusion-transmitted CMV (TT-CMV), transfusion services offers two options:

- CMV-safe: since CMV achieves latency in leukocytes, leukocyte reduction appears to prevent TT-CMV [15–17].
- CMV-seronegative: these units are collected from donors who are seronegative for past or current CMV infections and appear to be the most effective method to reduce TT-CMV [16, 17].

     iv. Providers must know for what infections their blood components are tested as each country has different regulations and each donor center has varying procedures within the regulations.

  i. Acute hemolytic transfusion reaction (AHTR)

       i. Acute hemolysis within 24 hours of cessation of transfusion.

      ii. Possible symptoms: fever, back/flank pain, renal failure, shock, death.

  j. Transfusion-associated graft versus host disease (TA-GvHD)

       i. Engraftment of transfusion-donor lymphocytes into recipient with subsequent organ failure from 2 days to 6 weeks after cessation of transfusion. Almost always universally fatal.

ii. Possible signs/symptoms: maculopapular rash, diarrhea, fever, liver failure, death

iii. Can be prevented by treating cellular blood products with gamma or x-ray irradiation or pathogen-reduction technology that crosslinks DNA

k. Transfusion-associated iron overload

i. The accumulation of excessive transfusion-derived iron in the cytoplasm of liver, myocardial, and endocrine cells, catalyzing free radicals and may eventually lead to organ failure.

ii. Each RBC unit contains 200–250 mg of elemental iron.

iii. Monitor liver and cardiac iron loading with T2* or R2* MRI and serial serum ferritin levels.

iv. Treated with serial phlebotomy or medications that chelate metals such as deferoxamine (Desferal®) or deferasirox (Exjade®; Jadenu®).

Post-HCT Considerations

1. RBCs

a. Routine RBC transfusion support

i. Know local guideline for transfusion triggers in HCT but decision to transfuse should be made on a case-by-case and day-by-day basis.

- Transfuse 1 RBC unit at a time until symptoms of anemia are relieved or patient is returned to a safe hemoglobin range (7–8 g/dL in stable, non-cardiac inpatients) [18].

ii. RBCs should be compatible to both donor and recipient ABO antibodies and donor's RhD status (see Table 12.4).

iii. All products must be irradiated or pathogen reduced to prevent TA-GvHD.

b. Complications prolonging RBC transfusion dependence

i. Pure red cell aplasia (PRCA) [19]

- Occurs in major ABO-incompatible HCTs because recipient's B lymphocyte pool generating naturally occurring ABO antibodies survive transplant and prevent sufficient formation and maturation of donor's incompatible RBCs.

- Findings include reticulocytopenia (1%) lasting more than 60 days post-HCT with absence of erythroid precursors in marrow but with engraftment of other cell lineages.

Table 12.4 Acceptable ABO and Rh compatibility during post-HCT period

	Blood Group		Blood Products		
	Recipient	Donor	RBCs	Platelets[a]	Plasma
Compatible	A	A	A, O	A, AB	A, AB
	B	B	B, O	B, AB	B, AB
	O	O	O	A, B, AB	A, B, AB
	AB	AB	AB, A, B, O	AB	AB
Major Incompatibility	O	A	O	A, AB	A, AB
	O	B	O	B, AB	B, AB
	O	AB	O	AB	AB
	A	AB	A,O	AB	AB
	B	AB	B, O	AB	AB
Minor Incompatibility	A	O	O	A, AB	A, AB
	B	O	O	B, AB	B, AB
	AB	O	O	AB	AB
	AB	A	A, O	AB	AB
	AB	B	B, O	AB	AB
Bi-directional	A	B	O	AB	AB
	B	A	O	AB	AB
RhD	Rh neg	Rh neg	Rh neg	Rh neg	N/A
	Rh neg	Rh pos	Rh pos or neg	Rh pos or neg	N/A
	Ph pos	Rh pos	Rh pos or neg	Rh pos or neg	N/A
	Rh pos	Rh neg	Rh neg	Rh neg	N/A

[a]Plasma-compatible platelets

- Risk increased with group A donors and non-myeloablative preparative regimens.
- Patients may be dependent on RBC transfusions for years, leading to transfusional iron overload (see section above).
- May be treated with rituximab (Rituxan®) 375 mg/m^2 IV weekly x 4 weeks.

ii. Passenger lymphocyte syndrome

- Seen in minor-incompatible BM and PBSC HCTs when functional, donor-derived B lymphocytes produce ABO antibodies incompatible with recipient RBCs.
- Hemolysis typically begins within 7–10 days after transplantation; should be considered in the differential as an etiology for early post-transplant hyperbilirubinemia.
- May cause compatible donor RBCs to lyse ("hyperhemolysis").
- Not described following HCT derived from umbilical cord blood presumably as infant B lymphocytes have not yet been sensitized to ABO.

    iii. Transplantation-associated thrombotic microangiopathy (TA-TMA) (for additional details, see Chap. 38)

- Characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage, including renal impairment
- Definitive management is discontinuation of implicated drugs (calcineurin inhibitors, sirolimus (Rapamune®).
  - Weak or conflicting evidence for therapeutic plasma exchange, rituximab (Rituxan®), ACE inhibitors, and eculizumab (Soliris®)
- Supportive care with RBC and platelet transfusions

2. Platelets

    a. Platelets express HLA and HPA (human platelet antigens). Soluble ABO antigens can be adherent to platelet surfaces.

    b. Note: RBCs that express Rh antigens can contaminate the plasma in which platelets are suspended.

    c. At a minimum, platelet units should be compatible with HCT donor (see Table 12.4).

      i. If compatible platelets cannot be identified in time, consider:

- Platelets from donors with low anti-A and anti-B titers
- Platelets suspended in Platelet Additive Solution, rather than all plasma
- ABO-incompatible platelets suspended in all plasma are acceptable but have a shorter circulating half-life.

      ii. If RhD-negative unit cannot be found in a timely fashion, give RhD-positive unit.

- Alloimmunization to RhD has followed after as little as 0.03 ml of RhD-positive RBCs.
- Due to severe immunosuppression, HCT patients are at low risk of developing RhD antibodies [20, 21].
- Consider giving Rh immunoglobulin (RhoGAM®) to RhD-negative patients who must receive RhD-positive platelets and who are thought to be at high risk (such as females of childbearing potential).

    d. Platelet refractoriness

      i. Defined as an inappropriately low platelet count increment following repeated platelet transfusions

      ii. Causes include platelet consumption (large thrombosis, Kasabach–Merritt syndrome), loss (ongoing hemorrhage), destruction (disseminated

intravascular coagulopathy, medications), sequestration (hypersplenism, sinusoidal-obstruction syndrome/veno-occlusive disease), or immune-mediated

iii. Consider immune-mediated causes if 1 hour post-transfusion corrected count increment (CCI) < 5000 following on two consecutive days:

$$CCI = \frac{\text{body surface area}\left(\text{m}^2\right) \times \left(\text{postcount} - \text{precount}\left(\frac{PLT}{\mu L}\right)\right) \times 10^{11}}{\text{Number of platelets transfused}\left(\text{assume } 3.0 \times 10^{11}\right)}$$

- However, an increment of >15 K/μL generally rules out immune-mediate platelet refractoriness.

iv. Two possible immune mechanisms:

- HLA alloimmunization

  - More common.
  - HLA alloantibodies can form following exposure to HLA antigens through pregnancy, transfusion of platelets, or transfusion of other blood components contaminated by WBCs.
  - Leukoreduction of blood products decreases alloimmunization to HLA antigens.
  - Diagnosed by testing whether the patient has HLA antibodies present, the strength (avidity) of the antibody, and how prevalent the cognate HLA allele is in the population.

    A Panel Reactive Antibodies (PRA) or calculated PRA (cPRA) analysis estimates the % of donors to which the patient is expected to be refractory.

  - If PRA or cPRA is above a pre-set cutoff, patient should receive platelets from donors who match the recipient, lack the cognate alleles to which the patient has HLA antibodies, and/or is crossmatch-compatible on platelet crossmatching.

    Local transfusion policy will determine the PRA or cPRA cutoff. Matched platelets take longer to procure than random-donor platelets; therefore, extra communication needed between clinical team and TS to maintain adequate in-house inventory to meet the need of the patient.

    1. Consider a slow continuous infusion of random-donor platelets if no matched platelets available and patient needs emergent platelets

- HPA alloimmunization

  - Rare.
  - HPA antibodies can form following exposure to HPA antigens from others through pregnancy or transfusion of platelets.
  - Diagnosed by assessing the patient for HPA antibodies.
  - If HPA antibodies are found, the patient should receive platelets from donors who match the recipient, lack the cognate allele to which the patient has HPA antibodies, and/or is crossmatch-compatible on platelet crossmatching.

    Matched platelets take longer to procure than random-donor platelets; therefore, extra communication needed between clinical team and TS to maintain adequate in-house inventory to meet the need of the patient.

Post-Engraftment Considerations

1. Once the recipient is stably engrafted:

   a. RBCs should be completely of the donor's blood type

      i. For example, if a blood group A recipient received a graft from group O donor, blood type should appear as group O RBCs once fully engrafted.

   b. However, because the recipient's original ABO antigens are still expressed on endothelial cells, plasma analysis should demonstrate a combination of donor and recipient ABO antibodies.

      i. For example, if a blood group A recipient (still expresses group A antigens on endothelial cells) received a graft from a group O donor, the donor's anti-A should slowly disappear due to continual exposure to recipient's A antigen on endothelial cells, and therefore, patient should eventually only show anti-B in the serum.

2. There are no data available to verify lifetime need for irradiated blood products; however, most centers recommend that all cellular blood products be irradiated until the recipient is stably engrafted, transfusion-independent and off all immunosuppressive medications.

   a. There are no reliable tests to measure complete immunologic reconstitution and therefore not reliable measure of decreased risk for TA-GvHD.

3. Patients may remain transfusion dependent on RBCs and/or platelets long after engraftment

   a. If the patient received >50–100 RBC units, monitor for iron overload (see Transfusion-associated iron overload above)

4. All allogeneic HCT recipients, regardless of whether they are transfusion dependent or not, must have a summary of their transplant and transfusion history including:

   a. Their original ABO/Rh
   b. ABO/Rh of their donor
   c. Suggested ABO/RhD blood products to administer if future transfusions needed. This summary is a priority if patient receives care at another facility.

   This summary should be given to the patient's local provider and TS to be on file in case of emergency transfusion needs.

5. Following stable engraftment of ABO-incompatible HCTs, the decision to change a recipient's historical blood type to that of the donor is typically made in conjunction with the transplant clinical team and the TS laboratory team.

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Chapter 13
Anticoagulation and Antiplatelet Guidelines

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Introduction

Patients undergoing hematopoietic cell transplant (HCT) are at risk for both arterial and venous thrombosis, similar to patients with solid organ malignancies, as well as for increased bleeding. Use of anticoagulant and antiplatelet agents in this population can be challenging given unique risk factors for both thrombosis and bleeding including frequent, significant disease- or treatment-related thrombocytopenia, systemic inflammation related to infection, graft-versus-host disease (GvHD) and malignancy itself, and multiple drug–drug interactions. Proper care of these patients requires understanding appropriate indications and contraindications for anticoagulant and antiplatelet therapy, as well as selection of the safest, most effective agent(s).

Providers directing HCT for patients with hematologic malignancies are often faced with one of two scenarios: how to manage anticoagulant and/or antiplatelet therapy for patients already on these drugs, and how to manage patients who develop new indications for these drug classes during the HCT process. Indications for anticoagulation typically fall under three main categories: (1) venous thromboembolic disease (VTE), (2) atrial fibrillation (AF), and (3) mechanical cardiac valves. Indications for antiplatelet therapy typically include (1) primary prevention for cardiovascular events (myocardial infarction and ischemic stroke), (2) secondary prevention of future cardiovascular events, and (3) primary prevention of thromboembolic stroke with prosthetic cardiac valves.

Though data and guidelines for the appropriate management of anticoagulant and antiplatelet therapy in patients specifically with hematologic malignancies undergoing HCT are limited, herein critical concepts are highlighted and available data summarized to guide clinicians performing HCT. A summary of recommendations is found in Table 13.1.

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Table 13.1 Summary of recommendations

VTE	
Prophylaxis	Mechanical thromboprophylaxis, encourage, ambulation, prophylactic-dose LMWH unless platelets $<25 \times 10^9$/L
Treatment	If platelets $\geq 50 \times 10^9$/L: Therapeutic-dose LMWH (preferred), DOACs on case-by-case basis. If platelets $<50 \times 10^9$/L, can either transfuse platelets to 50 or reduce anticoagulation to prophylactic dosing; no data to say one strategy is superior. If unable to maintain platelets $>25 \times 10^9$/L, consider holding anticoagulation if >30 days since VTE. Consider careful prophylactic dose LMWH if within first 30 days of VTE. Treat for 3 months (provoked). If malignancy-associated, treat for 3 months AND continued until hematologic remission, whichever is longer.
Catheter-associated thrombosis	Guidelines recommend treating with therapeutic anticoagulation for at least 3 months, or as long as catheter remains in place, whichever is longer. LMWH preferred. Catheter may be kept if still functioning and needed for treatment. If severely thrombocytopenic or otherwise high bleeding risk; some data to suggest removal of catheter alone, *without* anticoagulation, may adequate. Decide on case-by-case basis.
Isolated distal (calf) thrombosis	Treat same as proximal VTE.
Incidental, subsegmental PE	Treat same as proximal VTE.
Atrial fibrillation	
Treatment	CHA_2DS_2-VASc ≥ 2: anticoagulation with therapeutic-dose DOAC or LMWH Peri-transplant period: for most patients, can hold anticoagulation in immediate peri-transplant period as daily stroke risk remains low. If very high CHA_2DS_2-VASc (≥ 7), recommend switching DOAC to LMWH, and holding all anticoagulation if platelets $<50 \times 10^9$/L.
Prosthetic heart valves	
Mechanical	For most patients, replace warfarin with LMWH, reduce to prophylactic dose if platelets $<50 \times 10^9$/L, and stop all anticoagulation if platelets $<25 \times 10^9$/L. Daily stroke risk is low off anticoagulation. For high-risk patients (multiple valves, mitral position, ball-in-cage, prior stroke, AF, or heart failure): consult with cardiology, may warrant careful continuation of warfarin in peri-transplant period. Stop ASA if platelets $<30 \times 10^9$/L.
Bioprosthetic	Delay transplant until >90 days after valve replacement, when warfarin can be discontinued. If unable to delay, replace warfarin with LMWH in peri-transplant period. Stop ASA if platelets $<30 \times 10^9$/L.
Coronary artery disease	
Primary prevention	Hold all antiplatelet therapy

Table 13.1 (continued)

Secondary prevention	If possible, delay HCT until ≥6 months after coronary stent placement, when many patients will be able to transition from DAPT to single-antiplatelet therapy. If unable to delay HCT, consult with cardiology. Continue DAPT as long as platelets ≥50 × 10^9/L. If platelets <50 × 10^9/L, may reduce to single-antiplatelet therapy, or continue DAPT depending on risk. If platelets <30 × 10^9/L, strongly consider stopping all antiplatelet agents.
Acute coronary syndrome	DAPT as long as platelets ≥50 × 10^9/L. If platelets < 50 × 10^9/L, may reduce to single-antiplatelet therapy, or continue DAPT depending on risk. If platelets <30 × 10^9/L, strongly consider stopping all antiplatelet agents.

LMWH low molecular weight heparin, *DOACs* direct oral anticoagulants, *VTE* venous thrombo-embolism, *AF* atrial fibrillation, *ASA* aspirin, *HSC* hematopoietic cell transplantation, *DAPT* dual antiplatelet therapy

Types of Antiplatelet Therapy

1. Aspirin (ASA)

    a. Mechanism: Irreversibly acetylates and inhibits cyclooxygenase-1 (COX-1) enzyme in platelets, preventing synthesis of prostaglandins including the pro-thrombotic molecule thromboxane A_2. Reduced thromboxane A_2 prevents platelet activation and aggregation. At higher doses, ASA also blocks COX-2, conferring additional anti-inflammatory and analgesic effects.
    b. Half-life: 15–20 minutes.
    c. Duration of action: ~5 days.

2. P2Y$_{12}$ receptor antagonists

    a. Clopidogrel (Plavix®)

        i. Mechanism: parent drug inactive; requires *in vivo* conversion to active metabolite via cytochrome P450 enzymes (primarily CYP2C19). Irreversibly blocks P2Y$_{12}$ receptor on platelets, preventing ADP-mediated platelet activation and aggregation
        ii. Half-life: parent drug 6 hours, active metabolite 30 minutes
        iii. Duration of action: ~5 days

    b. Ticagrelor (Brilinta®)

        i. Mechanism: parent drug and active metabolite (formed via CYP3A4/5) equally active. Non-competitively and reversibly binds P2Y$_{12}$ receptor, preventing ADP-mediated platelet activation and aggregation.
        ii. Half-life: parent drug 7 hours, active metabolite 9 hours.
        iii. Duration of action: 1–2 days.
        iv. Due to reversible binding to P2Y$_{12}$ receptor, free drug may bind to and inhibit transfused platelets.

  c. Prasugrel (Effient®)

     i. Mechanism: parent drug inactive; requires *in vivo* conversion to active metabolite via cytochrome P450 enzymes (primarily CYP3A4). Irreversibly blocks $P2Y_{12}$ receptor on platelets, preventing ADP-mediated platelet activation and aggregation.
     ii. Half-life: active metabolites ~7 hours.
     iii. Duration of action: ~5 days.

Types of Anticoagulants and Important Drug Interactions

1. Heparins

  a. Mechanism: binds and facilitates ability of antithrombin to inactivate coagulation factors Xa and/or thrombin (see below for specific mechanisms).
  b. Unfractionated heparin (UFH)

     i. Thrombin and factor Xa inhibition via enhanced antithrombin activity, as well as inhibition of factors IX, XI, XII, plasmin, and inhibition of fibrinogen conversion to fibrin.
     ii. Intravenous (IV) or subcutaneous (SQ) routes of administration.
     iii. Useful due to immediate onset, short half-life, rapid adjustability, safety in renal failure
     iv. Can cause heparin-induced thrombocytopenia (HIT), leading to thrombocytopenia and thrombosis, increased time outside of therapeutic range (below and above) due to variable effects and need for titration over hours.

  c. Low molecular weight heparin (LMWH)

     i. Factor Xa inhibitor via enhanced antithrombin activity.
     ii. SQ route of administration.
     iii. Data in VTE suggest superior safety and efficacy compared with UFH, likely due to more consistent pharmacokinetics and thus exposure to therapeutic drug levels [1].
     iv. Multiple trials showing improved efficacy at prevention of VTE recurrence compared with warfarin in cancer patients [2].
     v. Substantially lower risk for HIT compared with UFH with much more rapid onset.
     vi. Disadvantages include need for renal clearance. LMWH dose should be reduced with progressive renal dysfunction, and avoided if CrCl < 30.

  d. Fondaparinux (Arixtra®)

     i. Pentasaccharide that inhibits factor Xa via enhanced antithrombin activity.
     ii. Essentially no risk for HIT, rapid onset of action.

      iii. Disadvantages include renal clearance and prolonged half-life of elimination (~20 hours). Fondaparinux dose should be reduced with progressive renal dysfunction, and avoided if CrCl < 30.

2. Vitamin K antagonist (VKA)

   a. Warfarin (Coumadin®)

      i. Mechanism: inhibits vitamin K epoxide reductase enzyme within hepatocytes, preventing recycling of vitamin K and consequently impaired gamma carboxylation of vitamin K-dependent coagulation factors II, VII, IX, and X.

      ii. Largely replaced by direct oral anticoagulants for most indications, though still the preferred anticoagulant in certain scenarios (mechanical cardiac valves, "triple-positive" antiphospholipid antibody syndrome,[1] [APS]) [3, 4].

      iii. Disadvantages include many drug–drug interactions, drug-exposure highly diet-dependent, prolonged half-life.

3. Direct oral anticoagulants (DOACs)

   a. Thrombin inhibitor

      i. Dabigatran (Pradaxa®)

   b. Factor Xa inhibitors

      i. Apixaban (Eliquis®)
      ii. Rivaroxaban (Xarelto®)
      iii. Edoxaban (Savaysa®)
      iv. Betrixaban (Bevyxxa®) (only approved for primary prophylaxis).

   c. Advantages

      i. Oral, fixed dosing
      ii. No routine monitoring required
      iii. Limited drug–drug interactions
      iv. Compared to VKA in the non-cancer population: equivalent efficacy for VTE recurrence, superior efficacy for embolic stroke prevention in non-valvular atrial fibrillation, less bleeding risk including intracranial hemorrhage [5, 6]. Note: *At the time of publication, Betrixaban is approved only for VTE prophylaxis in hospitalized patients, not for stroke prophylaxis in AF or VTE treatment*.
      v. Accumulating evidence for efficacy and safety for treatment of acute VTE and non-valvular AF in patients with cancer [7–11].

   d. Disadvantages

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[1] (Positive for lupus anticoagulant; anticardiolipin IgG or IgM antibodies >40 GPL or MPL or >99th percentile; and anti-beta-2-glycoprotein IgG or IgM antibodies >99th percentile).

    i. Despite increasing evidence and use in patients with malignancies, those with *hematologic* malignancies were significantly underrepresented or excluded from major trials [2, 7, 8, 12].

    ii. Limited evidence in morbidly obese, altered gastrointestinal anatomy (including post-bariatric surgery and post-Whipple procedure), end-stage renal disease (ESRD), and liver disease.

    iii. Enteral absorption required (challenging with nausea/vomiting, GvHD, or impaired absorption).

    iv. Contraindicated in pregnancy and breast-feeding [13].

    v. Contraindicated for stroke prophylaxis for mechanical cardiac valves [3].

    vi. Evidence for inferior efficacy in high-risk "triple positive" APS [4].

    vii. FDA-approved reversal agents exist for both thrombin (idarucizumab [Praxbind®]) and Xa (Andexanet Alfa [Andexxa®]) inhibitors, though these may not be widely available [14, 15].

4. Important drug interactions

    a. Heparins: no relevant drug interactions

    b. Warfarin: many drug interactions through cytochrome P450 enzymes (mostly CYP2C9); avoid use in peri-transplant period if possible

    c. DOACs: [16] given many unique drug–drug interactions but no reliable method for determining DOAC drug levels, recommend consulting with pharmacy before use

        i. P-glycoprotein (P-gp) interactions (critical for all DOACs)

- P-gp inhibitors increase dabigatran exposure: antimicrobials (azoles, clarithromycin [Biaxin®]), immune suppressants (cyclosporine, tacrolimus), hormonal therapy (enzalutamide [Xtandi®], abiraterone [Zytiga®], tamoxifen [Soltamox®], tyrosine kinase inhibitors (TKI; ibrutinib [Imbruvica®], imatinib [Gleevec®], idelalisib [Zydelig®], sunitinib [Sutent®], BRAF inhibitors (vemurafenib [Zelboraf®], venetoclax [Venclexta®].

- P-gp inducers reduce dabigatran exposure: Rifampin [Rimactane®], carbamazepine [Tegretol®], phenytoin [Dilantin®], chemotherapy (doxorubicin [Adriamycin®], vinblastine [Velban®], etoposide [Vepesid®]).

        ii. Cytochrome P450 interactions (critical only for Xa inhibitors)

- CYP3A4 inhibitors decrease Xa-inhibitor metabolism, increasing exposure: antimicrobials (azoles, clarithromycin, protease inhibitors for HIV), immune suppressants (cyclosporine, tacrolimus, sirolimus, chemotherapeutics (anthracyclines, vinca alkaloids, alkylating agents), TKIs (dasatinib [Sprycel®] imatinib, idelalisib), hormonal therapy (abiraterone, tamoxifen, bicalutamide [Casodex®]).

- CYP3A4 inducers increase Xa-inhibitor metabolism, decreasing exposure: antimicrobials (rifampin), anticonvulsants (carbamazepine, phenytoin), chemotherapeutics (paclitaxel [Taxol®]), hormonal therapy (enzalutamide).

Venous Thromboembolism (VTE)

1. VTE prophylaxis

   a. Hematologic malignancies can carry a high risk of VTE similar to solid tumors.

   b. Despite periods of thrombocytopenia, the incidence of VTE in patients undergoing HCT is as high as 5% without any form of thromboprophylaxis. The incidence appears higher in allogeneic transplants due in part to acute GvHD [17].

   c. Optimal thromboprophylaxis in HCT should consist of the following:

      i. Frequent ambulation should be encouraged for all HCT patients during hospitalization.

      ii. Mechanical thromboprophylaxis should be encouraged; anecdotal evidence suggests a possible increase ecchymoses in setting of thrombocytopenia, however the authors favor using mechanical methods. Data best support intermittent pneumatic compression (IPC) devices [18].

      iii. Pharmacologic thromboprophylaxis has not been prospectively examined in HCT patients, though retrospective data suggest prophylactic-dose LMWH may be safe in certain patients with platelets as low as 25×10^9/L [19–21].

2. Choice of anticoagulant for VTE

   a. LMWH remains the preferred anticoagulant for treatment of VTE in the acute peri-transplant period given the relative abundance of data, minimal drug–drug interactions, quick onset and clearance, and SQ route of administration.

   b. The use of DOACs during or after HCT for patients requiring long-term anticoagulation can be determined on a case-by-case basis, keeping in mind drug–drug interactions, impaired absorption, and other organ dysfunction (renal, hepatic). There is accumulating evidence for efficacy and safety of DOACs for treatment of acute VTE in patients with cancer, though hematologic malignancies were heavily underrepresented or excluded from trials, and increased rates of GI and GU bleeding were seen in patients with underlying predispositions [7–9]. Nevertheless, major cancer-specific guidelines now list DOACs as acceptable in patients with low bleeding risk and no drug interactions with systemic cancer-directed therapy [22]. Note: *At the time of publication, none of the DOACs are currently FDA-approved for use in patients with cancer, and patients with thrombocytopenia have been routinely excluded from trials of DOACs.*

   c. Catheter-directed thrombolysis (CDT) for DVT should be avoided in the majority of cases, extrapolating from non-cancer patients with lower-extremity DVT; a large randomized controlled trial did not show benefit of CDT over anticoagulation alone for prevention of post-thrombotic syndrome, recurrent DVT, or death, but did show higher bleeding rates [23].

d. Systemic thrombolysis for pulmonary embolism (PE) should only be considered for patients with massive PEs with hemodynamic instability (systolic BP <90 mmHg) [24]. Even in these scenarios, one must consider the high risk of major bleeding with thrombolysis which will likely be amplified in the setting of thrombocytopenia.

e. Inferior vena cava (IVC) filters for acute VTE should only be considered after careful, multidisciplinary discussion on a case-by-case basis and should be reserved for patients in whom there is an absolute contraindication to anticoagulation (thrombocytopenia alone does not constitute an absolute contraindication unless severe, persistent, and unresponsive to platelet transfusions). Two randomized trials in a general population failed to demonstrate a benefit of IVC filters added to anticoagulation, but demonstrated increased rates of progressive/recurrent DVT [25]. Retrospective data in cancer patients have not shown any benefit of filters [26].

3. Duration of anticoagulant therapy

   a. Determined by both the circumstances of the thrombosis and its location [27].
   b. Provoked VTE (due to reversible causes such as surgery, trauma, immobility, estrogen, etc.) requires only 3 months of anticoagulation.
   c. Unprovoked VTE generally requires indefinite (lifelong) anticoagulation.
   d. Cancer-associated VTE: Duration of anticoagulation is not supported by robust evidence, though anticoagulation is generally recommended for 3–6 months minimum, and continued as long as the patient's cancer remains "active" (currently receiving treatment or otherwise not in remission) [22, 27, 28].

4. Special VTE scenarios

   a. Catheter-associated thrombosis (CAT)

      i. The incidence of total CAT (screened or symptomatic) can be as high as 60% with peripherally inserted central catheters (PICCs). Symptomatic CAT occurs in ~3–7%. The highest incidence for CAT occurs after a dwell time of ~14 days [29, 30].
      ii. The incidence of PE with upper extremity thrombosis is less than lower extremity, though anticoagulation is still recommended based on extrapolation from data on treatment of lower extremity DVT as well as a desire to prevent post-thrombotic syndrome. Patients with a history of line-associated thrombosis are also at increased risk of VTE at other sites.
      iii. Prophylaxis: Major guidelines recommend against thromboprophylaxis specifically for prevention of CAT [31, 32]. A large meta-analysis showed a marginal benefit of LMWH prophylaxis for reducing CAT in cancer patients, but did not show mortality benefit and was unable to exclude potentially increased bleeding risk [33].
      iv. Treatment: Major guidelines recommend therapeutic anticoagulation as long as the catheter remains in place (may be kept if still needed and functioning), and continued for 3 months after catheter removal, based

largely upon data from lower extremity DVT [34]. Ongoing trials are examining alternative treatment strategies.

    v. Some data suggest that removal of catheter alone (without anticoagulation) may be adequate therapy for CAT [35]. Robust evidence supporting this strategy is lacking, but this may be considered for those at high risk of bleeding (severely thrombocytopenic, recent surgery, coagulopathy).

   vi. Given the low risk of long-term sequela, thrombolytic therapy should only be considered in limited scenarios with massive thrombosis (e.g. superior vena cava syndrome).

b. Isolated distal leg vein thrombosis (tibial, peroneal, gastrocnemius, soleus):

    i. Major guidelines suggest that some patients without cancer and with isolated distal thrombosis can be observed without anticoagulation [27].

   ii. However, a newer meta-analysis suggests significant benefit of anticoagulation and supports treating distal vein thrombosis the same as proximal vein (popliteal and above) VTE [36].

  iii. In addition, these authors suggest that cancer of any type conveys additional thrombogenic risk and warrants treatment similar to proximal veins.

c. Incidental subsegmental PE (SSPE):

    i. Up to 50% of PEs in patients with cancer are incidentally discovered.

   ii. Major guidelines for patients without cancer suggest that some patients with incidental SSPE without DVT can be observed without anticoagulation [27].

  iii. Major cancer-specific guidelines suggest treating anyone with SSPE as long as bleeding risk is low and any of the following are present: multiple SSPEs, concurrent DVT, or symptoms [28].

   iv. These authors favor treating all patients with cancer-associated SSPE of any type in light of data suggesting equivalent rates of VTE progression/recurrence regardless of symptoms [37].

d. High risk, acquired thrombophilias.

    i. Patients with high-risk thrombophilias such as "triple positive" APS have exceedingly high risk for recurrent thrombosis, even on anticoagulation.

- Data suggest warfarin is superior to DOACs for secondary thrombotic prophylaxis in triple-positive patients [4].
- Data for LMWH in this population are limited, though this agent is still often used in refractory cases with recurrent thrombosis [38].
- These authors recommend LMWH during the peri-transplant period for patients with pre-existing or newly diagnosed APS with thrombosis, regardless of the antibody profile.

5. Anticoagulation in the setting of thrombocytopenia

a. Robust data are lacking on the safety of anticoagulation in patients with hematologic malignancies and thrombocytopenia.

b. A platelet count <50 × 10⁹/L is generally considered the threshold below which therapeutic anticoagulation confers a prohibitively high bleeding risk, though this number is solely the result of expert opinion and has not been studied in prospective trials [39].

c. Current major guidelines suggest several strategies for managing anticoagulation for VTE in the setting of cancer and thrombocytopenia depending upon the individual patient's risk of progressive/recurrent thrombosis and hemorrhage. Options include: [39, 40].

   i. Full-dose, therapeutic anticoagulation with transfusion to maintain platelets >40–50 × 10⁹/L

   ii. Prophylactic- (reduced) dose anticoagulation while platelets are <50 × 10⁹/L but >25 × 10⁹/L, and temporary discontinuation of all anticoagulation while platelets <25 × 10⁹/L

d. Randomized trials are lacking to compare these two strategies, but a systematic review found no evidence of superiority with one strategy over the other [40].

e. Given the high risk of recurrent thrombosis in the first 30 days after acute VTE, it is generally recommended that full-dose anticoagulation be attempted at least during this period.

f. For those in whom it is difficult to maintain a platelet count at the targets listed above, those patients with more remote VTE (index event >30 days prior) or with lower-risk VTE (distal extremity, incidental subsegmental PE), reduced dose anticoagulation without transfusion support is reasonable during periods of thrombocytopenia.

Key Points
- LMWH remains the preferred anticoagulant for patients undergoing treatment for hematologic malignancy and pre-existing or newly diagnosed VTE; DOACs can be considered on a case-by-case basis in stable patients without thrombocytopenia, medication interactions, or high risk of bleeding following appropriate risk benefit counseling.
- Duration of anticoagulation for VTE in the setting of cancer should be at least 3–6 months, continued longer if cancer remains "active."
- No definitively superior strategy exists for balancing thrombosis and bleeding risks when using anticoagulation in the setting of thrombocytopenia from cancer therapy; can give full dose anticoagulation with transfusion support, or give reduced dose anticoagulation alone.

Atrial Fibrillation/Flutter

1. Stroke and bleeding – Risk stratification

   a. Cancer patients have an increased risk of developing atrial arrhythmias compared to individuals without cancer [41].

Table 13.2 CHA$_2$DS$_2$-VASc Scoring and Annual Stroke Risk

	Condition	Points
C	Congestive heart failure (or left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently >140/90 mmHg (or treated hypertension on medication)	1
A$_2$	Age ≥75 years	2
D	Diabetes mellitus	1
S$_2$	Prior stroke, TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

CHA$_2$DS$_2$-VASc Score	Stroke Risk %
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	12.5
9	15.2

    b. All patients with non-valvular atrial fibrillation/flutter (NVAF) should be risk-stratified to determine their risk for cardioembolic cerebrovascular accident (CVA) and need for anticoagulation.

        i. The most widely used prediction rule is the CHA$_2$DS$_2$-VASc, which predicts cardioembolic embolic stroke risk based on the presence or absence of particular risk factors [42] (Table 13.2).

        ii. Cancer is not included as a risk factor in the CHA$_2$DS$_2$-VASc score, and therefore the added impact of cancer on cardioembolic stroke risk is difficult to predict with this score.

        iii. The relative risk of cardioembolic stroke risk in patients with NVAF and cancer vs. no cancer is not well described. Therefore, currently available data suggest that patients with NVAF and cancer vs. no cancer should undergo similar risk stratification [41].

          • Patient with a CHA$_2$DS$_2$-VASc score ≥2 should receive therapeutic anticoagulation [42].

          • Patients with a CHA$_2$DS$_2$-VASc = 0 should not receive anticoagulation specifically for AF.

          • Therapeutic anticoagulation can be considered for CHA$_2$DS$_2$-VASc = 1, though guidelines differ on this recommendation [42, 43].

    c. Several bleeding risk scores have been developed specifically for patients with NVAF contemplating, or currently receiving, anticoagulation.

    i. The Hypertension, Abnormal liver or renal function, Stroke [history of], Bleeding [prior or major risk for], Labile INR [within therapeutic range <60% of time], Elderly [>65 years], Drugs [predisposing to bleeding] (HAS-BLED) score is the most well-validated and widely supported in non-cancer patients with NVAF, though this tool has not been validated specifically in cancer patients [42].

   ii. Bleeding risk with anticoagulation in cancer patients with NVAF can be more difficult to predict due to other risk factors not captured by traditional risk scores.

  iii. Importantly, high bleeding risk scores should not justify withholding long-term anticoagulation if there is a concurrent, high CHA_2DS_2-VASc score ($\geq$2), but can be used to identify modifiable bleeding risk factors, inform risk–benefit discussions regarding temporary interruption, and justify more frequent clinical or laboratory monitoring [42, 43].

2. Anticoagulant choice

  a. LMWH has historically been used only as bridging therapy peri-operatively and when initiating warfarin; data for long-term cardioembolic stroke prophylaxis in NVAF are limited, even in non-cancer patients. Major guidelines make no mention of LMWH for long-term stroke prophylaxis. However, given the benefits of LMWH in the setting of cancer, limited drug–drug interactions, and other benefits mentioned in section "Types of Anticoagulants & Important Drug Interactions" (1), LMWH may be a reasonable choice for short-term stroke prophylaxis in HCST patients with AF and very high stroke risk.

  b. DOACs have become the preferred anticoagulant class for patients with NVAF without cancer and are endorsed by major guidelines [43]. Data for DOACs in cancer patients with NVAF are accumulating [10, 11]; the largest published study showed comparable rates of cardioembolic stroke prevention and reduced bleeding with DOACs compared to warfarin [10].

  c. Warfarin has historically been the anticoagulant of choice for patients with NVAF and cancer due to a larger body of evidence, though this therapy is also problematic during HCT for many reasons (see section "Types of Anticoagulants & Important Drug Interactions" 2) and should therefore be avoided.

  d. Aspirin and $P2Y_{12}$ antagonists, alone or combination, should not be used for stroke prevention in NVAF [42, 43]. Commonly cited data for efficacy of ASA are based on a single trial [27], and multiple recent trials have demonstrated that ASA has comparable bleeding rates but inferior efficacy at stroke prevention compared with DOACs [44].

3. Anticoagulation recommendations in HCT

  a. It is important to involve cardiology consultants for appropriate management of prosthetic heart valves well in advance of planned HCT.

b. Data on the efficacy/safety of therapeutic anticoagulation for atrial arrhythmias in the setting of severe thrombocytopenia are limited, as thrombocytopenia was an exclusion criterion for major clinical trials of warfarin and DOACs.

   i. A prospective cohort study comparing patients with AF and mild thrombocytopenia (platelets $50–100 \times 10^9$/L) receiving reduced-dose DOACs to patients with normal platelet counts receiving full-dose DOACs found similar bleeding rates and mortality. Most patients had thrombocytopenia from cirrhosis and not cancer. Also, the trial was not powered to detect a difference in CVA [45].

   ii. Another trial in patients with AF undergoing percutaneous coronary intervention followed by triple therapy (ASA, clopidogrel, and warfarin) compared patients with (platelets $<150 \times 10^9$/L) and without thrombocytopenia. No differences in bleeding or cardiovascular events were seen [46].

c. For patients currently on anticoagulation for atrial fibrillation/flutter, decisions must be made on a case-by-case basis, taking into consideration the day-to-day risk of CVA (typically low) as well as the risk of major or clinically relevant non-major bleeding:

   i. For a majority of patients undergoing HCT, it is most reasonable to hold anticoagulation in the immediate peri-transplant period given the low daily stroke risk.

   ii. If a patient has a very high (≥ 7) CHA$_2$DS$_2$-VASc score or has had a CVA within the previous 3 months, consider replacing oral anticoagulants with LMWH in the immediate peri-transplant period and holding therapy while platelets are $\leq 50 \times 10^9$/L.

   iii. Resumption of pre-transplant oral anticoagulant of choice will be reasonable for most patients once platelets are $\geq 50 \times 10^9$/L, but may be limited by other risk factors such as drug interactions or impaired enteral absorption due to mucositis, nausea/vomiting, and/or gastrointestinal GvHD.

Key Points
- Patients with atrial fibrillation/flutter undergoing HCT should be risk-stratified for cardioembolic stroke with the CHA$_2$DS$_2$-VASc score, similar to non-cancer patients.
- The HAS-BLED score may be used to identify modifiable bleeding risk factors for patients with atrial fibrillation/flutter undergoing HCT, though generally should not affect treatment decisions given its unknown applicability to cancer patients.
- LMWH is the anticoagulant of choice in the immediate peri-transplant period for patients with very high CHA$_2$DS$_2$-VASc scores (≥ 7) or recent stroke, severe thrombocytopenia, and/or impaired oral intake/enteral absorption. Otherwise, consider holding anticoagulation entirely during the peritransplant period, decided on case-by-case basis with cardiology.

Prosthetic Heart Valves

1. Thromboembolic risk

   a. The foreign surface of prosthetic cardiac valves, particularly mechanical valves, serves as potent stimulator of the contact pathway of coagulation. This can lead to (1) valve leaflet thrombosis, (2) valve stenosis, and (3) thromboembolism including ischemic stroke, visceral infarction, and limb ischemia.

   b. Thromboembolic stroke risk is highly variable and depends on multiple factors including the valve material, valve type, location and number of implanted valves, surgical vs. transcatheter implantation, and the presence of other prothrombotic comorbidities.

      i. Stroke risk is higher with the following valve characteristics: mechanical, ball-in-cage, mitral position, ≥2 valves, AF, and heart failure.

      ii. For mechanical aortic valves, the annual thromboembolism rate is ~4% without any anticoagulation and ~1% with warfarin. These rates can be up to twice as high with mechanical mitral valves [47].

      iii. For bioprosthetic heart valves including transcatheter aortic valves (TAVR), the risk of thromboembolism is highest within 3 months of implantation and before endothelialization, ~4%; the annual risk thereafter is similar to that of mechanical valves treated with warfarin, ~1%. These patients generally do not require ongoing anticoagulation [3].

      iv. There are minimal data on the daily risk of valve thrombosis and thromboembolism with or without anticoagulation. Data on patients with mechanical valves and intracranial hemorrhage due to anticoagulation have demonstrated low rates of recurrent thromboembolism when warfarin was held for up to 2–3 weeks; therefore, daily thromboembolic risk appears relatively low off of anticoagulation [48].

2. Anticoagulant choice

   a. Warfarin is almost exclusively used for CVA prophylaxis with mechanical valves and has the most supporting data. However, for the same reasons listed in sections. "Venous Thromboembolism" and "Atrial Fibrillation/Flutter", warfarin is not ideal in HCT patients. Therefore, anticoagulant choice should be carefully discussed with cardiology, and in higher-risk scenarios (e.g. mitral valve), warfarin may still be preferred.

   b. DOACs (specifically, dabigatran) were tested against warfarin for thromboembolic stroke prevention with mechanical valves, though dabigatran led to significantly higher stroke and bleeding rates, leading to early trial closure. DOACs therefore remain contraindicated with mechanical heart valves [3].

   c. LMWH has historically been used only as bridging therapy and not for long-term thromboprophylaxis in patients with mechanical valves. However, a meta-analysis of cohort and case–control studies showed no difference in

thromboembolic or bleeding rates with LMWH compared with UFH or warfarin when used for short durations in patients with mechanical valves [49]. Therefore, LMWH is likely safe to use for patients undergoing HCT in the immediate peri-transplant period.

3. Anticoagulation recommendations in HCT
   a. It is important to involve cardiology consultants for appropriate management of prosthetic heart valves well in advance of planned HCT.
   b. Mechanical valves.

      i. If a patient is at lower risk for embolic stroke (single, bileaflet aortic valve without AF or heart failure), these authors recommend stopping warfarin prior to HCT and considering replacement with therapeutic LMWH if indicated.

         • Consider reducing LMWH to prophylactic dose once platelets decrease to $\leq 50 \times 10^9$/L and holding LMWH once platelets decrease to $\leq 25 \times 10^9$/L.

      ii. If a patient is at higher risk for stroke (mitral valve, multiple valves, prior stroke, AF or heart failure), continuing warfarin may still be preferred.

         • When platelets approach 50×10^9/L, discuss with cardiology whether to continue warfarin or hold warfarin and replace with prophylactic-dose LMWH.
         • If warfarin is continued, very close monitoring of the INR is advised as variation in oral intake and drug interactions are expected in the peri-transplant period.

      iii. ASA should be discontinued at platelet counts $<30 \times 10^9$/L or in the event of bleeding.
      iv. LMWH at prophylactic dose may be resumed once platelets are consistently $\geq 25 \times 10^9$/L and in the absence of bleeding.
      v. ASA and warfarin may be resumed once platelets are consistently $\geq 50 \times 10^9$/L, provided no major drug–drug interactions exist and with close monitoring of INR. Continue warfarin + ASA indefinitely thereafter.

4. Bioprosthetic valves

   a. If patient is on warfarin within the initial 3 months post-valve implantation at time of HCT, consider postponing HCT. If HCT cannot be postponed, discontinue warfarin and consider replacing with LMWH during the peri-transplant period as described in section "Prosthetic Heart Valves" (3.a), in coordination with cardiology.
   b. Consider discontinuing ASA once platelet count falls below 30×10^9/L.
   c. ASA may be resumed once platelets are consistently $\geq 50 \times 10^9$/L. Continue ASA indefinitely thereafter.

Key Points

- Prosthetic heart valves carry a significant risk for thromboembolic complications. Mechanical valves generally require both anticoagulation and antiplatelet therapy, while bioprosthetic valves generally require only antiplatelet therapy long term.
- While warfarin is standard of care in patients with mechanical heart valves, its long half-life and numerous drug–drug interactions raise safety concerns in the peri-transplant period. Very high-risk patients may need ongoing warfarin therapy in the peri-transplant period, but will require INR monitoring with careful attention to drug–drug interactions and absorption issues.
- While the daily risk of thromboembolism without anticoagulation is low, for lower-risk patients in whom anticoagulation cannot be held entirely, these authors recommend replacing warfarin with LMWH in the peri-transplant period and for as long as patients are at risk for severe thrombocytopenia and variable oral intake/absorption.
- All antiplatelet medications should be held at platelets counts $\leq 30 \times 10^9$/L, and all anticoagulation should be held at platelets counts $\leq 25 \times 10^9$/L.

Bridging Anticoagulation

1. Bridging therapy is meant to substitute anticoagulants with long half-lives (e.g. warfarin) with anticoagulants with short half-lives (e.g. LMWH) to ensure therapeutic anticoagulation is administered up to the point at which anticoagulation must be held (e.g. for invasive procedures).
2. Bridging therapy has limited indications, with newer data suggesting more harm than benefit in the form of excess bleeding.
3. The need for bridging depends on the type of anticoagulant, degree of thrombotic risk, and procedural bleeding risk.
4. Bridging is typically performed only for patients on warfarin; therefore, very few patients undergoing HCT should require bridging therapy as these authors recommend LMWH for most anticoagulation indications.
5. For patients who require anticoagulation for VTE, these authors recommend delaying procedures for 3 months post-VTE rather than bridging, if possible.
6. DOACs do not require bridging given their short half-lives and can typically be discontinued at scheduled points prior to procedures, depending on the patient's renal function and procedural bleeding risk.
7. Typical bridging procedure for patients on warfarin

    a. Warfarin is held ~5 days prior to planned procedures.
    b. Therapeutic-dose LMWH is initiated ~3 days prior to procedure or once INR is <2.0.
    c. The last dose of LMWH is given ~24 hours prior to procedure.

   d. LMWH is restarted ~24–48 hours after procedure concurrently with warfarin and at the discretion of the proceduralist, taking into consideration risk for procedure-related bleeding.
   e. LMWH is stopped once INR is ≥2.0 and the patient has been on warfarin for at least 5 days.

8. Indications for bridging for patients on warfarin.

   a. VTE [50]

      i. VTE within the past 3 months
      ii. Severe thrombophilia (APS, ATIII deficiency)

   b. Atrial fibrillation/flutter [51]

      i. CHA_2DS_2-VASc ≥7.
      ii. CHA_2DS_2-VASc 5–6, if procedural bleeding risk is low.
      iii. CVA or other arterial thromboembolism within the previous 3 months

   c. Mechanical heart valves [50]

      i. Mitral mechanical valve of any type
      ii. Aortic, *plus* at least one additional risk factor (multiple mechanical valves, ball-in-cage type valve, CVA ≤6 months ago, AF, left ventricular dysfunction, or hypercoagulable condition)

> **Key Points**
> - Bridging anticoagulation is only necessary for patients taking warfarin; the strongest indications for bridging therapy for patients on warfarin are recent (<3 months) VTE, very high (≥7) CHA_2DS_2-VASc score, and mechanical mitral valves or aortic valves with other cardiovascular risk factors
> - If patients are receiving LMWH around the time of HCT, no bridging therapy is needed as LMWH has a short half-life and can be held shortly before planned procedures.

Arterial Thrombosis

1. Thrombotic/bleeding risk

   a. Major clinical trials of antiplatelet therapy for cardiovascular disease typically excluded patients with cancer or with thrombocytopenia (platelets <100 × 10^9/L); therefore, risks of thrombosis and bleeding using antiplatelet agents in these populations are not well described.

    b. While chemotherapy-related thrombocytopenia may increase bleeding risk, it may also increase the risk of arterial thrombotic events, with several studies showing an association between progressive thrombocytopenia, thrombotic events, and even mortality [52, 53].

    c. Given the lack of consensus, communication with cardiology is essential when managing antiplatelet and anticoagulant medications in all the scenarios listed below.

2. Primary prevention

    a. A significant portion of the population is on ASA or other antiplatelet agents for primary prevention of cardiovascular events including myocardial infarction (MI) and CVA.

    b. Emerging data in certain populations suggest that ASA for primary prevention of first MI or CVA is either ineffective or balanced by equally significant major bleeding risk [8, 9].

    c. In HCT recipients taking antiplatelet agents for primary prevention, these authors recommend stopping the medication during the peri-transplant period at least until platelet counts and bleeding risk return to pre-transplant baseline.

3. Secondary prevention

    a. Secondary prevention refers to the prevention of further acute coronary syndromes (ACS) including unstable angina, ST- or non-ST elevation MI, CVA, or other arterial thromboembolic events in those patients who have already experienced such an event. Such patients take antiplatelet agent(s), anticoagulants, or occasionally both, for secondary prevention.

    b. The benefits of antiplatelet therapy for secondary prevention are much more significant than for primary prevention and remain important mainstays of treatment. This approach also requires more nuanced management in the setting of HCT and thrombocytopenia.

    c. Data for the efficacy and safety of antiplatelet agents in the setting of thrombocytopenia (including cancer) are limited, as patients with platelets $<100 \times 10^9$/L were typically excluded from major cardiovascular trials.

    d. It is important to involve cardiology consultants for appropriate management of antiplatelet therapy well in advance of planned HCT.

4. Patients with pre-existing coronary stents

    a. Dual-antiplatelet therapy (DAPT) with ASA + $P2Y_{12}$ inhibitor (e.g. clopidogrel) is mandatory immediately after stent placement to prevent in-stent thrombosis provoked by the metal stent surface. Bare metal stents (BMS) are quickly endothelialized and thus require shorter durations of DAPT, while drug-eluting stents (DES) prevent rapid endothelialization and thus require longer durations of DAPT.

    b. The duration of DAPT also depends on the context in which stents are placed (elective for refractory stable angina vs. emergent for ACS).

   c. Any stent placed in the setting of ACS generally requires 12 months of DAPT followed by single-antiplatelet therapy indefinitely [54].

   d. Stents placed electively for refractory angina generally require at least 1 month of DAPT for BMS and 6 months for DES, followed by single-antiplatelet therapy indefinitely [54].

5. Management of antiplatelet therapy in HCT for patients with stents

   a. If possible, for patients with coronary stents, consideration should be given to delaying HCST until at least 6 months after ACS, or after the "at risk" periods for elective stent placement, as above [53].

   b. If patients with coronary stents require urgent HCT within the "at risk" periods, consultation with cardiology is essential for safe management. Antiplatelet management strategies have been suggested as follows: [52, 53]

      i. If platelets are $\geq 50 \times 10^9$/L, continue DAPT.

      ii. If platelets are $<50 \times 10^9$/L but $\geq 30 \times 10^9$/L, management recommendations differ; strongly consider DAPT in coordination with cardiology consultants. May consider single-antiplatelet therapy with $P2Y_{12}$ inhibitor alone.

      iii. If platelets are $<30 \times 10^9$/L or clinically evident bleeding develops, consider stopping all antiplatelet therapy for as short a time as reasonably possible.

   c. If patients with coronary stents require HCT outside of the "at risk" periods, it may be possible to treat with single-antiplatelet therapy alone and hold therapy once platelets are $<50 \times 10^9$/L. Consultation with cardiology should be undertaken.

6. Management of antiplatelet therapy in HCT patients after coronary artery bypass grafting (CABG)

   a. The benefit of DAPT after CABG is not as clearly defined as after coronary stent placement; guidelines suggest DAPT is reasonable, but not mandatory [54]. Consult cardiology for specific recommendations on a case-by-case basis.

   b. Patients who undergo CABG should all be on single-antiplatelet therapy indefinitely at minimum.

   c. Thresholds for stopping/starting antiplatelet agents should follow guidelines listed in Table 13.1.

7. Patients who develop ACS during HCT

   a. As noted above, ACS can occur despite thrombocytopenia; therefore, chest pain or other concerning symptoms should trigger evaluation for cardiac causes regardless of platelet count.

   b. Data suggest improved outcomes with the use of antiplatelet medications even in the setting of thrombocytopenia, though as noted above, hard cutoffs above which antiplatelet agents are safe are not clear [52].

c. Management of antiplatelet therapy in HCT patients who develop ACS [52, 53].

   i. If platelets are ≥ 50–100×10^9/L, continue DAPT as indicated for patients with normal platelet counts.
   ii. If platelets are $<50 \times 10^9$/L but $\geq 30 \times 10^9$/L, management recommendations differ; strongly consider DAPT in coordination with cardiology consultants. May consider single-antiplatelet therapy with $P2Y_{12}$ inhibitor alone.
   iii. If platelets are $<30 \times 10^9$/L, consider withholding all antiplatelet therapy, though therapy may be given on case-by-case basis with careful coordination with cardiology.
   iv. Adjunctive measures and medications to minimize bleeding risk:

   - Ensure proton pump inhibitor therapy for all.
   - Avoid ticagrelor or prasugrel given higher bleeding risk than clopidogrel.
   - Use radial vascular access rather than femoral.
   - Use BMS or second-generation DES to minimize duration of required DAPT.

Key Points
- In patients already taking antiplatelet drugs for primary prevention prior to HCT, these authors recommend stopping these drugs in the peri-transplant period.
- In patients already taking antiplatelet drugs for secondary prevention prior to HCT, these authors recommend: continue DAPT as long as platelets $>50 \times 10^9$/L. If platelets are $<50 \times 10^9$/L but $\geq 30 \times 10^9$/L, one can consider DAPT or single-antiplatelet therapy with $P2Y_{12}$ inhibitor in consultation with cardiology. If platelets are $<30 \times 10^9$/L, consider withholding all antiplatelet therapy.
- Cardiology consultation is essential for safe management of antiplatelet agents during HCT.

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Chapter 14
Engraftment

Lyndsey Runaas, Parameswaran Hari, and Saurabh Chhabra

Introduction

The primary and earliest hallmark of success following HCT is the return of normal hematopoiesis. Patients and clinicians eagerly await the return of blood counts as an early "sign" of a successful transplant. Understanding this process of engraftment, or the establishment of normal hematopoiesis following a stem cell transplant, is critical. It does not occur all at once, but instead occurs in waves, with a very stereotypical pattern of neutrophils arriving first, followed by sustained platelet and red blood cell production. Generally, engraftment begins about 10–21 days following infusion of the stem cell product, though the kinetics of cell recovery is influenced by many factors. These factors include those related to the host (i.e. presence of splenomegaly), the underlying disease requiring transplant (i.e. sickle cell anemia), the donor (i.e. ABO incompatible or marrow graft source), the conditioning regimen (i.e. myeloablative versus non-myeloablative), and post-transplant management and/or complications (i.e. medications, infections).

Engraftment

1. Engraftment after transplantation is defined by achievement of count recovery including

    a. Absolute neutrophil count (ANC) $\geq 500/mm^3$ for 3 consecutive days
    b. Platelet count of $\geq 20,000/m^3$ for 3 consecutive days and no transfusions for 7 days

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   c. Hematocrit ≥25% for at least 20 days without transfusions

2. Typical timing of cell recovery

   a. *Autologous* transplant recipients

      i. Neutrophil recovery is typically seen 10–14 days after transplant, although timing varies based on the use of granulocyte-colony stimulating factor (G-CSF; e.g. Neupogen®).

      ii. Cell recovery may be seen 1–2 days earlier in patients receiving myeloid growth factors from day 1 after transplant.

      iii. Platelet and red blood cell independence may be more variable and slower.

      iv. Bone marrow biopsies are not routinely performed post-autologous transplant to assess engraftment.

   b. *Allogeneic* Transplant Recipients

      i. Initial neutrophil recovery can be seen by the third week after marrow or stem cell infusion but is quite variable and can be influenced by (see Table 14.1):

        • Stem cell source

          – Peripheral blood stem cell (PBSC) transplants average 10–14 days until first signs of neutrophil recovery.

          – Bone marrow grafts average 21 days until first neutrophil recovery.

          – Umbilical cord grafts can be even longer; duration of neutropenia can be shortened by identifying donor cord blood products with the highest nucleated cell counts.

Table 14.1 Factors affecting engraftment

Patient-Specific	
Disease indication for transplant	e.g. *Myelofibrosis, aplastic anemia, sickle cell anemia*
Massive splenomegaly	
Donor-specific anti HLA antibodies	
Donor-specific	
ABO incompatibility	
Transplant-specific	
Graft source	*PBSC* versus *bone marrow*
Conditioning regimen	*RIC* versus *myeloablative*
Post-transplant factors	
Infections	*Commonly viral such as CMV, EBV, HHV6*
GvHD	
Medications	*Bactrim, mycophenolate mofetil*

HLA human leukocyte antigen, *PBSC* peripheral blood stem cell, *RIC* reduced intensity conditioning, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HHV6* human herpes virus 6, *GvHD* graft-versus-host disease

- GvHD prophylaxis

  - Calcineurin inhibitor/prednisone: Shortest time to engraftment (10–15 days).
  - Long course methotrexate/calcineurin inhibitor: Longest duration of time to engraftment (21–26 days).
  - Marrow grafts performed with post-transplant cyclophosphamide average 15 days [1] until the first signs of engraftment are observed.

ii. Platelet engraftment generally follows ANC recovery. Transfusion independence typically seen within 5–7 weeks post-stem cell infusion and is generally delayed compared with the autologous setting.

iii. Hemoglobin and hematocrit studies are poor indicators of engraftment and hematopoietic recovery.

  - Patients receiving an ABO incompatible donor transplant may continue to produce host-specific isohemagglutinins for months to years (see also Chap. 12). These can result in immune-mediated hemolysis, diminished reticulocyte activity, and delayed red blood cell (RBC) transfusion independence.

iv. Assessment of full engraftment in the allogeneic setting requires assessment by bone marrow biopsy (generally performed between days 30 and 90 days post HCT).

v. Lineage-specific chimerism studies are recommended to demonstrate full donor hematopoiesis, especially after reduced intensity conditioning (RIC).

vi. Chimerism studies are evaluated by either variable nucleotide tandem repeats [VNTR] for sex-matched donor/recipient pairs, or fluorescent *in situ* hybridization [XY FISH] for sex mismatched donor/recipient pairs. In the reduced intensity conditioning (RIC) setting, lineage-specific chimerisms are especially important to assess (e.g. CD3 and CD33 sorted peripheral blood cell chimerism).

  - *Full chimerism* is considered 100% donor-derived lineage.
  - *Mixed chimerism* is considered <100% donor-derived lineage, a mixture of host and donor cells.
  - Peripheral blood chimerisms of both CD3$^+$ and CD33$^+$ populations are assessed in schedules determined by individual institutional guidelines; assessment of these two lineages—lymphoid and myeloid—can sometimes be utilized as a means for early detection of relapsed disease (e.g. myeloid lineage CD33-expressing malignancies).
  - While the decision to assess chimerism on peripheral blood or a bone marrow specimen remains clinical, bone marrow chimerism is generally considered a more sensitive assay [2].

Complications of Engraftment

1. Engraftment Syndrome (ES)

   a. A major complication of ASCT characterized by non-infectious fevers and a spectrum of systemic clinical manifestations such as rash, diarrhea, hepatic dysfunction, and capillary leak occurring in the peri-engraftment period. See Table 14.2 for defining criteria.

   b. ES has been documented in patients who undergo ASCT for plasma cell disorders such as multiple myeloma (MM), POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin abnormalities) syndrome, light chain amyloidosis, lymphoma, breast cancer, and multiple sclerosis. The highest incidence (approximately 50%) is believed to be in ASCT for POEMS syndrome.

   c. Symptoms typically occur within 3 days before to 7 days after neutrophil engraftment. Most cases are mild, and some require systemic steroid therapy for management; however, occasional fatalities have been reported.

   d. Variants or subsets of ES have been described as autologous GvHD, capillary leak syndrome, auto-aggression syndrome, or peri-engraftment respiratory distress syndrome.

   e. Although the existence of acute GvHD in the ASCT setting has been questioned, the current consensus is to consider all cases of peri-engraftment, GvHD-like phenomena under the ES umbrella.

   f. Incidence of ES after ASCT is reportedly 10–29% in MM and 10% in lymphoma. The latter typically has a milder clinical course.

   g. Severe ES (2–4%) is characterized by an inadequate response to steroid therapy, multi-organ involvement, histologic findings consistent with acute GvHD, and potential mortality.

   h. Risk is increased in patients with MM who receive novel agent induction (e.g. imide therapy) prior to transplant, while the use of cyclophosphamide in the pretransplant treatment period reduced the risk. Female gender and the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) are also associated with an increased risk [3].

Table 14.2 Criteria for the diagnosis of engraftment syndrome

	Spitzer criteria	Maiolino criteria
Requirements	3 major OR 2 major +1 minor	Major +1 minor
Major criteria	Non-infectious fever, skin rash or pulmonary edema	Non-infectious fever
Minor criteria	Weight gain, hepatic dysfunction, renal dysfunction or transient encephalopathy	Skin rash, pulmonary infiltrates, or diarrhea
Timing of symptoms relative to engraftment	4 days within ANC 0.5×10^9/L	1 day within neutrophils present

Adapted from Cornell et al. [3]

i. Pathogenesis is unclear but believed to be related to the development of auto-reactive T cells (that recognize self major histocompatibility complex (MHC) and self-peptides) which escape regulatory T-cell (T-reg)-mediated suppression in the setting of diminished T-reg activity induced by medications such as lenalidomide (Revlimid®). Proinflammatory cytokines in the immune milieu are thought to predispose to this autoreactivity state.

j. Management (see Fig. 14.1)

   i. Accurate early diagnosis is made by systematic exclusion of other causes of fever, rash, diarrhea, and other ES symptoms.
   ii. Majority of cases resolve spontaneously.
   iii. Early initiation of systemic steroids is key in patients with persistent and or severe symptoms lasting beyond 48–72 hours. Doses vary from 0.5 to 1.5 mg/kg of methylprednisolone based on the severity and number of organs involved.
   iv. Rapid taper of steroids is recommended once a response has been established (usually 48–72 hours). The author's practice is to taper to 10 mg daily of prednisone or equivalent over a 7–10-day period.
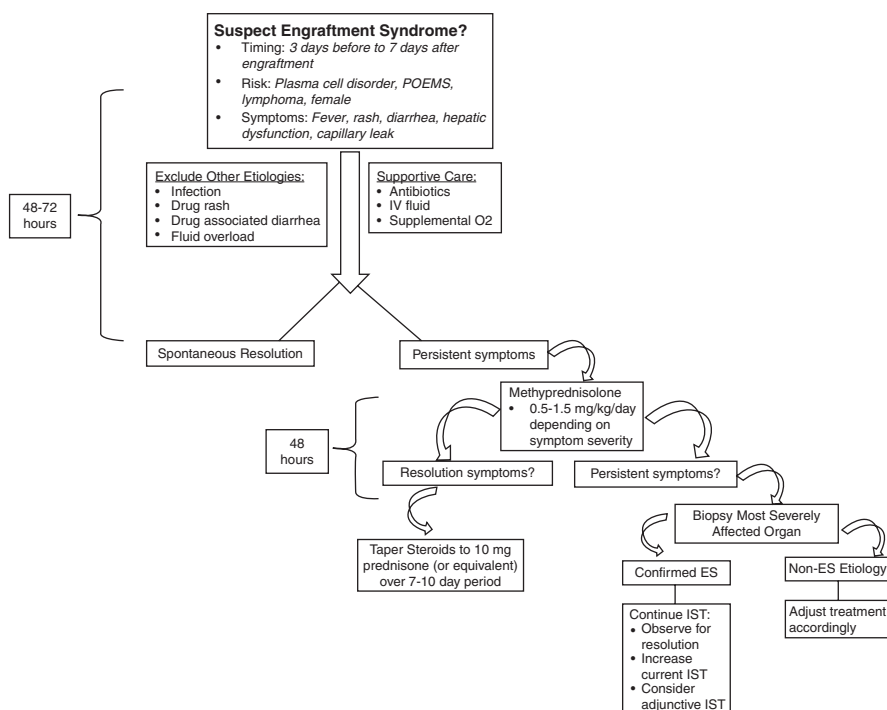
Fig. 14.1 Management algorithm of engraftment syndrome. POEMS Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin abnormalities syndrome, ES engraftment syndrome, IST immune suppressive therapy

    v. Additional immunosuppression as an adjunctive to steroids is reserved for biopsy proven, severe cases with multi-organ involvement. Therefore, biopsy of the most severely involved organ is mandatory when managing patients with non-response to steroids.

Foundation for the Accreditation of Cellular Therapy (FACT) Standards for the Review of Engraftment

1. Transplant centers need to systematically collect and analyze data regarding engraftment among their transplant recipients as an important quality standard. Ongoing audits of patient engraftment data are a measure of quality for HCT programs.
2. See FACT website (http://www.factwebsite.org/Standards/).

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Chapter 15
Acute Myeloid Leukemia and Allogeneic Hematopoietic Cell Transplant

Curtis Lachowiez and Rachel J. Cook

Introduction

Acute myeloid leukemia (AML) is predominantly a disease of the elderly. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER database) cite [1, 2]:

– Median age at diagnosis of 68 years
– Median age at death of 72 years
– Incidence of AML is approximately 5.2 per 100,000 individuals
– Slight male to female predominance [2]
– Five-year overall survival (OS) rate of approximately 27.4% [2]

   Due to recent advancements in molecular sequencing, understanding of the pathophysiology of AML has undergone rapid expansion. Intensive anthracycline-based chemotherapy developed in the 1980s remains frontline therapy for the majority of patients with AML who are considered fit enough to undergo induction chemotherapy [3–5]. Select subgroups have benefited from targeted therapy when harboring mutations in IDH1/IDH2, FLT3-ITD, or CD33+ AML [6–9]. While complete remission (CR) can be obtained in 60–80% of younger adults and 40–60% of older (age ≥60) adults with standard induction, relapse remains a formidable issue [3, 22]. Relapse rates range from 30% to >90% depending on patient and disease factors [3, 10, 22]. Early risk stratification is imperative to define a patient's risk of

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relapse and guide therapy, as allogeneic hematopoietic cell transplant (allo-HCT) currently remains the best curative option for certain subtypes of AML.

Key Points
1. AML occurs at a median age of 68 years.
2. Allogeneic hematopoietic cell transplantation is the only curative therapy currently for certain subtypes of AML.

Risk Stratification

Risk stratification has become increasingly complex.

1. AML historically was classified morphologically using the French-American-British (FAB) classification scheme [14].
2. In 2002, the World Health Organization (WHO) further subclassified AML to include clinical factors such as the presence of AML arising from a precursor state such as myelodysplastic syndrome (MDS) and clonal cytogenetic abnormalities based on the observation of distinct outcomes related to patient factors such as age, previous disease states, and karyotype [16–19].
3. Cytogenetic risk correlates with likelihood of achieving CR (84% favorable vs. 55% unfavorable) and with OS [18].

    a. A risk stratification schema based on cytogenetic analysis using a large cohort of 1612 patients enrolled in the MRC AML 10 trial classified patients into favorable, intermediate, and adverse groups, correlating with rates of CR, relapse, and OS for patients undergoing chemotherapy and consolidation with HCT [19].
    b. A high percentage of AML patients (42%) had normal cytogenetics, a group that historically has been classified as intermediate risk [19, 20].

4. Utilization of next-generation sequencing (NGS) (see also Chap. 59) enabled the identification of molecular markers to risk stratify patients at the greatest risk of relapse and adverse outcomes [13].

    a. This tool has proven useful among patients with a normal karyotype, allowing patients to be reclassified into either favorable- or adverse-risk groups based on certain mutations [20].
    b. Such stratification also guides treatment.

        i. Patients with mutated FLT-3, MLL, and NRAS demonstrated improvement in relapse-free survival (RFS) and OS following matched allo-HCT [20].

Table 15.1   2018 ELN risk stratification in AML

Favorable risk	Intermediate risk	Adverse risk
t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22) CBFB-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD low Biallelic mutated CEBPA	Mutated NPM1 and FLT3-ITD high Wild-type NPM1 without FLT3-ITD or with FLT3-ITD low (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); MLLT3-KMT2A Cytogenetic abnormalities not classified as favorable or adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.2) or t(3;3) (q21.3;q26.2) GATA2,MECOM(EVI1) −5 or del(5q); −7; −17/abn(17p) Complex karyotype Monosomal karyotype Wild-type NPM1 and FLT3-ITDhigh Mutated RUNX1 Mutated ASXL1 Mutated TP53

Döhner et al. [3]. © the American Society of Hematology

    ii. Molecular stratification of patients in the ECOG 1900 trial led to the redistribution of previously intermediate-risk patients into favorable-risk (19% ➜ 26%) and adverse-risk (18% ➜ 39%) groups [21].

    iii. Genomic analysis of 200 patients with AML identified at least one pathogenic somatic mutation per patient and further characterized mutations into nine distinct functional categories [12]. This work led to the current risk stratification schema as outlined in the 2017 European Leukemia Net (ELN) guidelines shown in Table 15.1, in addition to upfront assessment of common molecular mutations at diagnosis that harbor prognostic or therapeutic benefit: NPM1, CEBPA, FLT-3, IDH1/2, TET2, ASXL1, and TP53 [3, 12].

5. Age is an independent risk factor for poor overall survival.

    a. Older patients have been shown more likely to have adverse molecular mutations and complex cytogenetics compared to younger cohorts [11].

    b. A 2012 study demonstrated among a cohort of younger (<60 years) versus older (≥60 years) AML patients, the older cohort was more likely to have intermediate- and adverse-risk disease with inferior OS across all risk groups [11].

6. Relapse rates for favorable-, intermediate-, poor-, and very poor-risk patient groups of 35–40%, 50–55%, 70–80%, and >90% have been seen respectively (the most recent ELN guidelines only recognize three risk groups: favorable, intermediate, and adverse) [3, 10]; this risk was substantially decreased in patients undergoing allo-HCT [10].

7. Treatment considerations need to balance the relapse risk reduction with the risk of treatment-related mortality (TRM) as the benefit of allo-HCT varies significantly across risk groups. Current guidelines recommend consideration of allo-HCT for patients with intermediate- or adverse-risk disease [3].

8. Current National Marrow Donor Program (NMDP) guidelines recommend early consultation with a transplant specialist for patients with primary induction failure (PIF), minimal residual disease (MRD) positivity post-induction therapy, all molecular or cytogenetic intermediate- or high-risk patients, patients with therapy-related AML (tAML) or secondary AML (sAML), patients in their first relapse (particularly within 6–12 months of induction), and patients in CR other than CR1.

   a. All patients should have high-resolution HLA typing done at the time of AML diagnosis [86, 87].

   b. Patients with relapse or PIF have particularly poor outcomes. Historically, transplantation of patients not in CR is controversial; however, transplant in select patients resulted in 3-year OS of 19% among AML patients with PIF or relapsed disease.

   c. The Duval Criteria utilizes a scoring system to stratify patients likely to benefit from transplant [88].

Key Points
1. Flow cytometry, karyotyping (FISH and cytogenetics), and molecular testing for CEBPA, NPM1, FLT-3 ITD, RUNX1, IDH1/2, FLT-3 TKD, and TP53 should be performed on bone marrow at diagnosis for risk stratification.
2. Patients with early relapse, PIF, MRD post-induction, and tAML/sAML should be referred for transplant regardless of molecular or cytogenetic risk stratification.
3. All patients with AML should undergo high-resolution HLA typing at diagnosis.
4. The Duval criteria can be utilized to stratify patients with PIF or relapsed disease who may benefit from transplant.

Role of Transplant as Consolidation Therapy

1. The benefits of transplant on OS in AML were demonstrated in a 2009 JAMA meta-analysis comparing myeloablative conditioned (MAC) consolidative unrelated donor allogeneic or sibling matched HCT to autologous HCT versus cytotoxic chemotherapy in CR1 [22].

   a. Allogeneic HCT resulted in improved RFS and OS benefits among both intermediate-risk (RFS benefit: hazard ratio (HR) 0.76, OS benefit: HR 0.84) and adverse-risk patients (RFS benefit: HR 0.69, OS benefit: HR 0.60) [22].

2. Consolidative allo-HCT results in an immunological response driven by a continued graft-versus-leukemia (GvL) effect, as evidenced by decreased relapse among a cohort of patients undergoing sibling donor HCT with acute or chronic graft-versus-host disease (GvHD) [26].

   a. For patients with intermediate- or adverse-risk disease, allo-HCT should be considered as first-line consolidation therapy.
   b. Unrelated (URD)-HCT is a viable and more readily available option for patients without a matched sibling donor that is commonly used and associated with comparable outcomes [24]. Over 75% of Caucasian patients with European ancestry have a matched unrelated donor [23]. A 2011 review found 47% of HCT occurring in CR1 were performed using URD-HCT [27].
   c. Despite these advances, ethnic and racial disparities remain a challenge in regards to suitable donor availability [23].
   d. Increasing fidelity of HLA typing, use of alternative donor sources such as haploidentical transplantation (haplo-HCT) or umbilical cord blood transplantation (UCB), and improved GvHD prophylaxis have increased the donor pool and decreased the number of patients without a donor substantially [23].
   e. A prospective analysis of high-risk AML patients demonstrated an increased OS benefit from transplant and no difference in cumulative incidence of relapse or death between sibling and URD HCT [25]. While this trial included haplo-HCT, the sample size was too small to draw significant conclusions.

> **Key Points**
> 1. Consolidative transplant in CR1 results in prolonged RFS and OS for patients with intermediate- and high-risk AML.
> 2. A matched sibling donor is available in approximately 30% of patients. A matched unrelated donor can be identified in approximately 75% of Caucasian patients; however, underrepresented minorities have lower chances of finding a match.
> 3. Alternative strategies including haploidentical donors, cord blood transplant, and permissive mismatched donors have further increased the donor pool for transplant.

AML Disease Assessment Prior to Allogeneic HCT

Assessment of disease status has traditionally been performed at day 14 following induction (to assess the need for re-induction, though this approach has been called into question by several clinical trials) and at marrow recovery [29].

1. Morphologic CR on a recovery marrow is defined as <5% bone marrow blasts with an ANC >1000 cells/mm^3, platelets >100,000 cells/mm^3, and the absence of circulating blasts, blasts with auer rods, or extramedullary disease [3].

2. Complete remission with incomplete hematopoietic recovery (CRi) meets criteria for CR but with a platelet count or ANC less than that required for CR in a patient that is not transfusion dependent [3].

   a. Patients achieving CRi have inferior long-term outcomes when compared to patients in CR following induction [28].

3. Patients with intermediate- or adverse-risk cytogenetic or molecular studies have higher rates of relapse following consolidation [10]. Identification of patients who would benefit most from HCT and those at highest risk of relapse post-HCT has led to rapid advances in risk stratification and identification of molecular targets for pre-emptive post-transplant maintenance therapy.

4. Residual disease pre-transplant has been associated with reduced leukemia-free survival [46].

   a. With the clinical incorporation of NGS, the ability to identify patients with leukemic clones not previously identified on morphological examination of a recovery marrow is now commonplace.

   b. MRD (also termed measurable residual disease) is defined as the persistence of leukemic cells after chemotherapy at numbers below the sensitivity of detection level of routine morphology, typically a detection level of $1:1 \times 10^4$ to 1×10^6 cells compared to 1:20 cells using conventional morphology [30, 31].

   c. 2017 ELN guidelines recommend assessment for MRD via multi-parameter flow cytometry (MFC) or real-time quantitative PCR (qPCR) [3] with the recommended goal of MRD levels <0.1% in the bone marrow aspirate to be considered MRD-negative [31].

   d. Molecular MRD is more nuanced, requiring consideration of the sensitivity and stability of certain mutations throughout treatment, attention to clones that may be pre-leukemic clones or associated with age-related clonal hematopoiesis (ARCH), and recognition of germline clones based on variant allele frequency (VAF) at diagnosis and following therapy.

      i. If a germline mutation leading to an AML predisposition syndrome is suspected, confirmatory testing via an alternative histology should be completed (i.e., hair follicle, skin, and buccal swab) [31].

   e. The polyclonal nature of AML and relative lack of sensitivity and stability of certain somatic mutations throughout a patient's treatment course limits the selection of mutant clones acceptable for MRD measurement.

      i. Increasingly sensitive assays for assessment of common pathogenic mutations (i.e., recent improvements in FLT3-ITD detection assays) in addition to identification of a mutation or combination of mutations that are believed to be driving the disease are necessary to mitigate these pitfalls [30–32].

      ii. While NGS is highly sensitive at identifying clonal mutations in CR1 prior to transplantation (a unique mutation can be found in approximately 93% of patients), not all mutations are suitable for MRD monitoring [40].

Table 15.2 Current ELN recommended molecular markers for MRD

Marker
NPM1, RUNX1-RUNX1T1, CBFB-MYH11, or PML-RARA

Adapted from Schuurhuis et al. [31]. © the American Society of Hematology

    iii. Current molecular mutations in addition to antibody panels utilized in MFC suitable for assessment of MRD based on ELN recommendations are shown in Table 15.2 [30].

  f. MFC is another method of measuring MRD with a higher rate of detection albeit slightly lower sensitivity ($1:1 \times 10^3$–$1:10^5$ cells) [33].

    i. MRD by MFC is an independent predictor of decreased RFS and OS among AML patients with MRD present following induction therapy [38].

    ii. MFC utilizes a specific panel of cell surface markers in conjunction with fluorochrome-labeled antibodies to identify individual leukemia-associated immunophenotypes (LAIPs) [33]. LAIPs can be monitored over the course of treatment to assess for MRD.

    iii. Limitations of MFC again include the following:

- The polyclonal nature of AML leading to heterogeneity of LAIPs over the course of treatment.
- The ability for the leukemic cells to "shift" their LAIP due to the extinction of the clone being monitored (leading to a false-negative MRD status).
- The potential for a LAIP to be associated with normal background hematopoiesis (leading to false-positive MRD status) [33, 34].

    iv. Utilizing multiple LAIPs can reduce the likelihood of false-positive or -negative results [33–35].

    v. One advantage of MFC over MRD is its increased applicability.

- MFC has the ability to identify LAIPs in approximately 90% of patients with AML, compared to approximately 50% of patients who have an identifiable mutation suitable for MRD monitoring [33, 34, 39].

  g. Strategies including NGS with targeted sequencing may improve the applicability of molecular MRD testing to an expanded patient population [36, 37, 40].

  h. Currently, no standard exists for the timing of measuring MRD post-induction, which remains an active area of investigation [33].

    i. The presence of persistent leukemic clones via NGS at a VAF as low as 1% on day +30 following induction was associated with decreased progression-free survival (7.9 months vs. 25.6 months) and event-free survival (EFS) [39].

    ii. Among intermediate-risk patients analyzed for mutation clearance following induction, the presence of at least 1 detectable mutation was associ-

ated with reduced EFS and OS (EFS: 8.8 vs. 25.6 months, *p*-value: 0.003; OS:19.3 months vs. 46.8 months, *p*-value: 0.02) respectively [39].

Key Points
1. Morphologic CR on a recovery marrow is defined as <5% bone marrow blasts, an ANC >1000 cells/mm³, platelets >100,000 cells/mm³, and the absence of circulating blasts, blasts with Auer rods, or extramedullary disease.
2. Disease assessment at day +14 can aid in determining the need for re-induction but is becoming less valuable as up-front risk assessment improves.
3. MRD can be measured using MFC, molecular PCR/NGS, or both.
4. The presence of MRD following induction is associated with significantly decreased overall survival.

MRD in Transplant

1. MRD positivity among patients undergoing HCT is associated with an increased cumulative incidence of relapse (CIR) compared to MRD-negative patients (66% vs. 17%), RFS (5-year RFS 31% vs. 74%), and OS (5-year OS 41% vs. 78%) [40].
2. Time to relapse inversely correlated to the level of MRD as measured by VAF [40].
3. Additional factors associated with reduced OS in multivariate analysis include
   a. reduced intensity conditioning (RIC) compared to myeloablative conditioning (MAC)
   b. mutations in TP53 and KRAS, respectively [40].
4. MRD analysis using NGS can detect patients with a low risk of relapse post-transplant with a negative predictive value (NPV) of 84%.
   a. A subset of leukemic clones in BCOR, RUNX1, SETBP1, and SMC identify patients that appear more sensitive to HCT [40].
   b. While DNMT3A mutations have inconsistently correlated with adverse post-remission outcomes, the impact of other identified clones typically associated with ARCH in CR has yet to be fully defined [40, 41].
   c. A 4 log reduction in NPM1 levels post-induction therapy is associated with increased OS compared to a <4 log reduction (>4–5 log reduction: 3-year OS, 91.2% vs. <4 log reduction: 3-year OS 40.8%) [42].
      i. A <4 log reduction was found to be an independent predictor of decreased OS in addition to FLT3-ITD and an abnormal karyotype [42].

  ii. Patients with less than a 4-log reduction in NPM1 levels undergoing HCT
      had an HR of 0.25 for OS, a benefit that was not observed among patients
      with a >4 log reduction in NPM1 levels [42].

5. Relapse following HCT remains problematic. A study from the European Group
   for Blood and Marrow Transplantation (EBMT) observed a relapse rate of 32%
   among patients undergoing reduced intensity conditioning (RIC) HCT after
   achieving CR [43].
6. The presence of MRD prior to HCT was associated with high-risk features
   including adverse-risk AML, older age, multiple lines of therapy to achieve CR1,
   and incomplete count recovery [44].

   a. One-year OS was reduced in patients who were MRD positive (48.8% vs.
      66.9%), in addition to an increased rate of relapse (1-year relapse incidence:
      MRD-negative 6.9% vs. MRD-positive 42.7%) [44].
   b. Patients with FLT-3 ITD mutations who were MRD negative at transplant
      demonstrated survival similar to those with wild-type (wt) FLT-3 [44].
7. The presence of MRD post-transplant correlates with outcomes.

   a. MRD positivity at day +30 is associated with an increased risk of relapse (HR
      11) and decreased OS (HR 4.3) [45].
   b. One-year CIR among MRD-positive patients post-HCT is increased at day
      +100 (75%) and day +180 (100%) [45].
   c. Patients' risk groups and 1-year incidence of relapse demonstrate the signifi-
      cance of both pre- and post-HCT MRD:

      i. Day +30 MRD positive: 78%
      ii. Day +30 MRD negative and ELN intermediate risk and age >60 and/or
          pre-HCT MRD positive, or ELN adverse risk: 27%
      iii. Day +30 MRD negative, ELN intermediate risk and age <60 and negative
           pre-HCT MRD, or ELN favorable risk: 4–5%

> **Key Points**
> 1. MRD and the depth of MRD correlate with outcomes in HCT.

FLT-3-Mutated AML

1. FLT3-ITD

   a. Mutations in the transmembrane Fms-like tyrosine kinase (FLT-3)-commonly
      internal tandem duplication (ITD) mutations within the juxtamembrane
      domain (JMD) are seen in approximately 25% of cases of NK AML and asso-
      ciated with refractory disease, increased relapse risk, and poor OS [48–50,
      51]. HCT can improve outcomes among FLT-3 ITD+ patients.

b. The allelic ratio (AR; ratio of mutated alleles to wild-type alleles) of the mutation has a critical impact on outcomes, with a higher (i.e., >0.5) AR associated with higher relapse rates and decreased OS [50].

c. Patients with an FLT3-ITD AR >0.5 receiving an HCT in CR1 have improved RFS and OS compared to patients receiving only cytotoxic chemotherapy or autologous HCT, a result not seen among FLT-3 ITD[+] patients with an AR <0.5 [49].

d. Patients with mutated FLT-3 ITD with AR <0.5 and co-occurring NPM1 mutations have survival similar to intermediate-risk patients without FLT-3 mutations, with comparable rates of relapse risk (38 vs. 20), OS (56 vs. 47), and leukemia-free survival (LFS) (56 vs. 53) compared to patients with a wild-type FLT-3 ITD (wtFLT-3) [53].

e. Conversely, patients with co-mutations in NPM1 and a high AR FLT-3 ITD[+] are at increased risk of relapse, and benefit from allo-HCT compared to alternative consolidation therapies (5-year RR 20% vs. 80%, 5-year OS: 22% vs. 70%). This benefit is also seen among patients with wtNPM1 and any AR of mutated FLT-3 ITD, but not patients with mutated NPM1 and low FLT-3 ITD AR, or wtFLT-3 [53].

2. FLT3-TKD

a. Mutations in the tyrosine kinase domain (TKD) are seen in approximately 7% of patients and have a variable impact on survival [52].

b. The presence of co-mutations in NPM1 and FLT3-TKD is associated with significantly decreased rates of relapse (24%) compared to patients with only TKD mutations (70%), NPM1 mutations (58%), and NPM1-mutated patients with FLT-3 ITD[+] (50%) [54].

c. When censored for transplant as a consolidation strategy, patients with FLT-3 TKD/NPM1-mutated AML had a trend toward improved OS compared to NPM1-mutated patients (median, NR vs. 24.6 months) [54]. Thus, the presence of FLT-3 TKD[+]/NPM1^{+} AML appears to confer an exceptionally favorable-risk subgroup with potentially better outcomes than NPM1^{+} AML, though this has yet to be confirmed in larger cohorts.

3. Other co-occurring mutations with FLT-3 ITD[+] are associated with adverse outcomes. Co-mutations in Wilms' Tumor 1 gene (WT1) and FLT-3 ITD are associated with significantly lower CR rates and RFS compared to WT1 mutations and wtFLT3 [55]. DNMT3A co-mutations are also associated with inferior outcomes in the presence of FLT-3 ITD mutations [56].

Targeted Therapy

Increased focus on targeted therapy has resulted in the approval of multiple new agents for the treatment of AML, implementing their effects by targeting molecular mutations (i.e., FLT-3, IDH1/2), proteins critical for pro- and anti-apoptotic pathways (i.e., BCL-2), antibody drug conjugates (ADCs), or epigenetic modifiers [47]. While the diverse polyclonal nature of AML has not led to remission rates seen with agents such as the tyrosine kinase inhibitor (TKI) imatinib (Gleevec®) in chronic myeloid leukemia, the future of targeted therapy for AML remains promising.

1. FLT-3 inhibitors

    a. Relapse rates for FLT-3-ITD⁺ patients post-HCT are approximately 30–59% compared to 16–19% for patients with wtFLT-3 [73, 74].
    b. Targeted therapies have emerging roles in both pre- and post-transplant maintenance therapy.
    c. Numerous TKIs targeting the ATP-binding site on the intracellular domain of the FLT-3 receptor tyrosine kinase (RTK) have been developed including type 1 inhibitors that bind to the ATP-binding site when the RTK is in the active conformation [sunitinib (Sutent®), lestaurtinib (CEP-701), midostaurin (Rydapt®), crenolanib, and gilteritinib(Xospata®)], and type 2 inhibitors that bind to the hydrophobic region in juxtaposition to the ATP-binding domain when the receptor is in the inactive state and prevent receptor activation [sorafenib (Nexavar®), quizartinib (AC220), and ponatinib (Iclusig®)] [57].
    d. Sorafenib (Nexavar®)

        i. A multi-kinase inhibitor that has shown modest efficacy in AML as monotherapy; however, resistance mechanisms (including the development of D835 mutations in the TKD domain leading to constitutive activation of the RTK and thereby negating the effectiveness of type 2 inhibitors) limited its clinical use [57, 58].
        ii. When combined with standard chemotherapy in patients under age 60, sorafenib prolongs survival at the cost of increased toxicity [59, 61, 62].

            • The survival benefit is unclear in patients age 60 or greater with studies demonstrating mixed results [60, 65].
            • Administered with induction therapy and as maintenance following allo-HCT, sorafenib demonstrated superior 3-year LFS (15.8% vs. 22.2%, 18.8% and 46.1%) and 3-year OS (84.6% vs. 74.9%, 78.1% and 50.9%) compared to patients receiving sorafenib pre-transplant, post-transplant, or no FLT-3-directed therapy, respectively [69].
            • Prospective studies evaluating the addition of sorafenib to conditioning regimens for HCT and post-HCT maintenance therapy in patients with FLT-3 mutations are ongoing (CTN: NCT03247088).

- Maintenance therapy post-HCT resulted in improved OS (2-year OS 81% vs. 62%) and progression-free survival (PFS) (82% vs. 53%) following HCT [63].
- The results of the phase II randomized Sormain trial evaluating the efficacy of maintenance sorafenib following HCT at the 2018 annual meeting of the American Society of Hematology demonstrated significant improvement in 2- year RFS (85% vs. 53.3%) [64]. OS is anticipated to be released with final publication of the study results.

e. Midostaurin (Rydapt®)

  i. Early studies of midostaurin in patients with FLT3-mutated disease demonstrated a significant total blast (peripheral blood or bone marrow) reduction (71% vs. 42%) [66].

  ii. The CALGB10603 (RATIFY) trial is the first large multicenter study evaluating the efficacy of midostaurin added to induction and consolidation, and continued as maintenance therapy for 1 year [8, 67].

- Median OS was 74.5 months with midostaurin versus 25.6 months with placebo.
- Midostaurin use had an HR for death of 0.78, and improved 4- year OS (51.4% vs. 44.3%) [8].
- More patients in the midostaurin arm had improved event-free survival (time to relapse, death, or failure to achieve CR) (median 8.2 months vs. 3.0 months) and disease-free survival (DFS) (26.7 months vs. 15.5 months) compared to placebo, and a trend toward improved 4-year OS was seen (63.7% vs. 55.7%) among patients undergoing HCT.
- A sensitivity analysis demonstrated a 24.3% lower risk of death among patients receiving midostaurin when censored at the time of transplant [8]. This survival benefit may be due to the higher albeit non-significant rate of CR1 achieved in the midostaurin arm compared to placebo (58.9% vs. 53.5%, p-value 0.15), or the improved DFS allowing more patients to proceed to HCT in CR1. The authors noted no benefit in OS was seen with midostaurin compared to placebo when patients underwent transplant in a later CR [8].
- A study evaluating the role of midostaurin consolidation therapy following HCT has recently been completed demonstrating safety in the post-HCT setting and a trend toward improved PFS. (CTN: NCT01883362, Maziarz et al.).

f. Quizartinib (AC220)

  i. A phase 2 study demonstrated the potency and efficacy of quizartinib among FLT-3+ (AR >10%) patients aged ≥60 with refractory AML or disease relapse within 1 year of induction therapy, or patients age ≥18 who had undergone salvage chemotherapy or HCT [70].

- Quizartinib was associated with a composite CR (CR, CR with incomplete platelet recovery (CR_p), and CR with incomplete hematological recovery (CR_i)) rate of 56% in the FLT-3$^+$ cohort versus 36% among the FLT-3$^-$ cohort [70].
- Adverse events included febrile neutropenia, anemia, thrombocytopenia, neutropenia, leukopenia, QTc prolongation, and pneumonia [70].

ii. Results of the phase III QUANTUM-R study evaluating the efficacy of quizartinib were presented at the 2018 ASH meeting.

- Three hundred sixty-seven patients with relapsed/refractory AML within 6 months following standard therapy with or without a history of HCT were randomized to receive quizartinib or one of three standard-of-care (SOC) regimens consisting of low-dose cytarabine; mitoxantrone, etoposide, and intermediate dose cytarabine (MEC); or fludarabine, cytarabine, granulocyte colony stimulating factor (G-CSF), and idarubicin (FLAG-Ida).
- Patients were able to continue on quizartinib maintenance following allo-HCT [71].
- Median OS was 6.2 months with quizartinib versus 4.7 months in the SOC arm. There was no significant difference in EFS between the quizartinib arm versus SOC (6.0 months vs. 3.0, p-value 0.1071).
- The composite CR was 48% with quizartinib versus 27% with SOC.
- Thirty-two percent of patients receiving quizartinib went on to HCT, compared to 12% in the SOC arm, and 62% of quizartinib patients received post-HCT maintenance therapy [71].

iii. A phase 1, multicenter dose-escalation study of quizartinib post-HCT in FLT-3$^+$ AML demonstrated promising results [75].

- Quizartinib was dosed at either 40 mg/day or 60 mg/day for 28-day cycles.
- Seventy-seven percent of patients received quizartinib for >1 year, and 38% completed 24 cycles.
- OS ranged from 13 to 142 weeks with approximately 70% patients surviving ≥50 weeks and 1 relapse [75].
- The most common grade 3 or 4 adverse events of quizartinib therapy included neutropenia, leukopenia, anemia, thrombocytopenia, and lymphopenia [75].
- The rate of GvHD was 69%, not significantly different than rates reported among other studies [75].

g. Gilteritinib (Xospata®)

i. Gilteritinib demonstrated potent efficacy among patients with relapsed/refractory AML, with 40% of patients responding, and 8% achieving CR, 4% CR_p, 18% CR_i, and 10% PR [76].

ii. Gilteritinib demonstrated efficacy against FLT-3 ITD$^+$ and FLT-3 D835 (TKD) relapsed/refractory patients with an overall response rate of 49% compared to 12% among patients with wtFLT-3 and patients with prior TKI treatment (overall response rate [ORR]: 42%) or without (ORR: 56%) [72, 76].

iii. The addition of gilteritinib with standard anthracycline-based induction and consolidation chemotherapy followed by gilteritinib maintenance also demonstrated promising results [78].

- Among the FLT-3$^+$ group ($n = 23$), CR$_c$ was 91.3%, compared to 56% in FLT-3$^-$ group [78].
- FLT-3$^+$ patients receiving ≥80 mg/day of gilteritinib had CR$_c$ rates of 90% versus 60% in FLT-3$^-$ patients [78].

iv. Based on these trials, the FDA approved gilteritinib for the treatment of FLT-3$^+$ relapsed or refractory AML [79].

v. At the time of publication, a BMT CTN-sponsored, phase 3 randomized, placebo-controlled trial of gilteritinib as maintenance therapy following HCT is ongoing, along with studies evaluating the role of FLT-3 inhibition as a component of induction or maintenance therapy pre- or post-transplantation [68, 77].

Key Points

1. Patients with FLT-3-positive AML should receive FLT-3-targeted therapy with midostaurin, or enroll in a clinical trial utilizing FLT-3 inhibitors in addition to induction.
2. HCT in conjunction with targeted therapy should be considered in patients with MRD-positivity.
3. Clinical trials utilizing midostaurin, sorafenib, or gilteritinib should be considered for maintenance therapy following achievement of CR both pre- and post-HCT.
4. For patients with relapsed/refractory FLT-3$^+$ AML, gilteritinib should be considered in combination with cytotoxic therapy.

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2. IDH inhibitors

a. Isocitrate dehydrogenase gene (IDH1 and IDH2) mutations are also amenable to targeted therapy.

i. IDH1 and IDH2 are commonly mutated in cytogenetically normal AML and play a critical role in cellular metabolism by catalyzing the conversion of alpha-ketoglutarate to the oncometabolite R enantiomer of 2-hydroxyglutarate (R-2HG) [6, 80, 81].

ii. R-2HG has demonstrated the ability to block cellular differentiation and promote proliferation via inhibition of TET2 and the downstream effects

of demethylation *in vitro*, providing evidence of the pivotal role of IDH mutations in leukemogenesis [82, 83].

b. Ivosidenib (Tibsovo®)

  i. Ivosidenib demonstrated efficacy in patients with IDH1-mutated, relapsed, or refractory AML.

- In the primary efficacy population, CR or CR_p was achieved in 30.4% of patients with a CR in 21.6%.
- The median duration of CR/CR_p was 8.2 months and 9.3 months for CR.
- Median OS was 8.8 months with 50.1% of patients with a CR/CR_p surviving a median of 18 months.
- Patients who achieved mutational clearance of *IDH1* had a median CR duration of 11.1 months versus 6.5 months and OS of 14.5 months versus 10.2 months.
- Ivosidenib was well tolerated at doses of 500 mg daily.
- Grade 3 or higher adverse events included QT prolongation, the IDH differentiation syndrome, anemia, thrombocytopenia, leukocytosis, febrile neutropenia, and diarrhea [7].

c. Enasidenib (Idhifa®)

  i. Among patients with relapsed or refractory AML with IDH mutations R140 and/or R172 (activating mutations giving IDH2 its neomorphic enzymatic activity [84]), the ORR with enasidenib was 40.3% (35.4% for R140 mutations, and 53.3% for R172 mutations), with 19.3% obtaining CR (17.7% for R140 mutations, and 24.4% for R172 mutations) [6].

  ii. Median OS was 19.7 months for patients who achieved CR and 14.4 months for a partial CR.

  iii. Grade 3/4 adverse events occurred in 41% of patients, with the most common (>5%) being indirect hyperbilirubinemia, the IDH differentiation syndrome, anemia, and thrombocytopenia [6].

d. Combination therapy

  i. Ongoing studies are evaluating the addition of targeted therapy with cytotoxic induction therapy.

- A phase 1 study demonstrated the addition of ivosidenib or enasidenib to anthracycline-based induction therapy was associated with a CR rate of 66% and 55%, respectively, and CR_i/CR_p rates of 12% and 14%, respectively, among patients with predominantly intermediate- and adverse-risk AML with a median age of 63 years [85].

  – These results were driven by robust responses among patients with *de novo* AML among the ivosidenib group (CR: 93% in *de novo* vs. 46% in sAML with ivosidenib; CR: 73% *de novo* vs. 63% sAML enasidenib).

- Ninety-one percent of ivosidenib patients and 43% of enasidenib patients achieving CR or CR_i/CR_p demonstrated mutational clearance.
- MFC assessment of patients in CR demonstrated 89% of ivosidenib patients and 58% of enasidenib patients had no MRD.
- Grade 3/4 adverse events occurring in ≥10% of patients included febrile neutropenia, hyperbilirubinemia, pulmonary/urinary tract infections, colitis, hyper/hypotension, electrolyte disturbances, and acute kidney injuries [85].

e. To date, IDH inhibitors have not been evaluated in the post-HCT setting for maintenance therapy.

Key Points
1. Consideration should be given to the use of enasidenib (Idhifa®) or ivosidenib (Tibsovo®) in patients with IDH1 and IDH2 mutations.
2. No data currently exist on IDH1/2 inhibitor maintenance following HCT.

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Chapter 16
Acute Lymphoblastic Leukemia

Richard T. Maziarz and Gerhard C. Hildebrandt

Introduction

Allogeneic hematopoietic cell transplantation (HCT) has been a standard and effective therapy in the management of patients with all stages of acute lymphoblastic leukemia (ALL). Transplant providers face multiple considerations when evaluating patients with ALL and assessing the risks and benefits of its application. These include age, and whether the subject is considered a pediatric case, an adolescent/young adult (AYA) (age 16–40), or an elderly patient. Utilization of HCT options can be applied in the upfront setting as consolidation of induction therapy in patients in first clinical remission (CR), for patients with minimal residual disease (MRD) determinations after induction therapy, or for patients with relapsed or refractory disease. Cell of origin, molecular and cytogenetic characteristics, and phenotypic subtypes influence decision-making. For example, higher risk settings that still mandate early HCT include Philadelphia (Ph) + B-cell ALL where the translocation of chromosomes 9 and 22 creates the proliferative driver mutated P190 BCR ABL (and in less number of cases, P210) fusion protein, Ph-like ALL, and early T-cell precursor ALL; all more malignant natural histories when treated with standard chemotherapy induction approaches.

Given the high cure rate associated with chemotherapy in the management of pediatric ALL, the focus of this chapter will be on adult patients with ALL [1–3].

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Utilization of HCT for the adult patient with ALL may be more critical as these patients have a lower expected cure rate. However, given age and comorbidities, the risks of nonrelapse mortality (NRM) are consequently increased after allogeneic HCT. Regarding determining the role of transplantation, there were multiple early studies that supported this approach but the study that marks the modern era approach to adult ALL HCT was the Medical Research Council (MRC) UKALL XII/Eastern Cancer Oncology Group (ECOG) 2993 study, the largest available study ever performed in which 1646 adult patients were randomized [4–6]. This myeloablative transplantation study utilized randomization by donor availability in which patients who were identified as having HLA-matched sibling were assigned to an allogeneic HCT procedure arm. If the patient did not have a matched sibling, they were randomized to ongoing chemotherapy for 30 months or alternatively, autologous HCT. In this setting, when restricting the analysis to Ph (−) ALL, the availability of a matched sibling donor was associated with the superior overall survival reported at 53% versus 45% at 5 years, ($p = 0.01$). This survival difference was seen in patients with standard risk ALL (defined by age and molecular characteristics), but not in high-risk patients due to increased nonrelapse mortality (NRM) of 36% observed at 2 years. Also importantly, chemotherapy was found to be superior to autologous HCT with a higher 5-year overall survival (OS) rate (46% vs 37%, $p = 0.03$.) This particular study, published by Goldstone et al. in 2008 [5], served to define myeloablative transplantation approaches for the adult ALL subject. Its importance was highlighted by the subsequent observation that of the 609 patients who had documented relapse, less than 10% 5-year survival was observed, demonstrating to what was felt to be "myth of second remission" as many patients had refractory relapses [7].

A subsequent evidence-based review sponsored by the American Society of Blood and Marrow Transplantation (ASBMT) [currently known as the American Society for Transplantation and Cellular Therapy (ASTCT)] endorsed this approach that allogeneic HCT be considered over chemotherapy for adult patients in all risk groups but recognized that this recommendation applied to patients through age 35 (evidence = grade A) [8]. Over age 35, higher treatment-related mortality (TRM) diminished the survival advantage. For patients without a donor, autologous transplantation was felt equivalent to chemotherapy and only provided a benefit of a shorter treatment interval but was associated with a high relapse rate. In that same analysis, there was no recommendation for any particular induction therapy but that the goal was to achieve CR. Grade B evidence included observations of superiority of allogeneic HCT over chemotherapy in CR2, the equivalence of outcomes when using matched related and matched unrelated donors, and the use of cord blood transplantation if no adequate family or unrelated donors were available. The data were not robust enough to define an optimal conditioning regimen, but it was felt that total body radiation (TBI) should be strongly considered. The study also noted that reduced intensity conditioning (RIC) may deliver similar outcomes to myeloablative therapy for patients in CR. Finally, a meta-analysis published by Gupta et al., in 2013 analyzing 13 prior randomized trials of 2962 Ph(-) ALL patients demonstrated an overall benefit of HCT over a no donor approach [9]. Specifically, it

confirmed the benefit for patients under age 35, for male patients, and for those with standard risk disease with a trend to benefit seen in other subgroups.

Since this time, multiple advancements in the management of adults with ALL have emerged, thus changing all modern standards for transplantation approaches for these patients. These advancements will be reviewed in subsequent sections.

MRD Assessments and HCT Decision-Making

1. There have been multiple analyses of prognostic factors in adult allogeneic HCT for ALL [1, 3]. These include the following:

   a. Age which is likely a continuous variable associating higher risk with increasing age, with a commonly used cutoff of age >35 or 40 based on previous studies.

   b. Immunophenotype has also been characterized where T lineage ALL with presenting white blood counts $>100 \times 10^9$/L and B lineage ALL with presenting white blood cell counts $>30 \times 10^9$/L were considered high risk.

   c. Failure to attain a CR within 4 weeks after treatment initiation also has been associated with worse outcome.

   d. Similar to AML, cytogenetics are being used to define risk categories [10, 11].

      i. Hyperdiploid karyotype with >50 chromosomes and t(12;21) (p13;q22) translocation in B-cell precursor ALL are associated with an excellent prognosis.

      ii. t(1;7))p32;q35) and t(1;14)(p32;q11) translocations, interstitial 1p32 deletion, TAL1 dysregulation, t(11;14)(p15;q11), and 5'LMO2 deletion and LMO2 dysregulation are associated with favorable outcome in T-ALL.

      iii. Intermediate risk prognostic markers for B cell–ALL include trisomy 21 or trisomy 8, t(1;19), as well as deletion 6 q.

      iv. High-risk prognostic cytogenetic markers have traditionally included the Ph positive abnormality, involvement of the MLL locus at 11q23, t(4;11), a hypodiploid (<44 chromosomes) or high hyperdiploid (near tetraploid presentation), complex cytogenetics defined >5 abnormalities, and monosomy 7.

      v. Immunophenotyping has suggested that CD20 is a poor prognostic disease indication while cortical TPN and Ticlid CD1a positivity was a good prognosis [12–14].

   e. Finally, important clinical measure of disease prognosis was based on time to response to induction therapy with failure to gain CR within 4 weeks of induction (although some studies have extended this to 8 weeks) as highly predictive of eventual relapse.

2. What is emerging in the modern age as one of the key predictors of relapse is the level of MRD after primary therapy [15]. As such, assessment of MRD has now been incorporated into many clinical trials and has become an SOC for patients with adult ALL [3].

   a. Sensitivity is critical and assays should have a sensitivity of at least 10^{-4} as this degree of detection can impact treatment decision-making.
   b. One early study, which demonstrated the impact of MRD$^+$ status after induction therapy, was performed by the German Multicenter Study Group for Adult ALL (GMALL). This study showed that after induction therapy, that the presence of MRD was the only significant factor in multivariate analysis to predict OS with 80% OS identified in those patients who were in molecular CR at 16 weeks versus 42% having failed to meet this target [16].
   c. Other subsequent trials showed a similar impact of MRD and decision-making for ALL. Analysis combined data from two trials, that of the GRAALL-2003/GRAAL-2005, demonstrated that HCT could overcome MRD$^+$ ALL after induction, inclusive of patients age 15 through 55 [17]. Additional benefit was not identified in those patients who were MRD$^-$ after induction.
   d. In a summary of a recent large meta-analysis of 806 patients treated in five different ALL studies, clearance of MRD following frontline therapy was critically important in predicting overall survival with a hazard ratio of 0.28 [15].
   e. These observations have so influenced the field that MRD status is currently used to inform the decision-making regarding consolidative HCT for CR 1 ALL patients.

      i. The PETHEMA ALL-AR03 trial identified patients with high-risk Ph(–) ALL and assigned patients to HCT based upon the presence or absence of MRD after consolidation [18].

         a. HCT was limited to those patients with a poor early morphologic response or persistent MRD disease status.
         b. At 5 years, the disease-free survival (DFS) was 55% for those receiving chemotherapy and 32% per those assigned to the HCT group.

      ii. As such, it is anticipated that stratification for aggressive management of CR 1 patients will be driven by a depth of response.
      iii. Older patients that may not be able to tolerate intensive regimens designed to achieve MRD$^-$ status will still be able to be considered for first remission transplantation, balancing the associated previously reported prior TRM with the utilization of reduced intensity conditioning. These approaches have been performed in small institutional studies but also within registry studies to provide satisfactory outcomes but have not been assessed in a randomized study with myeloablative transplantation after intensive induction regimens.

The Impact of Age on HCT Decision-Making

1. The afore mentioned MRC/ECOG study demonstrated superiority of allogeneic HCT using myeloablative conditioning compared to chemotherapy for adult patients where the benefit was seen in patients through age 35. Over that age, TRM neutralized the immunologic benefit of the transplant allograft.
2. Recognition that toxicity was negating the benefit of an allogeneic HCT for older patients contributed to expansion of RIC for the procedure. Recent retrospective registry analyses have suggested that limiting myeloablative conditioning for ALL patients have been met with acceptable outcomes [19–22].
3. Recent studies have demonstrated that patients in the AYA age group can benefit from more intensive, asparaginase-containing chemotherapy induction therapy.

    a. Pediatric ALL induction regimens are intensive and have been associated with increasing cure rates for the young patient.
    b. Examination of patients within the AYA age group (see also Chap. 9) treated on pediatric regimens versus adult regimens demonstrated significant improvement in overall survival when treated with the more intensive upfront pediatric induction regimens [23].
    c. Recently, the CALGB-sponsored, US intergroup 10403 study analyzed utilization of frontline pediatric ALL induction therapy administered to adults through age 40 [24].

        i. A 66% projected 3-year DFS and 73% projected OS was observed
        ii. Additionally, the critical impact of MRD was confirmed. Those patients who had detectable disease had a 54% 3-year DFS versus 85% for those that were negative.

    d. Thus, current recommendations support the use of pediatric-inspired intensive induction regimens in the AYA population to gain MRD negative status and in that case, continue with chemotherapy consolidation and maintenance.
    e. Allogeneic HCT in the AYA population shall be reserved for those patients with persistent MRD and for the small subset of patients with high-risk features [1].

The Impact of Immunotherapy Utilization on HCT Decision-Making

1. Incorporating immunotherapeutic tools into the standard chemotherapy approaches for patients with ALL has had the greatest impact on HCT, particularly in patients with relapsed, refractory disease. It is generally recognized that refractory ALL has only limited success with salvage HCT. Unconjugated or conjugated antibodies and bispecific antibody constructs, as well as emerging

immune effector T-cell therapy are now creating clinical options for patients who otherwise lacked these options.

2. CD20 expression on B-cell ALL has historically been considered a high-risk feature. However, introduction of rituximab (Rituxan®) into the standard induction hyper CVAD regimen for patients age < 60 was associated with improved 3-year OS, 75% versus 47%, $p = 0.003$ [12]. Similar results were reported within the GRALL-2005 study where the event-free survival (EFS) was significantly higher in patients with CD20+ ALL when treated with rituximab [14]. Currently, introduction of rituximab during induction is now standard after the identification of CD20 surface antigen in patients with newly diagnosed B-cell ALL.

3. Blinatumomab (Blincyto®) is a bi-specific antibody construct that leads to host T-cell B-cell coupling interactions by binding surface CD19 on the B-cell and CD3 on the T-cell. (See also Chap. 57).

   a. This drug was shown to be effective for relapsed, refractory CD19+ B-cell ALL in adult patients aged 18–80 when compared to SOC salvage chemotherapy for which the United States Food and Drug Administration (FDA) approval was granted [25]. OS was improved (median 7.7 vs 4.0 months) with improved complete remission or with incomplete hematologic recovery (CR/Cri) status (44% vs 25%). Duration of remission was 7.3 versus 4.6 months with fewer adverse events experienced by the patients. Notably though, in both arms, 24% of patients were capable of proceeding to salvage allogeneic HCT and with censoring patients at the time of HCT for survival, there was again improvement of blinatumomab with 6.9 versus 3.9 months, $p = 0.004$.

   b. Similarly, in a phase 3 study assessing pediatric and AYA patients experiencing first relapse of their B-cell ALL, inclusive of ages 1–30, lower toxicity, superior MRD clearance (21% vs 79%), increased percentage of patients proceeding to transplant (45% vs 73%), and superior 2-year OS was observed (59% vs 79%) [26].

   c. Most recently, blinatumomab has been incorporated into a phase 2 study of induction chemotherapy in adult patients where hematologic remissions were achieved but MRD > 0.001% was observed. Using blinatumomab as consolidation, 78% of patients gained a complete MRD response after a single cycle. The 18-month relapse-free survival (RFS) was 54% with a median OS of 36.5 months [27].

   d. These successful studies have led to introduction of blinatumomab into multiple studies as the frontline therapy along with chemotherapy.

      i. The addition of this agent has led to increased remission rates in patients with relapsed disease, allowing patients to proceed to HCT who otherwise would have been considered to be ineligible due to resistant disease.

      ii. The important impact of blinatumomab added to primary induction therapy may prove to provide deeper complete remissions and decrease the

number of patients with MRD[+] status after induction, thus decreasing the number of ALL patients who actually proceed to allogeneic HCT.

4. Inotuzumab ozogamicin (Besponsa®) is a CD22-targeted immune conjugate utilizing caliceamicin as a specific cytotoxic agent toward CD22-expressing B lymphoblasts. The drug received FDA approval based upon its use in a phase 3 study for relapsed, refractory CD22^{+} B-cell ALL patients, aged 18–79 [28].

   a. Similar to the blinatumomab study, patients were randomized to receive either the immune conjugate or SOC salvage chemotherapy. CR rates were significantly higher in the study group (80.7% vs 29.4%) and of those patients who gained CR status, significantly more patients demonstrated MRD negativity, (78.4% vs 28.1%, $p < 0.001$). Significantly there was improved 2-year OS in the study group of 23% versus 10%, and notably, 41% of patients were able to proceed to HCT versus 11% with standard salvage chemotherapy. Thus, inotuzumab was an effective bridge to HCT in patients who otherwise would have been considered ineligible.

   b. Importantly and similar to previous studies with gemtuzumab (Mylotarg®), sinusoidal occlusive syndrome (SOS) was observed in patients after receiving inotuzumab and particularly, 21% of patients who proceeded to transplant developed SOS compared to only one patient of the standard therapy recipients, including some fatalities.

5. Chimeric antigen receptor T cell therapy: Tisagenlecleucel (Kymriah®) is an autologous immune effector cell therapy (see also Chap. 52) in which a chimeric gene construct is incorporated into the genome of host T cells after lentiviral infection. On expression, this construct can recognize target cell CD19 surface expression. The drug has now been FDA approved for relapsed, refractory ALL in patients through age 25.

   a. In the registration ELIANA study, a phase 2 trial of relapsed, refractory CD19^{+} ALL of patients aged 3–23, CR rates at 3 months were 81%, with all patients in remission gaining MRD negativity as determined by multicolor flow cytometry [29]. Twelve-month EFS was 50% with an OS of 76%. Updated data demonstrated a 24-month RFS of 62%. Notably, all patients at study entry had measurable, active relapsed, refractory ALL, and many of the recipients had actually failed allogeneic HCT.

   b. Multiple new studies are emerging including utilization of CAR-T cells in the upfront setting for patients aged 1–25, where tisagenlecleucel is used after consolidation for patients with MRD[+] status.

      i. An interesting study from Stanford demonstrated that CAR-T targeting CD22 can effectively rescue patients who fail CD19 directed immune effector cell therapy [30].

      ii. Additionally, the Center for International Blood and Marrow Transplant Research (CIBMTR) cellular therapy registry has reported "real world"

evidence that these deep responses in patients with relapsed, refractory ALL can be reproduced and observed in patients, including those with patient characteristics that would have made them otherwise, ineligible for trial participation [31].

Ph⁺ ALL

Ph⁺ ALL, one of the most frequent ALL subtypes in the adult patient population, presents a current challenge with respect to management. Historically, the outcomes of Ph⁺ disease were very poor (5-year OS 5–20%), and allogeneic HCT was considered the only way to achieve long term remission and cure [32, 33]. Currently, this approach has been significantly upgraded due to the introduction of tyrosine kinase inhibitors (TKIs) as the first-line therapy with TKI therapy leading to higher rates of MRD negative state at the time of transplant. Regardless, when decided on the management approach, additional factors such as relapse risk after transplant, especially in the older patient population, treatment-related morbidity, and mortality must be taken into consideration.

1. Complete hematologic remission (CHR) can be achieved by combining either intense induction chemotherapy [34–40] or less intense regimens [41–44] with a TKI in about 90–100% of cases but also with a TKI +/− prednisone alone [45, 46]. MRD responses vary between regimens, and TKIs but seem to be most promising with ponatinib (Iclusig®) with up to 83% of patients achieving a complete molecular remission (CMR) and 97% achieving a major molecular response (MMR) [40, 44, 47].

   a. Historically, allogeneic HCT was limited to the younger and fit population, receiving myeloablative conditioning, often TBI-based, in both the MRD⁻ and MRD⁺ state. Achieving high CHR rates along with high CMRs and MMRs even with less intense induction chemotherapy has led to an increase in older patients being transplant-eligible with up to 80% patients in CHR receiving an allogeneic HCT in the current age [48].

   b. Despite knowing that less intense conditioning regimens are associated with higher relapse rates and significantly inferior survival, this strategy often presented the only chance for improved long-term progression-free survival [49, 50].

   c. This outcome has recently changed with the introduction of novel treatment modalities such as inotuzumab, blinatumumab, and third generation TKIs such as ponatinib, when second line ALL treatments have been shown to induce high levels of MRD negative states either in MRD+ or hematologically relapsed ALL patients [25, 27, 51, 52]. Therefore, allogeneic HCT should and can now be preferably performed in the MRD negative state.

   d. Another challenge in the management of Ph+ ALL patients in the current age is the larger population of older patients undergoing allogeneic HCT, as their

risk of treatment-related morbidity and mortality after myeloablative conditioning can be high [52, 53]. For these patients, evidence is growing that RIC allogeneic HCT, especially in the MRD negative state, allows for mitigation of treatment-related toxicity and mortality, leading to improved long-term progression-free survival (PFS) [54].

e. *In summary*, induction chemotherapy including a TKI followed by allogeneic HCT leads to OS of 50–70% at 2–4 years, and therefore has been considered SOC in transplant eligible patients [37, 40, 55, 56].

2. Relapse in Ph+ ALL patients remains a significant problem after allogeneic HCT, and efficacious preventive and therapeutic approaches remain a priority for development.

   a. Some studies have explored the preventive use of TKIs as maintenance therapy after transplant, demonstrating a reduction in cytogenetic and hematologic relapse and improved PFS, whereas others have not [54, 57–61].

      i. Molecular MRD-triggered initiation of TKI administration as an alternative to preemptive maintenance has shown promising results as well, and a comparison between MRD- triggered start of imatinib versus preemptive start of imatinib (Gleevec®) after allogeneic HCT did not show differences in OS [62, 63].

      ii. TKIs usually are relatively well tolerated after allogeneic HCT, have a limited toxicity profile, and are "easy to take" for the patients.

      iii. Studies directly comparing first (imatinib) versus second (dasatinib [Sprycel®], nilotinib [Tasigna®]) or third generation (ponatinib [Iclusig®], bosutinib [Bosulif®]) TKIs with respect to efficacy and toxicity are lacking. BCR/ABL kinase domain mutations are frequent in Ph+ ALL, and a personalized approach based on mutation profile and on clinical comorbidities favoring one TKI over the other TKI is often used in clinical practice.

      iv. Whether preemptive or MRD-triggered TKI after allogeneic HCT is chosen often results from the patient's performance status, peripheral blood cell counts, the ability to perform recommended close molecular monitoring by quantitative polymerase chain reaction (qPCR) after HCT, and cost coverage status for molecular monitoring and drug supply. Whether dasatinib, due to its better CNS penetration, provides a benefit in patients with CNS involvement at diagnosis compared to other TKIs is not known.

   b. Hematologic relapse after allogeneic HCT is challenging, and various approaches, such as TKI therapy alone, blinatumumab alone, or inotuzumab alone or in combination with chemotherapy depends on the clinical context, as does the decision whether the patient may benefit from a second allogeneic HCT.

   c. Considering the high rate of transplant-related morbidity and mortality with allogeneic HCT, both autologous HCT and nontransplant treatment options for Ph+ ALL have been progressively explored.

    i. The Alliance Group demonstrated the feasibility of autologous HCT followed by imatinib with a promising outcome in their CALGB Study 10001 where OS and DFS were similar between those that underwent autologous HCT and allogenic HCT [64].

   ii. A recent European Society of Blood and Marrow Transplant (EBMT) Acute Leukemia Working Party retrospective analysis compared autologous HCT for MRD⁻ Ph⁺ ALL with allogeneic HCT [65].

- While the incidence of relapse was much higher (47% vs 28% [matched sibling donor HCT] and 19% [unrelated donor HCT]), nonrelapse mortality was decreased in these groups (2% vs 18% vs 22% respectively), resulting in comparable leukemia-free survival at 2 years (52% vs 55% vs 60%) and similar 2-year OS (70% vs 70% vs 69%).
- Of note, in the autologous HCT group, 95% of patients received TKI post-HCT, while in the matched sibling and unrelated donor allogeneic HCT groups only 51% and 43%, respectively, were given TKI post-transplantation.

  iii. Autologous HCT may provide an alternative to allogeneic HCT in patients where a suitable donor cannot be identified, yet it still requires a certain patient performance status due to the need of a myeloablative conditioning and an MRD⁻ state at the time of transplant as well as an MRD⁻ stem cell collection product.

  d. To spare both conditioning toxicity and allogeneic HCT-related sequelae like acute and chronic GvHD, nontransplant approaches are being assessed [40].

    i. Most recently, an update of the prior report by Jabbour et al. was reported on the combination of hyper-CVAD alternating with high-dose methotrexate/cytarabine in combination with ponatinib as frontline therapy for ALL. Excellent outcomes were seen with an OS of 73% and CMR rate of 84%. For patients not undergoing allogeneic HCT in CR1, a 3-year OS rate of 90% was seen [66], suggesting that nontransplant approaches could evolve to be a new SOC with confirmation needed in phase III randomized trials.

Ph-like ALL

1. In 2016, the updated World Health Organization (WHO) classification of hematopoietic neoplasms added a new entity, designated BCR/ABL1-like B-ALL (Philadelphia-like or Ph-like ALL). This ALL subtype was first reported by Mullighan, et al. [67] and den Boer, et al., in 2009 [68], and represents about 10–20% of newly diagnosed and 20–30% of adult B-cell ALL [69–72]. By definition, the disease is BCR/ABL negative, MLL negative, ETV/RUNX1 negative, and TCF3/PBX1 negative [70, 72]. Hyperdiploidy and other cytogenetic aberrations, including high-risk aberrations, can be found.

2. Ph-like ALL is characterized by its aggressive nature, often presenting with a high WBC, an overall poor response rate with a high rate of MRD positivity after induction, and an associated high relapse rate [67–70, 73, 74].

3. Studying the mutation profiles of 1725 patients with B-cell ALL, 90% of Ph-like ALL cases had activating kinase mutations [70]. Further analysis over the following years has now led to the understanding that Ph-like ALL encompasses a heterogeneous group of "Ph-like ALL subtypes" which are continuously expanded and revised as the body of experience grows.

4. Ph-like ALL subtypes are placed into one of four major subtype groups depending on their genetic profile [70, 75] with some minor differences between "clinically driven" and "pathologically driven" classification systems. The most recent classification has been reported by Jain et al. [75]:

   a. Alterations in JAK/STAT

      i. 50% of Ph-like ALL have CRLF2 mutations of which approximately half have activating JAK2 mutations. JAK2 wild type/CRLF2 rearranged cases often have mutations in JAK1, JAK3, FLT3, and IL7R.
      ii. 5% of Ph-like ALL have EPOR translocations.
      iii. JAK2 rearrangements are found in 7% of Ph-like ALL.
      iv. Rare: TSLP, IL2RB, and TYK2 mutations.
      v. In some classification approaches, CRLF2 mutation defines a separate subtype from the JAK/STAT pathway group [76].

   b. ABL class translocations are seen in 10% of Ph-like ALL including ABL1, ABL2, PDGFRB, PDGFRA (rare), and CSF1R.
   c. RAS mutations (KRAS, NRAS, NF1, PTNP11, CBL1, and BRAF) are seen in 4% of Ph-like ALL.
   d. Rare kinase alterations (NTRK3, FLT3, BLNK, FGFR1, DGKH, and PTK2B).

5. Diagnostic work-up for Ph-like ALL is complex but should be included in all newly diagnosed B-cell ALL patients irrespective of age. Depending on resources and time requirements, different approaches have been described: [68, 76, 77] a stepwise algorithm versus comprehensive unbiased testing [72, 78] (for an example of detailed workup recommendations, see Fig. 16.1).

6. If the diagnosis of Ph-like ALL can be made early on, a clinical trial should be considered as the first treatment choice. However, often treatment is initiated prior to having available molecular results, and in those cases, standard induction treatment of Ph-like ALL follows induction chemotherapy recommendations for Ph⁻ B-cell ALL. High rate of MRD positivity at the end of induction chemotherapy, the overall poor prognosis across all genetic Ph-like ALL subtypes [70, 79, 80], and reported associations of certain mutations (e.g., PDGFRB-R, IKZF1, CRLF2, JAK2 alterations) [71, 80–82] with even worse survival, often require intensified consolidation with allogeneic HCT and novel concepts incorporating targeted therapy.
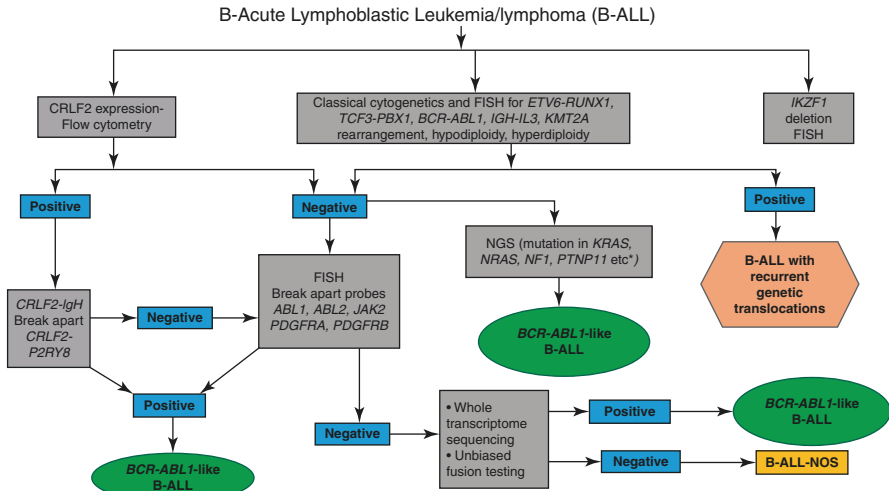
Fig. 16.1 Stepwise diagnostic algorithm for BCR-ABL1-like B-acute lymphoblastic leukemia. (Used with permission from Jain and Abraham [75])

7. At present, there is no absolute guidance whether to transplant all patients in CR1 or whether MRD negativity with intensified chemotherapy consolidation would provide comparable outcome without the risks of transplant-related morbidity and mortality.

   a. While allogeneic HCT is often recommended for adult MRD+ patients, some pediatric protocols include intensified chemotherapy, not necessarily followed by allogeneic HCT [76, 83, 84].

   b. Additionally, one recent analysis by the Italian Association of Pediatric Hematology/Oncology (AIEOP) showed no improvement in outcome with allogeneic HCT in children with high-risk ALL, still supporting early allogeneic HCT for its potential associated GvL effects [85, 86].

   c. A retrospective analysis of the European Working group for Adult Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the EBMT recommended allogeneic HCT in CR1 only in pediatric and adults with MRD+ Ph-like ALL [3], supporting an earlier report of a reduction in relapse risk in patients with high levels of MRD undergoing allogeneic HCT [87].

   d. The caveat with using MRD negativity as a decision point whether to proceed with allogeneic HCT in Ph-like ALL lies in the concern that the threshold for molecular MRD differs between ALL subtypes. Additionally even MRD− high-risk pediatric ALL patients remained at increased risk for relapse. Therefore, it may be reasonable to consider all Ph-like ALL patients as high risk, regardless of their MRD status [71, 76, 88–90].

8. Aldoss et al. [91], recently provided a very detailed perspective on the role of allogeneic HCT for Ph-like ALL, reiterating the value of allogeneic HCT in MRD⁺ Ph-like ALL and the lack of clarity in MRD⁻ patients.

   a. Long-term outcome data specific for Ph-like ALL patients achieving MRD negativity using pediatric/AYA protocols are lacking.
   b. For unfit younger patients unable to tolerate pediatric/AYA protocols in their full intensity or unfit younger or older patients receiving alternative chemotherapy regimens not as intensive as pediatric/AYA protocols who achieve MRD negativity, it is not clear whether their overall outcome benefits from allogeneic HCT in CR1 or in CR2 given the higher chance to achieve a remission, and potentially MRD negativity after relapse using novel agents such as blinatumumab, inotuzumab, or CAR T cells.

9. It is well known that outcomes of allogeneic HCT for patients with MRD positivity at the time of transplant, despite achieving MRD negativity after allogeneic HCT, are inferior compared to allogeneic HCT in the MRD negative state [92–94].

   a. For those patients not becoming MRD⁻ at the end of induction chemotherapy, attempts may be considered to potentially achieve an MRD negative state using intensified chemotherapy, novel agents like blinatumumab, inotuzumab, or targeted therapy such as ruxolitinib (Jakafi®) or other TKIs in preparation for transplant [76].
   b. This strategy has to be balanced against the delay in transplant and the associated increasing risk for hematologic relapse and the possible clinical worsening of the patient's overall performance status due to toxicities and therapy, potentially affecting transplant eligibility.

10. The role of maintenance after allogeneic HCT in patients with Ph-like ALL has not specifically been addressed. However, potential targets are defined by the underlying involved signaling pathways in Ph-like ALL [69, 80, 95–101].

    a. ABL kinase-activating mutations may be successfully targeted using TKIs like imatinib or dasatinib; this approach is already being used in Ph+ B-ALL.
    b. Alterations in the CRLF2/JAK/STAT signaling pathways could be targeted using JAK1-, JAK2-, or JAK3 inhibitors and for TYK2-mutated Ph-like ALL TYK2 inhibitors.
    c. RAS signaling mutations could be targeted using MEK inhibitors.
    d. FLT3 mutations may be targeted using FLT3 inhibitors.
    e. FGFR1 may be targeted using sorafenib (Nexavar®), ponatinib, or dasatinib [101].
    f. Of note, all these maintenance strategies are considered experimental. Some of these targeted therapies are currently being tested as first-line treatment approaches for Ph-like ALL.

Summary

HCT remains an SOC procedure for adult and pediatric ALL patients who present with either high-risk or relapsed disease, with the focus of the procedure at establishing immunologic host tolerance while contributing a GvL benefit to the recipient. The management of ALL has had significant advances in the past decade complicating the decision-making. It is critical for the transplant provider to remain aware of this evolution of care, including application of intensive upfront chemotherapy regimens for pediatric and AYA patients, utilization of MRD detection, and emergence and rapid expansion of immunotherapeutic options with antibody conjugates and immune effector cells. These advances have altered the landscape and created new transplant algorithms for ALL management.

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Chapter 17
Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Andy I. Chen

Introduction

Hematopoietic cell transplantation (HCT) is a key treatment modality in the management of advanced Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Autologous HCT (autoHCT) can be curative for relapsed or refractory HL and diffuse large B-cell lymphoma. In low-grade lymphoma, autoHCT also improves outcomes, and allogeneic HCT (alloHCT) can be curative in multiply relapsed disease. HCT is also effective in less common lymphomas like peripheral T-cell lymphoma and primary central nervous system (CNS) lymphoma. Maintenance therapy after transplant improves outcomes in HL, follicular lymphoma, and mantle cell lymphoma.

Hodgkin Lymphoma

1. Autologous hematopoietic cell transplantation (autoHCT) for relapsed or refractory Hodgkin lymphoma

   a. Improves freedom from treatment failure in relapsed disease
   b. Schmitz et al. [1]
      i. Dexa-BEAM ×2; if chemosensitive, then randomized to Dexa-BEAM ×2 vs. high-dose BEAM

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- Dexa-BEAM

  - Dexamethasone 8 mg po q8 h, days 1–10
  - Carmustine 60 mg/m^2 IV, day 2
  - Etoposide 250 mg/m^2 IV daily, days 4–7
  - Cytarabine 100 mg/m^2 IV q12 h, days 4–7
  - Melphalan 20 mg/m^2 IV, day 3

- High-dose BEAM

  - Carmustine 300 mg/m^2 IV, day -7
  - Etoposide 150 mg/m2 IV q12 h, day -7 to -4
  - Cytarabine 200 mg/m^2 IV q12 h, day -7 to -4
  - Melphalan 140 mg/m^2 IV, day -3

    Involved field radiation was recommended for all patients with residual lesions felt to represent active disease

  - 3-year freedom from treatment failure (FFTF) 34% vs. 55%, $p = 0.019$ ($n = 161$)
  - No benefit in overall survival (OS)

b. Pre-transplant positron emission tomography (PET) positivity is predictive of outcome [2].
   i. 5-year event-free survival (EFS) 31% vs. 75%, $p < 0.001$, for functional imaging positive vs. negative entering autoHCT

c. Brentuximab vedotin (Adcetris®) maintenance improves progression-free survival (PFS) after autoHCT in high-risk disease [3].
   i. High-risk criteria: primary refractory disease [progression of disease during treatment or a partial or transient response <60 days to primary induction therapy], relapse <1 year after completion of primary therapy, or extranodal disease at relapse
   ii. Significantly improves PFS: HR 0.57, $p = 0.001$ ($n = 319$) with median PFS of 42 vs. 24 months
   iii. Dosing: 1.8 mg/kg (capped at 100 kg) every 3 weeks × 16 cycles beginning 30–45 days post autoHCT
   iv. 5-year follow-up to this randomized phase 3 trial demonstrated brentuximab continued to provide patients benefit with 59% vs. 41% PFS compared to placebo [4]

2. AlloHCT

   a. Consider as rescue after failure of autoHCT [5]
      i. As an example, a French registry study of reduced intensity alloHCT for HL. Conditioning regimens included:

      - Busulfan ≤8 mg/kg ± purine analog
      - Cyclophosphamide ≤60 mg/kg ± purine analog
      - Total body irradiation (TBI) ≤6 cGy (fractionated) ± purine analog
      - Melphalan 140 mg/m^2 + purine analog

   ii.   3-year results: OS 63%, PFS 39%, non-relapse mortality (NRM) 16%, relapse 46%.
   iii. Disease status at time of alloHCT is the most important factor for outcome.

  b. Additional studies have been completed by the Center for International Blood and Marrow Transplant Registry (CIBMTR), European Society for Blood and Marrow Transplantation (EBMT), and other single institutional transplant centers across the United States and Europe that validate these results.

Diffuse Large and High-Grade B-Cell Lymphomas

1. AutoHCT for relapsed or refractory disease

  a. The seminal phase 3 randomized "Parma" study demonstrated both EFS and OS improved in patients receiving autoHCT [6]
    i.   Chemotherapy-sensitive intermediate or high-grade NHL in relapse ($n = 215$).
    ii. DHAP ×2; if chemosensitive disease by standard imaging, patients were randomized to DHAP ×4 vs. high-dose BEAC autoHCT.

      • DHAP dosing

        – Dexamethasone 40 mg po/IV daily, days 1–4
        – Cisplatin 100 mg/m^2 IV continuous infusion, day 1
        – Cytarabine 2000 mg/m^2 IV q12 h × 2 doses, day 2

      • BEAC dosing

        – Carmustine 300 mg/m^2 IV, day 1
        – Etoposide 100 mg/m2 IV q12 h, days 2–5
        – Cytarabine 100 mg/m2 IV q12 h, days 2–5
        – Cyclophosphamide 35 mg/kg IV daily, days 2–5
        – Mesna 50 mg/kg IV daily, days 2–5
    iii. 5-year EFS 46% autoHCT vs. 12% conventional chemo, $p = 0.001$
    iv. 5-year OS 53% autoHCT vs. 32% conventional chemo, $p = 0.038$

  b. Modern era imaging utilizing PET demonstrated pre-transplant response is predictive of outcome [7].
    i.   Deauville 1–3 response vs. Deauville 4 response after salvage therapy ($n = 129$) (see Table 17.1)

      • 3-year PFS 77% vs. 49%, $p < 0.001$
      • 3-year OS 86% vs. 54%, $p < 0.001$

Table 17.1 Deauville PET score

1	No uptake
2	Uptake ≤ mediastinal blood pool
3	Uptake > mediastinal blood pool but ≤ liver
4	Uptake > liver
5	Uptake markedly higher than liver and/or new lesion(s)

Table 17.2 International Prognostic Index (IPI) for large-cell lymphoma

Risk factors	
Age >60	
Performance status >1	
Elevated LDH	
Extranodal sites >1	
Stage III–IV	
Risk group	Number factors
Low	0–1
Low intermediate	2
High intermediate	3
High	4–5

2. AutoHCT as consolidation of first remission

   a. OS benefit in high-risk group in Southwest Oncology Group (SWOG 9704) randomized clinical trial [8]

      i. Eligibility: high-risk or high-intermediate-risk age-adjusted International Prognostic Index (IPI) (see Table 17.2)

      ii. Induction therapy: CHOP or CHOP plus rituximab (Rituxan®) (for CD20+ patients) q3 weeks with restaging after cycle 5

         • CHOP, rituximab dosing

            – Cyclophosphamide 750 mg/m^2 IV, day 1
            – Doxorubicin 50 mg/m2 IV, day 1
            – Vincristine 1.4 mg/m2 (max dose 2 mg) IV, day 1
            – Prednisone 100 mg/day PO, days 1–5
            – Rituximab 375 mg/m^2 IV, day 1

      iii. Randomized if chemosensitive: additional induction × 3 vs. one additional cycle of induction followed by autoHCT

         • AutoHCT conditioning

            – TBI 12 Gy in eight 1.5 Gy fractions BID on days -8 through -5
              OR
            – Carmustine 300 mg/m^2 day -6
              PLUS
            – Etoposide 60 mg/kg IV day -4 + cyclophosphamide 100 mg/kg IV day -2

      i.   Results seen in all subjects: improvement in 2-year PFS 69% vs. 55% (HR 1.72, $p = 0.005$), but no increased OS with 2-year OS 74% vs. 71% (HR 1.26, $p = 0.3$)

      ii.   In the high-risk IPI subset, benefit was seen: 2-year OS 82% vs. 64%, $p = 0.01$

      iii. However, these data remained controversial:

- Benefit was seen with additional subset analysis
- Only 47% of B-cell NHL patients received rituximab with CHOP

      iv. No OS benefit was observed in similar randomized European studies [9]

b. Double-hit lymphoma

      i.   Defined as a high-risk variant B-cell NHL with both MYC and BCL2 or BCL6 rearrangements.

      ii.   Conventional therapy with R-CHOP is associated with an expected OS <2 years.

      iii. Multiple chemotherapy regimens have been utilized as induction prior to autoHCT; no specific transplant conditioning regimen was defined.

      iv. Transplant was performed in first remission.

      v.   No difference was observed in the 3-year relapse-free survival (RFS) nor OS between autoHCT recipients and non-autoHCT recipients [10].

      vi. AutoHCT has limited utility in relapsed or refractory double hit lymphoma [11]. Consider novel therapies, alloHCT, or chimeric antigen receptor T-cell (CAR-T) therapy instead.

3. Transformed lymphoma [12]

a. Canadian registry analysis of transformed follicular ($n = 172$).

      i.   AutoHCT improves OS compared to rituximab-chemo alone: HR 0.13, $p < 0.001$.

      ii.   5-year PFS 55% autoHCT vs. 40% R-chemo, $p = 0.12$.

b. Note: alloHCT did not improve outcomes compared to rituximab-chemo.

4. Consider CAR-T or alloHCT for patients with diffuse large or high-grade B-cell lymphoma after failure of autoHCT

Follicular and Low-Grade NHL

1. AutoHCT for relapsed or refractory disease

a. Improves outcomes in randomized "CUP" study [13]

      i.   Relapsed follicular lymphoma ($n = 140$)

- Patients received three cycles of CHOP (see section "Diffuse Large and High-Grade B-Cell Lymphomas" for dosing) prior to restaging studies

ii. Chemosensitive responders were randomized to further chemotherapy or autoHCT ± stem cell product purging.

- HCT conditioning regimen: cyclophosphamide 60 mg/m^2 IV daily × 2 day + TBI (fractionated or unfractionated)

iii. PFS at 5 years was 8% vs. 31% for patients who receive chemo alone vs. purged or unpurged autoHCT; HR 0.3, $p = 0.009$.
iv. OS at 5 years was 33% vs. 54% for patients who receive chemo alone vs. purged or unpurged autoHCT; HR 0.4, $p = 0.026$.

b. AutoHCT is currently considered an acceptable treatment option for patients with early treatment failure [14]
   i. Early treatment failure is defined as relapse within 2 years of frontline immunochemotherapy.
   ii. AutoHCT <1 year after early treatment failure improves OS in registry analysis (HR 0.63, $p = 0.02$).

2. Rituximab (Rituxan®) maintenance after autoHCT [15]

a. Chemosensitive relapse, rituximab naïve ($n = 280$)
   i. Improves 10-year PFS 54% vs. 37%, HR 0.66, $p = 0.012$
   ii. No benefit in OS
   iii. Rituximab dosing: 375 mg/m^2 every 2 months × 4

b. No prospective data in patients pretreated with rituximab, but rituximab maintenance remains an option for those patients with disease not refractory to rituximab.

3. AlloHCT is an option for patients after failure of autoHCT or with multiply relapsed disease [16].

a. Registry analysis of HLA-matched donor alloHCT from 2001 to 2011 ($n = 1567$)

   i. 5-year results: OS 61%, PFS 52%, relapse 29%, TRM 19%
   ii. Predictors of worse survival

b. Chemoresistant disease
c. Older age
d. Heavy pretreatment
e. Poor performance status
f. Myeloablative regimen

Mantle Cell Lymphoma

1. AutoHCT improves PFS as consolidation in first response [17].
   a. Four to six cycles of CHOP induction (see section "Diffuse Large and High-Grade B-Cell Lymphomas" for dosing) followed by randomization

    i.   Two additional cycles of CHOP-like consolidation followed by interferon α 6×10^6 units SQ three times weekly
       OR

    ii. Dexa-BEAM for stem cell mobilization (see section "Hodgkin Lymphoma") followed by autoHCT

- HCT conditioning of TBI 12 Gy fractionated on days -6 to -4 and cyclophosphamide 60 mg/kg IV daily, days -3 and -2

  b. AutoHCT improved median PFS to 39 vs. 17 months when compared to chemotherapy alone, $p = 0.01$.

  c. No benefit in OS at 3 years: 83% vs. 77%, $p = 0.18$.

2. Introduction of intensified first-line regimens has demonstrated significant benefit.

  a. Nordic Mantle Cell Lymphoma 2 (MCL2) trial demonstrated long-term follow-up median OS and PFS of 12.7 and 8.5 years, respectively [18].

    i.   Maxi-CHOP

- Cycles 1, 3 5

  - Cyclophosphamide 1200 mg/m^2 IV, day1
  - Doxorubicin 75 mg/m2 IV, day 1
  - Vincristine 2 mg IV, day 1
  - Prednisone 100 mg po daily, days 1–5

- Cycles 2, 4, 6

  - Rituximab 375 mg/m^2 IV, day 1
  - Cytarabine 3 gm/m^2 IV q12 h, days 1 and 2

    Patient >age 60 reduced to 2 gm/m^2

    ii. Transplant conditioning regimen of either BEAM or BEAC

3. Rituximab maintenance improves PFS and OS after autoHCT [19]

  a. R-DHAP (see section "Diffuse Large and High-Grade B-Cell Lymphomas") induction followed by autoHCT then randomization to rituximab maintenance (375 mg/m^2 IV q2 months × 3 years) vs. observation

    i.   4-year PFS 83% vs. 64%, $p < 0.001$

    ii. 4-year OS 89% vs. 80%, $p = 0.04$, HR 0.50

4. Consider autoHCT or alloHCT in relapsed/refractory disease [20]

  a. Registry analysis: HCT more effective if completed earlier in treatment.

  b. AlloHCT improves disease control but increases toxicity and NRM.

Peripheral T-Cell Lymphoma

1. Consolidation of first remission [21]
   a. Phase 2 study ($n = 160$): CHOEP × 6 cycles induction followed by autoHCT ($n = 115$) for patients with a complete or partial response
      i. CHOEP dosing

         - Cyclophosphamide 750 mg/m^2 IV, day 1
         - Doxorubicin 50 mg/m2 IV, day 1
         - Vincristine 1.4 mg/m2 (max dose 2 mg) IV, day 1
         - Etoposide 100 mg/m^2 IV daily, days 1–3
         - Prednisone 100 mg po daily, days 1–5

      ii. HCT conditioning

         - High-dose BEAM (see section "Hodgkin Lymphoma"1)
           OR
         - BEAC (see section "Diffuse Large and High-Grade B-Cell Lymphomas")

   b. Excluded anaplastic lymphoma kinase positive (ALK$^+$) anaplastic large cell lymphoma (ALCL) due to good prognosis
   c. 5-year OS 51% and PFS 44%

2. Relapsed disease [22]

   a. AutoHCT for patients with chemosensitive ALCL based on registry analysis
   b. Consider alloHCT for other subtypes
   c. 3-year PFS 31% for alloHCT beyond first complete remission

Primary CNS Lymphoma

1 BEAM is considered suboptimal conditioning for CNS lymphoma.
2 Thiotepa-based autoHCT as consolidation of first response [23, 24].

   a. Thiotepa regimens: thiotepa/carmustine (Tt/BCNU) or thiotepa/busulfan/cyclophosphamide (TBC)

      i. Prospective studies Tt/BCNU ($n = 43$): 5-year OS 70% and EFS 67%
      ii. Retrospective series TBC ($n = 46$): 2-year OS 95% and PFS 92%

3. Thiotepa-based autoHCT in relapsed/refractory disease [25]

   a. Prospective study in relapsed/refractory CNS lymphoma after failure of high-dose methotrexate
      i. Cytarabine/etoposide salvage followed by TBC autoHCT if chemosensitive

    ii.   2-year PFS 43% in all patients ($n = 43$) and 58% in those completing autoHCT ($n = 27$)

    iii. 2-year OS 45% in all patients and 69% in those completing autoHCT

NHL with Secondary CNS Involvement

1. CIBMTR analysis of patients with prior secondary CNS involvement ($n = 151$) [26]

   a. For patients who underwent autoHCT with control of CNS disease, no significance differences were identified in PFS and OS when compared to patients with no prior CNS involvement.
   b. Patient with active CNS lymphoma at the time of autoHCT had higher relapse rates and lower PFS and OS compared to patient with control of CNS disease.

Restaging Guidelines After HCT in Systemic Lymphoma

1. Restage 3 months post-HCT:

   a. PET/CT
   b. Bone marrow biopsy if previously involved

2. Consider restaging again at end of maintenance therapy if applicable.
3. Routine surveillance imaging not recommended for lymphoma treated with curative intent in complete remission.

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Chapter 18
Multiple Myeloma

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Introduction

Multiple myeloma (MM) is characterized by the proliferation of monoclonal plasma cells in the bone marrow and usually the presence of a monoclonal protein in the serum and/or urine. Secondary end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone destruction (CRAB criteria) indicates symptomatic disease requiring therapy [1]. Furthermore, the presence of an abnormal serum free light chain ratio (>100, with involved free light chains >100 mg/l), two or more focal lesions in MRI or PET/CT as well as more than 60% monoclonal plasma cells in the bone marrow are myeloma-defining events according to the International Myeloma Working Group guidelines [2]. The introduction of novel agents and monoclonal antibodies revolutionized the treatment of MM in the last years and with every new

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drug approval, the value of ongoing utilization of autologous stem cell transplantation (ASCT) is questioned. However, recent phase III trials confirmed that combining novel agents with ASCT is associated with longer progression-free survival (PFS) compared to treatment with novel agents alone (Table 18.1) [3–6]. Although MM is still considered to be an incurable disease, long-lasting remissions over 10 years can be achieved making it difficult to determine if overall survival can serve as a primary endpoint for trials [7]. Furthermore, the outcome varies significantly among newly diagnosed patients based on risk stratification (Table 18.2) [8].

Table 18.1 Phase III studies comparing treatment with novel agents in combination with ASCT to treatment with novel agents alone

Study	n	Control arm	PFS (median in months)	p	OS	p
Palumbo et al., NEJM, 2014 [3]	273	MPR	43.0 vs. 22.4	$p < 0.001$	4-year OS: 81.6% vs. 65.3%	$p = 0.02$
Gay et al., Lancet Oncol, 2015 [4]	256	RCD	43.4 vs. 28.6	$p < 0.0001$	4-year OS: 86% vs. 71%	$p < 0.004$
Attal et al., NEJM, 2017 [5]	700	VRD	50 vs. 36	$p < 0.001$	4-year OS: 81% vs. 82%	Not significant
Cavo et al., ASH, 2016 [6]	1192	VMP	nr vs 44	$p = 0.002$	3-years OS: 85% vs. 85%	Not significant
Gay et al., ASCO, 2019 [86] Abstract 8002	474	KRD	Odds ratio 0.42[a]	$p = 0.021$	na	na

MPR melphalan, prednisone, lenalidomide; *RCD* lenalidomide, cyclophosphamide, dexamethasone; *VRD* bortezomib, lenalidomide, dexamethasone; *VMP* bortezomib, melphalan, prednisone; *nr* not reached; *na* not available
[a]Odds ratio in multivariate analysis

Table 18.2 International Staging System (ISS) and revised-ISS [8]

ISS stage	Criteria	5-year PFS (%)	5-year OS (%)
I	β_2-microglobulin < 3.5 mg/l Albumin ≥ 35 g/l	49	77
II	Not ISS I or ISS III	36	62
III	β_2-microglobulin ≥ 5.5 mg/l	30	47
Revised-ISS stage	Criteria	5-year PFS (%)	5-year OS (%)
I	ISS I Standard risk cytogenetics[a] LDH within normal range[b]	55	82
II	Not R-ISS I or R-ISS III	36	62
III	ISS III High-risk cytogenetics *AND/OR* LDH above the normal range	24	40

PFS progression-free survival, *OS* overall survival
[a]High-risk cytogenetics – del(17p) and/or t(4;14) and/or t(14;16)
[b]*LDH* lactate dehydrogenase

Assessment of Transplant Eligibility

There is no formal age cut-off for transplant eligibility in MM. Most phase III trials of ASCT have enrolled patients with an upper age limit of 65 years but other trials such as BMT CTN 0702 and CALGB 100104 allowed enrollment to 70 years of age. ASCT can be performed safely in older, medically fit patients [9, 10]. Therefore, transplant eligibility should be determined mostly on the basis of comorbidities. Table 18.3 summarizes the recommended assessments prior to ASCT at Roswell Park Comprehensive Cancer Center.

Table 18.3 Recommended assessments prior to ASCT

Examination/assessment	Time prior to ASCT
Physical examination	At admission

Blood test:
  Complete blood count including differential blood count
  Comprehensive metabolic panel (glucose, BUN, creatinine, sodium, potassium, calcium, liver function tests)
  Liver function tests (bilirubin, ALP, SGOT, SGPT, GGT)
  CRP, TSH, b-HCG (premenopausal)
  Coagulation tests (INR, PTT)
  Urinalysis (urine sediment, creatinine clearance in 24 h urine collection)
	30 days

Viral serology
  Hepatitis B (HBsAG, anti-HBc)
  Hepatitis C (anti-HBC)
  HIV (antibodies against HIV1+2)
  Treponema pallidum (IgG/IgM)
  HSV1, HSV2, and VZV (IgG/IgM)
	30 days

Central blood cultures of implanted port (aerobic and anaerobic)	30 days

Cardiopulmonary function:
  ECG
  Echocardiography
  Pulmonary function test (CO diffusion capacity, BGA)
	30 days

Menstruation prophylaxis in premenopausal patients	Start 4 weeks prior to admission

Optional
Contact blood bank if
  Daratumumab prior to ASCT (incorrect cross-match testing possible)
  HLA-antibodies (matching platelet concentrate necessary)
Chest CT scan
Rectal swab for MDRO screening
	Prior to admission

BUN blood urea nitrogen, *ALP* alkaline phosphatase, *SGOT* serum glutamic oxaloacetic transaminase, *SGPT* serum glutamate pyruvate transaminase, *GGT* gamma-glutamyl transferase, *CRP* C-reactive protein, *TSH* thyroid-stimulating hormone, *b-HCG* beta-human chorionic gonadotropin, *MDRO* multidrug-resistant organism

Induction Therapy

The common practice of bortezomib-based induction therapies is supported by large meta-analyses [11]. Recent phase III trials compared different combination partners for bortezomib (Velcade®) during induction therapy before ASCT.

1. The initial EVOLUTION phase I/II study appeared to demonstrate that VCD (bortezomib, cyclophosphamide, and dexamethasone) and VRD had similar outcomes [12].
2. The German GMMG MM5 trial showed that VCD (bortezomib, cyclophosphamide, and dexamethasone) is less toxic than PAd (bortezomib, doxorubicin, and dexamethasone) [13].
3. The French IFM2013-04 trial demonstrated higher rates of high-quality responses for VTD compared to VCD [14].

    a. However, VTD was associated with higher rates of neuropathy compared to VCD.
    b. Although there has never been a direct prospective, randomized comparison between VTD and VRD (bortezomib, lenalidomide, and dexamethasone), many centers utilize VRD as recently applied in the IFM/DFCI2009 phase III trial [5].

4. Currently, second-generation novel agents such as ixazomib (Ninlaro®) (in combination with lenalidomide and dexamethasone [IRD]) [15] and carfilzomib (Kyprolis®) (in combination with lenalidomide/dexamethasone [KRD] or cyclophosphamide/dexamethasone [KCD]) [16] are being tested as induction before ASCT with promising results.
5. The CASSIOPEIA trial investigating VTD with or without daratumumab (Darzalex®) before and after ASCT showed for the first time superiority of an induction regimen incorporating a monoclonal antibody [17].
6. Further results from trials incorporating monoclonal antibodies such as elotuzumab (Empliciti®) and isatuximab (e.g., Clinicaltrials.gov identifier NCT03617731) into induction therapy before ASCT are expected in 2019/2020.
7. Table 18.4 summarizes recent phase II/III trials on induction therapy before ASCT.

Stem Cell Mobilization

An adequate collection of mobilized peripheral stem cells is a crucial or successful outcome of autoHCT. A dose of $>2 \times 10^6$ CD34+ cells/kg is considered the minimum target dose to achieve optimal engraftment [18]. The main risk factors for poor mobilization are age >60 years, thrombocytopenia [19], extensive previous treatment with radiotherapy or alkylating agents [18, 20–23], and prolonged use of lenalidomide [24–27]. Stem cell mobilization can be performed with growth factors alone, a combination of growth factors with chemotherapy, or with chemokine receptor antagonists (Table 18.5).

Table 18.4 Summary of most common induction therapies before ASCT in recent phase II/III trials

Study	Regimen	Drugs	Common adverse events		% ≥VGPR
Mai et al., Leukemia, 2015 (n = 501), Phase III [11] Intravenous bortezomib n = 304 Subcutaneous bortezomib n = 197	Pad	Bortezomib 1.3 mg/m², d 1, 4, 8, 11 Doxorubicin 9 mg/m², d 1–4 Dexamethasone 20 mg/d, d 1–4, 9–12, 17–20 28-days-cycle	Infections Neuropathy Thrombosis Cardiac	25% 15% 6% 3% (all ≥ II)	34% after 3 cycles
	VCD	Bortezomib 1.3 mg/m², d 1, 4, 8, 11 Cyclophosphamide 900 mg/m², d 1 Dexamethasone 40 mg/d, d 1, 2, 4, 5, 8, 9, 11, 12 21-days-cycle	Infections Neuropathy Thrombosis Cardiac	22% 8% 3% 2% (all ≥ II)	37% after 3 cycles
Moreau et al., Blood, 2016 (n = 385), Phase III [14, 15] Subcutaneous bortezomib	VCD	Bortezomib 1.3 mg/m², d 1, 4, 8, 11 Thalidomide 100 mg/d Dexamethasone 40 mg/d, d 1–4, 9–12 21-days-cycle	Infections Neuropathy Thrombosis Cardiac	10% 3% 2% 0% (all ≥ III)	56% after 4 cycles
	VTD	Bortezomib 1.3 mg/m², d 1, 4, 8, 11 Cyclophosphamide 500 mg/m², d 1, 8, 15 po Dexamethasone 40 mg/d, d 1–4, 9–12 21-days-cycle	Infections Neuropathy Thrombosis Cardiac	8% 8% 2% 1% (all ≥ III)	66% after 4 cycles
Attal et al., NEJM, 2017 (n = 700), Phase III [5] Intravenous bortezomib	RVD	Bortezomib 1.3 mg/m², d 1, 4, 8, 11 Lenalidomide 25 mg/d, d 1–14 Dexamethasone 20 mg/d, d 1, 2, 4, 5, 8, 9, 11, 12 21-days-cycle	Infections Neuropathy Thrombosis Cardiac	9% 12% 4% (all ≥ III) Not reported	46% after 3 cycles

Table 18.4 (continued)

Study	Regimen	Drugs	Common adverse events		% ≥VGPR
Gay et al., ASCO, 2017 and ASH, 2018 (*n* = 474), Phase III [16]	KRD	Carfilzomib 20/36 mg/m², d 1, 2, 8, 9, 15, 16 Lenalidomide 25 mg/d, d 1–21 Dexamethasone 20 mg/d, d 1, 2, 8, 9, 15, 16 28-days-cycle	Infections Neuropathy Thrombosis Cardiac	5% Not reported 1% 1%	74% after 4 cycles
	KCD	Carfilzomib 20/36 mg/m², d 1, 2, 8, 9, 15, 16 Cyclophosphamide 300 mg/m², d 1–21 Dexamethasone 20 mg/d, d 1, 2, 8, 9, 15, 16 28-days-cycle	Infections Neuropathy Thrombosis Cardiac	3% Not reported 0% 2%	61% after 4 cycles
Moreau et al., ASH, 2016 [14] (*n* = 42), Phase II	IRD	Ixazomib 4 mg/d, d 1, 8, 15 Lenalidomide 25 mg/d, d 1–21 Dexamethasone 40 mg/d, d 1, 8, 15, 22 28-days-cycle	Infections Neuropathy Thrombosis Cardiac	19% 0% Not reported 2% (all ≥ III)	36% after 3 cycles
Moreau et al., Lancet, 2019 [17] (*n* = 1085), Phase III	VTD	Bortezomib 1.3 mg/m², d 1, 4, 8, 11 Cyclophosphamide 500 mg/m², d 1, 8, 15 po Dexamethasone 40 mg/d, d 1–4, 9–12 28-days-cycle	Neutropenia Lymphopenia Stomatitis Thrombopenia	15% 10% 16% 7%	78% after 6 cycles + ASCT
	VTD + Dara	VTD as above + Daratumumab (16 mg/kg IV QW C 1–2, Q2W C 3–6) Both arms 4 cycles before and 2 cycles after ASCT	Neutropenia Lymphopenia Stomatitis Thrombopenia	28% 17% 13% 11%	83% after 6 cycles + ASCT

Table 18.5 Mobilization strategies

Collection strategy	Agent	Advantage	Disadvantage
Growth factors alone	G-CSF (e.g., Neupogen®)	Moderate side effects [71] Cost-effective	Suboptimal in patients with risk factors for poor mobilization including lenalidomide pretreatment [26, 27, 72]
Chemo mobilization	G-CSF following chemotherapy	Higher cell yields than G-CSF alone [73–76]	Toxic side effects [73, 77–79] Not associated with better disease control [80, 81]
Chemokine receptor (CXCR4) antagonist	Plerixafor (Mozobil®)	Mobilization in patients with risk factors for poor mobilization [82–84] Rapid kinetics [85]	Higher costs

G-CSF granulocyte colony-stimulating factor

High-Dose Therapy

1. Melphalan 200 mg/m^2 is considered the standard of care [28] and usually administered intravenously in divided doses on days −3 and −2 or as a single dose on day −2 only before autoHCT.

    a. Dose reduction to 100 mg/m^2 is associated with an adverse outcome [29].
    b. To prevent anticipated toxicities in medically compromised patients (e.g., elderly patients or patients with cardiac disease), the melphalan dosage might be reduced to 140 mg/m^2 without apparent loss of efficacy compared to 200 mg/m^2 [30].
    c. Also in patients with renal insufficiency (RI) and dialysis-dependent renal impairment, melphalan should be reduced accordingly to obtain comparable results to patients with normal/mild RI and potentially achieve dialysis independence [31].

2. Tandem transplantation

    a. In the past, several studies addressed the question of whether a tandem autoHCT, that is, a second autoHCT usually within 6 months after the first, should be performed [32].
    b. In the era of novel agent-based induction and maintenance therapy, conflicting results from two prospective phase III trials have been reported.

        i. While the abovementioned EMN02/HO95 phase III trial demonstrated the inferiority of single versus tandem autoHCT [6], especially in patients with the high-risk disease [33], the StaMINA trial showed no significant differences for PFS and overall survival (OS) between single and tandem autoHCT, even in patients with the high-risk disease [34].

ii. In the author's practice, tandem autoHCT is offered to patients with the suboptimal response after induction therapy, FISH-based high-risk cytogenetics, or those patients not in complete remission after a first autoHCT.

Supportive Care

1. Patients with newly diagnosed MM are prone to infections due to the impaired humoral and cellular immunity caused by the proliferation of malignant plasma cells and the production of nonfunctional antibodies.
2. Infectious complications are the most common cause of death during the first 3 months of therapy, and one study suggested that antibiotic prophylaxis can reduce febrile episodes and death [35]. Table 18.6 summarizes the recommended prophylaxis.
3. General treatment of infectious complications such as neutropenic fever is discussed separately in this book. Furthermore, vaccinations need to be repeated after autoHCT, and one suggested schedule of administration is summarized in Table 18.7; an alternative schedule of administration is provided in Appendix 9.
4. Other common side effects of autoHCT for MM are nausea and vomiting as well as gastrointestinal mucositis.

Table 18.6 Summary of prophylaxis for most common transplant-related side effects

Infection prophylaxis				
Pathogen	Population	Drugs	Dosing	Timing
Bacterial	All newly diagnosed patients [35] Patients undergoing autoHCT	Levofloxacin	500 mg/d	12 weeks after initiating therapy until neutrophil recovery in autoHCT
Fungal	Patients undergoing autoHCT	Fluconazole	400 mg/d	d0–30 after autoHCT
Pneumocystis jirovecii	Patients undergoing autoHCT	Trimethoprim/ sulfamethoxazole	800/160 mg BID	d0–180 after autoHCT
Herpes simplex virus	Patients treated with proteasome inhibitors (PI) and/or monoclonal antibodies Patients undergoing autoHCT	Acyclovir	400 mg BID	Start and 3 weeks after PI d0–180 after CT

Table 18.6 (continued)

Infection prophylaxis				
Pathogen	Population	Drugs	Dosing	Timing
Varicella zoster virus	Patients treated with proteasome inhibitors (PI) Patients undergoing autoHCT	Acyclovir Inactivated-virus vaccine (Shingrix®)	400 mg BID	Start and 3 weeks after PI therapy d0–180 after autoHCT First dose 5–60 days before autoHCT Second/third doses at about 30, 60, and 90 days autoHCT [36]
Hepatitis B	All HBs-antigen and/or HBV DNA positive patients treated for MM patients including autoHCT	Lamivudine	100 mg/d	Start and 6 months after every MM therapy including autoHCT
Hepatitis C	All infected patients (hepatitis C RNA positive) should receive treatment	Prophylaxis not recommended		
Human immunodeficiency virus	All infected patients should receive highly active antiretroviral therapy	Prophylaxis not recommended		

Prophylaxis of other common side effects			
Side effect	Drug	Dosing	Comment
Nausea and vomiting	e.g., combination of		Improves nausea/vomiting and quality of life compared to granisetron and dexamethasone plus placebo [37]
	aprepitant	125 mg/d day 1; 80 mg/d days 2–4	
	granisetron	2 mg/d days 1–4	
	dexamethasone	4 mg/d day 1; 2 mg/d days 2–3	
Oral Mucositis	Palifermin (Kepivance®)	60 µg/kg/d Three doses before and three doses after ASCT	Improves quality of life, consider financial toxicity [38]
	Ice cubes	Oral administration during melphalan infusion	Reduces oral mucositis and febrile episodes without adding severe side effects or costs [39]
Prolonged neutropenia	Granulocyte-colony stimulating factor	50 µg/m²/d day 1 after ASCT until ANC ≥ 500/µl	Associated with faster engraftment [40], might reduce mucositis and febrile neutropenia, might cause engraftment or capillary leakage syndrome. Cost-effectiveness uncertain [41]

Table 18.7 Vaccinations recommended after autoHCT for MM (Roswell Park Comprehensive Cancer Institute Guidelines)

Pathogen	First dose after autoHCT (months)	Time points
Influenza (inactivated)	6	Yearly during flu season
Polio (inactivated)	6	3 doses, 1–3-month intervals (1 boost, 6–12 months after initial series)
Pneumococcal (conjugate)	6	3 doses, 1–3-month intervals (1 boost, 6–12 months after initial series)
Hemophilus influenza B (conjugate)	6	3 doses, 1–3-month intervals (1 boost, 6–12 months after initial series)
Hepatitis A and B	6	3 doses, 1–3-month intervals
Meningococcal	6	2 doses, 6-month intervals
Diphtheria, acellular pertussis, and tetanus toxoids	6	3 doses, 1–3-month intervals (1 boost, 6–12 months after initial series)
Measles, mumps, rubella (live)	24	2 doses, 2–3-month intervals
Varicella virus (live) or Shingrix®	24	2 doses, 2–3-month intervals

Maintenance Therapy After AutoHCT

Maintenance therapy in MM after autoHCT has been shown to improve OS. The commonly used agent is lenalidomide, whereas new approaches show also improved survival for maintenance therapy with bortezomib and ixazomib [3, 42–45].

1. Lenalidomide (Revlimid®)

    a. Lenalidomide is indicated as standard maintenance therapy after autoHCT in the United States and Europe.
    b. 4 randomized trials showed significantly improved PFS with lenalidomide maintenance therapy versus placebo or observation [3, 42–45].
    c. Meta-analyses demonstrated improved OS [45].
    d. Standard dosing: 10 mg po daily continuous, increase up to 15 mg daily if tolerated [45].
    e. Main side effects [46]

        i. Hematologic toxicity (neutropenia, anemia, thrombocytopenia)
        ii. Increased risk of secondary primary malignancies
        iii. Increased risk of venous thromboembolic events (VTE)
        iv. Gastrointestinal side effects (esp. diarrhea)
        v. Drug rash

    f. Concurrent medication [47, 48]:

        i. If no other risk factors for VTE: aspirin 81 mg/d po.
        ii. If other risk factors for VTE: low-molecular-weight heparin or full-dose warfarin.

        iii. Oral anticoagulants such as apixaban (Eliquis®) were successfully evaluated for VTE prophylaxis in IMiD-treated patients [49].

   g. Duration

      i. Three out of the four randomized phase III studies involved continuing maintenance treatment until disease progression.
      ii. Administration of lenalidomide beyond the achievement of complete remission (CR) is associated with better OS and therefore should be continued until disease progression if toxicities are tolerable [50].

2. Bortezomib (Velcade®)

   a. Bortezomib with induction and maintenance improved PFS compared to vincristine with induction and thalidomide with maintenance [51, 52].
   b. Improves outcome in patients with del(17p) [53].
   c. Standard dosing: 1.3 mg/m^2 sc every 2 weeks [51].
   d. Main side effects [54]:

      i. Hematologic toxicity (neutropenia, thrombocytopenia)
      ii. Peripheral neuropathy
     iii. Gastrointestinal side effects

   e. Concurrent medication:

      i. Herpes zoster prophylaxis with low-dose acyclovir [55]
   f. Duration: In studies discontinuation after 2 years [51]. Based on results from lenalidomide maintenance studies, treatment until progression might prolong survival and should be considered if no severe side effects occur.

3. Ixazomib (Ninlaro®)

   a. Improved post-autoHCT PFS by 5 months when compared to placebo [70]
   b. Standard dosing: 3 mg po every 2 weeks; may increase up to 4 mg if tolerated
   c. Main side effects:

      i. Hematologic toxicity (thrombocytopenia)
      ii. Peripheral neuropathy
     iii. Gastrointestinal side effects

   d. Concurrent medication:

      i. Herpes zoster prophylaxis with low-dose acyclovir.
   e. Duration: In studies, discontinuation after 2 years. Based on results from lenalidomide maintenance studies, treatment until progression might prolong survival and should be considered if no severe side effects occur.

Table 18.8 Revised response criteria for minimal residual disease (MRD)

Response MRD	Response criteria
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells in the bone marrow by NGF with a minimum sensitivity of 1 in 10^5 nucleated cells
Sequencing MRD-negative	Absence of clonal plasma cells by NGS in the bone marrow by NGS with a minimum sensitivity of 1 in 10^5 nucleated cells
Imaging plus MRD-negative	MRD negativity by NGF or NGS plus (a) Disappearance of increased tracer uptake found at baseline or preceding PET/CT or (b) Decrease to less mediastinal blood pool standardized uptake value (SUV) or (c) Decrease to less than that of surrounding normal tissue
Sustained MRD-negative	MRD negativity by NGF or NGS and in imaging for at least 1 year

NGF next-generation flow, *NGS* next-generation sequencing

Response Criteria

Historically, response criteria were based on the measurement of monoclonal protein in serum and urine as well as bone marrow plasma cell count. Response is categorized in stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), and progressive disease (PD). Revised criteria include new parameters of minimal residual disease (MRD) measured by flow cytometry or gene sequencing (Table 18.8). Furthermore, sensitive imaging techniques can detect extramedullary residual disease [57].

Salvage AutoHCT

Retrospective analyses demonstrated that salvage autoHCT after re-induction therapy is an option for patients with relapsed disease, particularly those with sustained remission ≥18 months after a first autoHCT procedure [58, 59]. Currently, there are only two published prospective randomized phase III trials comparing salvage auto-HCT after novel agent-based re-induction therapy to treatment with a novel agent alone in relapsed MM (Table 18.9) [60, 61]. While the study from the UK showed the superiority of salvage autoHCT over monotherapy with weekly cyclophosphamide, the German study could not show any differences in the intention-to-treat analysis. While major criticism of the study from the UK was the suboptimal control arm with weekly cyclophosphamide, the final analysis of the German study is still pending.

Table 18.9 Summary of current phase III trials for autoHCT for relapsed disease

Study	Arm	Re-induction	Consolidation	Maintenance	Common adverse events	Survival analysis
Cook et al., Lancet Oncol, 2014 [60] (n = 297)	autoHCT	PAd 4 cycles Bortezomib 1.3 mg/m², d 1, 4, 8, 11 Doxorubicin 9 mg/m², d 1–4 Dexamethasone 40 mg/d, d 1–4, 9–12, 17–20 (from cycle 2: 40 mg/d, d 1–4) 28-days-cycle	High-dose melphalan 200 mg/m² followed by autoHCT (7% did not receive autoHCT)	No maintenance	Infections 4% Neutropenia 75% Thrombocytopenia 72% Diarrhea 12% (all ≥ II)	Intention to treat (ITT); autoHCT vs. cyclophosphamide: PFS: (19 vs. 11 mo; $p < 0.0001$) OS (67 vs. 52 mo; $p = 0.022$)
	Control		Cyclophosphamide 400 mg/m² PO weekly for 12 cycles	No maintenance	Infections 0% Neutropenia 13% Thrombocytopenia 4% Diarrhea 1% (all ≥ II)	
Goldschmidt et al., ASH, 2018 [61] (n = 282)	autoHCT	RD 3 cycles Lenalidomide 25 mg/d, d 1–21 Dexamethasone 40 mg/d, d 1, 8, 15, 22 28-days-cycle	High-dose melphalan 200 mg/m² followed by autoHCT (30% did not receive autoHCT)	Lenalidomide 10 mg/d	Infections 33% Neutropenia 62% Thrombocytopenia 45% Oral mucositis 10% (all ≥°III)	ITT: autoHCT vs. RD until progression No significant PFS/OS differences Per protocol: PFS (23 vs 20 mo; $p = 0.09$) OS (not reached vs 57 mo; $p = 0.046$)
	Control		RD until progression	RD until progression	Infections 28% Neutropenia 25% Thrombocytopenia 11% Oral mucositis 2% (all ≥°III)	

Adoptive Cellular Therapies

1. Allogeneic transplantation (alloHCT)

   a. In contrast to autoHCT, alloHCT has the potential to generate an immunologic graft-versus-myeloma (GvM) effect.

      i. Studies comparing autoHCT and alloHCT as first-line therapy showed improved long-term OS for patients undergoing alloHCT, while transplant-related mortality (TRM) and toxicity mostly as a consequence of graft-versus-host disease (GvHD) were increased [62–65].
      ii. Whether alloHCTcan overcome high-risk disease features remains controversial since inclusion criteria for high-risk disease varied in the different studies [66–68].
      iii. As the incidence of TRM is 10–20%, alloHCT in MM should generally be reserved for young patients with primary relapsed/refractory disease, where transplant risk is relatively low (HLA-identical donor, no comorbidities) and no other novel therapy, for example, antibodies or chimeric antigen receptor T-cell is available.

   b. Studies comparing alloHCT to novel agents such as proteasome inhibitors, immunomodulatory agents, or monoclonal antibodies are lacking.

2. Chimeric antigen receptor T (CAR T) cell therapy

   a. CAR T cells are genetically engineered T cells utilizing a genetically engineered CAR targeting specific myeloma antigens, of which current studies are mainly directed against B-cell maturation antigen (BCMA).
   b. Phase I/II trials are presently investigating safety and efficacy for CAR T cell therapy for myeloma in heavily pretreated patients.
   c. Although overall response rates (ORR) up to 100% have been reported and the majority of patients achieved a VGPR or CR, long-term results have not been established to determine the durability of these responses [69].
   d. The observed toxicities of this therapy are similar to more established CAR T cell therapies in acute lymphoid leukemia (ALL) and aggressive lymphomas, most frequently grade 1–2 cytokine release syndrome (CRS) and neurotoxicity [69, 70].

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Chapter 19
HCT for Germ Cell Tumors

Brandon Hayes-Lattin

Introduction

Germ cell tumors have been a model of potentially curable malignancy since the advent of platinum-based chemotherapy. Even patients with relapsed or refractory germ cell tumors after initial conventionally dosed cisplatin-based chemotherapy can be cured with intensified dose chemotherapy, including high dose with autologous hematopoietic cell transplantation (autoHCT).

Diagnosis and Staging

1. Germ cell tumor may arise in gonads (testicular or ovarian) or extragonadal tissues (retroperitoneum, mediastinum, or central nervous system).

   a. Pure seminoma: By definition, germ cell tumors that produce alpha-fetoprotein (AFP) are not pure seminomas.
   b. Non-seminoma: While other histologies (including yolk sac tumor, embryonal carcinoma, choriocarcinoma, and mixed germ cell tumors) differ in their relative production of serum tumor markers and patterns of metastases, all non-seminomas are treated the same.

2. Testicular cancer is the most common solid tumor among young males in the United States, with 95% of testicular tumors being germ cell tumors.
3. Staging systems.

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Table 19.1 TNMS staging system

T (tumor)	T0: No evidence of tumor Tis: Intratubular, pre-invasion T1: Confined to testis
	T2: Invades beyond tunica albuginea or into epididymis
	T3: Invades spermatic cord
	T4: Invades scrotum
N (nodes)	N0: no lymph node involvement
	N1: single, <2 cm
	N2: multiple <5 cm/single 2–5 cm N3: any node >5 cm
M (metastasis)	M0: no metastatic spread
	M1: metastases present M1a: non-regional nodes or pulmonary metastases M1b: other distant metastases
S (serum markers)	SX: not done S0: normal S1: LDH <1.5× normal, hCG < 5000 IU/L, AFP < 1000 ng/mL S2: LDH 1.5–10× normal, hCG 5000–50,000, AFP 1000–10,000 S3: LDH >10× normal, hCG > 50,000, AFP > 10,000

a. Staging systems differ between pediatric and adult oncologists.
b. The adult American Joint Commission on Cancer staging system is based on tumor, nodes, metastases, and the serum tumor markers lactate dehydrogenase (LDH), human chorionic gonadotropin (hCG), and AFP (see Tables 19.1 and 19.2) [1].

Initial Therapy for Disseminated Testicular Cancer

1. The International Germ Cell Consensus Classification Group (IGCCCG) scoring system may be used to assign patients to prognostic groups and estimate outcomes of initial cisplatin-based chemotherapy treatment for those with stage II or stage III testicular germ cell tumor (see Table 19.3) [2].

    a. Approximately 20–30% of those with stage II or stage III disease will require additional therapy with surgery or chemotherapy for residual masses or for relapsed or refractory disease.
    b. TP53 and MDM2 alterations have been associated with cisplatin resistance, independent of the IGCCCG model [3].
    c. See Table 19.4 for common adult chemotherapy regimens. Common regimens for initial chemotherapy include:

        i. Bleomycin, etoposide, and cisplatin (BEP)
        ii. Etoposide and cisplatin (EP)
        iii. Etoposide, ifosfamide, and cisplatin (VIP)

Table 19.2 Stage grouping

0	Tis, N0, M0, S0
I	T1-T4, N0, M0, SX
IA	T1, N0, M0, S0
IB	T2-T4, N0, M0, S0
IS	Any T, N0, M0, S1–S3
II	Any T, N1-N3, M0, SX
IIA	Any T, N1, M0, S0–S1
IIB	Any T, N2, M0, S0–S1
IIC	Any T, N3, M0, S0–S1
III	Any T, Any N, M1, SX
IIIA	Any T, Any N, M1a, S0–S1
IIIB	Any T, Any N, M0, S2 Any T, Any N, M1a, S2
IIIC	Any T, Any N, M0, S3 Any T, Any N, M1a, S3 Any T, Any N, M1b, Any S

Table 19.3 The International Germ Cell Consensus Classification Group (IGCCCG) prognostic system for initial therapy of disseminated germ cell tumor

	Non-seminoma		Seminoma	
Good prognosis	Testis or retroperitoneal primary AND	56% of patients	Any primary site AND	90% of patients
	No non-pulmonary visceral metastases AND	PFS 89% @ 5 years	No non-pulmonary visceral metastases AND	PFS 82% @ 5 years
	Good risk markers (AFP < 1000 ng/mL and HCG < 5000 IU/L and LDH < 1.5 × upper limit of normal)	OS 92% @ 5 years	Normal AFP, any HCG, any LDH	OS 86% @ 5 years
Intermediate prognosis	Testis or retroperitoneal primary AND	28% of patients	Any primary site AND	10% of patients
	No non-pulmonary visceral metastases AND	PFS 75% @ 5 years	Non-pulmonary visceral metastases AND	PFS 67% @ 5 years
	Intermediate risk markers (AFP 1000–10,000 ng/mL or HCG 5000–50,000 IU/L or LDH 1.5–10 × upper limit of normal)	OS 80% @ 5 years	Normal AFP, any HCG, any LDH	OS 72% @ 5 years
Poor prognosis	Mediastinal primary OR	16% of patients		
	Non-pulmonary visceral metastases OR	PFS 41% @ 5 years		
	Poor risk markers (AFP >10,000 ng/mL or HCG >50,000 IU/L or LDH >10 × upper limit of normal)	OS 48% @ 5 years		

Table 19.4 Common conventional-dose adult germ cell tumor regimens

BEP	Bleomycin 100 mg/m^2 IV weekly on days 1, 8, and 15 Etoposide 100 mg/m^2 IV on days 1–5 Cisplatin 20 mg/m^2 IV on days 1–5
EP	Etoposide 100 mg/m^2 IV on days 1–5 Cisplatin 20 mg/m^2 IV on days 1–5
VIP	Etoposide 75 mg/m^2 IV on days 1–5 Ifosfamide 1200 mg/m^2 IV on days 1–5 + MESNA Cisplatin 20 mg/m^2 IV on days 1–5
VeIP	Vinblastine 0.11 mg/kg IV push on days 1–2 Ifosfamide 1200 mg/m^2 IV on days 1–5 + MESNA Cisplatin 20 mg/m^2 IV on days 1–5
TIP	Paclitaxel 250 mg/m^2 IV on day 1 Ifosfamide 1500 mg/m^2 IV on days 2–5 + MESNA Cisplatin 25 mg/m^2 IV on days 2–5

2. A randomized trial of intensified therapy for patients with poor-prognosis germ cell tumor and unfavorable tumor marker decline during initial BEP treatment showed improved progression-free survival (PFS) and a trend toward improved overall survival (OS), with minimal long-term toxicity and a reduction in salvage high-dose chemotherapy [4].

3. Incorporating high-dose chemotherapy into the first-line treatment of IGCCCG intermediate- or high-risk disease was not useful in a randomized trial comparing four cycles of BEP alone [5].

4. When feasible, complete surgical excision, such as retroperitoneal lymph node dissection (RPLND), may lead to durable responses. For RPLND after chemotherapy, surgical experience has been associated with superior outcomes. Patients with residual germ cell tumor in surgically removed disease benefit from conventional-dose adjuvant chemotherapy. However, there is no established role for adjuvant high-dose chemotherapy in that setting.

5. Several situations may be confused for relapsed or refractory disease and lead to inappropriate use of salvage therapy.

   a. Persistently elevated tumor markers

      i. AFP has a serum half-life of approximately 5 days; therefore, serum AFP that is falling consistent with that half-life may be observed until normalization. False-positive serum AFP is rare, but may occur with other tumors such as hepatoma or with liver inflammation.

      ii. hCG has a serum half-life of approximately 18–24 hours; however, the pattern of decline of hCG may be variable among patients with very high hCG levels. False-positive hCG may occur with marijuana use, and there may be assay crossreactivity with serum luteinizing hormone (which may be elevated with testosterone deficiency and can be evaluated for by a trial of supplemental testosterone).

      iii. Rising serum hCG and/or AFP may represent disease in chemotherapy-sanctuary sites including the contralateral testis or the brain, which may be cured with surgery rather than systemic salvage chemotherapy.

    b. Residual radiographic abnormalities

       i. Twenty to 50% of patients with disseminated disease at diagnosis will have residual radiographic changes after initial cisplatin-based chemotherapy.

      ii. In the absence of rising serum tumor markers, options include surgical resection or active surveillance.

- Radiographic persistence or even progression with negative serum markers may be due to benign teratoma elements.
- Nodular lung lesions after bleomycin chemotherapy may be due to bleomycin-induced pulmonary injury rather than tumor.

6. Rising tumor markers portend active disease and are an indication to proceed with salvage chemotherapy.

Salvage Therapy for Relapsed/Refractory Disease

1. Prognostic factors after failure of first-line cisplatin-based chemotherapy have been studied in a large retrospective cohort, and include seminoma versus non-seminoma histology, primary site, prior response, progressive-free interval, tumor marker levels at salvage, and sites of metastatic disease (see Tables 19.5 and 19.6) [6].
2. Conventional-dose chemotherapy salvage regimens lead to complete remission among 30–60% of patients, but long-term relapse-free survival in only about 20% [7]. These conventional-dose salvage regimens have not been compared to each other in randomized trials. Options include:

Table 19.5 Prognostic factors after failure of first-line cisplatin-based chemotherapy: prognostic score

Factor	Score 0	Score 1	Score 2	Score 3
Primary site	Gonadal	Extragonadal		Mediastinal
Prior response	CR/PR marker −	PR marker +/ SD	Progressive	
Progression-free interval	>3 months	<3 months		
AFP at salvage	Normal	<1000	>1000	
HCG at salvage	<1000	>1000		
Liver/brain/bone metastases	No	Yes		
Score sum	Add above	Range (0–10)		
Score grouping	(0) = 0	(1–2) = 1	(3–4) = 2	(5+) = 3
Histology factor	−1 for Pure Seminoma			
FINAL SCORE	−1 to 3			

Table 19.6 Prognostic factors after failure of first-line cisplatin-based chemotherapy: progression-free survival

Final prognostic score	Risk category	2-year progression-free survival	3-year overall survival
−1	Very low	75.1%	77.0%
0	Low	51.0%	65.6%
1	Intermediate	40.1%	58.3%
2	High	25.9%	27.1%
3	Very high	5.6%	6.1%

    a. Etoposide, ifosfamide, and cisplatin (VIP)
    b. Vinblastine, ifosfamide, and cisplatin (VeIP)
    c. Paclitaxel, ifosfamide, and cisplatin (TIP)

3. The appropriate timing of referral for high-dose chemotherapy with autoHCT is at the initiation of salvage therapy to allow for coordination of stem cell collection and efficiency of proceeding to high-dose chemotherapy.
4. High-dose chemotherapy with autoHCT leads to durable relapse-free survival in upward of 50–60% of patients in retrospective and phase 2/3 studies.

    a. Two tandem high-dose chemotherapy cycles with carboplatin and etoposide (CE) is the standard of care in the United States [8].
    b. Conditioning regimen consists of carboplatin 700 mg/m^2 and etoposide 750 mg/m^2 × 3 days with each transplant.

        i. $N = 364$, median age 32 (range 17–70). 2-year PFS 60%, 2-year OS 66%.
        ii. $N = 303$, autoHCT as second-line therapy: 2-year PFS 63%
        iii. $N = 61$, autoHCT as third-line or later therapy: 2-year PFS 49%

5. Large retrospective trials have demonstrated PFS and OS benefits for pursuing high-dose chemotherapy compared to only conventional-dose chemotherapy at first salvage. However, more randomized trials are needed to more clearly establish high-dose chemotherapy as superior to conventional-dose at first salvage.

    a. Conventional-dose paclitaxel and ifosfamide followed by sequential high-dose carboplatin and etoposide (TI-CE) has been shown to be effective in patients with high-risk features including extragonadal primary site, incomplete response to first-line therapy, or relapse or incomplete response to ifosfamide-cisplatin–based conventional-dose salvage [9].

        i. Two cycles of paclitaxel 200 mg/m^2 on day 1 and ifosfamide 2 gm/m^2 days 2–4, followed by three cycles of carboplatin AUC 8 and etoposide 400 mg/m^2 × 3 days
        ii. $N = 107$, median age 31 (range 16–54). 5-year disease-free survival (DFS) 47%, 5-year OS 52%. No relapses were reported after 2 years.

    b. A randomized trial of four cycles of vinblastine, ifosfamide, and cisplatin (VeIP) or VIP versus three cycles followed by high-dose carboplatin at doses up to 550 mg/m^2 × 1 (based on renal function), etoposide 450 mg/m^2, and

cyclophosphamide 1600 mg/m^2 × 4 days (CarboPEC) showed an improved DFS but similar OS [10].

  i. N = 263, median age 30 (range 15–58). Overall response rates were similar at 67% versus 75%.

c. A randomized trial of sequential autoHCT (VIP-CE × 3) versus single auto-HCT (VIP × 3-CEC) was stopped early due to excess treatment-related mortality in the single CEC transplant arm (4% versus 16%), including sepsis and cardiac toxicity [11].

  i. Arm A, N = 111: VIP, followed by carboplatin 500 mg/m^2 and etoposide 500 mg/m^2 × 3 days. 5-year PFS 47%, 5-year OS 49%.
  ii. Arm B, N-105: VIP × 3 cycles, followed by carboplatin 550 mg/m^2, etoposide 450 mg/m^2, and cyclophosphamide 1600 mg/m^2 × 4 days. 5-year PFS 45%, 5-year OS 39%.

d. A randomized trial (TIGER, NCT02375204) is ongoing which compares conventional-dose TIP versus conventional-dose paclitaxel and ifosfamide followed by high-dose carboplatin and etoposide (TI-CE).

6. There is a clear role for considering autoHCT for patients with chemotherapy-refractory disease after initial or salvage conventional-dose chemotherapy as a curative option.

Salvage Strategies After Failure of High-Dose Chemotherapy

1. Surgery may still be curative for patients with failure after high-dose chemotherapy if limited sites of resectable disease are identified. Such "desperation" surgeries are best referred to centers of experience.
2. Systemic chemotherapy after failure of high-dose chemotherapy is palliative. Options include:

a. Single agent: gemcitabine, oxaliplatin, paclitaxel, or oral etoposide
b. Two-drug combinations: gemcitabine/oxaliplatin, gemcitabine/paclitaxel
c. Three-drug combinations: gemcitabine/oxaliplatin/paclitaxel, gemcitabine/cisplatin/paclitaxel

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Chapter 20
Hematopoietic Cell Transplant for Myelofibrosis

Rachel B. Salit

Introduction

Myelofibrosis (MF) can present as primary myelofibrosis (PMF) or evolve from polycythemia vera (PV) or essential thrombocythemia (ET). Regardless of the etiology, MF is characterized as a clonal stem cell disorder associated with elevated levels of pro-inflammatory and pro-angiogenic cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interferon-gamma (IFN-γ), resulting in a bone marrow stromal reaction that includes varying degrees of reticulin and collagen fibrosis and osteosclerosis. The median age at diagnosis of MF is 60–65 years. The clinical course is heterogeneous with a median life expectancy in nontransplanted patients ranging from less than 2 years to more than 10 years. MF frequently involves the spleen, resulting in massive splenomegaly, severe constitutional symptoms, a hypermetabolic state, and cachexia. Worsening cytopenias and increasing numbers of circulating blasts and eventually leukemic transformation commonly mark disease progression. Allogeneic hematopoietic cell transplantation (HCT) is currently the only treatment with proven curative potential for patients with MF. In the last decade, the numbers of patients undergoing HCT for MF have more than doubled as reduced intensity conditioning (RIC) and non-sibling donor sources have increased accessibility. The following chapter will review the staging systems and other disease and non-disease related risk factors that guide decision-making, as well as choice of donor sources and conditioning regimens, and post-transplant complications which contribute to outcomes following transplantation.

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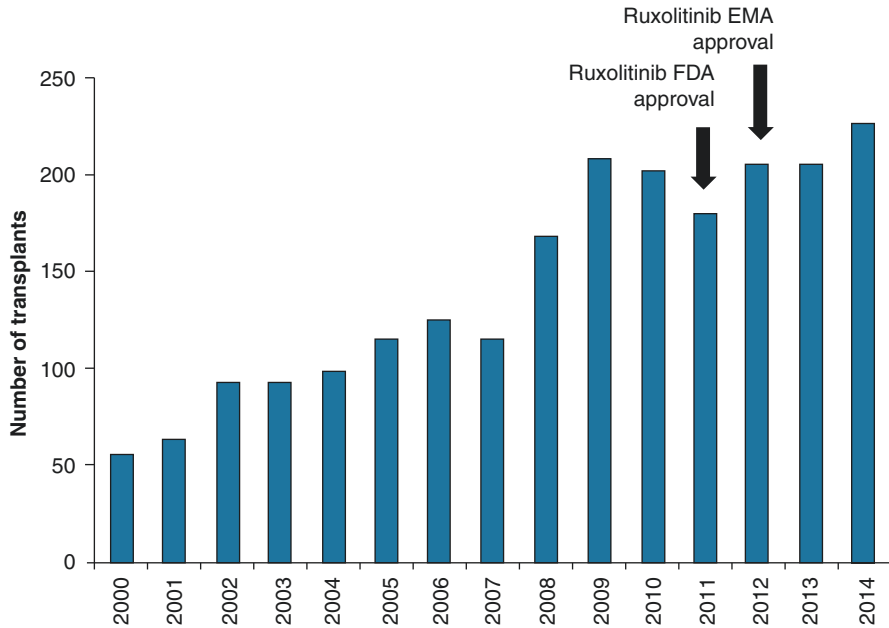
Fig. 20.1 Trends in transplantation for myelofibrosis [81]

Risk Classification

1. A variety of prognostic scoring systems based on clinical characteristics have been created with the aim of identifying higher risk patients (Fig. 20.1). These systems can stratify those who may benefit from HCT or experimental therapies (Table 20.1).
2. Dynamic International Prognostic Scoring System (DIPSS) and Mutation-Enhanced International Prognostic Scoring System (MIPSS) scoring systems have only been validated for PMF. However clinically these scoring systems are also used in patients with post-polycythemia vera (PV) and post-essential thrombocythemia/essential thrombocytosis (ET) myelofibrosis (MF).

Nontransplant Options for Treatment

1. Cytopenias (mainly anemia)

   a. Erythropoietin [1] (Epogen®, Procrit®, Aranesp®)
   b. Corticosteroids [2]
   c. Androgens (Danazol®) [3]
   d. Thalidomide [4] (Thalomid®)
   e. Lenalidomide [5, 6] (Revlimid®)

Table 20.1 Risk scoring systems

Scoring system	Parameters (points/weight)	Risk (points)	Median overall survival (years)
DIPSS [71]	Age > 65 (1) Symptoms (1) Hgb < 10 (2) WBC > 25 (1) Circulating blasts >1% (1)	Low (0) Int-1 (1) Int-2 (2–3) High (>4)	>15 14.2 4.0 1.5
DIPSS Plus [72]	DIPSS Score (0–3) RBC transfusion dependence Platelets <100 Adverse cytogenetics	Low (0) Int-1 (1) Int 2 (2–3) High (4–6)	15.4 6.5 2.9 1.3
MIPSS70 [73]	Symptoms (1) Hgb < 10 (1) WBC > 25 Circulating blasts >1% (1) Marrow fibrosis grade >2 (1) Platelets < 100 (2) Absence of CALR type 1 (1) High-risk mutations (1) >2 High-risk mutations (2)	Low (0–1) Int (2–4) High (>5)	27.7 7.0 2.3
MIPSS70 Plus [73]	Symptoms (1) Hgb < 10 (1) Circulating blasts >1% (1) Absence of CALR type 1 (2) High-risk mutations (1) >2 High-risk mutations (2) Adverse cytogenetics (3)	Low (0–2) Int (3) High (4–6) Very high (>7)	20 6.3 3.9 1.7

2. Splenomegaly, constitutional symptoms, elevated blood counts, increased blasts

    a. Ruxolitinib (Jakafi®) [7–10]
    b. Ruxolitinib + hypomethylating agents (Azacitadine [Vidaza®], Decitabine [Dacogen®])
    c. Fedratinib (Inrebic®)
    d. Hydroxyurea [11, 12]
    e. Interferon [13]
    f. Splenectomy/splenic radiotherapy [14]
    g. Clinical trials

Indications for Transplant

1. Disease criteria:
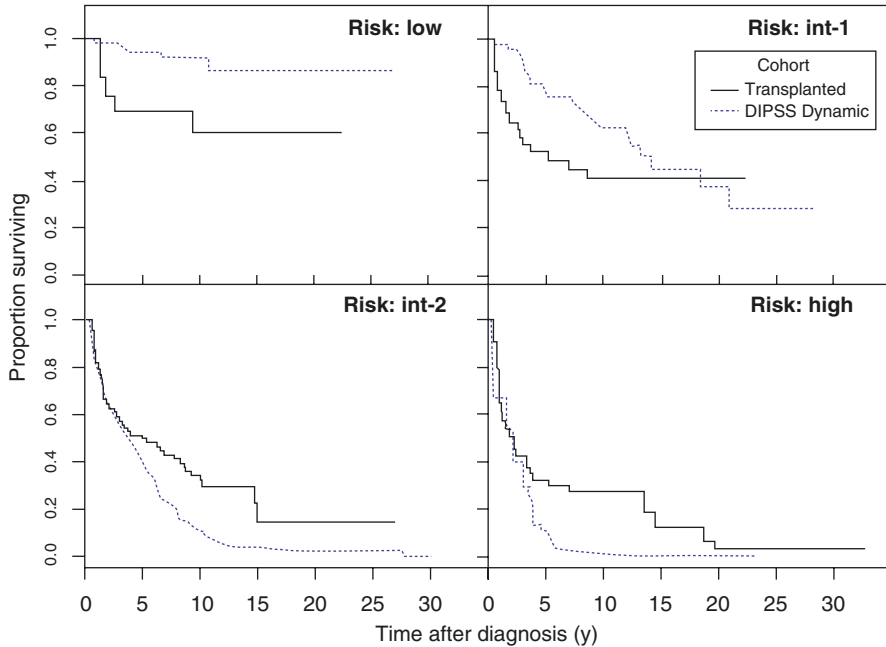
Fig. 20.2 Survival: non-transplant vs. transplant by DIPSS risk [15]

- a. Risk of transplant-related complications is justified in transplant-eligible patients with <5 years of expected survival [15].
- b. Dynamic international prognostic scoring system [for primary myelofibrosis] (DIPSS) data (Fig. 20.2) indicate consideration of:
    - i. patients in the intermediate-2 and high-risk groups only
    - ii. intermediate-1 risk patients with "high-risk features" or younger age

2. Driver mutations: Mutations in three genes have been identified as "driver mutations."

- a. Janus kinase (JAK) 2 (JAK2; nonreceptor tyrosine kinase) is essential for signal transduction via class 2 cytokine receptors in normal hematopoiesis.
- b. Myeloproliferative leukemia protein 1 (MPL1) serves as a receptor for the megakaryocyte stimulating ligand thrombopoietin.
- c. Calreticulin (CALR) serves as a chaperone for protein folding but is also involved in calcium metabolism, thereby co-regulating cell proliferation and function.
    - i. Patients with CALR type 1 may be observed for extended periods of time because of the relatively indolent course with a median life expectancy of more than a decade without transplant [16, 17].

    d. Patients without driver mutations (triple negative) should be considered for transplant early in the disease course since the projected overall survival is shortened in comparison to patients who have one of the driver mutations [16, 18].

3. Somatic mutations

    a. Mutations in ASXL1 are considered indicative of high-risk disease that should lead to consideration of HCT even in the absence of advanced disease, particularly in PMF [19–21].

    b. Mutations in IDH1 and IDH2 are considered high-risk features for disease progression and decreased progression-free survival (PFS) in PMF [22, 23]. These mutations should lead to consideration of HCT, even though preliminary results suggest that they also impact PFS post-HCT.

    c. Mutations in EZH2, often associated with increased circulating blasts, have been associated with reduced survival. While relevant HCT outcome data are not available, this mutation may lead to earlier consideration of HCT than for patients with the same disease characteristics in its absence [24].

    d. Mutations in SF3B1 correlate with shortened life expectancy, particularly in patients with PV and ET [25].

    e. Mutations in SRSF2 are associated with shortened survival in post-ET MF. In PMF the prognosis is affected most severely if seen in combination with IDH mutations, and the treatment strategy should include early HCT [23].

    f. TP53 mutations are also considered to be indicative of high-risk disease. However, TP53 mutations appear to be rare in the chronic phase of PMF. Although transplant data are limited, HCT should be considered for these patients [26].

    g. Considering all currently available mutation data, the strongest signal for disease progression and leukemic transformation in the non-HCT setting comes from the number/combinations of mutations [22, 27].

    h. Patients with multiple mutations are less likely to respond to JAK2 inhibitor therapy, thus identifying patients who should be closely monitored and offered HCT at the earliest sign of progression.

4. Age considerations

    a. The upper age limit of transplantation for MF varies depending on the individual transplant center; transplants in patients aged 70 and higher are commonly performed at some centers.

    b. MF is not currently a diagnosis covered for HCT by Medicare. In 2016, the Medicare Access Study was opened which offered coverage with evidence determination therefore allowing access to HCT Medicare-covered patients who enroll in this study.

    c. Some retrospective studies have reported an association between older age and inferior transplant outcomes [28, 29].

    d. Other studies using more recent cohorts and patients undergoing reduced intensity conditioning (RIC) transplants show no significant association between age and HCT outcomes [30, 31].

    e. Decreased performance status and increased comorbidities, which are often associated with age, are a better predictor of HCT outcome than age alone.

5. Donor options

    a. Stem cell source

       i. The European LeukemiaNet/European Society for Blood and Marrow Transplantation (ELN/EBMT) International Working Group considers peripheral blood the most appropriate source of hematopoietic stem cells for human leukocyte antigen (HLA)-matched sibling and unrelated donor (URD) transplants [32].

    b. Donor selection data on matched sibling versus URD versus mismatched donor

       i. Use of mismatched donors has resulted in inferior HCT outcomes consistently in several studies [29, 30].

      ii. A prospective study from the Myeloproliferative Disorders Research Consortium (MPD-RC) found inferior survival (32% vs 75% at 25 months) and higher nonrelapse mortality (NRM) (59% vs 22% at 25 months) when using URDs compared with matched sibling donors [33].

      iii. Several other studies have found no significant difference in outcomes between matched sibling and well-matched URD [29, 31, 34].

      iv. The European LeukemiaNet/European Society for Blood and Marrow Transplantation (ELN/EBMT) International Working Group concluded that patients with DIPSS int 2- or high-risk disease lacking HLA-matched sibling or URD, should be enrolled in prospective clinical trials using HLA nonidentical donors [32].

      v. A recent report by Takagi et al. suggests that successful engraftment can be achieved after RIC umbilical cord blood transplantation (UCBT) for MF [35].

      vi. Preliminary data by a French group presented in abstract form at American Society of Hematology (ASH) 2013 looking at myeloablative conditioning (MAC) and RIC UCBT for PMF, ET and PV (12 patients had transformed to acute myeloid leukemia (AML)) demonstrated only 64% engraftment but 44% 2-year survival [36].

      vii. In the 2011–2014 interval, survival was shown to be not significantly different between matched sibling and alternative donors (Fig. 20.3) [37].

Timing of Transplantation

1. No prospective studies have evaluated the optimal timing of HCT in MF.

Fig. 20.3 Comparison of outcomes between HLA identical sibling and alternative donor grafts in the 2000–2010 vs 2011–2014 period. (**a**) Cumulative incidence of transplantation-related mortality (TRM) stratified by transplantation period (2000 to 2010 and 2011 to 2014). (**b**) Cumulative incidence of relapse stratified by transplantation period (2000 to 2010 and 2011 to 2014) [37]
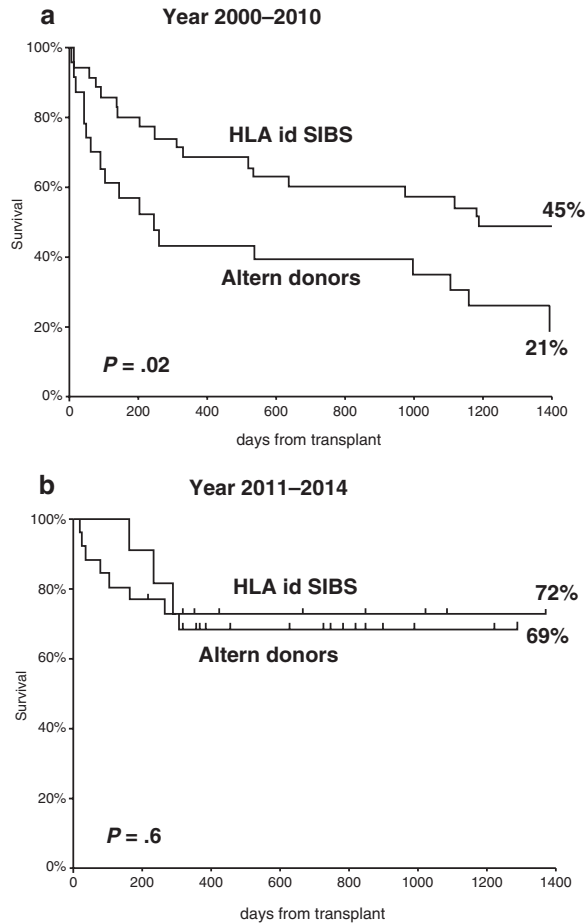
2. No decision analyses have rigorously compared outcomes of HCT to nontransplant therapies.
3. The goal is to proceed with transplant before leukemic transformation.
4. Optimal timing of transplantation is becoming a major decision-making challenge in patients responding well to Janus kinase (JAK)-inhibitor therapy.
5. In a large retrospective study, higher survival (91% vs 56%) and lower non-relapse mortality (NRM) were observed in patients who had clinical improvement on JAK-inhibitor therapy at the time of transplant [38].

   a. The median duration of response to ruxolitinib (Jakafi®) is about 3 years.
   b. Patients may acquire new comorbidities, particularly extramedullary hematopoiesis and fibrosis in organs such as the lungs, which may jeopardize their candidacy for and outcome of transplant.
   c. Patients may also acquire new mutations at an accelerated rate while receiving therapy which could carry a more severe prognosis.

  d. Patients may be greatest served by HCT performed either at the time of best response to ruxolitinib or approximately 8–24 weeks after its initiation.
  e. Many patients undergo HCT as they start to lose response.
  f. Patients should undergo transplant before leukemic transformation, as this secondary diagnosis carries a much worse prognosis [39].

Special Considerations in Work-up

1. Portal hypertension (HTN)

   a. Results in increased risk of hyperbilirubinemia and veno-occlusive disease of the liver/sinusoidal obstruction syndrome (VOD/SOS).
   b. Screening for asymptomatic portal HTN using upper endoscopy and abdominal Doppler ultrasound should be considered [40].

2. Splenomegaly

   a. Spleen size is a risk factor for poor HCT outcomes, including engraftment and mortality [41, 42].
   b. No consistent data on pretransplant splenectomy are available [43–45]. However, one recent retrospective study shows there may be an event-free and overall survival benefit [46].
   c. Splenectomy may carry up to 9% mortality risk [47].

3. Pulmonary hypertension

   a. Pulmonary HTN is a known complication of MF, although the etiology is poorly understood [48].
   b. Results in increased risk of heart failure and pulmonary complications.
   c. Screening for patients with asymptomatic or suspected pulmonary HTN with transthoracic echocardiogram and chest CT should be considered in work-up [49].
   d. If suspicion is high, right heart catheterization (RHC) is indicated.

4. Iron overload

   a. Heavily transfused MF patients should undergo evaluation including serum ferritin and transferrin saturation measurements.
   b. If iron overload is suspected, liver iron concentration should be assessed by MRI.

Conditioning Regimens

1. In the early era of HCT for MF (early 2000s), high-dose cyclophosphamide with busulfan or total body irradiation (TBI) were most commonly used [50].
2. Regimen-related toxicity was high, and survival was 30%–40%

3. During the last decade early NRM has been considerably reduced by using newer and lower intensity regimens.

   a. Intravenous (IV) busulfan [51]
   b. Targeted busulfan [52]
   c. Reversed order cyclophosphamide followed by busulfan [31, 53]
   d. RIC, most commonly fludarabine in combination with busulfan/melphalan or low-dose TBI [29, 33, 41, 54–56].

4. No prospective data are available comparing MAC to RIC in MF.
5. Multiple retrospective studies have made this comparison and overall demonstrate similar outcomes [54, 55, 57].
6. NRM is lower with RIC, but relapse is higher.
7. In a retrospective study of nonmyeloablative vs RIC, lower intensity was found to be associated with increased graft failure [58].

Transplant Outcomes (Table 20.2)

1. Post-transplant outcomes strongly depend on pretransplant risk features as listed above including:

   a. Dynamic International Prognostic Scoring System (DIPSS) or DIPSS-Plus score [31, 59]
   b. High-risk molecular features [60]
   c. Large spleen (>22 cm) [41]
   d. Age [29]
   e. Stem cell source [15, 33, 61]
   f. Comorbidities and performance status.
   g. Conditioning regimens [29, 54]

Pretransplant Therapy with JAK-inhibitors (Table 20.3)

1. Potential benefits of using JAK inhibitors in transplant protocols [7, 8].

   a. Reduction of splenomegaly
   b. Decreasing constitutional symptoms
   c. Improvement in performance status and well being

2. Potential post-transplant benefits include:

   a. Faster hematologic recovery due to reduction in splenomegaly
   b. Decreased severity of graft-versus-host disease (GvHD) and reduction in graft failure due to downregulation of cytokines
   c. Improvement in performance status leading to decreased nonrelapse mortality.

Table 20.2 Recent studies looking at transplant outcomes in patients with ET/PV and MF

Study	Patients, *n*	Conditioning regimen	Med age, *y*	Transplant-related mortality	Overall survival
Kroger 2009 [29]	103	Bu10/Flu180	55	16% at 1 year	67% at 5 years
Alchalby 2010 [39]	162	Bu/Flu	56	22% at 1 year	62% at 5 years
Robin 2011 [43]	147	Flu/Bu/Mel/TBI (87%) Cy/Bu, Cy/TBI (13%)	53	39%	39% at 4 years
Ballen 2012 [66]	117	Flu/Bu (*n* = 37) Bu/Cy (*n* = 80)	51	PV 22% at 1 year ET 27% at 1 year	ET 55% at 5 years PV 71% at 5 years
Scott 2012 [31]	170	HIC Bu/Cy; Cy/Bu; Flu/Bu (*n* = 152) Flu/TBI (*n* = 18)	52	34%	57%
Abelsson 2012 [57]	92	RIC (Bu/Flu) 52 HIC Cy/bu, Cy/TBI 40		5.8% RIC 17.5% HIC at 100 days	RIC 59% at 5 years HIC 49% at 5 years
Ditschkowski 2012 [74]	76	HIC (Cy/TBI, Flu/TBI) RIC (Treo/Flu)	51	28% at 1 year	PFS 50% at 5 years
Lussana 2013 [28]	250	RIC 170 HIC 80	56	28% at 16 months	55% at 3 years
Rondelli 2014 [33]	66	Flu/Mel (RIC)	56	16% at 1 year	75% at 2 years sibs 32% URD (6 months)
Gupta 2014 [30]	233	RIC (Flu/Bu, Flu/Mel, Flu/TBI)	55	24%	47% at 5 years
Kroger 2017 [60]	169	RIC 166 HIC 3	58	21% at 1 year	56% at 5 years
Robin 2017 [46]	85	RIC 70 HIC 15	53	32% at 2 years	PFS at 5 years 58% spleen out 42% spleen in
Samuelson 2018 [59]	233	RIC 42 (Flu/TBI) HIC 191 (Bu/Cy, Flu/Bu, Cy/TBI)	54	20% low/int-1 40% int-2/high	78% low/int-1 35% int-2/high

Bu busulfan, *Flu* fludarabine, *Mel* melphalan, *TBI* total body irradiation, *Cy* cyclophosphamide, *HIC* high-intensity conditioning, *RIC* reduced-intensity conditioning, *Treo* treosulfan

Other Post-Transplant Considerations

1. Splenomegaly

   a. Persistence of splenomegaly in the early post-transplant phase is consistent with expected delayed disease clearance and does not need specific management unless associated with pancytopenia.

Table 20.3 Studies using pre-transplant JAK inhibitors

Study	Number	Study design	Results	Conclusions
Robin, ASH abstract 2013 [75]	22	Prospective	Unexpected SAEs in three patients	Study closed early due to safety issues
Jaekel et al., BMT, 2014 [76]	14	Retrospective	GF, 1/14 treatment related sepsis 1/14	Tapering rux until conditioning did not result in unexpected SAEs
Stubig et al., Leukemia, 2014 [77]	22	Retrospective	1-year OS of 100% in patients with good resp to rux vs 60% in others	Continuing rux until conditioning without taper-no unexpected SAEs
Lebon et al., ASH abstract 2013 [78]	11	Retrospective	Good engraftment rates	Differing schedules of tapering
Shanavas et al., 2016 [38]	100	Retrospective	61% 2 years OS	Patients who stopped rux >6 days prior to conditioning did worse
Gupta et al., 2019 [79]	21	Prospective	61% 2 years OS	Study closed early due to high graft failure.
Salit et al., 2019 [80]	28	Prospective	100% engraftment 86% 2 years survival	Pre-HCT rux may improve post-HCT outcome

SAEs severe adverse events, *GF* graft failure, *rux* ruxolitinib, *OS* overall survival

  b. Post-transplant JAK inhibition has not been studied and may contribute to cytopenias.
  c. Persistence of splenomegaly late after transplantation, when associated with incomplete donor chimerism, is typically a sign of disease persistence or recurrence [32]. Treatment may consist of reduction of immunosuppression, donor lymphocyte infusion (DLI), or both.
  d. JAK inhibitors alone may reduce the spleen size and constitutional symptoms but will not increase donor cell chimerism or clear minimal residual disease.
  e. Splenomegaly appearing after HCT should raise the suspicion of hepatic VOD/SOS, post transplant lymphoproliferative disorders, infections, or relapse [32].

2. Graft failure (GF)

  a. Incidence in MF is reported between 5% and 25% [50, 54].
  b. Occurs significantly more frequently with donors other than siblings [33, 50].
  c. Splenomegaly is associated with primary GF [62].

3. Poor graft function

  a. In the presence of poor graft function, bone marrow should be assessed by biopsy to determine cellularity, persistence of fibrosis and osteosclerosis, and donor/host chimerism [32].

   b. Chimerism studies on peripheral blood CD3+ and CD33+ cells and unfractionated bone marrow cells are necessary to establish the degree of donor cell engraftment and may assist in the decision regarding withdrawal of immunosuppression (in an effort to achieve complete donor cell engraftment).

   c. In patients with poor graft function, use of growth factors may be beneficial.

   d. In patients with a late decline in graft function who have full donor chimerism and no evidence of active GvHD, an infusion of donor hematopoietic stem cells is recommended [32].

   e. In patients with GF and no autologous reconstitution, the only available option that holds any promise is a second allogeneic HCT.

4. GvHD

   a. Some studies have reported higher rates of GvHD in MF patients [33, 51, 53, 54].

5. Relapse

   a. Can be clinical, morphologic, cytogenetic or molecular [62]

   b. Testing for disease-specific markers such as JAK2, CALR, and MPL1 mutations has been shown to be beneficial in detecting minimal residual disease after HCT [63, 64]. These molecular markers can be monitored by polymerase chain reaction (PCR) or by direct sequencing.

   c. In patients who relapse after allogeneic HCT and do not have severe GvHD, reduction of immunosuppressive drugs or DLI are currently considered the treatment strategies of choice [65].

   d. In patients who fail to achieve complete remission despite these measures, a second allogeneic HCT may be considered.

   e. Patients relapsing with constitutional symptoms or splenomegaly may benefit from treatment with a JAK2 inhibitor.

Secondary MF (PV and ET)

1. Most transplants for PV and ET are carried out when MF has developed, or the disease has progressed to acute leukemia.
2. Several reports suggest that patients with secondary MF may have a higher probability of post-HCT OS than patients with PMF [53, 66]

Leukemic Transformation

1. MF, and rarely ET and PV, may progress to acute leukemia
2. Overall prognosis is inferior for patients whose disease has undergone leukemic transformation [39, 53, 67].

3. Probability of OS is higher if patients respond to induction type chemo-therapy.
4. Both relapse and nonrelapse mortality following HCT is higher in patients transplanted after leukemic transformation.
5. Nontransplant options such as hypomethylating agents and JAK inhibitors have been somewhat successful [68–70].

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Chapter 21
Chronic Myeloid Leukemia

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Introduction

Chronic myeloid leukemia (CML) is generally viewed as a less common leukemia, typically diagnosed in the seventh decade of life or beyond in the United States (US). However, age at presentation varies widely across different global regions with the median age at diagnosis in the latter part of the fourth decade in Africa and Asia [1] and in the fifth decade in Europe and Latin-American populations. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) database [2] describe the somewhat distinct profile of CML in the US:

– Median age at diagnosis of 65 years
– Incidence of approximately 1.9 per 100,000 individuals
– Slight male-to-female predominance
– Nearly 9000 new cases diagnosed per year
– Steadily increasing prevalence with 54,000+ people living with CML as of 2016
– Five-year overall survival (OS) rates of 69%, lower than observed in clinical trials to date

CML was the first human cancer linked to a discrete genetic anomaly, the Ph chromosome [3]. Sequential research into the structure and function of its product, the constitutively activated BCR-ABL kinase, led to the initial proof-of-principle study of the first ABL tyrosine kinase inhibitor (TKI), imatinib mesylate (a.k.a., STI571, Gleevec®/Glivec®). Over a period of 15 years, five oral agents have been approved for use in accelerated and blast phase CML and Ph+ acute lymphoid leukemia (ALL). These include imatinib, nilotinib (Tasigna®), dasatinib (Sprycel®),

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bosutinib (Bosulif®), and ponatinib (Iclusig®). Initial therapy with the cytoreductive alkylating agent, hydroxyurea (Hydrea®), is often deployed at initial presentation; its use should be limited given the risk for augmentation of myelosuppression common during initial TKI therapy.

While TKI therapy dominates the treatment of CML, early discussion and triage of appropriate patients to allogeneic hematopoietic cell transplant (HCT) remains appropriate. Presentation in the advanced phase, irrespective of subsequent response, should warrant proceeding to HCT if possible. Circumstances in which HCT should be strongly considered include failure to achieve protective levels of response such as partial or complete cytogenetic remission, sequential resistance/intolerance to multiple lines of therapy leading to exhaustion of treatment options and CML proliferation, and development of complex or high-risk cytogenetic changes both within the CML clone and in Ph- clones. In the case of chronic phase (CP) CML with indications or preference for HCT as the optimal path to stable remission or cure, all efforts should be made to avoid progression to advanced phase disease.

Key Points

1. In the US, CML typically occurs in the seventh decade; however, there is significant worldwide variability in the typical age at diagnosis.
2. TKI therapy has become the mainstay of treatment for CML with high rates of response and multiple oral agents targeting the BCR-ABL kinase; treatment-free remission (TFR) is feasible and increasingly the goal of therapy.
3. Allogeneic HCT remains an option for advanced phase CML and certain circumstances.

Making the Diagnosis and Monitoring Response in CML

1. The majority of CP CML patients are diagnosed based on abnormal blood counts, typically found incidentally. Presenting signs and symptoms include fatigue, weight loss, abdominal symptoms from splenic enlargement, and "B" symptoms including unexplained fevers and night sweats.
2. Beyond CP CML is defined as either accelerated phase or blast phase:

   a. Accelerated phase CML is defined by the World Health Organization (WHO) [4] criteria:

      i. 10–19% blast cells in the blood or bone marrow
      ii. Basophils in blood $\geq 20\%$
      iii. Persistent thrombocytopenia (platelet count $<100 \times 10^9$/L) unrelated to therapy
      iv. Thrombocytosis (platelet count $>1000 \times 10^9$/L) unresponsive to therapy

    v. Increasing spleen size and increasing white blood cell (WBC) count unresponsive to therapy

    vi. Cytogenetic evidence of clonal evolution (the appearance of additional genetic abnormalities that were not present at the time of diagnosis)

  b. WHO-recommended criteria for the diagnosis of blast phase CML are ≥20% blast cells in blood or bone marrow, extramedullary blast proliferation, or large foci or clusters of blasts in the bone marrow biopsy.

3. Bone marrow biopsy and aspirate given suspicion of CML is warranted to rule out occult advanced disease, maximize chances of obtaining adequate karyotyping, and identify disease features that might impact the course of TKI treatment and adverse events such as increase in fibrosis.

4. Bone marrow karyotype remains a gold standard method to identify the Philadelphia chromosome with a target of $n = 20$-cell assessment examining for t(9:22); additional clonal changes in Ph$^+$ and Ph$^-$ cells aid in risk assessment and plan for response monitoring.

5. Clonal cytogenetic changes are divided into "major route" and "minor route" [5], with different implications therein; major route changes (trisomy 8, a second Ph, isochromosome 17q or trisomy 19) were associated with diminished response and survival. Subsequent studies [6] identified additional specific "minor" routes with a significant impact on prognosis, including 3q26 rearrangement and −7/del(7q).

6. Fluorescence in situ hybridization (FISH) is an additional standard method of identifying the Ph chromosome, typically in a 200-cell count assay; examination and quantitation of the active fusion on chromosome 22 as well as the integrity of the derivative chromosome 9 historically have been important, with loss/partial loss of derivative 9 signaling genetic instability and greater risk of poor response; however, in the era of TKI therapy, loss of der 9 may be more equivocal [7].

7. Polymerase chain reaction (PCR) has evolved to be not only a standard diagnostic identifier for Ph$^+$ leukemia but also the main assay to assess response over time during TKI therapy, from early to late/deep response and gains increasing importance as a measure for TFR.

  a. CP CML is most often characterized by a p210 fusion product, whereas Ph$^+$ ALL is most often identified by p190 fusion; however, p190 fusion (+) CML and variant fusions leading to products of 210–230 kD have been reported [8].

  b. Variation in transcript type—e13a2 versus e14a2—is evident, as well as the presence of both transcripts admixed; e14a2 fusion type has been associated with improved response [9].

8. While subtle increased sensitivity has been reported in Ph$^+$ ALL, bone marrow sampling for quantitative PCR (qPCR) is not required, and the overwhelming majority of data regarding qPCR response and prognostic value have been derived from peripheral blood PCR, simplifying monitoring of CP CML for patients and providers.

9. Reporting of qPCR ideally is based on the International Scale (IS), normalizing BCR-ABL transcript levels to +/− 100% untreated levels and facilitating the development of established milestones representing a logarithmic reduction in disease burden (Tables 21.1 and 21.2).

Table 21.1 Response expectations over time on TKI therapy, NCCN [15] and ELN [17] Guidelines

Timepoint	NCCN optimal	ELN optimal	NCCN warning	ELN warning	NCCN failure	ELN failure
Baseline	NA	NA	NA	High-risk ELTS, high-risk ACA	NA	NA
3 months	≤10%	≤10%	>10%	>10%	NA	>10% confirmed within 1–3 mo
6 months	>1–10% and/ or ≤ 1%	≤1%	NA	>1–10%	>10%	>10%
12 months	≤1%	≤0.1%	>1–10%	>0.1–1%	>10%	>1%
>15 months	≤1%	NA	NA	NA	>1–10% and/ or > 10%	NA
Anytime		≤0.1%		>0.1–1%; Loss of ≤0.1%		>1%, resistance mutations, High-risk ACA

TKI tyrosine kinase inhibitor, *NCCN* National Comprehensive Cancer Network, *ELN* European Leukemia Net, *NA* not applicable, *ELTS* EUTOS long-term survival score, *ACA* additional chromosomal abnormalities

Table 21.2 Comparison, criteria, and procedure for treatment-free remission, NCCN, and ELN

NCCN 2020 Criteria [15]	ELN 2020 Criteria [17]
Age ≥ 18 years	–
Chronic phase CML; no prior history of accelerated or blast phase CML	CML in first CP only (data are lacking outside this setting) (mandatory requirement)
Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits	Motivated patient with structured communication (mandatory requirement)
Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (BCR-ABL1 ≤ 0.0032 IS)	Access to high-quality qPCR using the IS with a rapid turnaround of PCR test results (mandatory requirement)
Monthly molecular monitoring for 1 year, then every 2 months for the second year, and every 3 months thereafter (indefinite) IS recommended for patients who remain in MMR (MR3; BCR-ABL1 ≤ 0.1% IS) after discontinuation of TKI therapy	Patient's agreement to more frequent monitoring after stopping treatment. This means monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter (mandatory requirement)

Table 21.2 (continued)

NCCN 2020 Criteria [15]	ELN 2020 Criteria [17]
–	First-line therapy or second-line if intolerance was the only reason for changing TKI (minimal requirement)
Prior evidence of quantifiable BCR-ABL1 transcript	Typical e13a2 or e14a2 BCR–ABL1 transcripts (minimal requirement)
On approved TKI therapy for at least 3 years	Duration of TKI therapy >5 years (>4 years for 2GTKI) (minimal requirement)
Stable molecular response (MR4; BCR-ABL1 ≤ 0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart	Duration of DMR (MR^4 or better) >2 years (minimal requirement)
–	No prior treatment failure (minimal requirement)
–	Duration of TKI therapy >5 years (optimal requirement)
–	Duration of DMR >3 years if MR^4 (optimal requirement)
–	Duration of DMR >2 years if MR$^{4.5}$ (optimal requirement)
Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, BCR-ABL1 kinase mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months	–

NCCN National Comprehensive Cancer Network, *ELN* European Leukemia Net, *CML* chronic myeloid leukemia, *CP* chronic phase, *TKI* tyrosine kinase inhibitor, *qPCR* quantitative polymerase chain reaction, MR4.5 = molecular response 4.5, also known as complete molecular response, *IS* International Scale, *MMR* major molecular response, *MR3* molecular response 3, *DMR* durable molecular response, *MR4* molecular response 4

Defining Response in CML

1. Hematologic response in CML is defined [10] as WBC count <10,000/mm^3, platelet count <450,000/mm^3, the presence of <5% myelocytes plus metamyelocytes, the presence of <20% basophils, the absence of blasts and promyelocytes in peripheral blood, and the absence of extramedullary involvement of CML.
2. Cytogenetic response is defined by a reduction in the proportion of cells positive for the Ph$^+$ chromosome typically measured by karyotype or FISH:

   a. Minimal cytogenetic response: 36–95% Ph$^+$ metaphases
   b. Partial cytogenetic response: 1–35% Ph$^+$ metaphases

   c. Major cytogenetic response (MCyR): 0–35% Ph+ metaphases

   d. Complete cytogenetic response (CCyR): 0% Ph+ metaphases

3. Molecular response (MR) falls into several well-defined categories:

   a. Early molecular response (EMR) [11]: generally accepted as ≤10% IS; may be individualized to note 1 log reduction from the patient's baseline level

   b. MR2: ≤1% IS; accepted to equate to the conventional threshold of CCyR where the karyotype and FISH studies normalize (0% Ph+)); 2 logs below the typical initial level

   c. MR3: ≤0.1% IS; developed as a milestone during the landmark IRIS study of frontline imatinib [12]; prognostic value validated in key studies, offering protection from progressive disease and a greater likelihood of deeper response; 3 logs below typical initial level

   d. MR4: ≤0.01% IS; associated with eligibility to consider TFR

   e. MR4.5: ≤0.0032% IS; also referred to as complete molecular response (CMR); practically representing transcript detectability threshold in typical commercial and academic laboratories

Risk Stratification in CML

1. The Sokal Score [13] has consistently remained prognostic in the pre-TKI and the current TKI era; may apportion more patients to intermediate and higher risk based on age and development during the chemotherapy era.

2. Calculation of the Sokal Score should be performed at initial diagnosis:

   a. Sokal Score = exp.([0.0116 × (age in years – 43.4)] + [0.0345 × (spleen size in cm – 7.51)] + [0.188 × ((platelets in 10^9/L/700)^2–0.563)] + [0.0887 × (blasts in % – 2.10)]])

   b. Sokal Score categories: Low (<0.8), Intermediate (0.8–1.2), High (>1.2)

3. The EUTOS long-term survival score (ELTS) was developed from the European Treatment and Outcomes Study (EUTOS) dataset [14] and is felt superior to judge the risk of CML-related death:

   a. ELTS Score = 0.0025 × (age in completed years/10)^3 + 0.0615 × spleen size below costal margin +0.1052 × blasts in peripheral blood +0.4104 × (platelet count/1000)$^{-0.5}$

4. National Comprehensive Cancer Network (NCCN) guidelines [15] in the US incorporate risk stratification into decision-making regarding frontline TKI choice:

   a. For Sokal lower risk patients, imatinib included equally with nilotinib, dasatinib, and bosutinib as first choices

   b. For Sokal higher risk patients, nilotinib, dasatinib, and bosutinib as first choices with the highest level of evidence to support; imatinib listed as an additional option

5. Careful consideration of comorbid illness is suggested to incorporate into TKI choice and treatment decision-making in CML; Charlson Comorbidity Index (CCI) [16]:

   a. Strong negative association between CCI and overall survival in CML
   b. No negative effect of CCI on remission rates and progression to advanced phases in CML

Response Milestones and Kinetics: Treatment Guidelines

1. Traditional response milestones irrespective of treatment choice include the following:

   a. Complete Hematologic Response->Complete Cytogenetic Response->Major Molecular Response->Deep Molecular Response.
   b. NCCN and European Leukemia Net (ELN) guidelines [17] describe the timing of response expectations, with categorization of response as "optimal"/(green), "warning"/(yellow), or "failure"/(red) at time-based milestones.
   c. Key baseline factors include risk stratification (Sokal, ETLS) and "high-risk" additional chromosomal abnormalities (ACA) [5]:

      i. ACA includes +8, a second Ph-chromosome (+Ph), i(17q), +19, −7/7q-, 11q23, or 3q26.2 aberrations, and complex aberrant karyotypes.

   d. Key milestones based on IS reported qPCR levels ranging from 0.1% to 10%.
   e. Deep molecular response (MR4: ≤0.01% IS; MR4.5: ≤0.0032% IS) is not included in ELN or NCCN guidelines as expected response milestones but rather target responses for consideration of TFR.

Treatment-Free Remission (TFR)

1. Cessation of TKI therapy in patients maintaining deep remission for a prolonged period of time was first reported in a pilot trial of 12 patients in 2007 [18].
2. Subsequent larger trials have been performed, and both NCCN and ELN guidelines have now described criteria and framework by which patients may be considered for and undergo attempt at treatment cessation.
3. Meta-analysis of >500 patients in 15 cohort studies who discontinued imatinib for treatment-free remission demonstrated ~50% success rate and reproducibility of TFR [19].
4. Relapse and need for retreatment with TKI occurs within the first 6 months of TFR attempt in ~80% of cases; loss of MMR and need for retreatment >18 months after cessation appears very rare.
5. Retreatment, generally with the same TKI prior to cessation, yields return to pre-TFR molecular response in ~95% of cases.

6. Approximately 25% of patients discontinuing TKIs experience "TKI withdrawal syndrome" [20]. This syndrome generally manifests as musculoskeletal symptoms that peak 6–8 weeks after cessation and rarely persist, potentially linked to KIT reactivation and subsequent inflammation.
7. Rare events of response loss, mutation identification, and disease progression have been noted, and further research is needed to properly quantify risk and cause for such events.

Resistance Testing, Mutations, and Subsequent Lines of Therapy

1. Resistance to therapy can be observed in 10–15% of patients after initial TKI therapy (~15% after imatinib, <10% after initial therapy with second-generation TKIs nilotinib, dasatinib, bosutinib).
2. The best-described mechanism for TKI resistance is point mutation at key amino acid residues in the ATP-binding pocket where drug binding/inhibition occurs; while >100 mutations have been identified, there are a crucial key number of mutations which affect TKI efficacy to variable degrees [21].
3. Key inquiry at the discovery of clinical resistance includes ensuring proper adherence/compliance with recommended therapy as this may represent one of the more common causes.
4. ABL kinase domain mutation testing is of the highest yield for patients who fail to meet response (CHR, CCyR, MMR) or who have substantive response loss.
5. Predicted response milestones to TKI therapy based on mutations generally have been inferred from phase 2 clinical trials of second-generation agents after imatinib therapy; NCCN guidelines give practical guidance as follows [15]:

    a. Mutations contraindicated for bosutinib: T315I, V299L, G250E, F317L
    b. Mutations contraindicated for dasatinib: T315I/A, F317L/V/I/C, V299L
    c. Mutations contraindicated for nilotinib: T315I, Y253H, E255K/V, F317L/V/I/C, G250E
    d. Mutations contraindicated for ponatinib, omacetaxine, HCT: none

TKI Therapy: Imatinib (Gleevec®)

1. Sequential landmark discoveries supported the sole and central role of the Ph+ chromosome and resultant "driver" BCR-ABL fusion in disease pathogenesis in CML; however, comprehensive and lasting remission, and potentially curative effect of small molecule inhibitor was not predicted to come from research focused on inhibition of the BCR-ABL tyrosine kinase.

2. Imatinib is the prototype TKI for Ph⁺ leukemias, moved into clinical trials for CML in 1998 as the lead small molecule (prior name STI-571) for development as an inhibitor of several protein tyrosine kinases including the ABL tyrosine kinase, C-KIT, and PDGF.

3. Preclinically, imatinib was found to specifically inhibit or kill proliferating myeloid cell lines containing BCR-ABL without effect on normal cells [22].

4. Phase I clinical trials demonstrated remarkable safety and efficacy in CP CML and heralded in a new era of "targeted therapy" [23]; a phase III trial of imatinib unequivocally set a new standard for CP CML therapy, imatinib 400 mg daily, compared to the now historic comparator interferon-alpha with cytarabine [12].

5. Imatinib remains a gold standard treatment option for CP CML, viewed particularly favorable for patients with comorbid medical conditions and lower risk disease; however, it is suitable for CP CML in general.

6. Higher doses of imatinib have been studied (600–800 mg); 600-mg dosing remains the standard for accelerated phase CML and may offer an advantage as initial therapy or as immediate escalation for suboptimal early response [24].

7. Adverse events specifically associated with imatinib include periorbital and generalized edema, myalgias and muscle cramps, gastrointestinal effects including diarrhea, hypophosphatemia, and potential pigment changes in the skin and hair.

TKI Therapy: Nilotinib (Tasigna®)

1. Nilotinib was developed as a derivative of imatinib with the goal of narrowing the affected kinase spectrum and increasing potency against BCR-ABL, potentially offering a better adverse event profile and greater activity against ABL kinase domain mutations.

2. An initial study of nilotinib in the post-imatinib salvage setting showed remarkable efficacy and good safety; comparative phase III Evaluating Nilotinib Efficacy and Safety in Clinical Trials - newly diagnosed patients (ENESTnd) trial against imatinib [25] yielded higher rates of early response and deep molecular response as well as protection against progression to advanced phase disease.

3. Initial reports from earlier studies and comparative toxicity in the randomized phase III ENESTnd trial have demonstrated the potential for nilotinib to increase the risk of metabolic disease (hyperglycemia/diabetes, hyperlipidemia) as well as vascular occlusive events (VOEs), with a suggestion of association with dose (400 mg BID >300 mg BID).

4. In addition to pre- and post-nilotinib electrocardiogram testing to screen for potential QT prolongation and thus arrythmia risk, careful vascular disease risk assessment and monitoring during therapy are warranted to identify new or evolving metabolic disease and VOEs. Guidelines have been published urging baseline and sequential cardiovascular risk assessment for patients treated with nilotinib [26].

5. The exact mechanism of action for nilotinib-associated vascular occlusive disease and metabolic disease remains to be elucidated; in vitro and limited clinical

studies have suggested vascular endothelial effects favoring a pro-thrombotic state [27].

6. In addition to the possibility of metabolic disease and VOEs which are of relatively low likelihood but have greater potential for morbidity, nilotinib has the potential to cause other adverse effects, including lipase elevation and pancreatitis, follicular skin rash, myalgias and arthralgias, headache, and fatigue, as well as other effects.

7. The standard dosing of nilotinib is 300 mg twice daily in the frontline setting and 400 mg twice daily in subsequent lines of therapy; it is meant to be taken "fasting" (no food 2 hours prior and one hour after dosing).

TKI Therapy: Dasatinib (Sprycel®)

1. Dasatinib was initially developed as an inhibitor of the SCR (gene related to the Rous sarcoma virus) family of kinases and was found to be a potent inhibitor of the ABL kinase and suitable for Ph+ leukemias; like its companions in the second generation of such inhibitors, it was developed with the goal of greater potency against BCR-ABL and activity against ABL kinase domain mutations.

2. An initial study of dasatinib in the post-imatinib salvage setting also showed remarkable efficacy and good safety; comparative phase III trial against imatinib yielded higher rates of early response and deep molecular response as well as protection against progression to advanced phase disease [28].

3. Initial dosing of dasatinib in the salvage setting was 140 mg; subsequent dose optimization studies shifted the recommended dose down to 100 mg based on comparable efficacy and lower toxicity [29]. Additional studies are needed to identify the optimal dose of dasatinib particularly in the frontline setting with 50 mg daily under consideration based on a single-center phase II study [30].

4. Comparative toxicity in the randomized phase III Dasatinib versus Imatinib study in Treatment-naive Chronic Myeloid Leukema patients (DASISION) trial demonstrated the potential for dasatinib to have distinct pleural and pericardial toxicity and a significant degree of pleural effusions in ~20% or more of patients over time with the potential to occur de novo after several years of therapy; more rare pericardial effusions have been noted as well as less than 1% incidence of pulmonary arterial hypertension felt to be therapy related [31].

5. Other toxicities attributed to dasatinib include headache, diarrhea, bleeding, dyspnea, and among the TKIs used in the frontline, the highest degree of myelosuppression (although seen with all TKIs to a degree).

6. Baseline echocardiography may be helpful to assess baseline cardiac function [26], changes related to pulmonary hypertension, and rule out antecedent pericardial effusion to best manage symptoms or question of pericardial or pulmonary arterial toxicity from dasatinib; however, baseline chest radiographs are not recommended. Symptom-directed evaluation and management of pleural effusions (drug hold/reduction, diuretics, pulse steroids, thoracentesis when indicated) is the best practice to minimize morbidity.

7. The standard dosing of dasatinib is 100 mg daily in the frontline setting and beyond in CP, while accelerated phase CML warrants 140 mg dosing. Optimization of all TKI dosing schemas has been undertaken and lower doses (50 mg) continued to gain interest as an optimized dose to reduce the incidence of pleural effusions.

TKI Therapy: Bosutinib (Bosulif®)

1. Bosutinib, similar to dasatinib, was developed as a dual inhibitor of the SCR family of kinases and the ABL kinase, thus applicable for Ph+ leukemias. Targeting a narrower repertoire of kinase targets, initial studies showed clear efficacy against BCR-ABL, against ABL kinase domain mutations, and a distinct side effect profile.
2. Bosutinib in the post-imatinib salvage setting, similar to nilotinib and dasatinib, showed remarkable efficacy and good safety [32]. In addition, studies evaluated bosutinib in patients with ≥2 TKI therapies prior and yielded reasonable rates of efficacy in the third line or beyond [33].
3. Phase III study of bosutinib in comparison to imatinib was performed in multiple studies, with the acronyms BELA and BFORE, for the purpose of proving superiority. Data from the BELA trial failed to meet the primary endpoint of improved complete cytogenetic response at 12 months, despite higher rates of major molecular response and reduction in progression risk [34]. The subsequent BFORE trial, utilizing the optimized dose of 400 mg of bosutinib, demonstrated superior molecular response at 12 months, facilitating movement of bosutinib into the frontline setting [35].
4. The initial dosing of bosutinib in the salvage setting was 500 mg daily. Key observations regarding dose reductions for toxicity, notably gastrointestinal and hepatic, with preserved response suggested that 400 mg daily was optimal and ultimately was identified in the BFORE trial as the best frontline dose.
5. Toxicity observations in all phases of bosutinib investigation have included higher rates of gastrointestinal effects, namely diarrhea, typically rapid in onset but limited in duration. Aggressive early management to avoid dehydration and higher grade symptoms along with dose optimization has vastly improved the tolerance of bosutinib. In addition, hepatic enzyme elevation is observed more with bosutinib than other TKIs and requires ongoing monitoring and potential dose modification. Cardiovascular, vascular, and metabolic toxicities appear much lower with bosutinib.
6. Although added to the frontline options later than other TKIs, bosutinib offers a predictable and potentially avoidable side effect risk and thus a good alternative, with potential for improved response in patients. In addition, bosutinib is a good alternative in the third line and beyond to mitigate/avoid the toxicity of other agents used in such patients; a comparative study to the novel agent asciminib (ABL001) is ongoing [ClinicalTrials.gov Identifier: NCT03578367].

TKI Therapy: Ponatinib (Iclusig®)

1. Ponatinib was developed specifically with the goal of overcoming known resistance mechanisms in Ph⁺ leukemias, with a specific focus on the point mutation T315I (threonine/isoleucine substitution at amino acid position 315) known to, by steric inhibition, preclude activity of all other TKIs. In vitro studies demonstrated the ability of ponatinib to inhibit leukemic clones harboring the T315I mutation and limit outgrowth of de novo resistant clones [36].

2. An initial clinical study of ponatinib showed remarkable efficacy against patients with multi-TKI resistant CML [37]. While activity in blast phase disease was more limited and short-lived, chronic and accelerated phase CML response was comprehensive, including stable and deep responses. Activity against the T315I mutation in patients with more limited TKI exposure was the highest, with the majority of patients responding durably.

3. Larger phase II study of ponatinib (PACE study) [38] convincingly showed the majority of CP CML with multi-TKI resistance and patients with the T315I responded well; from this trial came initial reporting followed by temporary US Food and Drug Administration (FDA) prescribing hold and further investigation into the incidence of VOEs associated with ponatinib.

4. Now observed as a potential risk with several TKIs, VOEs and importantly signs or symptoms of potential cardiovascular, cerebrovascular, and peripheral vascular disease were noted in nearly half of patients in phase I studies and 15–20% of patients in subsequent studies. A randomized phase III study of ponatinib versus imatinib, designed to assay the performance of ponatinib in the frontline, was prematurely stopped due to an early signal of increased events [39].

5. While clearly a cause for concern and warranting specific screening and monitoring, several key elements of understanding are lacking regarding VOEs and TKIs, including adjudication regarding causality, understanding of the frequency and impact of underlying comorbid conditions, potential mechanisms of action, and potential appropriate mitigation strategies. Guidelines have been published in the leukemia and cardiovascular literature to outline prospective risk assessment and monitoring strategies to minimize such adverse events [26].

6. In addition to the prominent possibility VOEs, ponatinib also has the potential to cause other cardiovascular adverse effects, including heart failure and drug-induced hypertension; the latter is expected as ponatinib affects the vascular endothelial growth factor receptor (VEGFr), a known mechanism of hypertension seen with other targeted cancer drugs with a similar effect.

7. Hepatic toxicity, neuropathy, and ocular toxicity have been observed with ponatinib, as have lipase elevation and pancreatitis akin to that seen with nilotinib; follicular skin rash; abdominal pain; constipation, and headache, as well as other effects.

8. The current standard dosing of ponatinib is 45 mg daily with a reduction to 15 mg daily after a response is obtained. Based on analyses demonstrating toxicity reduction in association with dose reduction in phase II trials, a dose

optimization trial (OPTIC) is ongoing to confirm the optimal starting and maintenance dose for ponatinib [ClinicalTrials.gov Identifier: NCT02467270].

Other Recent Therapies for CML: Omacetaxine (Synribo)

1. Omacetaxine is a naturally occurring plant alkaloid found to be a reversible, transient inhibitor of protein elongation that triggers CML cell apoptosis in a manner not dependent on BCR-ABL signaling.
2. Previously as known as homoharringtonine (HHT), omacetaxine was studied in CML in several small trials and combined data from phase II studies of chronic and accelerated phase CML with ≥2 TKI therapies prior yielded reasonable rates of efficacy, albeit less than TKI-based therapy, with a non-TKI approach [40].
3. Omacetaxine is given by subcutaneous injection twice daily for 14 consecutive days of a 28-day cycle until a hematologic response is achieved, and then twice daily for 7 consecutive days over a 28-day cycle during maintenance therapy.
4. The most common adverse events include injection site reaction, diarrhea, nausea, neutropenia, febrile neutropenia, fever, infection, lymphopenia, anemia, weakness and fatigue, and thrombocytopenia.

Novel Therapy for CML: Asciminib (ABL001)

1. Asciminib was developed as a first-in-class allosteric inhibitor, specifically targeting the ABL myristoyl pocket ("STAMP"). BCR-ABL fusion causes loss of the autoinhibitory function of the myristoyl N terminus on the ABL kinase; allosteric binding of asciminib to the myristoyl site restores this regulatory function and BCR-ABL inhibition.
2. Due to its non-ATP-binding pocket mechanism of action, asciminib was developed as a means to overcome resistance based in ATP-binding pocket mutations and offered the potential to be combined with conventional ATP-pocket-binding TKIs for additive or synergistic effect [41].
3. A large phase I trial exploring a variety of dosing levels and schedules, treatment of all phases of Ph+ leukemia, and combination of asciminib with imatinib, dasatinib, and nilotinib is ongoing [ClinicalTrials.gov Identifier: NCT03578367]. The initial report of CP CML treated with single-agent asciminib [42] shows a high degree of safety and efficacy in multi-TKI-resistant patients. Pancreatic toxicity has been observed similar to nilotinib and ponatinib, as well as moderate myelosuppression; to date, no other major limiting toxicities have emerged nor has a vascular/cardiovascular safety signal.
4. Ongoing study of highly resistant T315I patients and higher dose asciminib, as well as combination approaches continue, holds great promise for this novel ABL inhibitor.

Role of Allogeneic Transplantation in CML in the Era of TKIs

1. Allogeneic HCT was highly successful for patients with CP CML and was a standard approach in the appropriate patients prior to the advent of TKIs.
2. Proceeding in early CP and avoidance of proximal therapy with interferon-based therapy maximized outcomes. In specialized centers, long-term success exceeded 80%.
3. In the TKI era, caution is advised to not dismiss allogeneic HCT as a curative option for CML patients. At present, evaluation of donors and planning in younger patients with poor response to TKIs, avoidance of progressive disease, and minimizing chronic toxicity from TKI therapy are important considerations.
4. The profile of patients proceeding to HCT at present likely represents a highly selected group of patients with significant resistance to TKIs and prolonged TKI exposure. While prior TKI use has not been associated with poor outcome for subsequent allografting, progressive disease and greater proportion of transplantation in advanced phases of CML will likely worsen the perception of allografting efficacy in CML.
5. Comparative outcomes in patients with the T315I mutation and treatment with ponatinib, representing one specific subset of patients with an uncertain long-term benefit versus risk, versus those proceeding to HCT, have been evaluated. Results suggested ponatinib efficacy in CP disease was initially superior. HCT and ponatinib were similar in the short term for accelerated phase; however, in blast phase CML, HCT was superior to ponatinib therapy, supporting the focused and informed use of allografting in CML as an important element of curative CML approach [43].
6. The use of TKIs in the post-transplant setting continues to be explored with reports of relapse risk reduction with the early addition of imatinib post-transplant, and more limited ability to deliver nilotinib in the post-transplant setting [44, 45]. Given the highly resistant nature of CP CML patients proceeding to transplant, more studies of highly potent TKIs including ponatinib and potentially asciminib are warranted.

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Chapter 22
Chronic Lymphocytic Leukemia

Alexey V. Danilov and Veronika Bachanova

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world. In the past decade, the introduction of novel targeted therapies resulted in a paradigm shift in CLL, with a diminished use of standard chemo-immunotherapy (CIT) regimens, and a widespread use of novel agents in both previously untreated and relapsed disease.

Novel targeted agents, FDA-approved in therapy of CLL and/or other lymphomas, include the following:

1. Bruton tyrosine kinase (BTK) inhibitors

    a. Non-selective: ibrutinib (Imbruvica®)
    b. Selective: acalabrutinib (Calquence®)

2. Phosphoinotiside-3 kinase (PI3K) inhibitors

    a. Idelalisib [PI3Kδ] (Zydelig®)
    b. Duvelisib [PI3Kγδ] (Copiktra®)

3. BCL2 inhibitor/BH3-mimetic

    a. Venetoclax (Venclexta®)

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Large randomized trials demonstrated the advantage of BTK inhibitors in prolonging progression-free survival (PFS) over CIT in both older and younger patients with CLL [1, 2]. Despite these data, allogeneic hematopoietic cell transplant (HCT) remains the only proven curative therapeutic approach in patients with CLL and should be considered in patients with high-risk disease features.

1. Factors limiting the widespread use of cellular therapy in CLL:

   a. Advanced age (70–72 years) at diagnosis
   b. Comorbidities at diagnosis (median number = 2) [3]
   c. Availability and sequencing of CIT and targeted agents with minimal or manageable side effects

2. Disease features predicting inferior outcomes in the CIT era, prompting evaluation of the eligible patients for HCT [4–9]:

   a. Chromosomal abnormalities – del(17p), del(11q), or complex karyotype ($\geq$3 chromosomal abnormalities) [10]
   b. Gene mutations (TP53)
   c. Unmutated IGHV (U-IGHV)
   d. Early relapse following chemo-immunotherapy (particularly fludarabine(Flu)-containing regimens)
   e. Others: CD38, CD49, ZAP-70, serum β_2-microglobulin, gene mutations [NOTCH1, SF3B1], etc.

3. However, in the era of targeted agents, many of those factors have been disputed to portend inferior prognosis. Consider the following data:

   a. Among patients who are treated with ibrutinib, traditional unfavorable features, such as presence of del(11q), del(17p), and U- IGHV may not be prognostic [11].
   b. In a randomized trial of ibrutinib versus chlorambucil in patients with previously untreated CLL (RESONATE-2), 18-month PFS was identical for patients with U- and M-IGHV [12].
   c. In a pooled analysis of large ibrutinib trials (RESONATE, RESONATE-2, and HELIOS), there was no association between U-IGHV, del(11q), trisomy 12 and complex karyotype and overall survival (OS) or PFS [13].
   d. Among patients treated with venetoclax-rituximab (MURANO study), the presence of a TP53 mutation and del(17p) and/or TP53 (but not del(11q) or U-IGHV) was predictive of shorter PFS [14].

4. Thus, unlike in the CIT era, early allogeneic HCT is no longer considered for most patients. *Selection of appropriate patients based on disease risk factors and comorbidities* remains the key issue when discussing cellular therapies in the era of targeted agents.

Note: Autologous cell transplantation is no longer offered as it does not improve survival in CLL compared with standard CIT [15].

5. European Research Initiative on CLL (ERIC) and the European Society for Blood and Marrow Transplantation (EBMT) proposed the following approach [16]:

    a. CLL high-risk-I (CIT-resistant, sensitive to novel therapies, TP53 abnormality present): cellular therapy should only be considered in highly select patients with low individual procedure-related risk.

    b. CLL high-risk II (CIT-resistant and novel therapy-resistant [independent of TP53 abnormality]): cellular therapy should be strongly considered in those patients if eligible.

6. Given a decline in use of CIT and presumed/proven low efficacy of CIT in patients who developed resistance to novel agents, one approach is to evaluate younger patients (<65) for allogeneic HCT under the following conditions:

    a. Patients with del(17p)/TP53 mutations/complex karyotype who have failed either a BTK inhibitor and/or venetoclax.

      i. In this case, treatment with second novel agent presents a window of opportunity to determine eligibility for cellular therapy.

    b. Patients who have progressed on both BTK inhibitor and/or venetoclax regardless of karyotype/TP53 status.

7. Fludarabine (Flu)-based reduced-intensity conditioning regimens are typically employed.

    a. Flu/low-dose total body irradiation (TBI)
    b. Flu/Cyclophosphamide (Cy) ± Rituximab
    c. Flu/Busulfan (Bu)
    d. Bendamustine/Flu/Rituximab [17]

8. Table 22.1 lists outcomes reported in three prospective single-center studies conducted at MD Anderson Cancer Center, Dana-Farber Cancer Institute, and Fred Hutchinson Cancer Center along with the German CLL study group. Each study enrolled between 76 and 90 patients [18–21].

9. CLL3X is a prospective phase II trial which enrolled 90 patients with high-risk CLL

    a. Median age 53 years
    b. Conditioning regimen: Flu/Cy

Table 22.1 Pooled outcome data [18–21]

Outcome measure	Frequency range (%)
PFS at 6 years	36–43
OS at 6 years	51–63
100-day mortality	<3
NRM	16–23
Acute grade 3–4 GvHD	7–20
Severe chronic GvHD	48–56

PFS progression-free survival, *OS* overall survival, *NRM* non-relapse mortality, *GvHD* graft-vs-host disease

    c. Outcomes [21]

        i. 4-year non-relapse mortality (NRM) 23%
       ii. Event-free survival (EFS) 42%
      iii. OS 65%
      iv. Acute graft-vs-host disease (GvHD) gr 2–4 45%, gr 3–4 14%
       v. Chronic GvHD 75%
      vi. At 10 year follow-up, NRM, relapse incidence, PFS, and OS were 20%, 46%, 34%, and 51%, respectively [22]

    d. Causes of death

        i. CLL progression > GvHD > infection

10. Thus, the high incidence of disease relapse (up to 50% in the long term) remains the key cause of mortality among patients with CLL undergoing allogeneic HCT, and novel strategies are needed to overcome this issue. For example, ibrutinib has been used successfully in patients who relapse after allogeneic HCT [23].

11. The following factors should be considered when making a decision regarding eligibility for HCT:

    a. Factors which predict outcomes of allogeneic HCT

        i. Refractory disease at presentation for HCT
       ii. Unfavorable patient and donor characteristics including advanced age, lower performance status, unrelated donor type, and unfavorable sex-mismatch (female donor/male recipient) [24]
      iii. T-cell depletion, prior alemtuzumab (Campath®) [25]
      iv. Mixed T-cell chimerism post-transplant
       v. Pre-transplant ibrutinib failure [26]
      vi. Transplant center characteristics such as team expertise, immune modulation strategies and quality of the follow-up program [24]

    b. Factors which are not predictive or are unknown:

        i. TP53 aberrations do not negatively impact outcome [16, 22, 25].
       ii. Complex karyotype requires further study.
      iii. Prior use of ibrutinib (in ibrutinib-responsive patients) [26].
      iv. HLA combinations [27].

12. Select novel strategies in cellular therapy relevant to CLL:

    a. Haploidentical HCT [28]

        i. 117 patients.
       ii. 38% received post-transplantation Cy as GvHD prophylaxis.
      iii. OS, PFS, NRM, and relapse at 5 years were 38%, 31%, 44% and 26%, respectively.
      iv. Results are similar to those with HLA-matched donors.

  b. Adaptive T-cell transfer-CAR-T therapy:

   i. Porter et al. [29] first demonstrated feasibility and long-term persistence of the immune effector cells
   ii. Turtle et al. [30]

   - 24 patients.
   - 19/24 ibrutinib-refractory, 6/24 venetoclax-refractory.
   - 23/24 had del(17p) or complex karyotype.
   - Overall response rate (ORR) 74% at 4 weeks (21% complete response; 53% partial response).
   - Absence of the malignant IgH clone in the bone marrow of responding patients was associated with 100% PFS at 6 months of follow-up.

   iii. In an early study, concomitant Ibrutinib has been shown to enhance CAR T cell engraftment and efficacy [31].

13. Richter's transformation (RS)

   a. CLL typically transforms into diffuse large B-cell lymphoma.
   b. Associated with very poor outcomes.

   i. The clonal relationship between the CLL and large cell component is the most important prognostic factor in RS [32].
   ii. Clonally unrelated RS has better prognosis compared to clonally related RS (median survival 5 years versus ~8–16 months).

   - Clonally unrelated RS should be approached as de novo diffuse large B-cell lymphoma.

   c. There are limited data to guide timing of autologous HCT as a consolidation strategy to primarily treat the large cell component versus allogeneic HCT to treat both diseases.

   i. Patients with chemotherapy-sensitive RS who underwent consolidative autologous HCT have improved RFS compared to patients who received allogeneic HCT [33].
   ii. Survival at 3 years is 59% after autologous HCT and 36% after allogeneic HCT. However, there is a selection bias based on sensitivity to initial CIT [33].

   d. Clinical trials should be considered for all patients with RS.
   e. One treatment approach involves early discussion of allogeneic HCT in patients with RS in the following groups of patients:

   i. Previously received CIT for CLL and are known to have TP53 aberration, regardless of RS-directed therapy
   ii. Developed RS on novel targeted agents, regardless of RS-directed therapy
   iii. Primary refractory to RS-directed therapy

    iv. Patients who experienced a relapse of large cell component following RS-directed therapy

    v. Patients <55 years of age with good performance status

f. CAR T cell therapy may have a role in RS; however, commercial products available at the time of this printing do not carry an FDA label for this disease indication.

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Chapter 23
Hematopoietic Cell Transplant for Severe Aplastic Anemia

Rabi Hanna

Introduction

Aplastic anemia (AA) is a blood disorder characterized by pancytopenia, bone marrow hypoplasia/aplasia, and the abscence of underlying malignancy. AA pathophysiology reflects the decrease in the cellularity of bone marrow and the decrease in the pool of hematopoietic stem cells (HSCs) below a threshold that could maintain mature blood cell production, ultimately leading to peripheral pancytopenia. Most patients have no identified underlying cause and are classified as idiopathic, but other etiologies include direct injury to HSCs, inherited genetic disorders, or an immune-mediated process. Treatment strategies include immunosuppressive therapy and/or allogeneic hematopoietic cell transplantation (HCT). Matched related donor (MRD) transplant is considered first-line therapy for young patients (<40 years) and elderly patients without significant comorbidities although improvements in matched unrelated donor (M-URD) transplants have been observed recently. These innovations have resulted in outcomes similar to MRD transplants in younger patients. Additionally, availability of alternative donors, in particular, haploidentical-related (haploID) donors, and the use of reduced-intensity conditioning (RIC) regimens have expanded the availability of allogeneic transplants to older patients.

Direct injury to HSCs may occur due to exposure to radiation, chemicals (benzene, solvents, glue vapors), medications (antiseizure medications, gold, arsenic, antithyroid medications, antibiotics such as sulfa and chloramphenicol), and infections (Epstein–Barr virus (EBV), seronegative hepatitis, human immunodeficiency virus (HIV), parvovirus, etc.). Inherited genetic disorders that lead to bone marrow failure include Fanconi anemia, dyskeratosis congenita, megakaryocytic thrombocytopenia, Diamond–Blackfan anemia, Schwachman–Diamond syndrome,

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thrombocytopenia absent radii, Pearson syndrome, and severe congenital neutropenia. Immune-mediated processes may also result in dysfunctional HSCs [1–5].

Autoimmune damage to HSCs contributes to most cases of acquired aplastic anemia (AA) (typically called idiopathic AA). It has been hypothesized that infections or different triggers could alter the immunologic appearance of HSCs and lead to autoimmune destruction of HSCs. This hypothesis is supported by the observation that many patients with AA respond to immune suppressive therapy [6, 7].

AA is divided into three groups based on marrow cellularity and peripheral blood counts:

1. Severe AA (SAA): Requires both of the following criteria [8]:

    a. Bone marrow cellularity <25% (or 25–50% if <30% of residual cells are hematopoietic)
    b. At least two of the following:

        i. Peripheral blood absolute neutrophil count (ANC) <500/μL (<0.5 × 10⁹/L)

        ii. Peripheral blood platelet count <20,000/μL
        iii. Peripheral blood reticulocyte count <20,000/μL

2. Very severe AA (vSAA): Diagnosis includes the same criteria for SAA above but ANC is <200/μL [9]
3. Nonsevere or moderate AA: Hypocellular bone marrow (as described for SAA) but the peripheral blood cytopenias do not fulfill the criteria for SAA or vSAA

Diagnosis of SAA

1. The differential diagnosis of AA includes hypoplastic myelodysplastic syndrome (MDS), clonal T-cell disorders, and AA associated with paroxysmal nocturnal hemoglobinuria (PNH). It is important to distinguish AA from hypocellular MDS because the two disease entities are treated differently.
2. Requires exclusion of a variety of inherited or acquired bone marrow failure syndromes with similar phenotypes. A quick and efficient diagnostic plan is important because time from diagnosis to "final" treatment is directly related to outcome regardless of the therapeutic option chosen.
3. Requires careful physical exam to identify any potential dysmorphic features that could be suggestive of inherited bone marrow failure.
4. Comprehensive laboratory work up to identify possible cause should include the following:

    a. Complete blood count and manual differential
    b. Reticulocyte count
    c. CD55/59 screen for PNH
    d. Serum aminotransferase
    e. Viral serologies for HIV, cytomegalovirus (CMV), Epstein Barr virus (EBV), hepatitis, and herpes simplex virus (HSV)

   f. Serum folate and vitamin B12 concentrations

   g. Hemoglobin F level

   h. Chromosome breakage test to screen for Fanconi anemia

   i. Bone marrow aspirate and biopsy with cytogenetics (usually normal in AA but likely to have abnormal karyotype in hypocellular MDS)

      i. It is common to find PNH clones of phosphatidylinositol glycan (PIG)-anchored proteins, such as CD55 and CD59, by flow cytometry assay of the bone marrow in approximately 20% of patients with AA [10].

        • Such clones can remain stable, diminish in size, or disappear.

        • Presence of a significant PNH clone with clinical or laboratory evidence of hemolysis or thrombosis is clinically important. Historically, the Ham test was used to support the diagnosis of PNH; however, more recently, diagnosis is made by flow cytometry. Urine should be examined for hemosiderin to exclude intravascular hemolysis, which is an important feature of hemolytic PNH.

   j. Human leukocyte antigen (HLA) testing

Treatment

The two major competing treatment strategies for SAA, allogeneic hematopoietic cell transplantation (HCT) and immunosuppressive therapy (IST) with antithymocyte globulin (ATG), date back to 1970 when the first series of successful marrow transplants from HLA-identical sibling donors was reported [11].

1. Generally, it has been accepted that HCT from a matched sibling is considered as the first line of therapy for children and young adult patients (<40 years) [8]. IST is reserved for those patients without a matched sibling or patients ≥40 years of age.

   a. The decision is more nuanced because some older patients can tolerate the toxicities of potentially curative HCT. Thus, HCT or IST may be appropriate, depending on disease severity, availability of a donor, and patient comorbidities.

   b. This decision is made on a case-by-case basis that considers the degree of cytopenias, life expectancy, and patient preferences [14].

2. HCT from an HLA-matched related donor (MRD)

   a. One of the early studies that proved that HCT is life saving for SAA is a prospective randomized trial comparing early bone marrow transplantation with conventional treatments.

      i. All patients with a matched sibling donor underwent HCT performed within 17–100 (median 33) days of original diagnosis. Patients without an MRD received conventional therapy including transfusion support with or without androgens.

    ii. Twenty-four of 36 HCT patients were alive (overall survival [OS] = 66.7%) at a median of 9 months with full marrow reconstitution compared with 12 of 31 patients (OS = 38.7%) who received conventional therapy (*p* = 0.006) [12].

   iii. This study demonstrated that early application of HCT appears to be an effective treatment for SAA.

b. Randomized prospective trials comparing HCT with IST in AA are lacking.

c. Meta-analysis by Peinemann et al. [13] reviewed 26 non-randomized controlled trials for patients with AA using either HCT or IST (7955 patients enrolled from 1970 to 2001). Young age and recent year of treatment were identified as factors contributing to improved survival in the HCT group.

d. Conceptual framework of allogeneic HCT is straightforward: replace the aplastic marrow in the patient with a marrow graft from a healthy donor. Three major transplant related problems exist [11]:

    i. Graft rejection
   ii. Acute graft-versus-host disease (GvHD)
  iii. Chronic GvHD

- Initially a frequent complication among patients with AA who received only cyclophosphamide conditioning; this complication was observed in >35% of patients transplanted in the early 1970s [15].
- Etiology is related to sensitization to HLA through previous transfusion of blood products. Early studies reported that previously transfused patients had a significantly lower OS compared with patients who had not received transfusions.
- Decreasing the number of transfused blood products along with irradiation and leukoreduction of platelet and RBC products aided in the reduction of graft rejection [16, 17]
- Other factors leading to a decrease in graft rejection include the following:

  - Intensifying conditioning regimen with addition of equine ATG at 30 mg/kg/dose × 3 days to cyclophosphamide 50 mg/kg/day × 4 days.
  - Data from the European Society for Blood and Marrow Transplantation (EBMT) showed cyclosporine + methotrexate as GvHD prophylaxis led to a decrease in graft rejection when compared with methotrexate alone [17]. This approach led to engraftment in 95% of patients with an OS of 90% at 2 years post-HCT with good long-term outcomes and limited number of late effects such as avascular necrosis, endocrine dysfunction, and very rare secondary malignancies [18, 19].
  - Immunosuppression aimed at preventing GvHD also had a role in controlling host-versus-graft (HvG) reactions.

- Mixed donor/recipient chimerism occurs in 44–55% of acquired AA patients following MRD HCT [19, 20]. Some patients may exhibit decline in donor chimerism during withdrawal of immune suppression (IS) and are

at risk for late graft rejection. Therefore, in contrast to the standard approach following HCT for malignant disorders, guidelines usually reinstitute IS for SAA patients with falling donor chimerism after HCT.

- Alternatives to high-dose cyclophosphamide (200 mg/kg) with decreased toxicity have been studied.

  - A randomized study comparing fludarabine 120 mg/m^2 + cyclophosphamide 100 mg/kg + rabbit ATG 9 mg/kg with cyclophosphamide 200 mg/kg + rabbit ATG showed no significant difference in graft rejection in the two arms (13.4% vs. 16.8%, respectively), or the incidence of acute or chronic GvHD and OS [21]
  - Another conditioning regimen approach is the combination of fludarabine 120 mg/m^2 + cyclophosphamide 1200 mg/m^2 + alemtuzumab (Campath®) 40–100 mg.
  - The combination of fludarabine + reduced-dose cyclophosphamide + either ATG or alemtuzumab appears to be an alternative conditioning regimen suitable for older patients, but due to the increased risk of graft rejection, the reduced-dose alternative regimens are not recommended for patients, especially children, who can tolerate the high-dose cyclophosphamide 200 mg/m^2 + ATG regimen.
  - Table 23.1 summarizes the results of selected studies of MRD HCT for SAA.

- In one report, the substitution of rabbit ATG (total dose 8 mg/kg) in place of equine ATG (90 mg/kg) as part of the conditioning regimen with cyclophosphamide 200 mg/kg prior to HLA-identical sibling bone marrow (BM) transplantation was associated with a decreased incidence of chronic GvHD (0% versus 34%, respectively).

  - However, there was increased risk of invasive fungal disease after transplantation, earlier CMV reactivation, and delayed lymphocyte recovery in rabbit ATG recipients.
  - Despite the decreased incidence of chronic GvHD, there was no difference in post-HCT OS between the two groups.

- Long-term outcomes for MRD HCT in children with SAA have been reported by Seattle group in 148 children (median age 12.8 years) [28].

  - GvHD prophylaxis was methotrexate on days +1, 3, 6 and 11 with cyclosporine.
  - With median follow-up of 25 years, the 5-year survival was 100% in the group that received cyclophosphamide + ATG.
  - The incidence of graft rejection was 7%, acute GvHD grades III–IV were 3%, and chronic GvHD was 10%.
  - This result demonstrates that allogeneic HCT using MRD should be used as the first-line therapy for children and young adults with SAA.

- The same conditioning regimen of cyclophosphamide + ATG in conjunction with a MRD HCT in older patients (> 40 years) is associated with decreased OS.

Table 23.1 HCT for SAA from an HLA-matched related donor; selected studies

Study (years of transplant)	Number of patients	Age	Conditioning regimen	GvHD prophylaxis	Overall survival	Graft rejection	Acute and chronic GVHD
Seattle (1988–2004) [22]	81	2–63 Median 25	Cyclo + ATG	CSP + MTX	88%	4%	Acute 24% Chronic 26%
EBMT 1998–2007 [23]	30	31–66 Median 46	Cyclo + FLU + ATG	CSP + MTX	77%	3%	Acute 10% Chronic 13%
CIMBTR 1994–2001 [24]	130	Median 23	Cyclo + ATG	CSP + MTX	80% at 5 years	11%	Acute 11% Chronic 32%
EBMT registry, children, 2000–2009 [25]	396	0–12	Mainly Cyclo; some Cyclo + FLU	Mostly CSP + MTX; some CSP + MMF+/−ATG	87% at 3 years	2%	Acute 8% Chronic 6%
EBMT registry, adolescents, 2000–2009 [26]	394	Median 15	Mainly Cyclo; some Cyclo + FLU +/− ATG	Mostly CSP + MTX; some CSP + MMF	86% at 3 years	8%	Acute 12% Chronic 8%
COSAH C-004A 2003–2010 [21]	43	18–60 Median 34	Flu + Cyclo+ Thymoglobulin; used PBSCs	CSP + short MTX	85.6% at 4 years	2.5%	Acute 23.3% Chronic 16.2%
UK-EBMT children, 2000–2009 [27]	21	8–62 Median 35	Flu + Cyclo+ Alemtuzumab	CSP	95%	9.5%	Acute 13.7% Chronic 4%

Cyclo cyclophosphamide, *ATG* antithymocyte globulin, *CSP* cyclosporine, *MTX* methotrexate, *EBMT* European Group for Blood and Marrow Transplantation, *FLU* fludarabine, *CIBMTR* Center for International Blood and Marrow Transplant Research, *MMF* mycophenolate mofetil, *COSAH* Cooperative Study Group A for Hematology, *PBSCs* peripheral blood stem cells, *GvHD* graft-versus-host disease

– A study from Seattle group evaluated 23 patients (age 40–68) with SAA who underwent MRD HCT between 1988 and 2008.

OS was 65% with median follow-up of 9.1 years.
It is important to note that 22% of patients died from infection prior to engraftment [29].

– A follow-up study by the EBMT added fludarabine to the cyclophosphamide + ATG regimen with the goal of decreasing the dose of cyclophosphamide in order to reduce organ cytotoxicity and intensify immunosuppression [23].

This combination resulted in improved 5-year survival of 77% in the fludarabine cohort compared to 60% in the cohort who did not receive fludarabine.
Patients between the ages of 30 and 40 years had a survival probability exceeding 80%.

• It is also important to mention that for SAA, it is not appropriate to use peripheral blood stem cells (PBSCs) as donor source, regardless of patients' age, due to the increased risk of GvHD.

– A retrospective analysis of 1886 patients with AA who underwent an HCT from a HLA-matched sibling between 1999 and 2009 evaluated either BM (n = 1163) or PBSCs (n = 723) as the source of stem cells [30].

Acute and chronic GvHD were more frequent in patients who received PBSCs vs BM.

• The major cause of death was GvHD with 2% versus 6% in BM vs PBSC recipients, respectively.
• This contributed to a survival advantage for recipients of BM rather than PBSCs and was statistically significant in patients aged 1–19 years (90% versus 76% $p < 0.00001$) as well as in patients aged over 20 years (74% versus 64%, $p = 0.001$). The advantage for recipients of BM over PBSCs was maintained above the age of 50 years (69% versus 39%, $p = 0.01$).
• Therefore, unlike in transplantation for pediatric malignancies, whereby PBSC may elicit beneficial graft-versus-leukemia effects, BM is clearly the preferred stem-cell source for acquired SAA patients.

HCT from HLA-Matched Unrelated Donors (M-URD)

1. HCTs using M-URDs have historically been considered second-line therapy for SAA patients who fail IST. Consequences of delayed M-URD include iron overload from chronic RBC transfusions, platelet transfusion refractoriness, poten-

tial life-threatening infections, and other comorbidities that can affect OS post-HCT.

2. Outcomes following M-URD HCT have steadily improved since the early 1990s. A retrospective study of 141 patients with SAA who underwent M-URD HCT between 1988 and 1995 showed an OS of 36% [31] compared with a recent pediatric series that showed an OS of 78–95% [23, 32]. This increase in OS is due in large part to improvements in supportive care during the IST phase of therapy, conditioning regimens, and high-resolution HLA typing leading to better unrelated donor matching.

3. An important prospective study sponsored by the National Marrow Donor Program (NMDP) looked into optimization of the conditioning regimen in M-URD HCT [33].

   a. The starting conditioning regimen was cyclophosphamide 50 mg/kg/day × 4 doses + equine ATG 30 mg/kg/day × 3 days + total body irradiation (TBI) 600 cGy.
   b. In this multicenter study, a total of 87 patients were enrolled between 1994 and 2004 with median age 18.6 years (range 1.3–53.5 years).
   c. The optimum TBI dose was 1 × 200 cGy.
   d. Graft failure occurred in 5% of patients and OS was 61% at median follow-up of 7 years.
   e. However, in the optimized conditioning that included TBI dose of 200 cGy, the 5-year OS in patients < age 20 was 78% compared with 50% for patients > age 20.

4. A recently completed phase I/II study by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) (study 0301, registered at www.clinicaltrials.gov [NCT00326417]) aimed to identify the optimal dose of cyclophosphamide in a M-URD HCT conditioning regimen that incorporated fludarabine, ATG, and low-dose TBI 200 cGy.

   a. All patients receive a fixed dose of ATG (either rabbit ATG 3 mg/kg IV or equine ATG 30 mg/kg IV daily on days −4 to −2), fludarabine 30 mg/m^2 IV daily on days −5 to −2, and low-dose TBI 200 cGy on day −1.
   b. Cyclophosphamide dosing was started at 150 mg/kg and decreased in steps of 50 mg/kg (to 100 mg/kg, 50 mg/kg, and 0 mg/kg).
   c. A total of 96 patients (median age 24.5 years, range 0.5–65) underwent M-URD HCT.
   d. Median follow-up after HCT was 17 months and 24 months for patients receiving cyclophosphamide 50 mg/kg and 100 mg/kg, respectively.
   e. OS at 1 year for patients receiving 50 mg/kg and 100 mg/kg were 97.4% (95% CI 82.8–99.6) and 80.5% (64.8–89.7), respectively [34].
   f. Early in the clinical trial, both the 0 mg/kg and 150 mg/kg dose schedules were discontinued due to poor outcomes.
   g. This study identified cyclophosphamide 50 mg/kg as the most desirable dose in combination with TBI 200 cGy, fludarabine 120 mg/m^2, and ATG for engraftment and early survival for M-URD HCT in patients with acquired SAA.

5. Another multicenter, retrospective study from the United Kingdom (UK) evaluated an alemtuzumab (Campath®)-based conditioning regimen [27].

   a. Twenty-nine patients received fludarabine 30 mg/m^2 for 4 days, cyclophosphamide 300 mg/m^2 for 4 days, and alemtuzumab with a median total dose of 60 mg (range 40–100 mg).
   b. Median age was 35 years (range 8–62).
   c. OS at 2 years was 83% with a cumulative incidence of graft failure of 14.5%.
   d. Acute GvHD was observed in only 13.5% patients (all grades I–II) and only 2 patients (4%) developed chronic GvHD.
   e. A low incidence of viral infections was seen.
   f. Factors influencing OS were HCT comorbidity index (92% with score 0–1 vs 42% with score ≥2, $p < 0.001$) and age (92% for age < 50 years vs 71% ≥ 50 years, $p < 0.001$).
   g. These data suggest that alemtuzumab-based M-URD HCT regimen for SAA results in durable engraftment with a low incidence of chronic GvHD even in elderly patients.

M-URD HCT as First-Line Therapy in Children

1. Despite the initial response to IST in children, there is considerable risk of relapse and long-term side effects of cyclosporine dependence as well as clonal evolution [35, 36].
2. Furthermore, in the case of incomplete response post-IST, children may suffer either from restrictions to sporting and other activities because of subnormal platelet and/or hemoglobin values, or from higher risks for infection due to suboptimal neutrophil count and prolonged cyclosporine treatment.
3. It is clear that event-free survival (EFS) is more meaningful than OS when studying outcomes of SAA in children.
4. These long-term concerns combined with the improvements in outcomes of M-URD HCT have encouraged many investigators to offer upfront transplant to children with SAA.
5. UK investigators reported an excellent estimated 5-year failure-free survival (FFS) of 95% in 44 consecutive children who received a 10/10 allele level HLA-matched unrelated donor; 40 of these children had previously failed IST [37].

   a. A follow-up study from the EBMT reported a cohort of 29 consecutive children with SAA who received M-URD HCT as first-line therapy after conditioning with fludarabine–cyclophosphamide–alemtuzumab.

      i. OS and EFS were 96% and 92%, respectively [38]. These results demonstrated that upfront M-URD HCT was similar to MRD HCT and superior to IST and M-URD HCT post-IST failure.

6. There is currently a North American randomized prospective trial of IST vs M-URD HCT in children with SAA (ClinicalTrials.gov number NCT02845596). The conditioning regimen used in this trial is based on BMT CTN results with reduced dose cyclophosphamide 50 mg/kg + fludarabine 120 mg/m^2 + ATG 90 mg/m^2 + TBI 200 cGy.
7. Bone marrow is the preferred source of HSCs for HCT for SAA.

   a. A CIBMTR study compared outcomes of patients with SAA who received 10/10 HLA-M-URDs between 2000 and 2008 after variety of standard conditioning regimens [39].

      i. Two hundred twenty-five patients received unmanipulated BM and 71 patients received PBSCs.
      ii. Engraftment was similar between the two sources, but the incidence of grades II–IV acute GvHD was 31% in the BM group vs 43% in the PBSC group.
      iii. Chronic GvHD was not different after adjusting for age.
      iv. Three-year OS was 76% in the BM group compared with 61% in the PBSC group.

Alternative Donor Transplantation for SAA

1. Fully matched unrelated donors (HLA-A, B, C, DRB1) from worldwide registries can be identified for about 80% of Caucasians; however, identification of a fully matched donor for persons of other races and/or ethnicities is much lower [40].
2. Despite potential benefits of umbilical cord blood (UCB) as source of HSCs for HCT in SAA (rapid accession of stored UCB units with better tolerance of HLA mismatch), published data for UCB in SAA show limited success due to low dose of HSCs obtained in single UCB associated with higher rates of graft rejection. The use of double cord blood units has decreased the risk of graft rejection but increased the rate of acute GvHD.

   a. The Japanese cord blood network reported outcomes of 31 patients with SAA (median age 28 years) who received single UCB. The overall engraftment was 55%, incidence of acute GvHD of 17% and cGvHD of 20%, with an OS of 41% at 2 years [41].
   b. A follow-up study in Japan with 12 SAA patients using fludarabine 125 mg/m^2 + melphalan 80 mg/m^2 + TBI 400 cGy and single CBU with median total nucleated dose (TNC) 2.5×10^7/kg showed an OS of 83.3% at median follow-up of 36 months [42].
   c. An EBMT report analyzed the outcomes of 71 patients who received UCB for SAA. This analysis demonstrated an OS of 45% in patients who received

a UCB with a TNC $> 3.9 \times 10^7$/kg compared to 18% for patients who received units with TNC $< 3.9 \times 10^7$/kg [43].

   d. A study by Francophone Society of Bone Marrow Transplantation and Cellular Therapy reported outcomes of 29 consecutive patients with SAA transplanted with UCB with TNC dose $\geq 4 \times 10^7$/kg between 6/11 and 10/15.

     i. Conditioning regimen included fludarabine + cyclophosphamide + ATG + TBI.

     ii. At a median follow-up of 38.8 months, engraftment was reported in 23 patients (88%) with cumulative incidences of grades II–IV acute and chronic GvHD of 45.8% and 36%, respectively, and OS was 88.5% [43]. Results from this study highlight the importance of UCB with a higher TNC dose/kg.

3. The use of posttransplant cyclophosphamide (PTCy) in the setting of haploidentical (haploID)-related donors has significantly expanded the access to HCT in malignant disorders; however, the use of haploID HCT in patients with SAA has only recently been attempted. Accordingly, published data are limited.

   a. In 2015, a Brazilian group published outcomes of 16 SAA patients (age 5–39 years) who underwent haploID HCT using the modified Hopkins regimen with fludarabine + rabbit ATG 2.5 mg/kg per day on days −4 to −2 + TBI 200–600 cGy with PTCy. HSC sources were BM ($N = 13$) or PBSCs ($N = 3$). The rate of neutrophil engraftment was 94% and platelet engraftment was 75%. Three patients developed acute GvHD with grades II–IV GvHD in two. Five patients died, and the 1-year OS was 67.1% [44].

   b. A prospective phase II study from the Hopkins group reported 13 patients with a median age 30 years (11–69 years) who underwent haploID HCT [45]

     i. A reduced-intensity regimen of rabbit ATG + fludarabine + cyclophosphamide + TBI 200 cGy was used.

     ii. All patients received BM with GvHD prophylaxis of PTCy 50 mg/kg/day IV on days +3 and + 4 along with mycophenolate mofetil (Cellcept®, MMF) on days +5 through 35 and tacrolimus from day +5 through 1 year.

     iii. G-CSF (Neupogen®) was administered from day +5 until ANC $> 1.5 \times 10^9$/L $\times 3$ days.

     iv. There was no reported graft failure, and mild GvHD occurred in two patients with OS 100%.

     v. The very limited transplant-related mortality suggests that this regimen will be feasible in elderly patients with SAA.

   c. Currently, haploID HCT with PTCy is being studied on a national level in North America by the BMT CTN (CTN 1502 CHAMP study; NCT02918292). This phase II study of haploID HCT uses an RIC regimen with a primary objective of assessing OS at 1-year post-haploID HCT in SAA patients up to the age of 75 years. The study opened in July 2017 and aims to finish enrollment in early 2021.

Conclusion

MRD HCT is considered first-line therapy for young patients (<40 years) and elderly patients without significant comorbidities. Improvements in M-URD HCT have been noted using reduced-dose TBI, adding fludarabine to lower-dose cyclophosphamide, and selecting donors who are better HLA matched to patients. These innovations have resulted in outcomes similar to MRD HCT in younger patients. Additionally, availability of alternative donors, in particular, haploID-related donors, using RIC regimens, and PTCy expands the availability of HCT to patients including older patients.

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Chapter 24
Inherited Disorders

Patrick C. DeMartino and Eneida R. Nemecek

Introduction

The landscape of pediatric hematopoietic cell transplantation (HCT) differs significantly from that of adults. Non-malignant diseases accounted for 41% of all pediatric allogeneic transplants performed in 2010 (Center for International Blood and Marrow Transplant Research [CIBMTR]). Patients typically have not received chemotherapy prior to HCT, and there is no need to eradicate a malignancy nor desire for graft-versus-tumor (GvT) effect. The decision to pursue transplant also differs in that many of these diagnoses are not acutely life-threatening, but instead impact quality or long-term duration of life. With reductions in transplant-related mortality (TRM) and increasing utilization of alternative donors, the indications for HCT for inherited conditions are expanding. The following is an overview of various inherited conditions for which HCT is indicated with an emphasis on common themes and general principles.

Primary Immunodeficiencies (PID)

PIDs are a group of inherited disorders of the innate and adaptive immune systems (see Table 24.1). The phenotypes of these disorders are diverse with clinical manifestations including severe infections, autoimmunity, and malignancy. For many of the disorders, HCT is the only curative option although other modalities such as gene replacement therapy are emerging. For patients with these diseases and

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Table 24.1 Primary immunodeficiencies potentially treated with HCT (incomplete list) based on the International Union of Immunological Societies classification system

Phenotypic classification	Diagnoses
Combined immunodeficiencies	Severe combined immunodeficiency, CD40 ligand deficiency, MHC class II deficiency
Combined immunodeficiencies with associated features	Wiskott-Aldrich syndrome, DiGeorge syndrome, DOCK 8 deficiency
Antibody deficiencies	Common variable immunodeficiency
Immune dysregulation	Familial hemophagocytic lymphohistiocytosis, Chediak-Higashi, Griscelli syndrome, X-linked lymphoproliferative disease, chronic active EBV, autoimmune lymphoproliferative syndrome
Phagocytic cell disorders	Chronic granulomatous disease, leukocyte-adhesion deficiency, severe congenital neutropenia

Adapted from J Silva 2018 [7]

MHC major histocompatibility complex, *DOCK8* dedicator of cytokinesis 8, *EBV* Epstein-Barr virus

without pre-transplant comorbidities, the outcome with HCT is excellent (i.e., 5-year overall survival (OS) >85%).

1. Severe combined immunodeficiency (SCID)

   a. SCID is a disease with many genetic causes, classically presenting with low or absent T cells with potential involvement of B and NK cells leading to severe infections and early death.
   b. Young children may present with graft-versus-host disease (GvHD) via engrafted maternal T cells.
   c. For nearly all types of SCID, the standard therapy is prompt HCT, with superior outcomes for patients transplanted prior to 3.5 months of age [1].
   d. Newborn screening for SCID is performed in most of the United States with the goal of performing curative therapy as early as possible though many still experience infectious complications.
   e. Pre-transplant

      i. SCID subtypes

         • The phenotypes vary with some having B or NK cell lines affected, and these differences impact outcomes. In general, patients with unaffected B cells have superior outcomes [2], whereas those with intact NK cells have poorer engraftment.
         • Adenosine deaminase (ADA) deficiency: a subtype for which enzyme replacement therapy is available and used as a bridge to curative therapy. A promising gene therapy for ADA deficiency appears efficacious and is approved for use in Europe [3].

   f. Pre-transplant infections (especially pulmonary) are associated with poorer outcomes.

g. Donor considerations

    i. HCT with a matched sibling donor (MSD) yields excellent outcomes, while transplants utilizing an unrelated donor (URD) versus haploidentical (haploID) donor is a challenging decision.

    ii. HaploID transplants result in slower immune reconstitution compared to URD transplants; however, this strategy is preferred over URD transplant if maternal T-cell engraftment.

    iii. Umbilical cord blood (UCB): More rapid acquisition of this product is especially desirable for SCID patients.

h. Conditioning

    i. Conditioning therapy may be omitted depending upon genotype and donor (e.g., those with intact B cells with MSD).

    ii. Cytoreductive conditioning regimens are tailored to patient, genotype, and donor. The European Society for Blood and Marrow Transplantation (EBMT) guidelines provide an excellent overview [4].

i. Outcomes

    i. 2-year OS 90% (95% CI, 80–95%) for patients with SCID transplanted from 2010 to 2014 with mean age at transplant of approximately 100 days [5].

    ii. At 1 year post-HCT, patients who received pre-HCT conditioning therapy had higher CD4 cell counts and required less IV immunoglobulin compared to patients who did not receive conditioning therapy, but there was no difference in OS at 2 years.

2. Non-SCID primary immunodeficiencies
Countless non-SCID PIDs may be treated with HCT; however the decision to pursue HCT is less clear and evolving in some situations. Reviewed here are two disorders demonstrating clear benefit from HCT.

a. Wiskott-Aldrich syndrome (WAS)

    i. Characterized by triad of eczema, microthrombocytopenia, and immunodeficiency. At risk for Epstein-Barr virus (EBV) lymphoproliferative disorder.

    ii. Improved outcomes if HCT occurs before 5 years of age [6].

    iii. Myeloablative regimen typically used. There is concern for mixed chimerism promoting post-transplant autoimmune cytopenias though the data are unclear.

b. Chronic granulomatous disease (CGD)

    i. Characterized by ineffective phagocytosis with recurrent or chronic infections of soft tissue and lung (bacterial or fungal) with poor growth and diarrhea.

  ii. Uncertainty exists regarding indications and timing for transplant given phenotypic variability. Early transplant in those with absent NADPH oxidase activity is beneficial.

  iii. Reduced intensity conditioning (RIC) appears effective with fludarabine, serotherapy (e.g., antithymocyte globulin, alemtuzumab [Campath®]), and targeted busulfan with 2-year event-free survival (EFS) >90% [7].

 c. Primary hemophagocytic lymphohistiocytosis (HLH)

  i. Also referred to as familial HLH, this inherited disorder of dysregulated immune activation presents with a variety of symptoms including fever, cytopenias, and hepatosplenomegaly (accepted diagnostic criteria exist) [8].

  ii. Numerous germline mutations are recognized with most involving cytotoxic pathways. Earlier age of presentation correlates with likelihood of identifiable genetic predisposition [9] promoting development of HLH in setting of some immune activation (i.e., EBV infection).

  iii. Indications for HCT: primary HLH given risk of recurrence. Secondary (non-familial) HLH also benefits from transplant in setting of recurrent or progressive disease.

  iv. Pre-transplant considerations:

  • Control of disease prior to transplant is critical. HLH-94 (etoposide [VP16] and dexamethasone) protocol remains standard induction therapy.

  v. Conditioning: RIC associated with lower TRM [10]

  vi. Outcomes: Italian cohort provides most recent data with 5-year OS and EFS of 71% and 60%, respectively [11].

Inborn Errors of Metabolism (IEM)

IEMs are a diverse spectrum of diseases caused by inherited disorders of lysosomal enzymes or peroxisome function. These diseases are characterized by progressive multi-system pathology, often with neurologic deficits and early death. Only a few IEMs demonstrate clear benefit from HCT, while many candidate indications exist including mitochondrial diseases and glycogen storage disorders (see Fig. 24.1). The rationale leading to HCT for IEMs are discussed below.

1. Cross-correction is the primary therapeutic mechanism. Wild-type donor leukocytes migrate and secrete the deficient enzyme, and this enzyme is taken up by enzyme-deficient host cells.

2. Neurologic disease progression does not halt as quickly as other organ systems, and HCT does not reverse existing deficits (aside from organomegaly). HCT is more efficacious when performed early in disease course.

3. Enzyme replacement therapy (ERT) is available for some diseases as first-line therapy or as adjunctive to transplant. Generally, this therapy does not improve CNS disease. Development of alloantibodies to ERT may limit utility. HCT can promote tolerance.
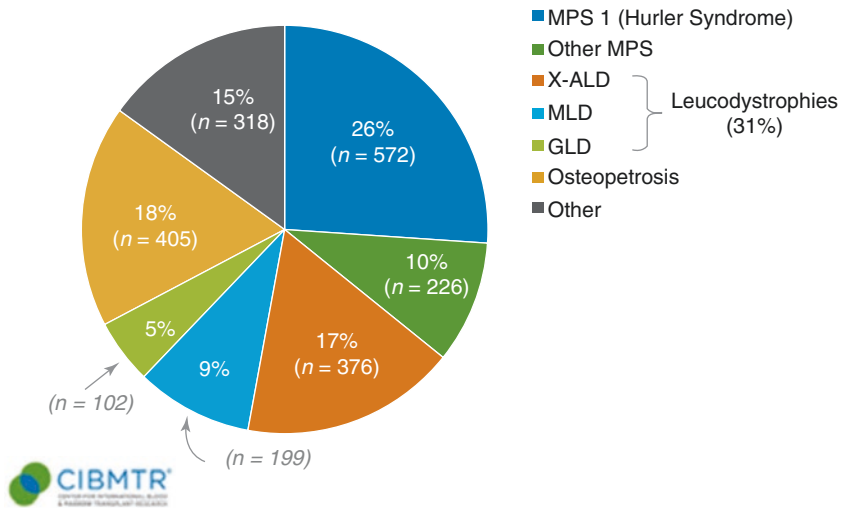
Fig. 24.1 Distribution of the various inborn errors of metabolism treated with hematopoietic cell transplantation. (*The data presented here are preliminary and were obtained from the Statistical Center of the Center for International Blood and Marrow Transplant Research. The analysis has not been reviewed or approved by the Advisory or Scientific Committees of the CIBMTR. The data may not be published without the approval of the Advisory Committees*)

4. Indications for HCT: The following diseases/syndromes are among the most commonly accepted though many more may be considered. In general, earlier transplant yields superior outcomes.

   a. Hurler syndrome (MPS-1H): one of the many mucopolysacchararidoses caused by a deficiency of alpha-L-iduronidase leading to neurologic, skeletal, and cardiorespiratory complications with early death. Hurler syndrome was the first IEM treated with HCT and remains most common.

   b. Cerebral adrenoleukodystrophy (C-ALD): The most severe phenotype of the X-linked ALDs presents in children with progressive neurologic disease and death within a few years. HCT should be pursued once demyelination is confirmed via MRI.

   c. Metachromatic leukodystrophy (MLD): MLD presents with central and peripheral demyelination leading to progressive motor dysfunction and death within a few years. HCT is utilized in juvenile/adult onset but not infantile subtype [13].

   d. Globoid cell leukodystrophy (GLD) or Krabbe disease: manifests in infancy with neurologic deterioration and death by 2 years of age. HCT is beneficial in those with less rapid phenotype with early detection but not for rapidly progressive infantile phenotype [14].

5. Newborn screen (NBS): Various lysosomal storage disorders (LSD) and C-ALD have been added to some states' NBS to promote rapid intervention. Concerns for the inclusion on NBS include difficulty in predicting phenotype, risk of curative HCT, and false positive results.
6. Pre-transplant considerations

   a. Comorbidities

      i. Pre-transplant ERT (if available) to optimize patient condition is safe and likely beneficial.
      ii. Rapid pre-transplant neurologic deterioration portends poorer outcome.

   b. Donor considerations

      i. UCB: excellent outcomes with rapid acquisition and reduced viral transmission.
      ii. MSD: Wild-type donors provide better correction of stored substrate than heterozygous donors.

7. Post-transplant considerations

   a. Significant disability is common given inability to reverse pre-transplant morbidity (e.g., skeletal disease in Hurler syndrome).
   b. Full donor chimerism and higher enzyme levels associated with improved outcomes [15].

8. Outcomes

   a. Much of the existing data is dated and likely underestimates survival.

      i. Hurler syndrome (1995–2007): 5-year OS and EFS 74% and 63%, respectively, for all patients transplanted; for those with MSD or 6/6 matched UCB, 5-year EFS 81% [17].
      ii. C-ALD with very early stage disease (1982–1999): 5-year OS 90% whereas more advanced disease (per MRI) with 5-year OS 45% [16].

9. Gene therapy

   a. Clinical trials are underway evaluating genetically modified autologous cell transplant with theoretical potential to achieve supra-physiologic synthesis of enzyme by donor cells.
   b. C-ALD: An autologous stem cell product transduced with lentiviral vector has demonstrated safety and able to stabilize disease.
   c. Long-term follow-up data are lacking comparing gene therapy to HCT [12].

Inherited Bone Marrow Failure Syndromes

The inherited bone marrow failure syndromes (IBMFS) are group of diagnoses typically presenting at a young age, manifesting with cytopenias and other clinical findings. Transplantation is curative for the hematologic manifestations of IBMFS though other disease-specific sequelae will persist and confer morbidity atop transplant-related late effects. The decision to pursue transplant is further complicated by the unpredictable phenotypes for most IBMFS.

1. Fanconi anemia (FA)

    a. FA is the most common IBMFS (1 case per 160,000 worldwide) and often presents with pancytopenia and physical anomalies (short stature, radial ray abnormalities, café-au-lait spots) with risk for MDS/AML.
    b. Average age at diagnosis is 7 years though some present in adulthood.
    c. Diagnosis is made via chromosomal breakage in T lymphocytes followed by gene sequencing. The underlying DNA repair defect presents challenges during and after transplant.
    d. Pre-transplant considerations

        i. Indication: significant bone marrow failure (not seen in all FA) or myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML).
        ii. Androgen therapy (i.e., danazol [Danocrine®]) can reduce transfusion needs pre-transplant.

    e. Donor considerations

        i. Must evaluate all related donors for FA.
        ii. HCT using URDs have survival approaching MSDs.
        iii. Bone marrow (BM) recommended over peripheral blood stem cells (PBSC) even with clonal evolution given importance of avoiding GvHD in FA.

    f. Conditioning regimen

        i. RIC with cyclophosphamide and fludarabine.
        ii. Total body irradiation (TBI) traditionally for URDs although recent data indicate TBI may be omitted [20].
        iii. Cohort receiving alternative donor transplant (2009–2014) with T-cell depletion and no radiation: 1-year OS and disease-free survival (DFS) of 80% and 77.7%, respectively.
        iv. Pre-transplant cytoreduction for patients with MDS/AML; one must account for significant chemotherapy-associated aplasia [18].
        v. Patients with biallelic FANCD1/BRCA2 mutations are best suited for cytoreduction.

g. Post-transplant considerations

    i. Significant risk for secondary malignancy (especially head/neck tumors); there is an additional risk in patients who develop chronic GvHD.

    ii. Estimated 15-year cumulative incidence of secondary malignancy of 15% (majority solid tumors) with an estimated 28% cumulative incidence of solid tumors by age 50 [19].

    iii. Follow-up with specialists to screen for head/neck or anogenital tract cancer is required. Patients should be advised to avoid carcinogens (i.e., tobacco, alcohol).

h. Outcomes

    i. 5-year OS is 76% for MSD donor (2000–2009) [19]

2. Dyskeratosis congenital (DC)

    a. DC presents at a variable age with initial skin/nail changes followed by bone marrow failure and pulmonary/hepatic fibrosis with risk for similar cancers seen in FA.

    b. Diagnosed via short telomere length per flow-FISH analysis.

    c. There are many overlapping themes between FA and DC, given the sensitivity to conditioning.

    d. Indication for HCT: significant bone marrow failure (majority with DC).

    e. Conditioning regimen: RIC with fludarabine; risk for pulmonary/hepatic toxicity.

    f. Post-transplant: similar to FA with increased risk for TRM via organ toxicity and secondary cancers.

    g. Outcomes: Meta-analysis of HCT for DC performed after the year 2000 estimated 5- and 10-year OS of 70% and 28%, respectively [22].

3. Diamond-Blackfan anemia (DBA)

    a. DBA is a congenital erythroid aplasia presenting with macrocytic anemia in infancy; various physical anomalies are seen though can be subtle or absent.

    b. Diagnosed via elevated erythrocyte adenosine deaminase activity.

    c. Medical management includes transfusions and corticosteroids, while a minority of patients will require HCT.

    d. Pre-transplant consideration.

        i. Indication: patients not responding to corticosteroids with persistent transfusion needs.

        ii. Ideally, consider HCT before 10 years of age.

    e. Donor considerations: Historically, only those with MSD are referred for transplant (screen sibling for carrier status). Recently improved URD/alternative donor outcomes make this a viable option [24].

    f. Conditioning regimen: myeloablative regimen with fludarabine and busulfan.

g. Post-transplant considerations: Iron overload from pre-transplant transfusions may require chelation or phlebotomy.

h. Outcomes: 5-year OS 87% for MSD with some evidence for improved OS if <10 years of age [21].

4. Shwachman-Diamond syndrome (SDS)

a. SDS classically presents with neutropenia, exocrine pancreatic dysfunction, and skeletal anomalies in infancy.

    i. Pancytopenia may occur and there is great phenotypic variability. Early-onset cytopenias (<3 months of age), even if mild, are associated with severe phenotype warranting transplant [23].

    ii. Like DBA, pathologic ribosomal biogenesis causes this syndrome.

b. Pre-transplant considerations

    i. Indication: patients with severe cytopenias, MDS, or leukemia (~20% of patients with SDS).

    ii. G-CSF (Neupogen®) may be considered pre-transplant for recurrent infections.

    iii. Androgens may be considered as in FA (with increased risk for liver toxicity).

c. Conditioning regimen: Consider RIC when possible given likelihood of organ toxicity (including cardiac).

d. Post-transplant: Unlike FA and DC, there does not appear to be increased risk of secondary malignancy.

e. Outcomes: CIBMTR study in progress at the time of this publication.

Hemoglobinopathies

An estimated 300,000 children are born annually with a severe hemoglobinopathy (sickle cell disease being most common, followed by β-thalassemia major) with a majority living in low- and middle-income countries [25]. Currently HCT is the only curative therapy; however, gene therapy appears promising. The decision to pursue transplant for a hemoglobinopathy is complex, balancing the severity (or predicted severity) of the phenotype versus the risk of transplant from a perspective in which the patient's priorities are paramount. The first allogeneic HCT for thalassemia occurred in the early 1980s, and this strategy has become an effective therapy worldwide. This section focuses on the two ß-hemoglobinopathies benefiting from HCT.

Table 24.2 Pesaro classification for predicting outcome of HCT for ß-thalassemia major

Risk factors	Class 1	Class 2 (1–2 risk factors)	Class 3
Hepatomegaly (>2 cm below costal margin)	No	Yes/no	Yes
Irregular chelation	No	Yes/no	Yes
Hepatic fibrosis	No	Yes/no	Yes

1. β-thalassemia major

   a. Thalassemia refers to an inherited quantitative defect in alpha or beta globin leading to ineffective erythropoiesis and anemia.
   b. β-thalassemia major causes severe anemia requiring lifelong transfusions.
   c. Despite improvements in medical therapy (transfusion and chelation), quality of life remains limited, and patients may elect for curative therapy via HCT despite the risks.
   d. Pre-transplant considerations.

      i. Indication: Any transfusion-dependent patient may be considered.
      ii. Earlier is better if >1 year of age.
      iii. The Pesaro classification is a prospectively validated tool to estimate transplant-related risk in children with β-thalassemia major. This tool is used to identify high-risk patients or those who may benefit from RIC [31] (see Table 24.2).
      iv. Additionally, sub-optimal transfusion therapy and age ≥ 18 years associated with higher treatment-related mortality.
      v. Viral hepatitis alone is not a contraindication.
      vi. Pre-transplant splenectomy may be considered in patients with hypersplenism; however, there are minimal data to inform this decision. Splenectomy is associated with faster engraftment and potentially worse OS [29].

   e. Donor considerations:

      i. MSDs or URDs are acceptable options. MSDs with the diagnosis of thalassemia minor is allowable. Ideally, alternative donors should only be pursued via trial enrollment.

   f. Conditioning regimen

      i. Myeloablative conditioning is standard.
      ii. RIC regimens are associated with poorer engraftment; partially related to extra-medullary hematopoietic system.

   g. Post-transplant considerations

      i. Mixed chimera can provide phenotypic resolution of thalassemia.
      ii. Management of iron overload is critical via phlebotomy or chelation.
      iii. High risk for hypogonadism given iron overload and conditioning.

h. Outcomes: The International Hemoglobinopathy Registry demonstrated 2-year OS and EFS of 91 ± 1% and 83 ± 1%, respectively, between 2000 and 2010 [26].

2. Sickle cell disease (SCD) see also Chap. 25

SCD is characterized by hemolytic anemia and vaso-occlusive complications conferring significant morbidity. The median life expectancy for a patient with SCD in the United States was approximately 40 years as of 2005. SCD remains a debilitating disease despite incremental improvements in medical therapy. Improving outcomes for HCT has allowed for a precipitous increase in the number of transplants being performed.

a. Pre-transplant considerations

   i. Indication: a highly individualized decision.
   ii. Historically reserved for severe disease (i.e., stroke, acute chest syndrome) with MSD. However, indications are expanding with recognition that transplantation at a younger age is associated with improved outcomes.
   iii. Phenotypic variability and an inability to predict later development of SCD-related morbidity complicate the decision.
   iv. The EBMT Inborn Error and EBMT Paediatric Working Parties recommend that patients with symptomatic SCD who have an MSD should undergo HCT as early as possible, preferably at pre-school age [30]
   v. Optimal age for transplantation: Younger appears better with regards to TRM. Children 10–21 compared to <9 years of age were found to have increased mortality (HR 21.2 95% CI 2.8–160.7) [28].

b. Donor considerations

   i. Largely limited to MSD and URD although this will evolve with advances in alternative donors.
   ii. Only an estimated 19% probability of finding fully matched unrelated donor in African Americans versus 75% in Caucasians of European decent [27].

c. Conditioning regimen

   i. Conditioning regimen: Myeloablative busulfan/cyclophosphamide with busulfan/cyclophosphamide with antithymocyte globulin yields excellent outcomes with MSD.
   ii. RIC for children has shown promise though is not standard.
   iii. Posterior reversible encephalopathy syndrome (PRES) is more likely to occur in patients with SCD undergoing HCT +/− calcineurin inhibitors exposure due to underlying vascular disease.

   d. Post-transplant considerations

      i. Risk of stroke is dramatically reduced though not eliminated.

      ii. Vaso-occlusive pain may occur over the first few months following transplant.

   e. Outcomes

      i. 2-year OS for MSD and URD of 94% and 74%, respectively (CIBMTR 2000–2013). Long-term follow-up and quality of life data are lacking.

      ii. SCURT (Sickle Cell Unrelated Transplant) trial (2015): URD with RIC in children with 2-year OS and EFS of 79% and 69%. PRES occurred in 34% of patients.

   f. Future directions

      i. Clinical trials exploring gene therapy are currently underway.

         • Potential approaches include adding an extra globin gene, gene editing to correct the mutation, or augmenting fetal hemoglobin production.

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PID

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Chapter 25
Hematopoietic Cell Transplant and Cellular Therapies for Sickle Cell Disease

Rabi Hanna

Introduction

Sickle cell disease (SCD) is an inherited blood disorder that was first described by James Herrick in 1910 [1]. In 1957, Vernon Ingram, PhD, described the underlying genetic mutation as a single point mutation in codon 6 of β-globin chain and its resultant expression of mutated hemoglobin S that triggers erythrocytes to take a characteristic sickled conformation [2]. SCD now includes a group of different genetic conditions that result in same pathology such as homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle β0-thalassemia [HbSβ0-thalassemia], sickle β+-thalassemia [HbSβ+-thalassemia], and other genotypes. SCD affects nearly 100,000 residents of the USA with estimates that it affects hundreds of thousands more worldwide. Annually there are 2000 new children in the United States (US) affected by SCD [3].

The abnormal sickle-shaped erythrocytes disrupt blood flow in small vessels and can cause vaso-occlusion in small vessels, which leads to distal tissue ischemia and inflammation with symptoms defining the acute painful sickle cell crisis. Repeated ischemia-reperfusion episodes are responsible for many of the acute and chronic complications affecting all major organs (anemia, hemolysis, acute splenic sequestration, stroke, cerebral silent infarcts, cognitive impairment, retinopathy, avascular osteonecrosis, leg ulcers, priapism, proteinuria, renal failure, cholelithiasis, hepato-cholangiopathy, pulmonary hypertension, etc.), resulting in substantial morbidity and contributing to early mortality [4].

The health and survival of children with SCD have improved considerably after implementation of newborn screening, penicillin prophylaxis, pneumococcal immunization, chronic transfusion, hydroxyurea (Hydrea®) utilization, and

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education about disease complications. However, unfortunately, the average projected life span of affected adults has not improved beyond the fifth decade [5, 6]. Thus far, hematopoietic cell transplantation (HCT) remains the only curative option, which could improve both quantity and quality of life. This chapter will review challenges and outcomes of HCT in patients with SCD, utilizing different conditioning regimens and different donor types as well as briefly promising new cellular therapies such as gene therapy that could offer a curative option.

HLA-Matched Related Donor Transplant (MRD) in Children

1. The first reported case of using HCT to cure SCD was in 1984 in an 8-year-old female, who also had acute myeloid leukemia (AML); her 4-year-old HLA-matched brother was her donor.

   a. Myeloablative (MA) conditioning regimen with cyclophosphamide 60 mg/kg/day × 2 doses and total-body irradiation (TBI) 11.5 Gy.
   b. Graft-versus-host disease (GvHD) prophylaxis consisted of methotrexate and prednisone.
   c. This regimen resulted in a cure of both her AML and SCD.
   d. Despite this successful case, widespread use of HCT to treat SCD has been limited due to its highly variable clinical outcomes.

2. Many studies have attempted to identify patients at risk for progressive organ damage with associated long-term poor outcomes.

   a. This includes patients with debilitating clinical events, such as stroke, recurrent acute chest syndrome, and recurrent painful vaso-occlusive crises, which contribute to the high morbidity and early mortality among patients with sickle cell disease.

3. Since the first reported case, multiple studies have been published using HCT for patients with SCD, supporting this therapy as a curative option.

   a. The first multicenter study included 22 children with symptomatic SCD, who underwent an MA regimen using busulfan 16 mg/kg, cyclophosphamide 200 mg/kg, and antithymocyte globulin (ATG) 90 mg/kg with an HLA-matched sibling donor. At the 4-year follow-up, disease-free survival (DFS) was reported at 73% and overall survival (OS) was 91% [8].
   b. Following that study, many groups have described a series of patients transplanted with an HLA-identical sibling with reported OS that varies between 91% and 100% and event-free survival (EFS) that varies between 73% and 100% [9].
   c. The addition of ATG resulted in a decrease in the 5-year cumulative incidence of graft rejection from 22.6% to 2.9%. Furthermore, its use was associated with an increased frequency of mixed but stable chimerism.

  d. GvHD was the principal complication, accounting for four deaths. Twenty percent of patients developed grade II or higher acute GvHD (aGvHD), 8.1% of whom developed grade III to IV aGvHD. The cumulative incidence of chronic GvHD (cGvHD) was 12.6% [10].
  e. The largest retrospective study published the results of 1000 HLA-identical transplants, performed between 1986 and 2013, and reported to the European Society for Blood and Marrow Transplantation (EBMT), Eurocord, and the Center for International Blood and Marrow Transplant Research (CIBMTR).

    i. Five-year EFS and OS of 91.4% (95% CI 89.6–93.3%) and 92.9% (95% CI 91.1–94.6%), respectively [11].
    ii. A multivariate analysis of age at the time of transplant was associated with improved OS and EFS.

      • Five-year OS was 95% (95% CI, 93–97%) and 81% (95% CI, 74–88%) for patients aged <16 years and those aged ≥16 years, respectively ($P < 0.001$).
      • The corresponding EFS was 93% (95% CI, 92–95%) and 81% (95% CI, 74–87%; $P < 0.001$).
      • Five-year probability of GvHD-free survival was 86% and 77% for patients aged <16 years and ≥16 years, respectively ($P < 0.001$).
      • The indications for HCT in most of these studies are summarized in Table 25.1.

  f. Another landmark clinical trial is the DREPAGREFFE (NCT01340404).

    i. A multicenter, prospective trial between 2010 and 2013 with a 3-year follow-up.
    ii. Enrolled patients with SCD aged <15 years, who were receiving chronic transfusions due to a history of abnormal transcranial Doppler (TCD).
    iii. Children with HLA-matched donors underwent HCT, while those without a suitable donor continued chronic transfusion.

Table 25.1 Summary of clinical indications for HCT in HLA-matched donors for SCD

Children with sickle cell disease (Hgb SS or Hgb SB thalassemia) ≤ 18	*Adults* with sickle cell disease (Hgb SS or Hgb SB thalassemia) >18
Stroke or central nervous system event lasting >24 hours	Stroke or central nervous system event lasting >24 hours
Abnormal MRI/MRA vasculopathy (silent stroke)	Impaired neuropsychological function with abnormal MRI/angiography
Recurrent acute chest syndrome	Recurrent acute chest syndrome
Recurrent vaso-occlusive painful episodes or recurrent priapism	Recurrent vaso-occlusive painful episodes

	Evidence of end-organ damage:
	  Pulmonary hypertension
	  Osteonecrosis
	  Renal insufficiency

	Red-cell alloimmunization

    iv. Thirty-two children were enrolled on each arm of the trial, and comparison between the two arms was analyzed using both genetic randomization and propensity-score matching as a sensitivity analysis.

    v. The primary end point was the velocity measure at 1 year. Secondary end points were the incidence of stroke, silent cerebral infarcts and stenosis, cognitive performance in comparison with siblings, alloimmunization, and iron overload.

    vi. There were no strokes or deaths in either group.

    vii. Highest TCD velocities at 1 year were significantly lower on average in the HCT group (129.6 cm/s) vs the chronic transfusion group (170.4 cm/s; $P < 0.001$).

    viii. Of the 25 analyzed secondary end points, four showed significant differences.

- The highest TCD velocity at 3 years of 112.4 cm/s in the HCT group vs 156.7 cm/s in the chronic transfusion group; difference, −44.3; $P = 0.001$
- Normalization rate at 1 year of 80.0% in the HCT group vs 48.0% in the chronic transfusion group; difference, 32.0%; $P = 0.045$
- Ferritin levels at 1 year of 905 ng/mL in the HCT group vs 2529 ng/mL in the chronic transfusion group; difference, −1624; $P < 0.001$
- Ferritin levels at 3 years of 382 ng/mL in the HCT group vs 2170 ng/mL in the chronic transfusion group; difference, −1788; $P < 0.001$

    ix. Additionally, children who underwent HCT reported better quality of life (QOL) than those receiving chronic transfusion only at 3 years (84.8 vs 73.2, respectively; difference, 11.6; $P = 0.001$), while their parents reported improved QOL at 1 year (88.3 in the HCT group vs 69.7 in the chronic transfusion group; difference, 18.6; $P < 0.001$) and 3 years (84.0 in the HCT group vs 73.1 in the chronic transfusion group; difference, 11.0; $P = 0.01$) [12, 13].

    x. *In summary*: Matched sibling donor HCT was associated with greater improvements in TCD velocities and many secondary end points without unexpected toxicity when compared with the chronic transfusion group. One important observation is that at the 3-year follow-up, three children receiving chronic transfusions developed new silent infarcts and two developed stenosis, while no patients in the HCT group developed either of these abnormalities. Although these differences were not statistically significant, this suggests a possible benefit of HCT in halting progression of cerebrovascular disease and vasculopathy.

4. These studies collectively demonstrate:

    a. Patients with symptomatic SCD who undergo HCT with an HLA-matched sibling donor have excellent outcomes.

    b. Patient age at transplant is important, supporting the notion that early transplant before end-organ damage occurs is fundamental to treatment success [14]

    c. DREPAGREFFE trial is a clear evidence of the advantage of early intervention before end-organ damage occurs, similar to studies in thalassemia major where transplant is performed as soon as a matched sibling donor is identified.

5. Studies in the US also show that HCT leads to substantial reductions in healthcare expenditures over time for SCD patients compared to SCD patients who receive supportive therapy alone, with the largest benefit noted among patients with MRDs and those who were younger at the time of transplantation.

    a. Merged data for 176 patients showed that the median total adjusted transplant cost per patient was $467,747.

    b. Healthcare utilization was lower among recipients of matched sibling donor HCT and those with low severity disease compared to those with other types of donor and disease severity types ($P < 0.001$ and $P = 0.022$, respectively).

    c. HCT early in the disease course was associated with significant reductions in admissions ($P < 0.001$), length of stay ($P < 0.001$), and cost ($P = 0.008$).

    d. Reduced posttransplant inpatient healthcare utilization indicates that HCT may provide a sustained decrease in healthcare costs over time [15].

6. Between 2011 and 2015, only 116 HCTs per year were performed on patients with SCD within the US, which some would consider a remarkably low number given the prevalence of this disease and the data accumulated to date.

    a. Multiple factors contribute to the low rates of HCT in this patient population.

       i. One of the major barriers to increased use of this therapy is limited donor availability. Studies assessing donor availability in the SCD population have found that only 14–25% of SCD patients have an HLA-matched related sibling [16]. However, even with less than one-third of patients potentially having a HLA-matched sibling donor, donor availability alone fails to fully account for the low utilization of HCT in this patient population of approximately 100,000 SCD in the US.

       ii. Sociocultural factors, both patient and provider related, may also contribute to this phenomenon [11, 17, 18].

- Parents of children with SCD and adult patients affected by the disease are willing to accept relatively high risk of mortality to achieve cure of the disease [19]
- Among healthcare providers, there are variable perceptions of acceptable up-front risk vs the opportunity for long-term cure [20].
- These observations suggest that clinician attitudes about and clinical practices of discussing HCT with families may play a role in the underutilization of this therapy in the SCD patient population [21].

HLA-Matched MRD Transplant in Adults

Most of the studies described above focused on HCT in children with SCD where MA HCTs proved to be a curative option. However, the potential toxicity of MA transplants may be prohibitive for adults, thus leading to the study of non-myeloablative (NMA) HCT with different degrees of reduced-intensity conditioning (RIC). RIC regimens have traditionally been associated with a higher incidence of graft rejection and GvHD. Reviewed below are several studies that successfully employed increased immunosuppression instead of MA conditioning, resulting in curative treatment option for adult SCD patients with comorbidities.

1. A minimally toxic regimen was first developed by the John Hopkins group using pretransplant fludarabine 150 mg/m^2 and TBI 200 cGy in seven patients. This approach was safe with no mortality and little or no aGvHD. However, after initial engraftment, all patients lost their graft after withdrawal of immunosuppression and experienced autologous recovery with disease recurrence [22].

2. This approach was modified by the group at the National Institutes of Health (NIH).

    a. A pilot study enrolled ten SCD patients (age range 16 to 45 years), who received a NMA conditioning regimen of alemtuzumab (Campath®) 1 mg/kg in divided doses and TBI 300 cGy followed by infusion of G-CSF (Neupogen®)-mobilized peripheral blood stem cells (5.5–31.7 × 10^6 cells/kg) from an HLA-matched sibling. Sirolimus (Rapamune®) was used for GvHD prophylaxis [23].

    b. An additional 20 patients were accrued (for a total of 30 patients evaluated, aged 16–65 years), who were transplanted between 2004 and 2013 with the same NMA regimen [24].

        i. Twenty-nine patients (96%) survived with a median follow-up of 3.4 years. One patient died from intracranial bleeding after graft failure.

        ii. Twenty-six patients (87%) had long-term stable donor engraftment without acute or chronic GvHD.

        iii. The mean donor T-cell chimerism was 48% (95% CI, 34–62%); myeloid chimerism 86% (95% CI, 70–100%).

        iv. Fifteen patients engrafted and discontinued immunosuppression medication with continued stable donor chimerism and no GvHD.

        v. Additional findings in this study included the resolution of hemolysis among engrafted patients, stabilization in brain imaging, a reduction of echocardiographic estimates of pulmonary pressure, and the ability to perform phlebotomy to reduce hepatic iron.

        vi. Another importance healthcare utilization finding was the significant decrease in the mean annual hospitalization rate from 3.23 (95% CI, 1.83–4.63) the year before HCT to 0.63 (95% CI, 0.26–1.01) the first year

Table 25.2 Selected studies of non-myeloablative conditioning (alemtuzumab + TBI 300 cGy) with HLA-matched sibling HCTs for patients with SCD

	Number of patients	Age (years)	Overall survival	Acute GvHD	Sustained engraftment
University of Chicago [26]	N = 13	17–40	100%	0%	92%
Saudi Arabia [27]	N = 51 17 children 34 adults	27 (14–39) 8.8 (4–14)	Adult 97% Peds 100%	Adult 0% Peds 12%	Adult 90% Peds 100%
Alberta Children's Hospital-Canada [28]	16 children	12 (3–18)	100%	0%	100%

GvHD graft-versus-host disease; *Peds* Pediatric

> after. This trend continued to further decrease to 0.19 (95% CI, 0–0.45) in the second year after and subsequently down to 0.11 (95% CI, 0.04–0.19) the third year after HCT.
>
> vii. Another important observation in RIC HCTs where mixed chimerism is common is that patients with myeloid chimerism ≥20% remained free of SCD symptoms, due to the greatly shortened red blood cell (RBC) life span in sickle cells and improved RBC survival of the donor cells. A minority of donor cells is adequate to reverse the sickling phenotype [25].

c. This RIC regimen was replicated at other transplant centers as summarized in Table 25.2. These data suggest that alemtuzumab + low-dose TBI conditioning creates adequate space in the bone marrow and depletes recipient lymphocytes to overcome the risk of graft rejection and facilitate donor engraftment. Additionally, the prolonged half-life of alemtuzumab contributes to in vivo depletion of donor alloreactive T cells, decreasing GvHD risk with very little transplant-related mortality or toxicity.

Alternative Donor Sources

One of the biggest challenges of expanding HCT to the SCD population is the lack of an HLA-matched family donor. In a cohort of 113 children with SCD receiving chronic RBC exchange transfusion therapy, only eight (7%) had identified an unaffected HLA-matched sibling [29] and only three patients (<3%) underwent HLA-matched HCT. In another collaborative study among 22 centers where 4848 patients with SCD were followed, only 14% were likely to have a HLA-identical sibling donor [30]. These data illustrate the important role of alternative donors to expand the access to this life-saving therapy. While several other stem cell sources such as mismatched unrelated bone marrow, umbilical cord blood, and haploidentical stem

cells from a parent or sibling are potential alternative options for HCT in SCD patients, these options are associated with increased risk of graft rejection and/or GvHD.

1. Matched unrelated donor (M-URD)

    a. The National Marrow Donor Program (NMDP) reports African Americans have low probability (16% to 19%) of finding an appropriate 8/8 HLA-matched donor [31].

        i. An important prospective phase II multicenter trial study, BMT CTN 0601 (SCURT: Sickle Cell Unrelated Transplant), aimed to evaluate the role of unrelated donors in SCD.

            • Twenty children with a median age of 14 years (range 4–19 years).
            • Preparative regimen consisted of distal alemtuzumab [Campath®] on days −23, −22, −21, and −20 followed by fludarabine 30 mg/m2/daily on days −8, −7, −6, −5, and −4 and melphalan 140 mg/m2 on day −3.
            • GvHD prophylaxis was a calcineurin inhibitor, short methotrexate 7.5 mg/m2 on days +1, +3, and +6, and methylprednisolone 1 mg/kg per day IV through day +28 [32]
            • The 1-year OS was 86% and 1-year DFS rate was 75%. The regimen was associated with 28% aGvHD (grade II to IV) and 38% chronic extensive GvHD.
            • Six patients died of GvHD, and one patient died following a second transplant.

        ii. Another approach has been CD34+ cell-selected, T-cell-depleted peripheral blood stem cell transplantation in the M-URD setting using an RIC reduced-intensity conditioning regimen including melphalan, thiotepa, fludarabine, and rabbit ATG.

            • A study by Gilman et al. [33] reported outcomes of ten patients (age 5–23 years); the 2-year OS was 90%, and EFS was 80%. This approach enabled stable myeloid engraftment (mean donor chimerism was 99%) with low GvHD rate; however, Epstein-Barr virus (EBV)-related post-transplant lymphoproliferative disorder (PTLD) occurred in three patients and one patient died as a consequence of treatment of PTLD.

        iii. A recent multicenter study reported HCT outcomes in adults with SCD using RIC regimen with busulfan 13.2 mg/kg, fludarabine 175 mg/m^2, and rabbit ATG 6 mg/kg.

            • Twenty-two patients with a median age of 22 years, range 17–36.
            • Seventeen patients had MRDs, and five patients received marrow from an 8/8 HLA-allele-M-URD.
            • One patient died from graft failure; OS was 80% with DFS at 3 years of 60%.

    iv. Currently there is another multicenter phase II clinical trial (BMT CTN #1503) testing busulfan, fludarabine, and ATG reduced-toxicity conditioning regimen in both HLA-matched sibling donor and HLA-M-URD bone marrow transplant (BMT) in adults with SCD. At the time of publishing, this clinical trial (NCT02766465) is recruiting and will compare BMT to the standard of care in individuals without a suitably HLA-MRD or M-URD.

2. Umbilical cord blood transplant (UCBT)

  a. Given the limited availability M-URD, it is reasonable to consider cord blood as an alternative donor source for HCT.

    i. Historically outcomes of UCBT in patients with SCD have been complicated by graft rejection as seen in the SCURT trial, which included a cohort of eight patients, who received unrelated UCBT [34].

- Patients were conditioned with alemtuzumab, fludarabine, and melphalan.
- GvHD prophylaxis consisted of cyclosporine A (CSA) or mycophenolate mofetil (Cellcept®, MMF) and tacrolimus (Prograf®).
- All patients engrafted neutrophils; however, five patients had autologous hematopoietic reconstitution equivalent to 62% graft rejection; the remaining three patients had sustained donor engraftment.
- One-year EFS was 37.5%; therefore, study enrollment into the UCBT cohort was prematurely suspended due to high rates of graft rejection.

    ii. Another study also reported a high incidence of graft rejection using a conditioning regimen of busulfan, fludarabine, and alemtuzumab, where only four out of eight patients engrafted with DFS of 50% [35].

    iii. The outcome following UCBT from an HLA-MRD is acceptable with 5-year EFS of 86% from a study by Soni et al. [36], who reported outcomes of 22 children with median age 5.2 years (range 1.8–11.7 years).

- Most patients received an MA regimen of busulfan, cyclophosphamide, and ATG.
- Three patients died from infectious complication of transplant, 5% developed aGvHD, and no chronic GVHD was reported.
- The author also investigated co-infusion of bone marrow cells from the same donor as the umbilical cord blood donor in 13 patients as a way to increase the cell dose and enhance engraftment.

    – Neutrophil engraftment occurred at a median day +17, which was 8 days less than UCBT group, none of the patients experienced graft failure, and the EFS was 100% after a median follow-up of 66 months (range: 33–91 months) [36].

    iv. More recent data suggest that the addition of thiotepa to the previous RIC regimen of fludarabine, melphalan, and alemtuzumab could improve outcomes in the setting of unrelated UCBT.

- Abraham et al. [37] reported outcomes of nine patients with median age of 4 years (range 3–10 years).
- One-year OS was 100%, and DFS was 78%.
- Of note the median total nucleated cell (TNC) dose was 5.9×10^7/kg (range 3.9–8.5), which was higher than the TNC dose in SCURT trial (median 4.5×10^7/kg with a range of 2.1–6.3×10^7/kg) and could be a contributing variable.
- This small patient study will need to be validated in larger trial before unrelated UCBT could be used more widely in SCD.

3. Haploidentical HCT (haploID)

    a. HaploID donors have increased the access to life-saving HCT therapy in many malignant disorders, especially with the success of T-cell-replete HCT products with posttransplant cyclophosphamide (PTCy) as the method for immune tolerance and prevention of GvHD [38]. A majority of patients will have parents, children, or siblings who can serve as donors.

    b. The John Hopkins regimen using T-cell-replete HCT with PTCy served as a platform for many studies that investigated the safety and efficacy of haploID HCT in patients with SCD.

        i. A study by Bolaños-Meade et al. [42] used a regimen consisting of rabbit ATG, fludarabine, cyclophosphamide, and TBI 200 cGy.

        ii. GvHD prophylaxis consisted of PTCy and mycophenolate mofetil (Cellcept®, MMF) with either tacrolimus or sirolimus.

        iii. Seventeen patients were transplanted using bone marrow as the stem cell source; 14 from HLA-haploID donors and three from HLA-MRDs.

        iv. With a median follow-up of 711 days, 11 patients had sustained engraftment (EFS = 65%) with no mortality. No cGvHD was reported in the patients who had sustained engraftment.

        v. This study provided evidence that haploID HCT is safe and feasible; however, this strategy was associated with a high rate of graft failure (43%).

        vi. A modified Hopkins regimen was investigated at the University of Illinois [39], increasing the TBI dose to 300 cGy (instead of 200 cGy) and using peripheral blood stem cells (PBSCs) instead of bone marrow.

- Eight patients were evaluated with a reported DSF of 75% and OS of 87.5%.
- Two patients developed aGvHD; only one patient experienced cGvHD but died later.

    c. Another approach was adding thiotepa to the conditioning regimen, which consisted of ATG 0.5 mg/kg on day −9 and 2 mg/kg on days −8 and −7 (total dose 4.5 mg/kg), fludarabine 30 mg/m^2 on days −6 to −2 (total dose 150 mg/m^2), cyclophosphamide 14.5 mg/kg on days −6 and − 5 (total dose 29 mg/kg), and TBI 200 cGy on day − 1 [40].

        i. GvHD prophylaxis included PTCy 50 mg/kg on days +3 and + 4, mycophenolate mofetil on days +5 to +35, and sirolimus instead of tacrolimus or cyclosporine to decrease the incidence of neurological complications such as PRES. Sirolimus target levels were 5–15 ng/mL for 1 year.

        ii. Outcomes were very encouraging with 93% (14 of 15) of patients experiencing >95% stable donor engraftment at 6 months and 100% OS. Two patients had grade III–IV aGvHD, one patient had mild chronic GvHD, and 86% of patients (6 of 7) were off immunosuppression therapy by 1-year posttransplantation.

    d. Other studies have utilized a similar RIC haploID HCT regimen with thiotepa or increased TBI dose to 400 cGy with excellent EFS of 88% and OS of 100% [41, 42].

    e. The preconditioning phase of RIC haploID HCT has also proved critical. Investigators have used hydroxyurea 30 mg/kg for 60 days prior to start of conditioning therapy or pulses of fludarabine and dexamethasone [43]. There is no clear advantage of one therapy over the others, and some therapies may be associated with increased mortality due to infection or macrophage activation syndrome as reported when hydroxyurea, hypertransfusion, and azathioprine (Imuran®) are used as preconditioning therapy [44].

        BMT CTN 1507 (NCT03263559) is an ongoing prospective phase II multicenter trial to evaluate the efficacy and toxicity of haploID BMT in children and adults with SCD after preconditioning with hydroxyurea and a conditioning regimen of ATG, fludarabine, cyclophosphamide, thiotepa, and TBI 200 cGy. Of note this study enrolls both adults and children but has different indications for each group. See Table 25.3 for indications for enrollment.

        i. This study, which aims to enroll 40 patients in each stratum with the primary end point or EFS at 2 years posttransplant, is expected to complete enrollment by the end of 2021.

    f. Another approach for haploID HCT by the NIH group is based on their success with NMA platform used with matched sibling donors that was discussed earlier (see section "HLA Matched MRD Transplant in Adults" a, b) [45].

        i. Conditioning consists of alemtuzumab and TBI 400 cGy total followed by infusion of a haploID product.

        ii. GvHD prophylaxis was sirolimus and dose escalation of PTCy.

Table 25.3 Indications for enrollment in BMT CTN 1507

Indication criteria for adults Ages 15–45.99 years at the time of enrollment	Indication criteria for children Ages 5–14.99 years at the time of enrollment
Clinically significant neurological event (stroke) or any neurological deficit lasting >24 hours	Evidence of overt stroke ischemia based on neuroimaging or clinical evidence of permanent neurological injury lasting for 24 hours, or both
History of two or more episodes of ACS in the 2-year period preceding enrollment despite the institution of supportive care measures (i.e., asthma therapy and/or hydroxyurea)	Abnormal TCD measurement with a timed average maximum mean velocity of ≥200 cm/sec in the terminal portion of the internal carotid or proximal portion of middle cerebral artery or if the imaging TCD method is used >185 cm/sec plus evidence of intracranial vasculopathy
History of three or more severe vaso-occlusive pain crises per year in the 2-year period preceding enrollment despite the institution of supportive care measures (i.e., a pain management plan and/or treatment with hydroxyurea); painful episodes related to priapism, osteonecrosis, or any sickle-related complication are acceptable	Silent cerebral infarct defined as an infarct-like lesion based on an MRI signal abnormality at least 3 mm in one dimension and visible in two planes on FLAIR or T2-weighted images (or similar image with 3D imaging) and documented neurological examination performed by a neurologist, demonstrating the participant has a normal neurological examination or an abnormality on examination that could not be explained by the location of the brain lesion(s)
Administration of regular RBC transfusion therapy, defined as receiving ≥8 packed RPB transfusions per year in the 12 months before enrollment to prevent vaso-occlusive clinical complications (i.e., pain, stroke, and ACS)	
An echocardiographic finding of TRJV ≥2.7 m/sec	

ACS acute chest syndrome, *TCD* transcranial Doppler, *MRI* magnetic resonance imaging, *RBC* red blood cell, *TRJV* tricuspid valve regurgitant jet velocity

   iii. It is notable there were few patients in their cohort with significant disease complications including cirrhosis, dialysis, and pulmonary hypertension. Despite the severe organ damage, patients tolerated the conditioning regimen with all patients alive at day +100.
   iv. PTCy improved donor engraftment with 83% engraftment at the 100 mg/kg dose compared with 33% in the patients who did not receive PTCy.

Gene Therapy

The concept that gene therapy could ameliorate human genetic diseases first emerged in the 1970s. This concept involves the delivery of a functional copy of the defective gene into a patient's own stem cells or manipulation of regulatory genes that are known to influence disease phenotype. This correction is achieved either via gene editing, gene silencing, or gene insertion/addition.

Because SCD arises from single amino acid substitution in "adult" βA-globin (Glu6Val) as a result of a single base substitution (A → T) in the first exon of the human βA-globin gene (HBB), SCD is an attractive target for curative approaches using gene therapy. Table 25.4 below summarizes the available clinical trials in the USA for gene therapy in SCD.

a. Gene transfer and addition strategies have significantly improved over the past decade and became more precise and efficient.
b. The first successful report of gene therapy for a patient with SCD was reported in 2017 [46].

   i. At age 13, this patient underwent bone marrow harvest. The bone marrow-enriched CD34+ cells were transduced with LentiGlobin BB305 vector.

- The patient received MA conditioning with intravenous busulfan (total AUC was 19,363).
- After a 2-day washout period, transduced CD34+ cells (5.6×10^6 CD34+ cells/kg) were infused.
- Red-cell transfusions were continued after transplantation until a large proportion of HbAT87Q (25 to 30% of total hemoglobin) was detected.
- A level of therapeutic anti-sickling globin (HbAT87Q) of ~50% with biological parameters typical of SCD trait was rapidly achieved.
- Subsequent multicenter clinical trials HGB-205/206 with the same vector demonstrated the importance of several factors especially the number of the transplanted CD34+ hematopoietic stem cells (HSCs) and transduction protocol [47].
- Initial studies showed importance of high CD34 and recommended infusing > an average of 7×10^6 CD34+ cells/kg with a vector copy number (VCN) ≥2 for BB305 LV. To achieve this number of CD34+ cells, recent studies used PBSC instead of marrow and along with plerixafor (Mozobil®) mobilization; collections yielded up to 24.5 x 10^6 CD34/kg [48, 49].

c. Gene editing (GE) studies, on the other hand, can be divided into those intended to elevate HgbF to therapeutic levels and those repairing the underlying sickle β^S-globin mutation.

Table 25.4 Current gene therapy trials for SCD in the USA

Clinical trial #	Phase	LV/nuclease	Site/sponsor
NCT02140554 (HGB206)	1/2	BB305 LV	BlueBird bio
NCT02186418	1/2	sGbG LV	Children's Hospital Medical Center, Cincinnati, OH
NCT02247843	1	βAS3-FB LV	University of California Children's Hospital
NCT03745287	1	CRISPR/Cas9 (BCL11A enhancer)	Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics

i. GE relies on the application of engineered nucleases with programmable specificity via zinc-finger nucleases and transcription-activator-like effector nucleases (TALENs) or CRISPR-Cas9 systems.

ii. In 2019, Erica Esrick, MD, presented an abstract at the American Society of Hematology (ASH) conference, reporting the outcomes of feasibility of gene therapy study NCT 03282656 that used BCH-BB694-transduced autologous CD34+ cells in three adult patients aged 21–26 years.

- BCH-BB694 is lentiviral vector (LVV) encoding a shRNA targeting BCL11A embedded in a microRNA scaffold (shmiR), allowing erythroid-specific knockdown to induce γ-globin expression and concomitantly and coordinately repress β-sickle globin expression [50].
- While early data suggest an acceptable safety profile, validation of BCL11A as effective target for HgbF induction in humans was shown. High numbers of F cells in circulation containing high levels of HgbF per F cell were seen, mitigating the cellular pathology of SCD.

d. Although these approaches seem very promising, challenges remain that need to be addressed:

i. Conditioning regimens used in conjunction with autologous gene therapies include MA doses of busulfan. These regimens carry risk for both early transplant-associated toxicity and late effects such as infertility and second malignancies. Therefore, novel regimens that could promote engraftment without such risks are needed to extend autologous therapies more broadly especially in adults with comorbidities.

ii. Access to therapy: The expected high cost of gene therapy is a barrier to a widespread utilization of this potentially transformative therapy especially in Africa where the burden of this disease is the highest.

Conclusion

Allogeneic HCT, especially from an HLA-matched sibling, has a long track record of an ability to cure SCD with limited toxicities. This treatment strategy has been utilized mostly in the severe phenotype of SCD; however, the recent data by DREPAGREFFE study encourage hematologists and transplant physicians to offer MSD HCT early in the disease course before patients suffer end organ or other severe disease manifestation. Only a limited percentage of patients have HLA-matched siblings; therefore, alternative sources of stem cells are needed. The data emerging regarding haploID HCT with PTCy for GvHD prophylaxis are especially exciting as this procedure will expand the donor pool for SCD patients. Additionally, haploID HCT studies have demonstrated sustained engraftment even with RIC regimens, which make this option especially attractive for adult SCD patients who have many comorbidities. Finally, gene editing and gene addition studies to replace the

abnormal gene or augment fetal hemoglobin production are ongoing; however, for these studies to be successful, gene transfer to the hematopoietic stem cell population must be efficient and provide long-term gene expression and cure.

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Chapter 26
Radiology Pearls for the Transplant Provider

Anupama G. Brixey and Steven L. Primack

Introduction

A wide variety of pulmonary and abdominal complications occur in hematopoietic cell transplant (HCT) patients and are a major cause of morbidity and mortality. Diagnosing these transplant-related diseases early is important to prevent irreversible complications and superimposed infections. Imaging plays a critical role in the diagnosis of all of the transplant-related pulmonary and abdominal complications discussed in this chapter. Therefore, it is important for the provider to be familiar with the general imaging appearance of these complications. The authors begin this chapter by defining commonly used radiologic terminology. This is followed by a discussion of specific pulmonary and abdominal diseases that occur in the neutropenic/pre-engraftment phase (1–30 days), early phase (1–3 months), and late phase (3 months–1 year) post-transplant periods, along with their imaging manifestations.

Chest

A wide variety of pulmonary complications, both infectious and non-infectious, can occur following HCT (Fig. 26.1). Historically, pulmonary complications were reported to occur in approximately 40–60% of all HCT patients [1] with a mortality rate close to 90% in patients requiring mechanical ventilation [2]. With the routine use of prophylactic antimicrobials, the rate of infectious complications has decreased, while non-infectious complications have become the major cause of

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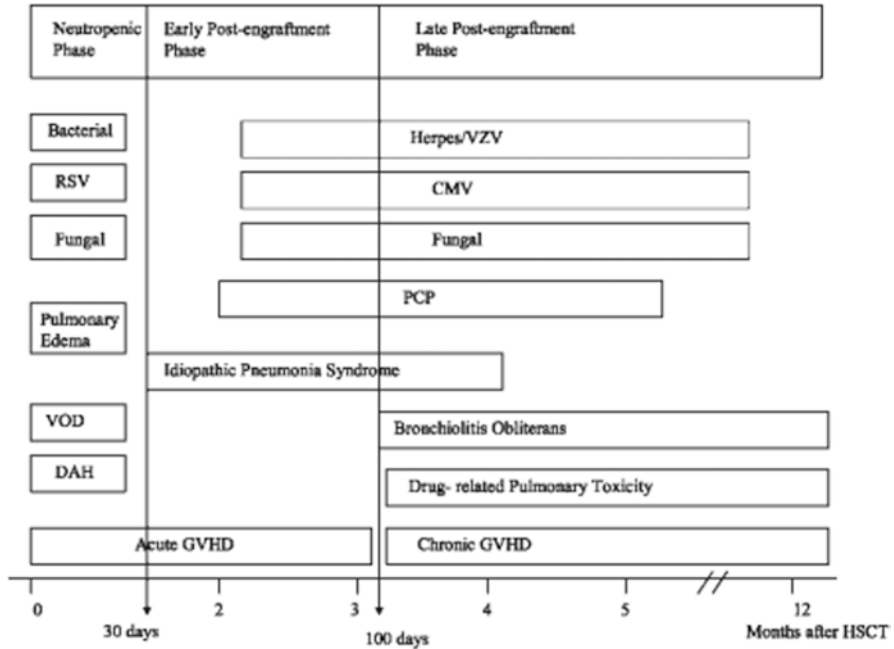
Fig. 26.1 Time period for occurrence of pulmonary complications after HCT (with permission from Gosselin and Adams [14]). Bacterial infections are not included in this diagram, but can occur during any time period. The term "bronchiolitis obliterans organizing pneumonia" (BOOP) is antiquated and has been replaced with "organizing pneumonia" (OP)

morbidity and mortality in HCT patients [3]. The type of pulmonary complication depends on the type of HCT (allogeneic vs autologous), type of conditioning regimen (myeloablative vs non-myeloablative), and time elapsed post-HCT [4, 5]. In general, infectious and non-infectious complications are more common in allogeneic transplants, in patients who have had a myeloablative conditioning regimen, and in those with either acute or chronic GvHD. More recent data suggest that the rate of pulmonary complications is approximately 49% in allogeneic transplants recipients versus 13% in autologous transplants recipients and is highest in patients with acute or chronic graft-vs-host disease (GvHD) at approximately 60% [4].

For proper interpretation of chest radiographic and computed tomography (CT) imaging, it is important for the provider to be familiar with the most commonly used chest radiology definitions and descriptions:

1. *Consolidation*: increased attenuation of lung parenchyma with obscuration of normal lung architecture/blood vessels
2. *Ground-glass opacity*: increased attenuation of lung parenchyma through which blood vessels/normal lung architecture appear indistinct but are still visible
3. *Air bronchograms*: visualization of air-filled bronchi surrounded by consolidated lung parenchyma
4. *Halo sign:* a ring of ground-glass attenuation surrounding a focal area of pulmonary consolidation

5. *Reverse halo sign*: a ring of consolidation surrounding a focal ground-glass opacity
6. *Nodule*: a focal rounded/oval area of increased attenuation on radiograph that is ≤3 cm in greatest dimension
7. *Mass*: a focal rounded/oval area of increased attenuation on radiograph that is >3 cm in greatest dimension
8. *Reticulation*: irregular linear opacities, typically in a lace-like network
9. *Infarct*: non-enhancing consolidation without air bronchograms, typically in a subpleural location

Neutropenic/pre-engraftment Phase (0–30 days)

During this period, patients essentially have no effective immune system and are, therefore, susceptible to a broad range of systemic infections. Despite the high prevalence of bacteremia, pulmonary manifestations of bacterial/fungal infections are *not* commonly seen in this time period. Supportive care and empiric antibiotic therapy are important in successful passage through the pre-engraftment phase. The most common complications during this phase are pulmonary edema (cardiogenic and non-cardiogenic), drug toxicity, and diffuse alveolar hemorrhaage (DAH), which will be discussed in further detail in this chapter. Bacterial/fungal infections and acute pulmonary GvHD are uncommon complications in this time period. Viral infections, with the exception of respiratory syncytial virus (RSV), are not common in this time period.

Idiopathic pneumonia syndrome (IPS) is a clinical diagnosis assigned to patients with widespread acute lung injury and absence of infectious organisms. However, recent data have shown that greater than half of patients that were previously given the diagnosis of IPS were later found to have infectious pathogens identified by modern polymerase chain reaction (PCR) testing [6]. By imaging, the findings of IPS include a broad differential of imaging diagnoses including non-cardiogenic pulmonary edema/acute lung injury, DAH, peri-engraftment syndrome, transfusion-related acute lung injury (TRALI), etc. [7, 8]. Therefore, these authors suggest that this term be avoided if possible since the findings are more often not "idiopathic" and falsely gives the impression that IPS is a specific diagnosis. Rather, during the work-up which often includes cross-sectional imaging, the patient may be given a diagnosis based on imaging findings (such as non-cardiogenic pulmonary edema).

1. Cardiogenic pulmonary edema
   Patients receive a large volume of fluid in the form of intravenous medications, blood products, total parenteral nutrition, etc., which can lead to cardiogenic (hydrostatic) pulmonary edema, exacerbated in the setting of cardiac and renal impairment (as a result of chemotherapy administration) and concomitant hypoalbuminemia.

   a. Clinical presentation
      i. Dyspnea
      ii. Orthopnea

Fig. 26.2 (**a**, **b**)
Hydrostatic/cardiogenic pulmonary edema: The hallmark of pulmonary edema is pulmonary vascular indistinctness with presence of thickened septal lines (Kerley B lines) at the periphery of the lungs. **a**. Chest radiograph in this patient with hydrostatic pulmonary edema; peri-hilar and lower lobe-predominant ground-glass and consolidative opacities are present along with small bilateral pleural effusions. **b**. Representative CT image in the same patient better delineates the lower lobe ground-glass opacities, thickened interlobular septae, and small bilateral pleural effusions, consistent with cardiogenic pulmonary edema
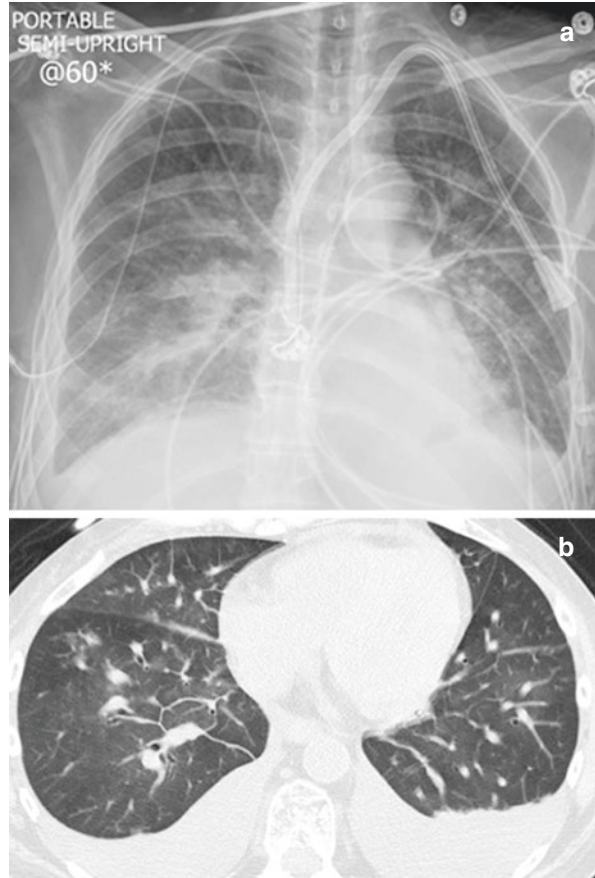
     iii.   Lower extremity edema
     iv.   Weight gain

  b. Radiographic/CT findings (Fig. 26.2a, b)

      i.   Pulmonary vascular indistinctness, best seen in the medial lower lobes
     ii.   Ground-glass and consolidative opacities
    iii.   Septal thickening (Kerley B lines)
    iv.   Pleural effusions and fissural fluid
     v.   Enlarged cardiac silhouette

2. Non-cardiogenic pulmonary edema (NCPE)

    Also known as increased capillary permeability edema, NCPE is due to decreased intravascular oncotic pressure from leakage of protein and exudative fluid through the capillaries. NCPE is an entity on a spectrum which can result in acute respiratory distress syndrome (ARDS) in its most severe form.

Fig. 26.3 *Non-cardiogenic edema*: In contrast to cardiogenic pulmonary edema, mixed ground-glass and consolidative opacities are diffusely present in non-cardiogenic edema reflecting a systemic process as the cause (in this case, sepsis). Pleural effusions may be present as well
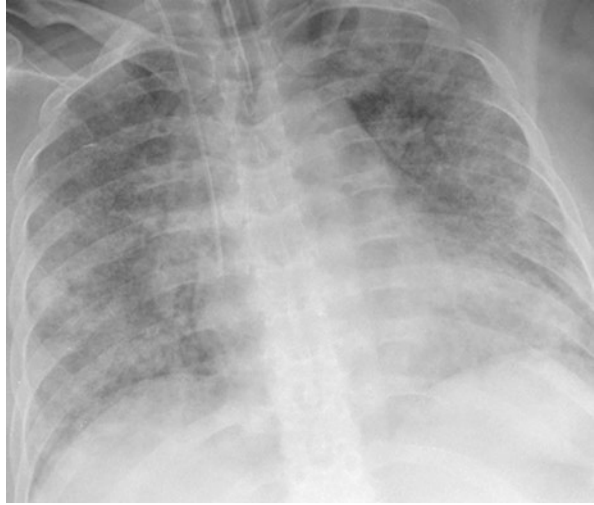
a. Common etiologies of NCPE in HCT patients include:

    i. Sepsis/systemic infection
    ii. Pneumonia secondary to infection
    iii. Drug toxicity
    iv. Total body irradiation (TBI)
    v. TRALI

b. Clinical manifestations include:

    i. Fever
    ii. Dyspnea
    iii. Erythroderma
    iv. Liver/renal/central nervous system (CNS) dysfunction

c. Radiographic findings (Fig. 26.3)

    i. Diffuse bilateral ground-glass and consolidative opacities, often with pleural effusions when severe.
    ii. Typically, there is no clinical or radiographic evidence to suggest a cardiac etiology (cardiomegaly, septal thickening, basilar-predominant opacities).
    iii. Diffuse distribution is an important clue that the underlying cause is systemic.
    iv. Response to fluid restriction and diuresis is minimal given that the mechanism is due to capillary leak as opposed to volume overload. Intubation for mechanical ventilation may be required if it progresses to ARDS, although this occurs in the minority of patients [9].

d. Also associated with peri-engraftment respiratory distress syndrome (PERDS) or simply peri-engraftment syndrome (see Chap. 14). PERDS has an average onset 7 days after HCT with a 20% mortality [7].

Fig. 26.4 *Diffuse alveolar hemorrhage (DAH)*: Axial CT image of the chest demonstrates bilateral diffuse ground-glass predominant opacities with smooth septal thickening. There is notable sparing of the subpleural lung parenchyma, which is commonly seen with DAH. The lack of pleural effusion makes severe pulmonary edema unlikely
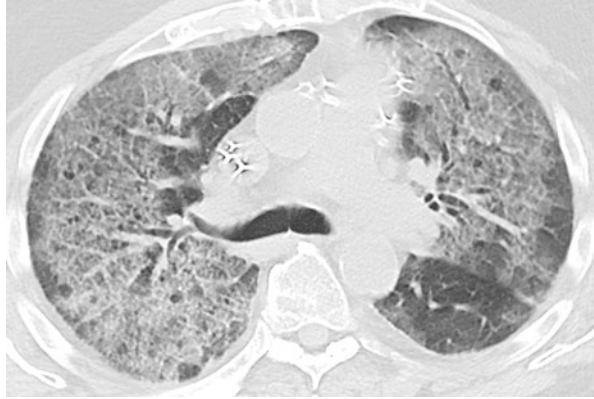
3. Drug toxicity

    a. Drug toxicity may occur during the neutropenic phase but more commonly occurs during the early post-HCT period (1–3 months); see "Early Phase" section below for discussion.

4. Diffuse alveolar hemorrhage (DAH)

    a. DAH is an underdiagnosed disease with an incidence ranging from 14% to 19% by bronchoscopy and up to 39% by autopsy [10, 11]. It occurs most frequently in the 2–3 weeks post-HCT and can be associated with an underlying infectious organism that may be the etiology for hemorrhage. It remains associated with high mortality.

    b. The exact pathophysiology of DAH is unclear but general risk factors include:

        i. Age >40
        ii. Severe mucositis
        iii. Identification of an infectious pathogen
        iv. Solid malignancy
        v. Conventional myeloablative transplant
        vi. Rapid neutrophil recovery
        vii. Grade III–IV acute GvHD

    c. Clinical presentation

        i. Acute onset dyspnea
        ii. Cough
        iii. Hypoxemia
        iv. Hemoptysis (rarely) and/or mild drop in hemoglobin
        v. Fever

    d. Radiographic/CT findings (Fig. 26.4)

        i. Rapidly progressive diffuse ground-glass and consolidation
        ii. Smooth septal thickening
        iii. Sparing of the subpleural lung parenchyma
        iv. Absent pleural effusions

    e. Definitive diagnosis requires bronchoalveolar lavage (BAL) which demonstrates increasingly bloody serial aliquots of lavage fluid.

5. Bacterial/fungal/viral infection

    a. Pulmonary manifestations of bacterial and fungal infections are uncommon during the neutropenic phase despite a high prevalence of bacteremia.

    b. Empiric use of broad-spectrum antimicrobial agents may prevent development of infectious pneumonia during this time period.

    c. Radiologic manifestations of common bacterial and fungal infections in HCT will be discussed in later sections, as they are more common during the early/late post-transplant period.

    d. Viral infection is more common in the early and late phases with the exception of RSV, which presents more commonly in the neutropenic phase possibly as a result of superimposed pneumonia [12].

6. Acute graft-versus-host disease

    a. Acute GvHD involving the lung is considered a very rare event. Typically, other organs such as the skin, liver, and gut are involved prior to pulmonary involvement.

Early Phase (1–3 months)

During the early period, 1–3 months after HCT, the most common pulmonary complications in both allogeneic and autologous transplants are drug toxicity, bacterial infection, invasive *Aspergillus*, and viral pneumonia (particularly cytomegalovirus (CMV)), all of which are discussed in detail in this chapter.

    Pulmonary cytolytic thrombi is a rare complication that only affects allogeneic HCT patients with acute or chronic GvHD and is more common in the pediatric population [13]. It consists of thrombi that are composed of products of cellular breakdown (hence the term cytolytic thrombi) with an imaging presentation of bilateral pulmonary nodules and adjacent peripheral pulmonary infarcts. Treatment consists of increased immunosuppression that usually results in resolution.

1. Drug toxicity

    a. Occurs most often in the first 100 days post-HCT. Common inciting agents include carmustine, busulfan, and bleomycin.

    b. Clinical symptoms

       i. Progressive dyspnea
      ii. Dry cough
     iii. Low-grade fever

    c. Radiographic/CT findings usually develop within days to weeks of symptom onset (Fig. 26.5).

    d. The pattern of injury varies and most commonly manifests as non-specific interstitial pneumonitis (NSIP), hypersensitivity drug reaction, organizing pneumonia, and diffuse alveolar damage (DAD) among others [14, 15].
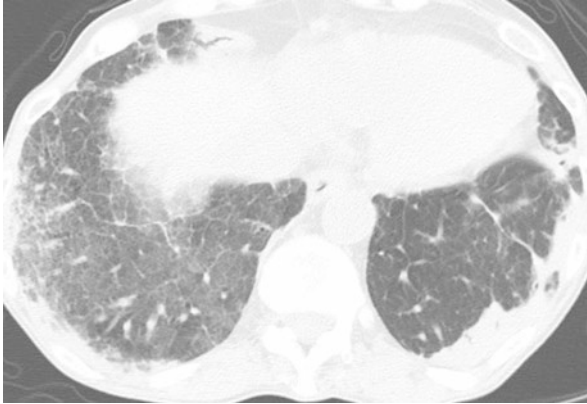
Fig. 26.5 *Drug toxicity*: Chest CT performed for new symptoms of shortness of breath demonstrates peripheral consolidation in bilateral lower lobes, left greater than right, as well as right lower lobe ground-glass opacities and subpleural reticular opacities. Clinical symptoms and CT findings developed after the patient was started on IVIG. The CT findings are most suggestive of organizing pneumonia versus non-specific interstitial pneumonia (NSIP), which was clinically thought to be related to IVIG-induced drug toxicity. After removal of the drug and initiation of high-dose steroids, pulmonary symptoms and chest CT abnormalities completely resolved

    i. NSIP presents on imaging as patchy ground-glass opacities, usually basilar-predominant. With continued drug exposure, the findings eventually progress to fibrosis with traction bronchiectasis. Carmustine and methotrexate are common inciting drugs with this pattern.

    ii. Hypersensitivity drug reaction presents as ill-defined upper lobe-predominant centrilobular nodules and patchy ground-glass opacities. Carmustine is a commonly involved drug.

    iii. With continuous/repeated exposure to the offending agent, hypersensitivity reaction can progress to or mimic the appearance of pulmonary fibrosis in an NSIP or usual interstitial pneumonia (UIP) pattern [16].

    iv. Organizing pneumonia (formerly referred to as BOOP) presents as peripheral and peri-bronchovascular ill-defined consolidation with bronchial wall thickening and ground-glass opacities. Bleomycin commonly results in an organizing pneumonia pattern of drug toxicity.

    v. Drug toxicity may present as DAD which is evident by rapidly progressive scattered or diffuse mixed ground-glass and consolidative opacities, usually favoring the mid to lower lung zones [15]. Bleomycin, busulfan, and carmustine are some of the commonly involved drugs.

    vi. If the offending agent is not removed in DAD, it will usually progress to fibrosis with architectural distortion.

2. Bacterial infection

    a. There is a high prevalence of bacteremia during the early phase post-HCT which can lead to bacterial pneumonia.

    b. Gram-negative and anaerobic bacteria, originating from oral mucosa or the gastrointestinal tract, are most commonly identified.

Fig. 26.6 *Bacterial pneumonia*: Focal consolidation with air bronchograms is the most common and characteristic imaging manifestation of acute bacterial pneumonia. This patient had a clear chest radiograph 6 days prior and was found to have pseudomonas bacteremia at the time of this chest radiograph

    c. Gram-positive bacteremia occurs most commonly secondary to long-term indwelling central venous catheters and as a result of upper GI tract mucositis.

    d. GvHD is a risk factor for the development of bacterial pneumonia.

    e. The radiographic appearance of bacterial pneumonia is similar to that of an immunocompetent host, with presence of focal or multifocal pulmonary consolidation containing air bronchograms (Fig. 26.6).

3. Opportunistic fungal infection

    a. Accounts for approximately 1–10% of all pneumonias in allogeneic HCT recipients [17]. Occurs less commonly in autologous HCT recipients.

    b. Infections are usually a result of ubiquitous fungi such as *Aspergillus* or *Mucoraceae* in the early phase post-transplant. *Aspergillus* is the most common pathogen and is usually angioinvasive or, less frequently, airway-invasive.

    c. *Aspergillus* is most frequently seen 1–4 months post-HCT, although this period is extended further in patients with chronic GvHD.

    d. Clinical symptoms

      i. Persistent fever

      ii. Cough

      iii. Hemoptysis, seen rarely

    e. Radiographic/CT findings

      i. May initially present as multiple scattered ill-defined nodules or as multifocal segmental/subsegmental areas of non-enhancing consolidation typically in a peripheral distribution and without air bronchograms (all features of pulmonary infarct).

Fig. 26.7 *Angioinvasive Aspergillus*: Focal right upper lobe consolidation without air bronchograms and with surrounding ring of ground glass (halo sign). The halo sign represents pulmonary hemorrhage as a result of vascular invasion of the *Aspergillus*. It is common to have two to three separate lesions in angioinvasive *Aspergillus*, and this patient had bilateral upper lobe lesions present

ii. On CT, these areas of consolidation are often surrounded by a halo of ground glass ("halo sign"), which is a result of hemorrhage surrounding the area of infarction (Fig. 26.7).

iii. Later in the disease course, the nodules/consolidation may cavitate and demonstrate an "air-crescent" sign on chest CT. This development signifies neutrophil recovery and improved prognosis. This finding is highly suggestive of angioinvasive *Aspergillus*.

iv. In a minority of HCT patients, *Aspergillus* only invades the airways. On chest CT, airway-invasive *Aspergillus* manifests as tree-in-bud nodularity. This radiographic/CT appearance combined with bronchoscopic identification of *Aspergillus* in an immunocompromised patient is considered diagnostic for infection, rather than colonization.

v. Imaging findings in mucormycosis (which includes *Mucor* pneumonia and *Rhizopus* pneumonia) often manifest in a solitary ground-glass opacity surrounded by a ring of consolidation ("reversed halo sign" or "Atoll sign"). In an HCT patient with fever, these findings are highly suggestive of mucormycosis (Fig. 26.8).

vi. Additional fungal infections in this time period include candidiasis, which is rare due to use of azole prophylaxis.

4. Cytomegalovirus (CMV)

    a. CMV pneumonia is the most common infection to occur in the early phase and usually occurs 1.5–3 months post-HCT. It occurs more commonly in allogeneic HCT patients [18].

    b. Risk factors

       i. Concurrent GvHD

Fig. 26.8 *Mucormycosis (genus Rhizopus)*: Focal left upper lobe ground-glass opacity surrounded by ring of consolidation (reversed halo sign or Atoll sign) as seen on both lung and soft tissue windows. In a post-transplant patient with fever, this finding is highly suggestive of mucormycosis. A solitary lesion is typical with this diagnosis
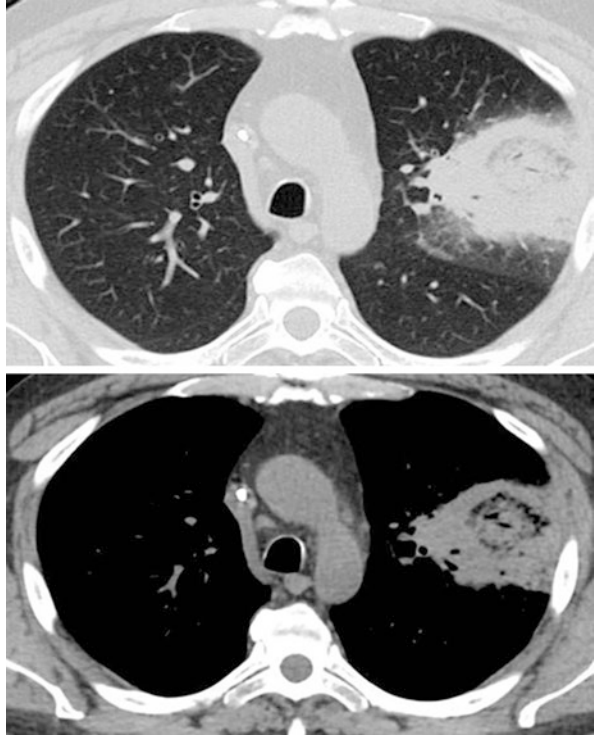
    ii. Recipient CMV sero-positivity prior to transplant
    iii. Transplantation of a sero-negative recipient from a sero-positive donor

c. Screening for recipient viral sero-positivity with early initiation of viral prophylaxis and use of leukocyte-reduced blood products in viral sero-negative recipients have all led to decreased incidence of clinically apparent disease (see Chap. 10).
d. Clinical symptoms

    i. Fever
    ii. Dyspnea
    iii. Non-productive cough
    iv. Hypoxia
    v. Respiratory failure and death if left untreated

e. Radiographic/CT findings (Fig. 26.9)

    i. Patchy, ground-glass predominant opacities
    ii. Numerous ill-defined centrilobular nodules, usually <5 mm in diameter

f. Additional viral infections to consider in post-HCT patients include varicella-zoster virus (VZV), Epstein-Barr virus (EBV) which is associated with post-transplant lymphoproliferative disorder (PTLD), and seasonal viral infections such as influenza, parainfluenza, RSV, and human metapneumovirus.

Fig. 26.9 *Cytomegalovirus (CMV) pneumonia*: Bilateral small centrilobular nodules greatest within the middle and lower lung zones along with patchy ground-glass opacities are the typical appearance of CMV pneumonia
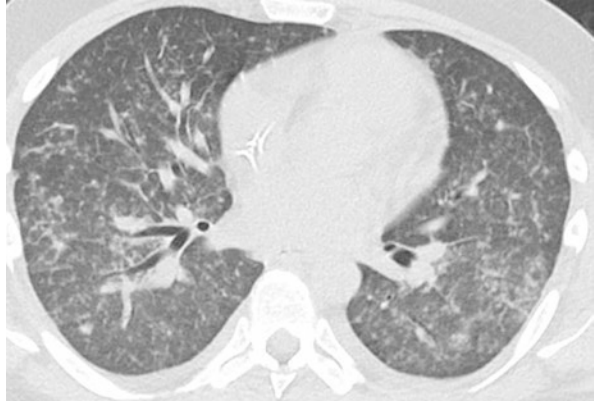
Late Phase (3 months–1 year)

In the late post-HCT period, which extends from 3 months to 1 year, the immune system continues to recover resulting in a reduction of transplant-related pulmonary complications in both autologous and syngeneic (twin-twin) HCT recipients. However, allogeneic HCT recipients often develop chronic GvHD, which in turn increases the risk of pulmonary infections and additional non-infectious pulmonary complications.

The term late-onset idiopathic pneumonia syndrome (LOIPS) refers to various interstitial lung diseases that develop post-HCT and include constrictive/obliterative bronchiolitis, organizing pneumonia (OP), NSIP, and DAD among others [19]. The most common type of LOIPS is bronchiolitis obliterans syndrome (BOS) which is the clinical manifestation of chronic pulmonary GvHD [20, 21]. Additional late phase pulmonary complications which include thoracic air leak syndrome, PTLD secondary to immunosuppression in the setting of HCT, and pulmonary arterial hypertension secondary to pulmonary veno-occlusive disease or as a result of BOS or other LOIPS are rare complications and will not be discussed in this chapter.

1. Chronic GvHD/BOS/constrictive bronchiolitis

   During the late period, autologous and syngeneic transplant recipients recover their immune function and experience a reduction in transplant-related pulmonary complications. In contrast, allogeneic HCT recipients become susceptible to chronic GvHD which is the most common and most clinically relevant complication [8, 20]. Incidence ranges from 2% to 26% [22].

   a. The pathologic correlate to chronic GvHD is constrictive/obliterative bronchiolitis which can be diagnosed by bronchoscopy, obtaining transbronchial lung biopsies which show bronchial wall thickening secondary to fibrosis and resulting in luminal narrowing and air-trapping. Alternatively, if biopsies are deemed too risky to obtain, patients can be given a clinical diagnosis (termed BOS) by fulfilling both of the following criteria based on pulmonary function testing (updated in 2014):

     i.   FEV1/FVC: <70% or 5th percentile predicted, *and* FEV1 <75% predicted (without reversibility with use of albuterol) with >10% decline in less than 2 years.

    ii.   Air-trapping manifests as hypoattenuation on expiratory CT, or manifests as small airway thickening or bronchiectasis on high-resolution inspiratory CT, *or* air-trapping manifests on PFTs as RV >120% predicted or RV/TLC > 90th percentile.

  iii.   See Chap. 33 for additional details.

b. Risk factors

     i.   Older age of recipient
    ii.   Sex matching of donor/recipient
  iii.   Acute GvHD
  iv.   Pre-transplant conditioning regimen
   v.   Stem cell source

c. Clinical symptoms

     i.   Chronic progressive dyspnea
    ii.   Wheezing
  iii.   Occasional non-productive cough

d. Radiographic/CT findings (Fig. 26.10a, b)

     i.   Hyperinflation on chest radiograph
    ii.   Mosaic attenuation, bronchial wall thickening, and possible bronchiectasis/bronchiolectasis on inspiratory chest CT
  iii.   Patchy peripheral-predominant areas of air-trapping on expiratory-phase chest CT

e. Patients with chronic GvHD are predisposed to bacterial, viral, and fungal pneumonias, either from primary immune dysfunction caused by GvHD itself or secondary to immune-suppressive therapies and associated hypogammaglobulinemia.

f. Oral and inhaled steroids are typically used to treat chronic pulmonary GvHD, but until recently [23], the decline in pulmonary function secondary to chronic pulmonary GvHD was considered irreversible. Current research efforts are aimed at prevention of chronic pulmonary GvHD recognizing that there is no effective treatment. Additional treatment options include pulmonary rehabilitation and lung transplantation in certain patients. Mortality remains extremely high.

2. Thoracic air leak syndrome

a. Defined as extra-alveolar air within the lungs, soft tissues, or mediastinum/pleura and includes spontaneous pneumothorax, subcutaneous emphysema, pneumomediastinum, and pneumopericardium.

b. Associated with obliterative bronchiolitis/BOS and mechanically ventilated patients. Occurs in 2.3% of all HCT patients and in 20% of patients with obliterative bronchiolitis/BOS [24].

Fig. 26.10 a, **b**. *Chronic GvHD manifest as constrictive bronchiolitis*: **a**. Inspiratory-phase axial CT image demonstrates mild mosaic attenuation. **b**. Expiratory-phase axial CT image demonstrates lack of expected diffusely increased attenuation of the lungs, but, rather, presence of bilateral lobular air-trapping consistent with constrictive bronchiolitis. The etiology in this case was secondary to chronic GvHD
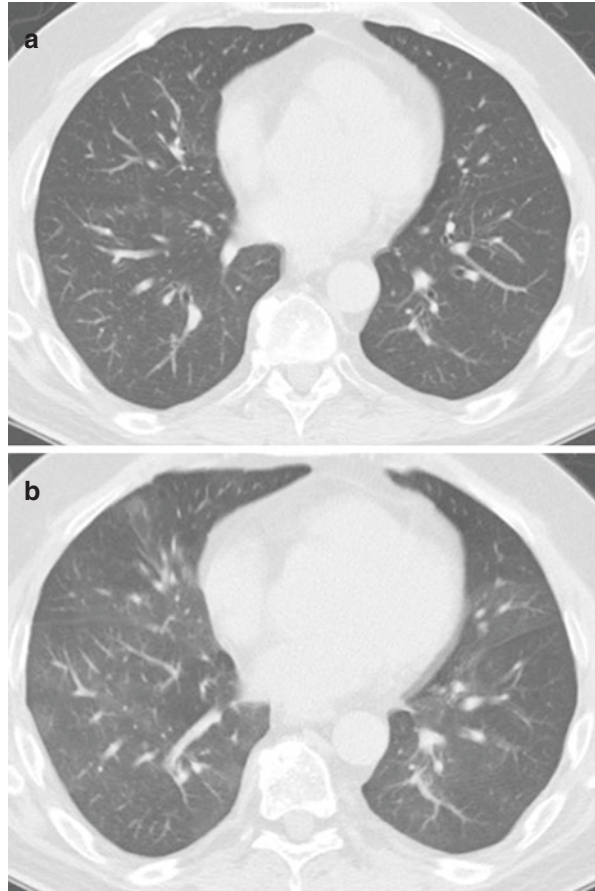
    c. Pathogenesis is thought to be from alveolar rupture leading to pulmonary interstitial emphysema and pneumothorax and eventually to pneumomediastinum as the air travels along the bronchovascular bundles [25].

    d. Presents with progressive dyspnea.

    e. Findings are usually progressive and often fatal (89%), although pleurodesis can be considered in stable patients.

3. Organizing pneumonia (OP)

    a. After constrictive/obliterative bronchiolitis, OP is the next most common LOIPS. Affects approximately 2% of allogeneic HCT recipients with median onset of 150 days [26].

    b. The etiology of OP is typically due to drug toxicity or infection. OP has previously been referred to as a manifestation of chronic pulmonary GvHD, but the most recent consensus statement defines constrictive/obliterative bronchiolitis as the only manifestation of chronic pulmonary GvHD and OP as being associated with GvHD but not synonymous with it.

Fig. 26.11 *Organizing pneumonia (OP)*: Bilateral peri-bronchovascular ground-glass opacities with peripheral ring of consolidation (reversed halo sign or Atoll sign) are commonly seen in organizing pneumonia. This patient had chronic GVHD, and the OP was favored to have developed as a result of chronic GVHD
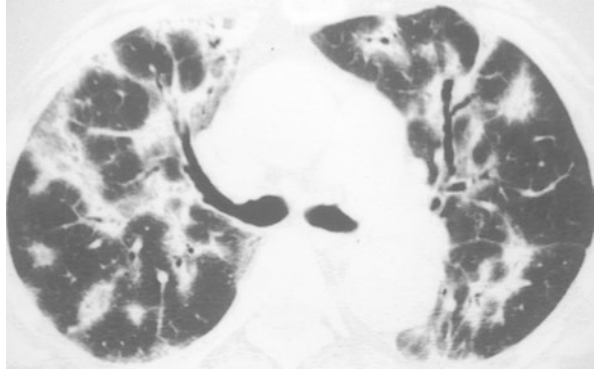
   c. Pathologically characterized by loose plugs of granulation tissue within small airways.

   d. Risk factors

      i. Allogeneic HCT
      ii. GvHD
      iii. CMV infection
      iv. Radiation as part of conditioning regimen

   e. Clinical symptoms

      i. Dyspnea
      ii. Fever
      iii. Cough, non-productive

   f. Radiographic/CT findings (Fig. 26.11)

      i. Multifocal, peripheral, mixed ground-glass/consolidative opacities, often in a peri-bronchovascular distribution

   g. Treatment is high-dose corticosteroids to which patients usually respond well.

   h. The radiographic/CT manifestations of additional less common LOIPS, such as NSIP and DAD, are discussed in section "Early Phase" above.

Abdomen

HCT recipients are also at risk for abdominal complications such as gastrointestinal GvHD, infectious enterocolitis (bacterial, fungal, and viral), VOD/SOS, and neutropenic colitis. Hemorrhagic cystitis is more common in the pediatric population. Additional less common abdominal complications in HCT patients include PTLD, tumor recurrence, and thrombotic microangiopathy, but will not be discussed in this chapter.

Fig. 26.12 *GvHD of the bowel*: Coronal CT image of the abdomen/pelvis demonstrates circumferential small and large bowel wall thickening and edema with mucosal hyperenhancement. Engorgement of the vasa recta adjacent to the involved bowel is also present
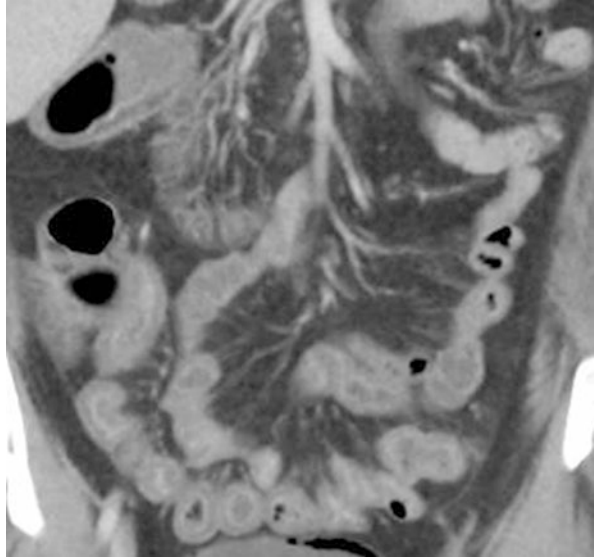
1. Gastrointestinal (GI) GvHD

    a. Acute GvHD occurs commonly in the GI tract, liver, and skin and has been reported in 30–70% of HCT patients [27]. The usual time of onset is 2–10 weeks post-transplant.
    b. The pathogenesis of GI GvHD is damage to the GI epithelium by donor lymphocytes, manifesting as inflammation within the walls of the GI tract anywhere between the esophagus and rectum.
    c. Clinical symptoms

        i. Nausea/vomiting/diarrhea.
        ii. Weight loss.
        iii. Abdominal pain.
        iv. Fever, on occasion.
        v. Skin rash and liver dysfunction are often present.

    d. Radiographic findings

        i. Multiple dilated and fluid-filled loops of bowel
        ii. Air-fluid levels may be seen
        iii. Pneumatosis intestinalis and perforation in severe cases

    e. CT findings (Fig. 26.12)

        i. Diffuse bowel wall thickening
        ii. Mucosal hyperenhancement of both mucosa and serosa ("halo sign")
        iii. Bowel wall dilation
        iv. Mesenteric inflammatory stranding
        v. Hepatomegaly

Fig. 26.13 *Pseudomembranous colitis*: Axial CT scan in a patient who developed pseudomembranous colitis (also known as *Clostridium difficile* colitis) following antibiotic therapy demonstrates colonic submucosal edema of the entirety of the colon. The small bowel is normal in appearance
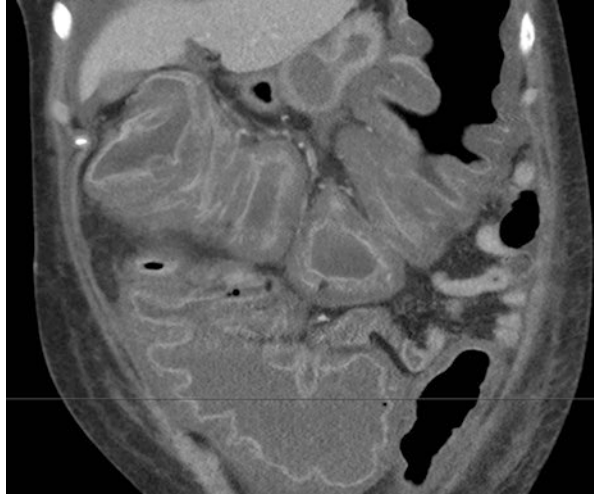
     vi. Ascites
    vii. Possible gallbladder and bladder hyperenhancement
   viii. Perforation and abscess in severe cases

2. Bacterial/fungal/viral abdominal infection

   a. Abdominal infections are common during the post-HCT period. The most frequently identified organisms are *Clostridium difficile (C diff)*, *Candida albicans*, and CMV.

   b. Neutropenic patients are at a higher risk for bacterial infections and are therefore placed on aggressive bacterial prophylaxis which may lead to overgrowth of normal bowel flora, such as *C diff*.

     i. Pseudomembranous colitis is the result of damaged colonic mucosa induced by toxins produced by *C diff* bacteria.
    ii. Clinical symptoms

- Copious watery, foul-smelling diarrhea.
- Often markedly elevated white blood cell count after resolution of neutropenia.
- Fever may be present.

   iii. Radiographic/CT findings (Fig. 26.13)

- Haustral thickening/edema, seen as "thumbprinting" on radiography.
- Marked wall thickening from submucosal edema, usually involving the entirety of the colon (pancolitis), but sigmoid colon and rectum are most commonly involved [28].
- Trapped enteric contrast between thickened haustral folds on CT, known as the "accordion sign."
- Inflammatory stranding adjacent to colon.

c. Abdominal candidiasis usually affects solid organs such as the liver, spleen, and kidneys.

    i. Infection most often manifests as numerous widespread micro-abscesses within solid organs.

    ii. Clinical symptoms

- Abdominal pain, especially painful hepatomegaly
- Fever

    iii. Imaging findings

- On sonography, micro-abscesses appear as multiple hypoechoic nodules ("bull's eye" lesions).
- On CT, micro-abscesses appear as hypoattenuating nodules with peripheral enhancement.

    iv. Although *Aspergillus* spp. are commonly seen in immunocompromised patients, infection with *Aspergillus* is more commonly systemic rather than localized to the GI tract.

d. CMV gastroenteritis is a leading cause of abdominal infection in the early post-HCT period.

    i. Clinical symptoms

- Abdominal pain.
- Nausea/vomiting/diarrhea.
- Fever.
- Hepatitis may develop.

    ii. Imaging findings

- Wall thickening of colon, small bowel (particularly terminal ileum), and stomach
- Mesenteric inflammatory stranding
- Ascites

3. VOD/SOS (see Chap. 32)

a. VOD/SOS (venoocclusive disease/sinusoidal obstruction syndrome) is thought to develop secondary to injury to the hepatic venous endothelium from the conditioning regimen resulting in hepatic sinusoidal obstruction, hepatic congestion, and eventually sinusoidal portal hypertension [29].

b. Onset is typically within 2–4 weeks post-HCT [27].

c. Clinical symptoms

    i. Painful hepatomegaly

    ii. Jaundice

    iii. Weight gain

    iv. Ascites

Fig. 26.14 a, **b**. *Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstructive syndrome (SOS)*: **a**. Coronal CT demonstrates hepatomegaly secondary to hepatic congestion as well as peri-hepatic ascites. **b**. Liver Doppler ultrasound demonstrates partial reversal of flow in the portal vein as a result of post-sinusoidal portal hypertension
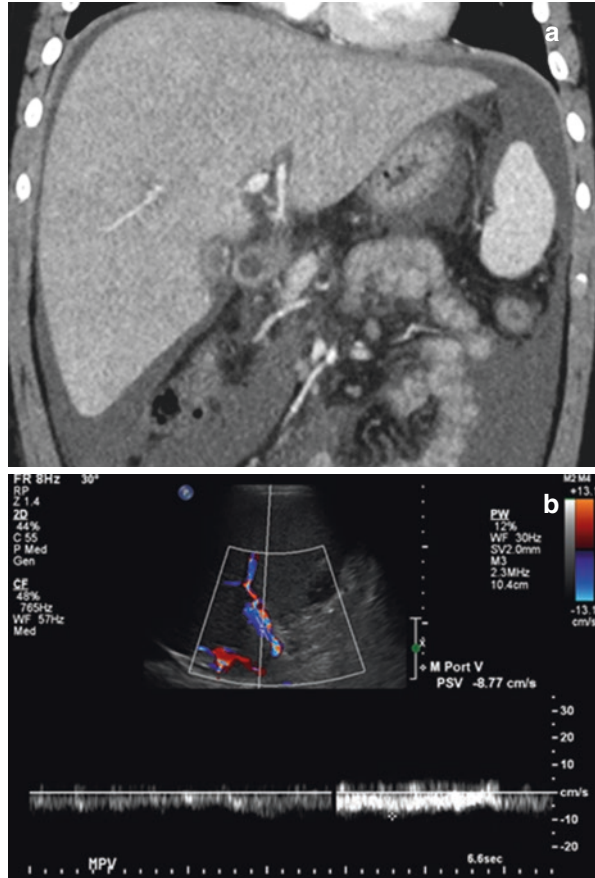
d. Imaging findings (Fig. 26.14a, b)

    i. Gray-scale ultrasound may show small caliber hepatic veins, gallbladder wall thickening, and ascites.

    ii. Liver Doppler shows increased phasicity of portal veins, with subsequent development of portal flow reversal by liver Doppler.

    iii. Periportal hypoechogenicity/hypoattenuation.

    iv. Hepatomegaly.

    v. Splenomegaly.

e. Liver biopsy may be required for definitive diagnosis.

4. Neutropenic colitis

a. Also known as typhlitis or cecitis, this entity is a necrotizing inflammatory condition centered on the cecum and potentially involving the ascending colon or terminal ileum.

Fig. 26.15 *Neutropenic colitis, also known as typhlitis*: Axial CT image demonstrates marked mural wall thickening of the cecum with adjacent peri-cecal inflammatory stranding and fluid in the right lower quadrant

b. Although the exact etiology is unknown, postulated theories suggest a combination of ischemia and infection in the setting of immune-compromise.

c. More common in children, but prevalence in adults is increasing.

d. Clinical symptoms

　i.　Right lower quadrant abdominal pain
　ii.　Severe diarrhea, possibly bloody
　iii.　Vomiting
　iv.　Fever

e. Imaging findings (Fig. 26.15)

　i.　Marked mural wall thickening and hyperenhancement of the cecum (and possibly terminal ileum and ascending colon)
　ii.　Peri-colic inflammation/inflammatory stranding
　iii.　Perforation in severe cases

f. Treatment is centered on antibiotics and bowel rest.

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Chapter 27
Acute Graft-Versus-Host Disease (GvHD)

Susan Schubach Slater

Introduction

Despite advances in molecular HLA typing, acute GvHD (aGvHD) remains the leading cause of morbidity and mortality among allogeneic hematopoietic cell transplant (HCT) recipients, reflecting the impact of polymorphic minor antigens that differ between recipients and donors. It is estimated that 30–50% of patients who undergo allogeneic HCT will develop grades 1–4 aGvHD; 14% of patients will develop grades 3–4 aGvHD [1].

Acute GvHD has historically been defined as occurring prior to day +100 post-transplant and chronic GvHD (cGvHD) as occurring after day +100. However, that arbitrary timeline has given way to defining GvHD based on clinical symptoms and pathologic findings. Three main categories of aGvHD are now recognized:

1. Classic aGvHD which occurs within the first 100 days post-transplant and typically results in an erythematous maculopapular rash, nausea, vomiting or diarrhea, and/or hyperbilirubinemia.
2. Persistent, recurrent, or late aGvHD which occurs after day +100.
3. Overlap GvHD includes patients with chronic GvHD that have clinical findings of aGvHD during cGvHD flares [2].

The overall outcome of aGvHD is dependent on the overall grade of GvHD and the patient's response to initial treatment.

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Pathophysiology

1. Three conditions are central to the development of aGvHD [3]:

    a. The patient must receive an infusion of immune-competent donor cells.
    b. The recipient must be unable to mount an appropriate immune response to these "foreign" cells, at least long enough for the donor cells to establish a chimeric state and mount an anti-host immunologic response.
    c. There must be an immunologic disparity between the recipient and donor cells.

The pathophysiology contributing to the development of GvHD is a complex interaction of donor T cells with host antigen-presenting cells (APCs) and involves numerous cytokines, chemokines, and immune cell subsets; however, the key mechanisms that perpetuate GvHD are not completely understood [4].

1. Tissue damage occurs as a consequence of the patient's malignancy, prior therapies, and/or the transplant conditioning regimen. This injury results in the release of inflammatory cytokines such as TNF-α, IL-1, and IL-2 leading to activation of the recipient's APCs.
2. These inflammatory cytokines and both patient and donor APCs interact with donor T cells leading to T cell expansion and release of additional inflammatory cytokines.
3. These activated T cells produce inflammatory cytokines and cellular mediators resulting in apoptosis in the target host cells, typically within the skin, gut, and liver target tissues.

This is a basic summary. For a more comprehensive and current understanding of the pathophysiology of GvHD, see Zeiser R and Blazar BR (N Eng J Med. 2017;377:2167–79).

Risk Factors[1] [5–8]

1. HLA disparity between donor and recipient.

    a. HLA DP disparity in HLA-A, HLA-B, HLA-C, and HLA-DRB1 matched pairs
2. Stem cell source: While the use of peripheral blood stem cell (PBSC) products has been clearly shown to influence the development of cGvHD, an association between PBSC products and aGvHD has been seen in the setting of certain myeloablative conditioning regimens.

    a. When analyzed independently, PBSC = marrow > cord blood

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[1] Historically, risk factors for GvHD have also included increased recipient age, cytomegalovirus positivity, and allo-sensitized donors (heavily transfused, prior pregnancies). However, more recent studies have found these etiologic factors not statistically significant.

b. Higher risk of GvHD is associated with the combination of

- PBSCs + total body irradiation + myeloablative conditioning + matched sibling donor
- PBSCs + myeloablative conditioning + unrelated donor

3. Regimen intensity (myeloablative > reduced intensity).
4. Immune suppressive regimen for GvHD prophylaxis (cyclosporine > tacrolimus); however, no impact on overall survival (OS) has been demonstrated.
5. Diagnosis of CML (possibly related to better functioning APCs due to minimal prior therapy) [9].
6. Pretransplant comorbidities as determined by the Hematopoietic Cell Transplant Comorbidity Index [10].

Incidence and Mortality [11, 12]

1. An estimated 30% of sibling donor recipients and 50% of unrelated donor recipients will develop grades 2–4 aGvHD; however, the incidence varies widely due to inconsistency of obtaining biopsies for definitive diagnoses, appropriate consideration of alternative etiologies, and absence of consensus guidelines for staging.

   a. Skin is usually the first organ involved and often coincides with engraftment
   b. Of patients who develop aGvHD, approximately 80% will have skin involvement, 50% gut involvement, and 50% liver involvement.

2. For patients alive at 60 days post-myeloablative HCT, only 5–8% will subsequently develop aGvHD; the advent of reduced intensity regimens has contributed to a change in the natural history with more frequent late presentation.
3. Over time, the prognosis of patients who develop aGvHD has improved due to advances in HCT practices, including more advanced HLA typing, better prevention and treatment of infections, and improved supportive care.

   a. A recent multicenter, retrospective analysis showed an increase in 12-month OS in patients with severe GvHD from 30% (1997–2006) to 42% (2007–2012) and decrease in the 1-year treatment-related mortality (TRM) from 58% to 38% in those same time frames [13].

4. Not surprisingly, patients who develop aGvHD experience longer hospital stays, more frequent readmissions and ICU admissions, higher inpatient mortality, and higher associated costs than patients who do not develop aGvHD [14, 15].

Clinical Presentation (See Table 27.1)

1. The median time to onset for symptoms of aGvHD is approximately 3 week post-transplant; however, this may be up to 3 months for patients receiving non-myeloablative conditioning regimens [16].
2. The primary organs affected by aGvHD are the skin, liver, and GI tract.

   a. *Skin*: Classically manifests as an erythematous, maculopapular rash +/− pruritis +/− pain involving the pinnae, palms, and soles. This rash often spreads to involve the neck and trunk with later involvement of the extremities. Severity is determined by the percentage of body surface area (BSA) involved (see Fig. 27.1) and may range from a mild, non-pruritic rash to bullous formation and desquamation reminiscent of toxic epidermal necrolysis.
   b. *Liver*: An elevated serum bilirubin is the typical manifestation of liver involvement, although elevated alkaline phosphatase may also be an indicator of impending disease. A variant of liver aGvHD has also been described that manifests as hepatitis with transaminitis and elevated alkaline phosphatase; however, these are not classic findings and are not specific.
   c. *GI*: Manifestations include anorexia, nausea, vomiting, diarrhea, and/or abdominal cramping. However, these are relatively nonspecific findings and may be attributed to the conditioning regimen, immune suppressive medications, or infection.

Table 27.1 Findings associated with GvHD

Organ	Clinical manifestations	Histologic findings	Alternate diagnoses
Skin	Erythematous maculopapular rash involving the palms, soles, pinnae, spreading to the trunk and later extremities. +/− pruritis. Bullae/desquamation in severe cases	Basal vacuolization, necrotic epidermal cells, lymphocytes in dermis, exocytosis in epithelium	Chemotherapy/radiation effect Drug eruption Viral exanthem Infection
Liver	Hyperbilirubinemia, jaundice. Possible hepatitis with transaminitis, elevated alkaline phosphatase	Bile duct damage, bile duct lymphocytic infiltration, endothelialitis	Sinusoidal obstructive syndrome Medication effect Extrahepatic obstruction TPN Infection Iron overload
GI	Anorexia, nausea, vomiting, diarrhea, abdominal pain/ileus, GI bleeding	Apoptosis, crypt cell necrosis and dropout, epithelial denudation	Chemotherapy/radiation effect GI tract infection (C. diff, CMV, etc.) Drug reaction
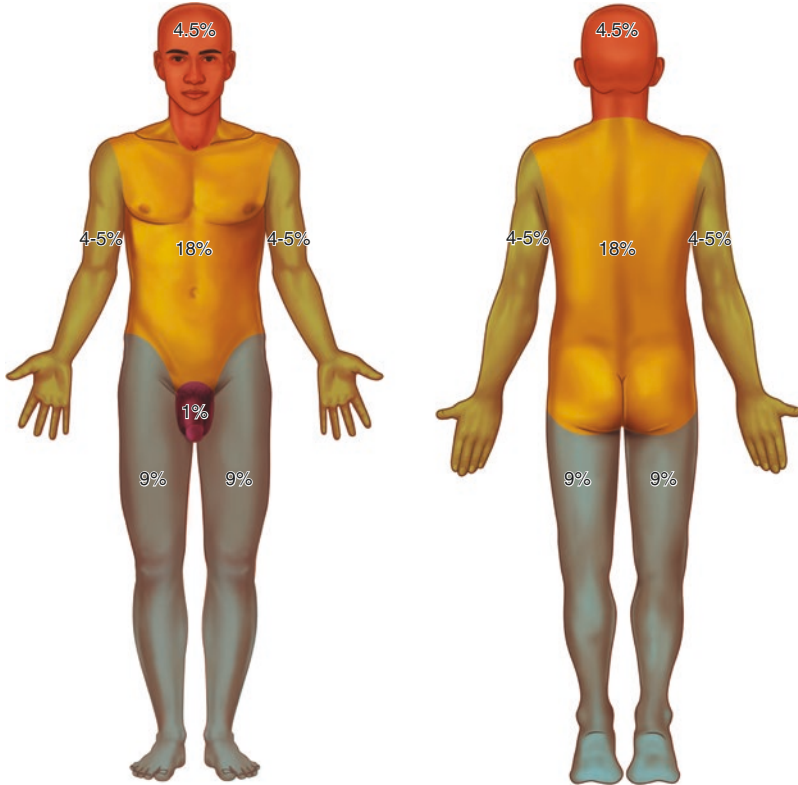
Fig. 27.1 Rule of nines (body surface area)

Evaluation

Tissue pathology is the gold standard for the diagnosis of GvHD; however, the sensitivity of biopsy testing is ~60%. Therefore, clinical correlation is necessary as many non-GvHD causes (tissue damage from the conditioning regimen, infection, medications, drug eruptions, viral exanthems) may mimic the pathologic findings of GvHD. The ongoing development of GvHD-specific biomarkers (see section "Biomarkers") may aid in the diagnosis of GvHD versus alternative diagnoses.

1. Skin:

   a. Dermatology consult for skin biopsy

      i. Biopsies may be of limited usefulness as pathology frequently demonstrates nonspecific findings that are nondiagnostic [17].
      ii. Criteria for diagnosis of aGvHD include evidence of basal vacuolization, dyskeratosis of keratinocytes, and sparse superficial perivascular mononuclear cell infiltrate [18].

2. Liver:

   a. Liver ultrasound to r/o sinusoidal obstructive syndrome (SOS), cholelithiasis, and/or biliary sludge.
   b. Consider liver biopsy for tissue diagnosis, either ultrasound-guided percutaneous or transjugular if patient is thrombocytopenic.

      i. Biopsies typically show bile duct damage, bile duct lymphocytic infiltration, portal inflammation, and ductopenia [19].

3. GI:

   a. Stools to r/o *Clostridium difficile* and other enteral pathogens.
   b. GI consult for endoscopy.

      i. There is no clear correlation between endoscopic findings and aGvHD stage.
      ii. Flexible sigmoidoscopy is as effective a tool as colonoscopy in obtaining a diagnosis [20].

   c. For patients who present with diarrhea or nausea/vomiting, rectosigmoid biopsies have a higher sensitivity, specificity, and positive predictive value than upper GI biopsies [21].
   d. To make the diagnosis of aGvHD, apoptosis must be present on pathology review; however, this finding is not exclusive to aGvHD [22].

      i. A small study of GI pathology identified a combination of lamina propria eosinophil (>15/10 HPF), combined with a lack of endocrine cell aggregates and apoptotic microabscesses as indicators of mycophenolate colitis rather than gut aGvHD [23].

Staging/Grading

Standardized staging of aGvHD is critical to evaluating the extent of disease, response to therapy, and prognosis. The most widely used Glucksberg staging criteria, developed in 1974, are organ-specific and based on the percentage of BSA involved, volume of diarrhea, and/or total bilirubin (see Table 27.2). These stages are then evaluated together, in combination with performance status, to determine an overall grade of aGvHD (see Table 27.3).

There have been attempts to modify the Glucksberg system to identify a correlation of patterns of organ involvement with treatment-related morbidity and treatment failure.

1. In 1994, following a consensus conference on aGvHD grading, the Minnesota group devised a system based on the Glucksberg criteria for organ staging, modified to include upper GI symptoms [24]. Additional retrospective analyses have

Table 27.2 Glucksberg organ staging

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No rash	<2 mg/dL	<500 mL/day or persistent nausea
1	Maculopapular rash ≤25% BSA	2–3 mg/dL	>500 mL/day
2	Maculopapular rash 25–50% BSA	3.1–6 mg/dL	>1000 mL/day
3	Generalized erythroderma	6.1−15 mg/dL	>1500 mL/day
4	Generalized erythroderma + bullous formation	>15 mg/dL	Severe abd pain, +/− ileus, +/− bleeding

Table 27.3 Glucksberg overall grading

Grade	Skin	Liver	Gut	ECOG performance
I	Stage 1–2	Stage 0	Stage 0	0
II	Stage 1–3	Stage 1 and/or	Stage 1	0–1
III	Stage 2–3	Stage 2–3 and/or	Stage 2–3	2–3
VI	Stage 2–4	Stage 2–4 and/or	Stage 2–4	3–4

Table 27.4 CIBMTR severity index

	Skin		Liver		GI	
Index	Stage (max)	Extent of rash	Stage (max)	Bilirubin (μmol/L)	Stage (max)	Diarrhea (mL/d)
A	1	<25%	0	<34	0	<500
B	2	25–50% or	1–2	34–102 or	1–2	500–1500
C	3	>50% or	3	103–255 or	3	>1500
D	4	Bullae or	4	>255 or	4	Pain, ileus

resulted in the refinement of this grading system to identify high-risk GvHD patients who may benefit from more aggressive up-front treatment. A free web-based program to determine standard vs. high-risk aGvHD for a given patient using this refined risk score can be found at http://z.umn.edu/MNAcuteGVHDRiskScore [25].

2. In 1997, the Center for International Blood and Marrow Transplant Research (CIBMTR) developed a severity index (see Table 27.4), which grades aGvHD based on organ involvement alone and groups patients with similar risks of treatment-related morbidity and treatment failure [26].

3. More recently, researchers at the University of Michigan devised consensus guidelines to standardize the diagnosis and clinical staging of aGvHD in an effort to decrease discrepancy in grading GvHD between centers.

    a. Identified barriers to consistent scoring across institutions included:

        i. Frequency of obtaining tissue biopsies from symptomatic patients.

ii. Consideration and exclusion of alternative diagnoses.
iii. Lack of consensus guidelines to address variables influencing staging of GvHD.
iv. Differences in reporting the timing of onset and severity of GvHD.

b. Keeping those challenges in mind, these researchers developed and validated a web-based data entry system that is now utilized in multiple clinical trials, including the current Bone Marrow Translant Clinical Trials Network (BMT CTN) efforts [12].

i. Staging takes into account upper GI symptoms of nausea, vomiting, and/or anorexia (see Table 27.5), symptoms that are not included in other staging systems.
ii. Additionally, researchers have developed guidelines for determining confidence levels of actual GvHD based on clinical symptoms +/− biopsy results (see Tables 27.6 and 27.7). These confidence levels may help in the

Table 27.5 Mount Sinai Acute GvHD scoring

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dl	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2–3 mg/dl	Persistent nausea, vomiting, or anorexia	Adult: 500–999 mL/day or 3–4 episodes/day Child: 10–19.9 mL/kg/day or 4–6 episodes/day
2	Maculopapular rash 25–50% BSA	3.1–6 mg/dl	–	Adult: 1000–1500 mL/day or 5–7 episodes/day Child: 20 – 30 mL/kg/day or 7–10 episodes/day
3	Maculopapular rash > 50% BSA	6.1–15 mg/dl	-	Adult: >1500 mL/day or >7 episodes/day Child: > 30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation > 5% BSA	>15 mg/dl	-	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume)

Used with permission from Elsevier; from Harris et at. [12]
Overall clinical grade (based upon most severe target organ involvement)
Grade 0: No stage 1–4 of any organ
Grade I: Stage 1–2 skin without liver, upper GI or lower GI involvement
Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI
Grade III: Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI
Grade IV: Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI

Table 27.6 Confidence level criteria

Confidence level	Pathologic evidence	Clinician assessment	Treatment for acute GvHD	Comments
Confirmed	Unequivocal pathologic evidence of GvHD	GvHD is the etiology for symptoms	Not applicable	GvHD is clearly present even if other etiologies may coexist simultaneously
Probable	Not required	GvHD most likely etiology for symptoms (as evidenced by treatment being provided)	Yes	GvHD is most likely present, but other etiologies may also explain the symptoms, and there is insufficient evidence to make a confirmed diagnosis
Possible	Not required	GvHD in differential diagnosis (but no treatment is being provided)	No	GvHD may be present, but other etiologies are favored to the degree that GvHD treatment is not initiated
Negative	Unequivocal evidence of a diagnosis other than GvHD (e.g., drug rash)	GvHD is not considered as an explanation for the symptoms	No *and* the symptoms resolve without GvHD treatment	A "negative" biopsy (e.g., normal skin) is not unequivocal evidence of a diagnosis other than GvHD

From Harris et at. [12]

Table 27.7 Biopsy results and confidence levels

Pathology results	Target organ confidence level		
	Treated as GvHD	Not treated but GvHD in differential diagnosis	Not treated and GvHD not in differential diagnosis
Positive	Confirmed	Confirmed	Confirmed
Equivocal	Probable	Possible	Possible
Nondiagnostic	Probable	Possible	Negative
Non-GvHD etiology	Probable	Negative	Negative

From Harris et at. [12]
GvHD confirmed in a biopsied target organ raises the confidence level from possible to probable for other target organs where GvHD is suspected, even in the absence of treatment

selection of patients for participation in clinical trials and result in more standardized data reporting.

For patients receiving therapy on a study protocol, one should become familiar with the staging system associated with that protocol to ensure accurate and consistent measurements of aGvHD.

Biomarkers

Elafin, an epithelial host-defense protein, has been validated as a biomarker of GvHD of the skin. Elevated plasma levels of elafin or elafin expression in skin biopsy samples correlate with GvHD, helping to distinguish aGvHD rash from other etiologies [27, 28]. Regenerating islet-derived 3-alpha (REG3α) has been validated as a biomarker for GvHD of the gut, enabling the distinction of GvHD-related diarrhea from non-GvHD-related diarrhea [29]. Additional biomarkers correlating to GvHD such as ST2 [30] and TNFR1 [31] have also been identified.

Historically, the diagnosis of GvHD has relied mainly on clinical findings and often inconclusive biopsy results. These findings have been evaluated in the context of identified biomarkers in an attempt to classify patients into low-, intermediate-, and high-risk groups. This classification allows for risk stratification to better customize initial and secondary treatments, predict prognosis, and allow for more meaningful interpretation of clinical trial results due to greater homogeneity in the enrolled patient population [32–34].

Recent/Active Multicenter Trials

1. BMT CTN 0302 (closed 2008): Initial Systemic Treatment of Acute GvHD: A Phase II Randomized trial Evaluating Etanercept, Mycophenolate Mofetil (MMF), Denileukin Diftitox (Ontak), and Pentostatin in Combination with Corticosteroids in [35]

   a. Efficacy, survival, and toxicity all favored MMF.
   b. Approximately 50% of patients receiving MMF did not achieve the target drug levels; patients with drug levels >0.5 mcg/mL at weeks 1 and 2 had a significantly greater proportion of complete and partial responses at days 28 and 56, suggesting an MMF dose higher than 1 gm BID as prescribed in the trial is necessary to achieve a response.
   c. These data supported further study of MMF as the primary therapy.

2. BMT CTN 0802 (closed 2011): A Multi-center Randomized, Double Blind, Phase III TRial Evaluating Corticosteroids with Mycophenolate Mofetil vs. Corticosteroids with Placebo as Initial Systemic Treatment of Acute GvHD [36]

   a. MMF dosing was increased to 1 g q8hr based on the data from CTN 0302.
   b. Study participation was terminated at interim analysis when no difference was observed between the two groups with regard to the rates of GvHD, GvHD-free survival, OS, development of cGvHD, rate of Epstein Barr virus (EBV) reactivation, and cumulative incidence of grade 3 infections.
   c. Benefit of adding MMF to corticosteroid therapy for the new diagnosis of aGvHD was not confirmed.

3. REACH1: A Study of Ruxolitinib in Combination with Corticosteroids for the Treatment of Steroid-refractory Acute Graft-Versus-Host Disease [37]

    a. Open label, phase II, single-arm study that enrolled 71 patients with steroid-refractory aGvHD grades 2–4.
    b. Initial dosing of 5 mg po BID, increased to 10 mg po BID after 3 days in the absence of toxicity.
    c. A 28-day overall response rate (ORR) was 58% with complete responses (CR) in 26.8%.
    d. Based on these data, the United States Food and Drug Administration (FDA) has approved ruxolitinib for this indication, while waiting for the results of a phase III study in Europe comparing ruxolitinib to the best standard of care.

4. BMT CTN 1501 (closed 2018): Randomized, Phase II, Multicenter, Open Label, Study Evaluating Sirolimus and Prednisone in Patients with Refined Minnesota Standard Risk, Ann Arbor 1/2 Confirmed Acute Graft-Versus-Host Disease [38]

    a. Patients >12 years of age received a loading dose of 6 mg po once with dose adjustments to maintain a trough level of 10–14 ng/mL with decrease in target range to 5–10 ng/mL once GvHD had completely resolved.
    b. Sirolimus tapering could be done at the discretion of the treating provider but was to begin no sooner than 56 days after initiation of therapy.
    c. The primary objective was to assess the response rate at day 28 in patients with *standard-risk* GvHD defined by both clinical status and biomarker studies.

        i. Day 28 CR/PR rates for patients receiving sirolimus and prednisone were similar (64.8% vs. 73%); however, response rates were higher in patients receiving sirolimus (66.7%) compare with patients receiving low-dose (≤ 0.25 mg/kg/day) steroids (31.7%)
        ii. There were no differences in the incidence of steroid-refractory GvHD, disease-free survival (DFS), relapse, non-relapse mortality (NRM), or OS supporting that sirolimus could be considered an alternative to initiation of steroids as presentation of standard-risk aGvHD.

5. BMT CTN 1703 (currently enrolling): A Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate Versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation [39]

    a. Randomized, phase III, multicenter trial.
    b. The primary objective is to compare 1-year GvHD-free, relapse-free survival.
    c. Aim to accrue 428 patients, 214 per arm, over a period of 36 months.

6. BMT CTN 1802 (accrual suspended): An Open-Label, Single-Arm, Multicenter Study, of Combination Anti-CD3/CD7 Immunotoxin (T-Guard) for Steroid-Refractory Acute Graft-Versus-Host Disease [39]

  a. Open-label, single-arm phase III, multicenter trial.
  b. The primary objective is to assess the rate of CR at day 28 in patients with steroid-refractory aGvHD treated with T-Guard.
  c. Aim to accrue 47 patients over a period of 12 months.

Treatment for the New Diagnosis of Acute GvHD

The standard mainstay of treatment for aGvHD is corticosteroids; however, not all patients achieve durable responses to steroids alone.

1. General treatment guidelines

   a. There is no consensus on the initial corticosteroid dosing or tapering schedule [40, 41].

      i. Should patient's rash progress to >50% of BSA or patient develop aGvHD involving the gut or liver, systemic steroids should be dosed at 1–2 mg/kg/day, depending on the current and potential predicted severity of aGvHD.
      ii. For patients with stage 1 and 2 disease, there is no evidence that beginning with 1 mg/kg/day of steroid results in worse patient outcomes overall. Additionally, no benefit has been shown with steroid doses >2 mg/kg/day.
      iii. To avoid potential side effects of protracted high-dose steroids, tapering should begin after 7 days of therapy regardless of response.

         • One could consider a stepwise decrease by 0.25 mg/kg/day every 5–7 days to a dose of 1 mg/kg/day and then continue to decrease by 10% every 7 days as tolerated [41].

   b. Maximize benefit of calcineurin inhibitors (CNIs) in combination with steroids by maintaining therapeutic drug levels (CSA ~200 ng/mL, tacrolimus ~8–10 ng/mL).

   c. The most important predictor of long-term survival is response to high-dose steroids.

      i. Response at day 28 of therapy is considered to be the best predictor of the 2-year TRM.
      ii. Due to infection and organ failure, steroid-refractory disease is associated with a high rate of morbidity and mortality.

   d. Ensure adequate antifungal and antiviral prophylactics are in place (see Chap. 10 for monitoring and prophylaxis guidelines). Change to IV formulation if absorption is questionable due to diarrhea.

      i. Acyclovir 800 mg po BID or 250 mg/m^2 IV daily.

- Weekly monitoring of cytomegalovirus (CMV) by polymerase chain reaction (PCR) remains critical as aGvHD often accompanies CMV reactivation.

ii. Maximize fungal coverage:

- Posaconazole (Noxifil®) 300 mg po BID × 3 doses, then 300 mg po daily (tablet); however, therapeutic drug levels may be difficult to achieve in patients with GI aGvHD due to absorption issues. Assessment of posaconazole levels will give insight regarding GI absorption.
- Voriconazole (VFend®) loading dose of 6 mg/kg po/IV × 2 doses and then 4 mg/kg po/IV BID.
- If patient is unable to tolerate azoles due to transaminitis, consider low-dose liposomal amphotericin 1 mg/kg IV daily or 3 mg/kg IV three times weekly.

iii. Consider surveillance for Epstein-Barr virus, adenovirus, and human herpes virus 6 due to profound T-cell suppression associated with GvHD therapy.

2. Organ specific

   a. Skin

   i. Stage 1 and 2 skin GvHD can be treated with topical steroids, such as triamcinolone 0.1% or betamethasone 0.1% cream or ointment. These moderate-dose topical steroids should be used only on the trunk and extremities. Hydrocortisone 1–2.5% is safe for application to the face, neck, and groin. If possible, wrap affected areas after application to provide occlusion to increase absorption.
   ii. Emollients to prevent breakdown of dry and fissured skin areas.
   iii. Keep skin clean and dry, using gentle hypoallergenic soaps.
   iv. Antipruritic agents (diphenhydramine 12.5–50 mg po q6hr, hydroxyzine 25 mg po QID)

   b. Liver

   i. Hold medications which may contribute to hyperbilirubinemia (particularly azoles).
   ii. Consider adding ursodeoxycholic acid (ursodiol, Actigall®) 12 mg/kg/day in divided doses to increase water solubility of bile salts and protect liver cells from toxic bile acids if patient is not already receiving this medication.

   c. GI

   i. NPO or stage I GvHD diet depending on symptoms.
   ii. IV hydration. Consider TPN early depending on severity of symptoms.
   iii. Change all immune suppression to IV formulation to ensure absorption.
   iv. Supportive care with antiemetics and antidiarrheals.

    v. Consider gram-negative prophylaxis or anaerobic protection in light of compromised mucosal integrity and functional neutropenia in the setting of high-dose steroids.

- Ciprofloxacin (Cipro®) 500 mg po BID or 400 mg IV BID
- Levofloxacin (Levaquin®) 400 mg po/IV daily

    vi. Oral nonabsorbable steroids may be considered as an adjunct to systemic therapy.

- Beclomethasone (orBec®) 1 mg po QID
- Budesonide (Entocort®) 3 mg po TID or 9 mg po daily

Steroid-Refractory Disease

There is no standard definition of steroid-refractory aGvHD; however, failure of therapy has been defined as the progression of symptoms after 3 days of high-dose steroids, no improvement after 7 days of therapy, or requirement for second-line treatment at any point during or after completion of steroid taper [42]. Approximately 50% of transplant recipients will respond to therapy; 60–75% of patients will require an additional therapy. The addition of second-line therapy is associated with a 1-year survival rate of 20–30%.

There is also no consensus on the best salvage therapy for steroid-refractory disease.

Multiple agents have been utilized with varying degrees of success. However, in the last 30 years, only one agent, ruxolitinib (Jakafi®), has been approved by the FDA for the systemic treatment of steroid-refractory aGvHD [37].

The choice of second-line therapy should be based on the effects of prior treatment, potential for drug interactions, toxicity profile, and provider/patient preference. A summary of agents that have been used in research trials as well as standard of salvage agents is provided in Table 27.8.

1. Kinase inhibitors

    a. Ruxolitinib (Jakafi®) [37, 43, 44]

        i. *Mechanism of action*: Inhibits dysregulated Janus-associated kinase (JAK) 1 and JAK2 signal tranducers and activators of transcription (STATs).

        ii. *Dosing and administration*: Starting dose of 5 mg po BID; may increase to 10 mg po BID after 3 days if absolute neutrophil count (ANC) and platelet counts are not decreased by $\geq$50% of baseline. Oral administration may limit efficacy.

        iii. *Adverse effects*:

- Pancytopenia

Table 27.8 Agents for salvage therapy in steroid-refractory GvHD

Drug	Class	Dose/route	Target organ	Current FDA approval
α₁-antitrypsin	Protease inhibitor	No defined standard dosing		α₁-antitrypsin deficiency
Alemtuzumab (Campath®)	MAB	10 mg IV/day × 5 doses	Skin, liver	B-cell CLL
ATG – equine (ATGAM®)	Immune serum	No defined standard dosing	Skin, GI, liver	Aplastic anemia; prevention/ treatment of renal transplant rejection
ATG – rabbit (Thymoglobulin®)	Immune suppressant	2.5 mg/kg IV × 4–6 days or 2.5 mg/kg QOD on days 1, 3, 5, and 7	Skin, GI, liver	Renal transplant rejection
Basiliximab (Simulect®)	MAB	No defined standard dosing	Skin	Prevention/ treatment of renal transplant rejection
Beclomethasone (orBec®)	Adrenal glucocorticoid	2 mg po q6hr of both immediate release and enteric-coated capsules	GI only	Orphan drug designation
Bortezomib (Velcade®)	Proteasome inhibitor			Multiple myeloma, mantle cell lymphoma
Brentuximab vedotin (Adcetris®)	Antibody drug conjugate	Maximum tolerated dose was 0.8 mg/kg q2 weeks x 4 doses		Hodgkin, non-Hodgkin lymphoma
Budesonide (Entocort®)	Adrenal glucocorticoid	3 mg po TID or 9 mg po daily	GI only	Crohn's disease
Etanercept (Enbrel®)	TNF inhibitor	25 mg SQ twice weekly × 4–8 weeks	GI	Ankylosing spondylitis, chronic plaque psoriasis, RA, juvenile idiopathic arthritis
Extracorporeal photopheresis	n/a	n/a	Skin, liver	Cutaneous T-cell lymphoma
Fecal microbiota transplantation	n/a	To be determined	GI	n/a
Infliximab (Remicade®)	TNF inhibitor	10 mg/kg/day IV weekly × 1–4 weeks	GI	Ankylosing spondylitis, chronic plaque psoriasis, RA, Crohn's disease, ulcerative colitis
Inolimomab (Leukotac®)	MAB	11 mg/day × 3 days or 5.5 mg/day IV × 7 days, then 5.5 mg IV QOD × 5 doses	Skin, liver	Investigational; granted temporary authorization in France for treatment of GvHD

Table 27.8 (continued)

Drug	Class	Dose/route	Target organ	Current FDA approval
Itacitinib	JAK1 inhibitor	200 – 300 mg po daily		n/a
Mesenchymal stromal cells	Biologic	$1–10 \times 10^6$/kg recipient body weight, dosing schedule varies	GI, liver	Orphan drug designation for treatment of steroid-refractory aGvHD in pediatrics only
Mycophenolate mofetil (Cellcept®)	Immune suppressant	1.5–3 gm po daily in two divided doses	Skin, liver	Prevention/ treatment of rejection in cardiac, renal & liver transplant
Natalizumab (Tysabri®)	MAB	300 mg IV on days 0 and 14		Crohn's disease
Pentostatin (Nipent®)	Antimetabolite, antineoplastic	1.5 mg/m^2 on days 1–3 and 15–17	Skin, GI, liver	Hairy cell leukemia
Ruxolitinib (Jakafi®)	JAK inhibitor	5 mg po BID, increase to 10 mg po BID if tolerated		Myelofibrosis; steroid-refractory aGvHD
Sirolimus (Rapamune®)	Bacterial macrolide antibiotic	15 mg/m^2 po load on day 1, then 5 mg/m^2 po daily × 13 days or 4–5 mg/m^2 po daily × 14 days without a loading dose; adjust dose to maintain a trough level of 4–12 ng/mL.	Skin, GI, liver	Prevention/ treatment of rejection in renal transplant
Tocilizumab (Actemra®)	MAB	8 mg/kg IV every 3–4 weeks until CR, then 4 mg/kg IV every 3–4 weeks	Skin, GI	Juvenile idiopathic arthritis, polyarticular juvenile RA, moderate to severe RA
Vedolizumab (Entyvio®)	MAB	300 mg IV on day 1, then at 2 and 6 weeks, then q8 weeks	Gut	Crohn's disease; moderate to severe ulcerative colitis. Orphan drug designation for aGvHD

MAB monoclonal antibody, *CLL* chronic lymphocytic leukemia, *RA* rheumatoid arthritis, *IL-2* interleukin 2, *TNF* tumor necrosis factor, *CR* complete response

- Peripheral edema
- Rash
- Hyperlipidemia
- CMV reactivation

b. Itacitinib (research study only)

  i. *Mechanism of action*: Selectively inhibits JAK-1, thereby inhibiting the phosphorylation of STAT proteins and the production of proinflammatory factors induced by other cytokines, including interleukin-23 (IL-23) and interleukin-6 (IL-6).
  ii. *Dosing and administration*: 200 or 300 mg po daily.
  iii. *Adverse effects*: undetermined; in studies has been shown to be less myelosuppressive than ruxolitinib.

2. Antithymocyte globulin (ATG)

a. ATGAM® (equine)

  i. *Mechanism of action*: Affects cell-mediated immunity by selectively destroying lymphocytes
  ii. *Dosing and administration*:

- Despite the fact that historically, ATG is the most commonly used second-line therapy, no standard regimen has been identified. ATG preparations should not be used interchangeably as their potency differs. Dosing examples: 10–15 mg/kg IV QOD × 6–7 doses, 15 mg IV BID × 8–10 doses, 30 mg/kg IV QOD × 6 doses, 15 mg/kg IV daily × 12 doses, or 40 mg/kg IV daily × 4 days.
- A test dose is recommended prior to the first dose of ATG. Inject 0.1 mL of a 1:1000 dilution intradermally into one arm with a control of 0.1 mL NS into the contralateral arm. A systemic reaction, including rash, tachycardia, dyspnea, hypotension, or anaphylaxis, is a contraindication for administration of the drug. If a wheal and/or erythema >10 mm occurs, consider an alternative therapy.
- Premedicate for all doses (excluding test dose) with acetaminophen 650 mg po, diphenhydramine 50 mg IV, and methylprednisolone (or equivalent) 50–100 mg IV.
- Meperidine 12.5–25 mg IV q1 hr prn rigors.

  iii. *Adverse effects*:

- Sepsis
- Anaphylaxis
- Serum sickness
- Dyspnea, pulmonary edema
- Chest/back pain
- Leukopenia, thrombocytopenia

- Rash, urticaria
- Fever, rigors
- N/V/D
- Renal function abnormalities
- Extravasation may result in tissue necrosis and nerve damage

b. Thymoglobulin® (rabbit)

  i. *Mechanism of action*: Affects cell-mediated immunity by selectively destroying lymphocytes
  ii. *Dose and administration*:

  - No standardized dosing has been established: 2.5 mg/kg IV daily × 4–6 days; 2.5 mg/kg IV on days 1, 3, 5, and 7 are included within the various schedules that have been reported.
  - No test dose is required.
  - Premedicate for all doses with acetaminophen 650 mg po, diphenhydramine 50 mg IV, and methylprednisolone (or equivalent) 50–100 mg IV.
  - Meperidine 12.5–25 mg IV q1hr prn rigors.

  iii. *Adverse effects*:

  - CMV reactivation, sepsis
  - Abdominal pain, N/V/D
  - Hypertension, tachyarrhythmias
  - Fever, rigors
  - Leukopenia, thrombocytopenia
  - Myalgias
  - Dyspnea
  - Dizziness, headaches

3. Etanercept (Enbrel®) [45]

  a. *Mechanism of action*: Dimeric soluble TNF receptor that inactivates TNF-α and TNF-β
  b. *Dose and administration*: 25 mg SQ twice weekly for 4–8 weeks
  c. *Adverse effects*: *Black box warning* – Increased risk for serious infections, including bacterial sepsis and invasive fungal and other opportunistic infections

    i. Abdominal pain, N/V
    ii. Headache
    iii. Injection site reaction
    iv. Rhinitis/URI
    v. Rare complications include the following: cytopenias, aplastic anemia, Stevens-Johnson syndrome, autoimmune hepatitis, and malignant lymphoma (children > adults)

4. Extracorporeal photopheresis (ECP) [46]

   a. *Mechanism of action*: The definitive mechanism of action is not completely understood. The leading hypothesis involves induction of cellular apoptosis, which results in modulation of antigen-presenting cell activation inducing immune tolerance and increased production of Tregs.
   b. *Procedure*:

      i. Through leukopheresis, a patient's blood is removed and then centrifuged. 8-methoxypsoralen is added to the buffy coat/plasma, which is then exposed to a UVA light source prior to being returned to the patient.
      ii. ECP is administered in multiple schedules. One typical schedule is that ECP is performed on two consecutive days, every 1–4 weeks for varying lengths of time depending on patient's response.

   c. *Adverse effects:*

      i. Vasovagal syncope/hypotension
      ii. Anemia/thrombocytopenia
      iii. Bleeding secondary to procedure-related anticoagulant
      iv. Central venous catheter-associated bacterial infections/sepsis
      v. Constitutional symptoms of nausea, fever/chills, and headache

5. Mesenchymal stromal cells (MSC) [47–50]

   a. *Mechanism of action*: Not clearly defined; however, proposed mechanisms include T-cell immune suppression, polarization of macrophage and monocyte population, induction of Tregs, and secretion of soluble factors that enhance tissue repair. This therapy is currently approved by the FDA as an orphan drug for steroid-refractory aGvHD in the pediatric population only.
   b. *Dose and administration*: $1–10 \times 10^6$ MSCs per kg recipient body weight with variable dosing schedules per specific clinical trial
   c. *Adverse effects*:

      i. No infusion-related toxicities have been reported with either cryopreserved or fresh product; however, there remains the possibility for infusional toxicity-related toxicities comparable to other cryopreserved products (see Chap. 12).
      ii. No long-term adverse events have been reported.
      iii. Costs of goods and manufacturing are higher than with other biologic or pharmacologic therapies.

6. Monoclonal antibodies

   a. Alemtuzumab (Campath®) [51]

      i. *Mechanism of action*: Binds to cell surface CD52 which is present on all B- and T lymphocytes, resulting in cell lysis.
      ii. *Dose and administration*: 10 mg/day IV × 5 doses.
      iii. *Adverse effects*:

- Increased risk of infection, specifically CMV reactivation/infection, EBV, and sepsis
- EBV-associated lymphoproliferative disorder, tumor lysis syndrome, or progressive multifocal leukoencephalopathy
- Autoimmune hemolytic anemia/thrombocytopenia
- Cardiomyopathy, CHF, cardiac dysrhythmia
- Pancytopenia
- Guillain-Barre syndrome
- Toxic optic neuropathy
- Goodpasture's syndrome (rapidly progressive glomerulonephritis with pulmonary hemorrhage)
- Rash, urticaria
- N/V/D
- Bronchospasm, dyspnea

   iv. As of 9/4/12, alemtuzumab is available only through compassionate use through the Campath Distribution Program of Genzyme.

b. Basiliximab (Simulect®) [52]

   i. *Mechanism of action*: An IL-2 receptor antagonist that inhibits IL-2 binding, preventing IL-2 mediated activation of lymphocytes and impairing immune response.
   ii. *Dose and administration*: No standardized dose has yet been defined. In trials, various doses have been utilized with varied response. Additional studies are required to determine optimal dosing.
   iii. *Adverse effects*:

- Acute allergic reaction
- CMV reactivation/infection
- Candidiasis
- Dysuria
- Cough, dyspnea
- Edema
- Hypertension
- Abdominal pain, vomiting
- Dizziness, weakness

c. Infliximab (Remicade®) [53, 54]

   i. *Mechanism of action*: Binds to soluble and transmembrane forms of TNF-α, neutralizing its activity and causing cell lysis.
   ii. *Dose and administration*: 10 mg/kg/day IV weekly for 1–4 weeks.
   iii. *Adverse effects*: *Black box warning* – Increased risk for serious infections, including bacterial sepsis and invasive fungal and other opportunistic infections. Rare cases of hepatosplenic T-cell lymphoma, usually fatal, have been reported in patients with Crohn's disease and ulcerative

colitis treated with infliximab and who were concurrently receiving treatment with azathioprine or 6-mercaptopurine.

- Acute coronary syndrome
- Erythema multiforme, Stevens-Johnson syndrome
- Pancytopenia
- Demyelinating disease of the CNS
- Abdominal pain, nausea
- Headache
- Fatigue
- Rare complications include the following: hepatotoxicity, drug-induced lupus erythematosus, and immune hypersensitivity reaction

d. Inolimomab (Leukotac®) [55, 56]

i. *Mechanism of action*: A murine anti-IL-2 receptor which blocks the activation of the alpha-chain of the IL-2 receptor (CD25): this may inhibit IL-2-mediated T-cell activation.
ii. *Dose and administration*: 11 mg/day IV × 3 days, 5.5 mg/day IV × 7 days, and then 5.5 mg QOD × 5 doses per manufacturer's instructions. Alternatively, 0.3 mg/kg/day IV × 8 days and then 0.4 mg/kg 3 times per week × 3 weeks. The optimum dose and duration of therapy have yet to be determined.
iii. *Adverse effects*:

- Human antimouse antibody response occurs frequently (allergic reaction to the mouse antibodies ranging from a mild rash to acute renal failure). There is no clear evidence of decreased effectiveness of the drug.
- Rates of infection are comparable to standard immune suppression alone.

e. Tocilizumab (Actemra®) [57, 58]

i. *Mechanism of action*: humanized anti-IL-6 receptor antibody that blocks IL-6 signaling.
ii. *Dose and administration*: 8 mg/kg IV weekly every 2–4 weeks, dose reduced to 4 mg/kg IV every 3–4 weeks once a complete remission was achieved.
iii. *Adverse effects*: *Black box warning* – Increased risk for infections, including bacterial sepsis and invasive fungal and other opportunistic infections. Evaluate for latent tuberculosis and treat if necessary prior to initiation of therapy. Monitor patients for signs and symptoms of infection, including tuberculosis, even if initial latent tuberculosis test is negative.

- Cytopenias
- Hypersensitivity reaction, anaphylaxis

- URI, nasopharyngitis
- GI perforation
- Hypertension
- Transaminitis
- Dizziness, headache

f. Vedolizumab (Entyvio®) [59]

    i. *Mechanism of action*: Reduces chronically inflamed GI parenchyma by binding to $\alpha_4\beta_7$ integrin, which mediates migration of lymphocytes to the GI mucosa and associated lymphoid tissue.

    ii. *Dose and administration*: 300 mg IV on day 1; repeat dosing at 2 and 6 weeks and then every 8 weeks thereafter.

    iii. *Adverse effects*:

- Nausea
- Arthralgias
- Headache
- Nasopharyngitis

g. Natalizumab (Tysabri®) [60]

    z. *Mechanism of action*: Inhibits adhesion molecules, preventing leukocyte migration into the inflamed gut mucosa

    ii. *Dose and administration: 300 mg IV on days 0 and 14*

    iii. *Adverse effects*: *Black box warning* – Increases the risk of progressive multifocal leukoencephalopathy

- Anemia
- Hypersensitivity reaction
- Arthralgias
- Headache, depression
- Nausea, diarrhea

7. Brentuximab vedotin (Adcetris®) [61]

a. *Mechanism of action*: CD30-directed antibody-drug conjugate including the microtubule-disrupting agent monomethyl auristatin E (MMAE), which binds to tubulin, disrupting the microtubule network leading to apoptosis.

b. *Dose and administration*: Yet to be determined; however, the dose-limiting toxicity was defined at 0.8 mg/kg.

c. *Adverse effects*: *Black box warning* – Progressive multifocal leukoencephalopathy may occur in patients with JC virus receiving brentuximab.

- Pancytopenia
- Sensory neuropathy
- Cough
- Fatigue
- Stevens-Johnson syndrome

- Anaphylaxis, hypersensitivity reaction

8. Mycophenolate mofetil (Cellcept®, MMF)

   a. *Mechanism of action*: The active metabolite, mycophenolic acid, inhibits the synthesis pathway of guanosine nucleotides, resulting in selective suppression of B- and T-cell proliferation and possibly preventing the recruitment of leukocytes to sites of inflammation.
   b. *Dose and administration*: 1.5–3 gm po or IV daily in two divided doses. IV and po dosing are equivalent.
   c. *Adverse effects*:

      i.   Hypertension, peripheral edema
      ii.   Hyperlipidemia
      iii. Electrolyte abnormalities
      iv.   Increased risk of opportunistic infection
      v.   Abdominal pain, N/V/D/C
      vi.   Weakness, headache, insomnia
      vii. Increased frequency of UTIs, renal function abnormalities
      viii. Dyspnea, cough, pleural effusions, pulmonary fibrosis
      ix.   Pancytopenia
      x.   Progressive multifocal leukoencephalopathy
      xi.   Rare complications include gastric ulceration/perforation

9. Nonabsorbable corticosteroids [62, 63]

   a. Beclomethasone (orBec®)

      i.   *Mechanism of action*: A synthetic corticosteroid with potent glucocorticoid but weak mineralocorticoid activity. The mechanism of its anti-inflammatory effects has not been clearly established.
      ii. *Dose and administration*: 2 mg po q6hr of both immediate release and enteric-coated capsules.
      iii. *Adverse effects*: Minimal adverse effects reported with oral dosing. Systemic absorption is similar to oral prednisone 2.5 mg po daily and <1 mg IV dexamethasone daily.

   b. Budesonide (Entocort EC®)

      i.   *Mechanism of action*: An anti-inflammatory corticosteroid with high affinity for the glucocorticoid receptor and low systemic bioavailability due to rapid first-pass metabolism in the liver.
      ii. *Dose and administration*: 3 mg po TID or 9 mg po daily.
      iii. *Adverse effects*:

           - Nausea, diarrhea.
           - Arthralgias.
           - Headache.

- Sinusitis, respiratory tract infection.
- Cushing's syndrome.
- Rare complications include the following: immune hypersensitivity reaction, glaucoma, cataracts, and increased risk of developing basal cell/squamous cell carcinoma or malignant melanoma.

10. Pentostatin (Nipent®) [64, 65]

   a. *Mechanism of action*: A nucleoside analog that inhibits adenosine deaminase, leading to increased levels of 2′-deoxyadenosine 5′- triphosphate (dATP) resulting in lymphocyte apoptosis
   b. *Dose and administration*: 1.5 mg/m^2 IV over 15–30 minutes on days 1–3 and 15–17. Reduce dose by 50% for ANC < 1000 and/or CrCl of 30–50 mL/min, and hold for ANC < 500 and/or CrCl < 30 mL/min.
   c. *Adverse effects*:

      i. Increased risk of infection
      ii. Cytopenias
      iii. Abdominal pain, N/V/D, anorexia
      iv. Stomatitis
      v. Headache, weakness
      vi. Transaminitis
      vii. Constitutional symptoms of fever/chills, fatigue
      viii. Rash/pruritis
      ix. Hyponatremia
      x. Acute renal failure
      xi. Microangiopathic hemolytic anemia/thrombotic thrombocytopenia purpura
      xii. Immune hypersensitivity reaction

11. Sirolimus (Rapamune®) [66–68]

   a. *Mechanism of action*: Inhibits IL-2, IL-4, and IL-15 stimulated T cell activation and proliferation, as well as inhibiting antibody production.
   b. *Dose and administration*: Load with 15 mg/m^2 po on day 1 and then 5 mg/m^2 po daily × 13 days or 4–5 mg/m^2 po daily × 14 days without a loading dose; adjust dose to maintain a trough level of 4–12 ng/mL.
   c. *Adverse effects*:

      i. Hemolytic uremic syndrome, nephritic syndrome, renal insufficiency
      ii. Thrombotic thrombocytopenia purpura
      iii. Thromboembolism, deep vein thrombosis
      iv. Interstitial lung disease/pneumonia, pulmonary hemorrhage
      v. Hyperlipidemia
      vi. Hypertension
      vii. Rash

        viii. Abdominal pain, nausea, diarrhea, constipation
         ix. Pancytopenia
          x. Increased risk of urinary tract infections
         xi. Increased risk of developing basal cell/squamous cell carcinoma or malignant melanoma

12. α_1-Antitrypsin (AAT) [69]

    a. *Mechanism of action*: Decreased production of TNFα and IL-1β; lowers levels of chemokines IL-8 and monocyte chemotactic protein-1
    b. *Dose and administration*: Two dosing cohorts of 90 mg/kg IV on day 1, followed by either 30 or 60 mg/kg/day on days 3, 5, 7, 9, 11, and 13
    c. *Adverse effects*:

        i. Transient leukocytosis
        ii. Transaminitis
        iii. Hypersensitivity reactions
        iv. Musculoskeletal pain
        v. Headache
        vi. Cough

13. Bortezomib (Velcade®) [70]

    a. *Mechanism of action*: Inhibits in vitro mixed lymphocyte responses and promotes the apoptosis of alloreactive T cells
    b. *Dose and administration*: 1.3 mg/m^2 IV or SQ
    c. *Adverse effects*:

        i. Cytopenias
        ii. Dysesthesia, neuropathy
        iii. Stevens-Johnson syndrome
        iv. Posterior reversible encephalopathy syndrome
        v. Cough, dyspnea
        vi. Arthralgias

14. Fecal microbiota transplantation (FMT)
    Studies are currently underway to determine the effect of disruption of the normal gut microbiome and its effect on GvHD. Loss of intestinal diversity has been shown to increase TRM. Obligate anaerobes have been shown to mediate intestinal homeostasis by inhibiting inflammation. Two small case studies have been completed using FMT with favorable results [71, 72].

Autologous GvHD

While GvHD is typically considered to be a complication of allogeneic transplant alone, an acute GvHD-like syndrome is recognized to occur in approximately 5–20% of autologous and syngeneic HCT recipients. It is thought the incidence of

autologous/syngeneic GvHD is underreported as symptoms mimic those of regimen-related toxicity, and currently this syndrome is incorporated into engraftment syndrome (see also Chap. 14).

The pathophysiology is not well understood but is thought to be related to a failure of self-tolerance through the thymic depletion of regulatory T cells following the conditioning regimen.

Target organs include the skin, GI tract, and liver; clinical symptoms and histopathologic findings are identical to those of allogeneic GvHD. Autologous/syngeneic GvHD most commonly affects the skin, is usually milder than allogeneic GvHD, and is often self-limiting, burning out in 1–3 weeks. Some patients however may require systemic steroids, and deaths have been reported, most commonly from complications of prolonged immune suppressive therapy (see Chap. 14 for suggested treatment algorithm).

Conclusions

Only 50% of patients with acute GvHD will experience long-term responses to therapy, and the likelihood of response decreases as the severity of the disease increases. Of those patients with steroid-refractory disease, the overall long-term survival rates fall to <20%. Patients with grade IV disease typically have <5% long-term survival.

Minimal improvement has been made in the last 15 years despite multiple new agents. Most studies have been small, and patient responses have been variable. Clinical practice relies mainly on institutional bias and provider experience. The emergence of the BMT CTN with focused multicenter clinical trials targeting GvHD will guide future therapies. Treating providers are encouraged to enroll patients on clinical trials to aid in identifying superior agents and determining standard, effective second-line therapy. Future trials should be multicenter studies with clearly defined response criteria and endpoints to "standardize" responses across institutions [73].

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Chapter 28
Chronic Graft-Versus-Host Disease

Maxwell M. Krem and Gerhard C. Hildebrandt

Introduction

In the late 1970s, clinical investigators reported a wasting syndrome in long-term survivors of allo-HCT associated with a high mortality rate [1]. This syndrome was soon identified as an immunologic complication of HCT, designated as chronic graft-versus-host disease (cGvHD). Treatment with steroids and dual-agent immunosuppressive therapy (IST) improved symptoms and survival [2]. Decades of further clinical and translational research led to the 2014 National Institutes of Health (NIH) cGvHD consensus criteria, a major advance toward uniform diagnosis, severity scoring, treatment, and design of clinical studies in the posttransplant setting [3].

GvHD is an alloimmune process mimicking autoimmune phenomena and involving dysregulation of the innate and adaptive immune system. Historically, the 100-day posttransplant mark served as the boundary for distinguishing cGvHD from acute GvHD (aGvHD); currently, the clinical features associated with cGvHD establish the diagnosis as opposed to a temporal relationship. The basis of treatment remains corticosteroids and other IST. Progress in the basic biological and clinical research of cGvHD has recently led to new classes of therapeutics and increased treatment options.

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Pathophysiology (See Fig. 28.1)

1. The outcome of grafting an immune system into an environment of ubiquitous "foreign" antigens, despite IST, is activation of the complementary processes of graft-versus-leukemia (GvL, the long-term therapeutic mechanism of allo-HCT) and GvHD.
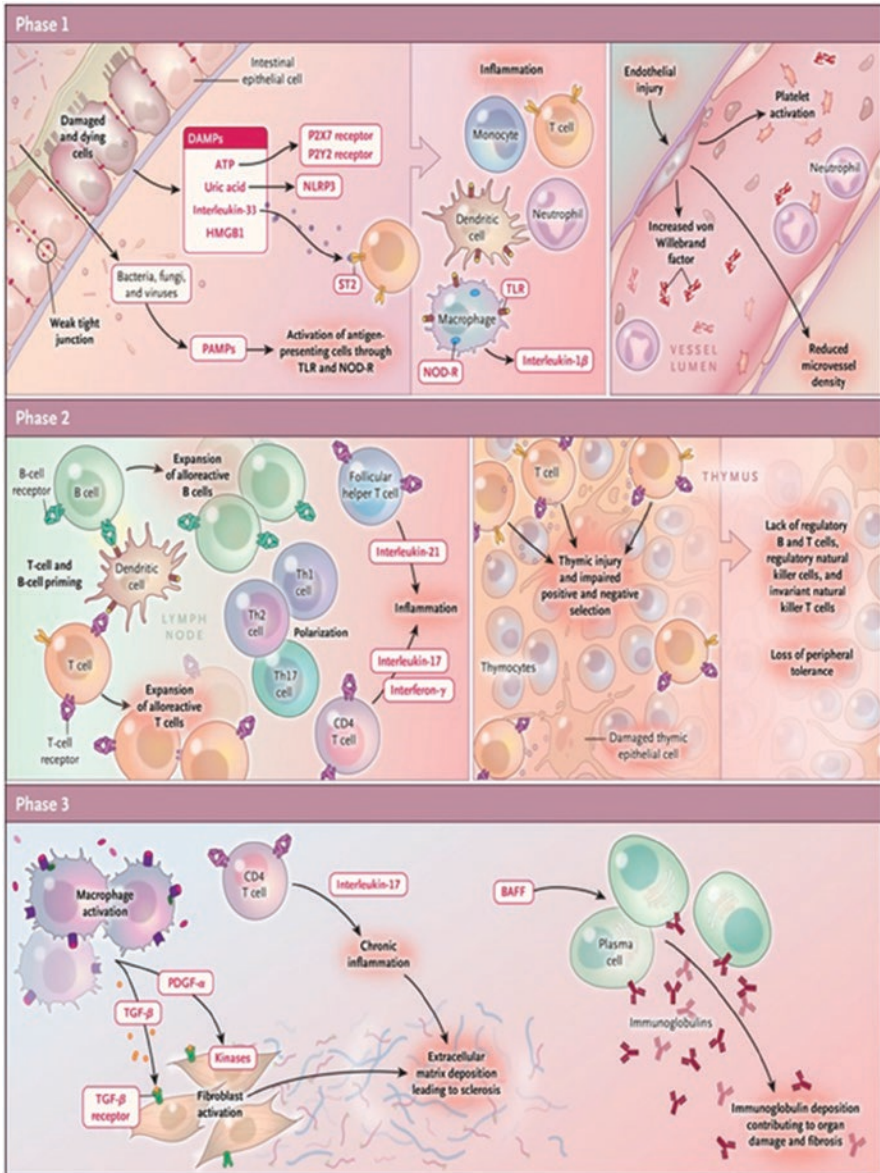
Fig. 28.1 Pathophysiology of chronic GvHD. (Zeiser and Blazar [5])

2. Mechanisms that contribute to cGvHD include [4, 5]:

   a. Host tissue damage with ensuing antigen exposure
   b. Inflammation
   c. Infection
   d. Innate and adaptive cell-mediated immunity (both T cells and B cells)
   e. Humoral immunity
   f. Fibrosis

3. Three phases of cGvHD pathogenesis are proposed [6]:

   a. Tissue injury leading to early inflammation
   b. Chronic inflammation with dysregulation of B-cell and T-cell immunity
   c. Tissue repair with fibrosis

4. The *early phase* of cGvHD involves the release of soluble inflammatory mediators, such as ATP, uric acid, IL-33, and lipopolysaccharide. This release triggers increased antigen presentation.
5. Endothelial injury also contributes to increased antigen exposure. T-helper 17 (Th17) cells are activated and released after tissue damage and have been isolated from patients with skin cGvHD.
6. Antigen presentation during the early phase of cGvHD leads to activation of immune effector donor-derived B and T cells during the *intermediate phase*.

   a. B cells produce antibodies against host tissues.
   b. Alloreactive T cells escape thymic selection.
   c. Thymic injury, increased IL-17, and increased IL-21 contribute to an environment of alloreactive effector cells that are insufficiently counterbalanced by regulatory T, B, and natural killer (NK) cells, leading to loss of immune tolerance.

7. During the *final phase* of cGvHD, activated macrophages elaborate platelet-derived growth factor (PDGF)-alpha and transforming growth factor (TGF)-beta, which in turn activate fibroblasts to deposit extramedullary matrix inappropriately, leading to sclerosis. Excess antibody production by plasma cells causes pathogenic immunoglobulin deposition, target organ damage, and fibrosis [5].

Epidemiology and Risk Factors

1. All patients who undergo allo-HCT are at risk of developing cGvHD. Estimates for the prevalence of cGvHD among allo-HCT patients range from 30% to 50%, with a median onset time of 5–6 months posttransplant [1, 5, 7].
2. A single-center retrospective review of 2941 recipients of the first allo-HCT identified risk factors for cGvHD including [7]:

   a. HLA-matched unrelated donor (MURD) as opposed to HLA-matched related donor (MRD)

    b. HLA-mismatched unrelated or related donor
    c. Female-to-male donor-recipient gender mismatch
    d. Peripheral blood stem cells as graft source
    e. Conditioning regimens not including antithymocyte globulin (ATG)

3. Additionally, prior grades 3 or 4 aGvHD and chronic myeloid leukemia (CML) as the underlying disease [5] have also been identified as risk factors for cGvHD.
4. While risk factors for developing aGvHD and cGvHD are similar, in particular, female-to-male transplant, use of peripheral blood grafts, and older patient age predispose uniquely to cGvHD as opposed to aGvHD.
5. A Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of 26,563 patients identified increasing incidence of cGvHD over a 12-year span, from 1995 to 2007. The principal reasons for this increase were more frequent use of peripheral blood stem cells, older patients undergoing transplant, and longer survivorship posttransplant [8].
6. A multicenter retrospective analysis of data from 1128 patients led to a score that predicts non-relapse mortality (NRM) and overall survival (OS) in patients with cGvHD. The following variables were included:

    a. Age at transplantation
    b. Female-to-male gender mismatch
    c. Disease status at transplantation
    d. Time to onset of cGvHD
    e. Karnofsky score
    f. Bilirubin
    g. Donor-recipient HLA match
    h. GvHD prophylaxis
    i. Prior acute GvHD
    j. Platelet count

The variables defined three risk groups: low, intermediate, and high. Five-year OS was approximately 70%, 50%, and 35% for the groups, respectively [9] (see Fig. 28.2).

Symptoms and Severity

1. cGvHD has the ability to affect most organs, with severity ranging from mild to debilitating or possibly fatal, particularly in the case of pulmonary cGvHD.
2. Manifestations specific to cGvHD include (see Table 28.1):

    a. Cutaneous sclerosis or morphea
    b. Cutaneous or oral lichen planus
    c. Esophageal strictures
    d. Bronchiolitis obliterans
    e. Fasciitis

Fig. 28.2 (**a**) Five year OS of patients with chronic GvHD by risk group. (**b**) Five year cumulative incidence of TRM of patients with chronic GvHD by risk group [9]
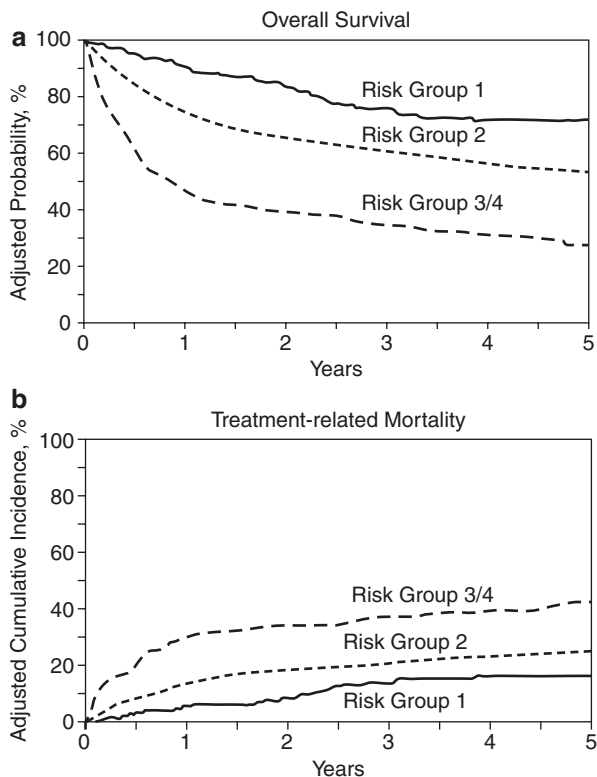
Table 28.1 Stigmata and clinical features of cGvHD

Organ or site	Diagnostic (adequate for the diagnosis of cGvHD)	Distinctive (seen in cGvHD but not aGvHD; insufficient to establish cGvHD diagnosis)	Other features (cannot be used to establish a diagnosis)	Common (seen with aGvHD and cGvHD)
Skin	Poikiloderma Lichen-type features Sclerotic features Morphea-like features Lichen sclerosis	Vitiligo	Sweat impairment Ichthyosis Keratosis pilaris Decreased pigmentation Increased pigmentation	Erythema Maculopapular rash Pruritis
Nails		Dystrophy Longitudinal ridging, splitting, brittleness Onycholysis Pterygium Destruction (usually symmetric, affects most nails)		

<div align="right">(continued)</div>

Table 28.1 (continued)

Organ or site	Diagnostic (adequate for the diagnosis of cGvHD)	Distinctive (seen in cGvHD but not aGvHD; insufficient to establish cGvHD diagnosis)	Other features (cannot be used to establish a diagnosis)	Common (seen with aGvHD and cGvHD)
Scalp and body hair		New alopecia (after recovery from chemoradiotherapy), scarring and non-scarring alopecia; scaling, papulosquamous lesions Loss of body hair, typically patchy (including eyelashes, eyebrows)	Thinning scalp hair, coarse or dull (not due to endocrine or other causes) Premature gray hair	
Mouth	Lichen-type features Hyperkeratotic plaques Sclerosis with decreased range of motion	Xerostomia Mucocele Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis Sicca Corneal ulceration	Excessive aqueous tearing Photophobia Periorbital hyperpigmentation Blepharitis	
Genitalia	Lichen-type features Vaginal strictures or stenosis	Ulcers Fissures Erosion		
GI tract	Esophageal webbing Strictures or stenosis in the upper third of the esophagus		Pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive
Liver				Total bilirubin, alk phos> 2x ULN ALT or AST > 2x ULN
Lung	Bronchiolitis obliterans diagnosis with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology		BOOP
Muscles Fascia Joints	Fasciitis Joint stiffness of contractures secondary to sclerosis	Myositis or polymyositis (proximal muscle weakness; myalgia is uncommon)	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergamma-globulinemia Autoantibodies (also AIHA, ITP)	

Table 28.1 (continued)

Organ or site	Diagnostic (adequate for the diagnosis of cGvHD)	Distinctive (seen in cGvHD but not aGvHD; insufficient to establish cGvHD diagnosis)	Other features (cannot be used to establish a diagnosis)	Common (seen with aGvHD and cGvHD)
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	
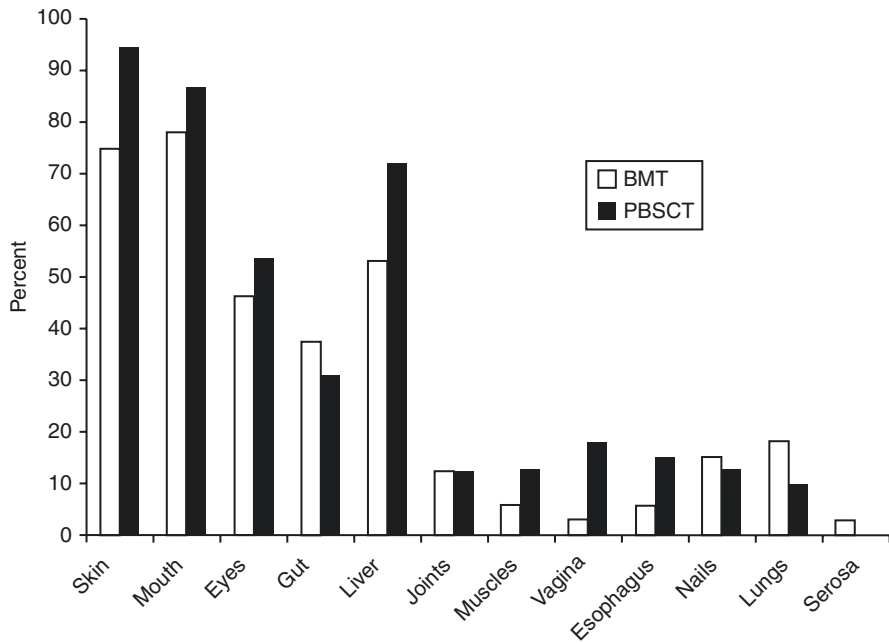
Fig. 28.3 Relative frequencies of chronic GvHD involvement by organ. (From Flowers and Martin [4])

3. The relative frequencies of involvement by organ are shown in Fig. 28.3.
4. Prior to publication of the NIH consensus criteria, the most commonly used staging scheme was the Fred Hutchinson Cancer Research Center system of limited versus extensive cGvHD.

   a. Limited involvement was defined as localized skin disease, hepatic dysfunction, or both.

b. Extensive involvement was defined as [10]:

- Limited involvement plus additional organ involvement
- Generalized skin involvement plus additional organ involvement

5. Contemporary symptom enumeration is performed concomitantly with severity scoring. This allows determination of the NIH global severity of cGvHD, measured as mild, moderate, and severe [3].
6. Organ manifestations and their individual contributions to global severity are described in Fig. 28.4, and summation of global severity is described in Table 28.2.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: [ ] **KPS ECOG LPS**	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† [ ] **SCORE % BSA** _GVHD features to be scored by BSA:_ **Check all that apply:** Maculopapular rash/erythema Lichen planus-like features Sclerotic features Papulosquamous lesions or ichthyosis Keratosis pilaris-like GVHD	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
SKIN FEATURES SCORE:	No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** Deep sclerotic features "Hidebound" (unable to pinch) Impaired mobility Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** Hyperpigmentation Hypopigmentation Poikiloderma Severe or generalized pruritus Hair involvement Nail involvement _Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
MOUTH _Lichen planus-like features present:_ **Yes** **No** _Abnormality present but explained entirely by non-GVHD documented cause (specify):_____	No symptoms	Mild symptoms **with** disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs **with** partial limitation of oral intake	Severe symptoms with disease signs on examination **with** major limitation of oral intake

Fig. 28.4 NIH organ severity score. (Jagasia et al. [3])

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* **Yes** **No** **Not examined**	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs). **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS

Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

GI Tract ***Check all that apply:*** Esophageal web/ proximal stricture or ring Dysphagia Anorexia Nausea Vomiting Diarrhea Weight loss ≥5%* Failure to thrive	No symptoms	Symptoms without significant weight loss* (<5%)	Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living

Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

LIVER	Normal total bilirubin and ALT or AP < 3 X ULN	Normal total bilirubin with AL T ≥3 to 5 x ULN or AP ≥ 3 x ULN	Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	Elevated total bilirubin > 3 mg/dL

Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

LUNGS** **Symptom score:**	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring O_2)
Lung score: % FEVI ☐	FEVI≥80%	FEVI 60-79%	FEVI 40-59%	FEVI ≤39%

Pulmonary function tests
    Not performed
Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Fig. 28.4 (continued)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7):___ Wrist/finger (1-7):___ Ankle (1-4):___	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	Contractures **WITH** significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)

Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3

GENITAL TRACT
(See Supplemental figure[‡])
    Not examined
Currently sexually active
        Yes
        No
	No signs	Mild signs[‡] and females with or without discomfort on exam	Moderate signs[‡] and may have symptoms with discomfort on exam	Severe signs[‡] with or without symptoms

Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2 severe – 3)

Ascites (serositis)___	Myasthenia Gravis___	Eosinophilia > 500/μl___
Pericardial Effusion___	Peripheral Neuropathy___	Platelets <100,000/μl___
Pleural Effusion(s)___	Polymyositis___	Others (specify):_____
Nephrotic syndrome___	Weight loss>5%* without GI symtoms___	

Ovearall GVHD Severity
(Opinion of the evaluator)   ☐ **No GVHD**   ☐ **Mild**   ☐ **Moderate**   ☐ **Severe**

Photographic Range of Motion (P-ROM)

† Skin scoring should use both percentage of BSA involved by disease signs <u>and</u> the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEVI scores whenever possible. FEVI should be used in the final lung scoring where there is discrepancy between symptoms and FEVI scores.

<u>Abbreviations:</u> ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).

‡ To be completed by specialist or trained medical providers (see Supplemental Figure).

Fig. 28.4 (continued)

Table 28.2 NIH global severity of chronic GvHD

Mild chronic GvHD
One or two organs involved with no more than score 1 *plus*
Lung score 0
Moderate chronic GvHD
Three or more organs involved with no more than score 1
Or
At least one organ (not the lung) with a score of 2
Or
Lung score 1
Severe chronic GvHD
At least one organ with a score of 3
Or
Lung score of 2 or 3

Key points
In the skin: Higher of the two scores to be used for calculating global severity
In the lung: FEV1 is used instead of clinical score for calculating global severity
If the entire abnormality in an organ is noted to be unequivocally explained by a non-GvHD documented cause, that organ is not included for calculation of the global severity
If the abnormality in an organ is attributed to multifactorial causes (GvHD plus other causes), the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score)

Posttransplant Follow-Up and Monitoring for cGvHD

1. Serial monitoring of organ systems impacted by cGvHD should be performed for the duration of a patient's life. A detailed cGvHD-focused assessment has been published [11], and a video demonstration of a patient assessment can be viewed at http://www.fredhutch.org/en/labs/clinical/projects/gvhd.html [12].
2. In addition to history and physical exam, annual evaluations should include:

   a. CBC with differential
   b. Metabolic panel with liver function tests
   c. Pulmonary function tests with adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) and residual volume (RV)
   d. Schirmer's test (considered useful for diagnosis of ocular cGvHD but not follow-up)
   e. Lipid profile
   f. Iron panel with ferritin
   g. Endocrine function tests such as thyroid function studies, testosterone, follicle-stimulating hormone, luteinizing hormone, estradiol, and/or hemoglobin A1c
   h. Bone densitometry
   i. Vitamin D as appropriate

3. For patients diagnosed with cGvHD, comprehensive evaluation should continue at 3–6-month intervals until at least 12 months after systemic therapy has ended [4].

Prophylaxis (See Also Chap. 11)

1. Prophylactic IST is essential for minimizing the risk and severity of cGvHD.
2. Standard prophylaxis includes:

   a. Calcineurin inhibitor (CNI) such as tacrolimus (Prograf®) or cyclosporine (e.g., Gengraf®, Neoral®).

   b. Antimetabolite such as methotrexate (MTX) or mycophenolate mofetil (Cellcept®, MMF).

   c. Some centers use antithymocyte globulin (ATG) as part of the preparative regimen for recipients of unrelated donor grafts or those being treated for nonmalignant hematologic disorders.

3. CNIs

   a. Tacrolimus (Prograf®).

      i. Initial IV dose is 0.03 mg/kg/day.

      ii. The IV-to-oral conversion ratio is 1:4, divided into two oral doses per day.

      iii. Therapeutic levels range from 5 to 15 ng/mL and are maintained until day +60 (patients at high risk of relapse) to day +90 posttransplant, with intent to taper off by day +180 in the absence of active GvHD, at a rate of 20–25% per month [13, 14].

   b. Cyclosporine (e.g., Gengraf®, Neoral®)

      i. Initial IV dose is 3 mg/kg/day.

      ii. The IV-to-oral conversion ratio is 1:3, divided into two oral doses per day.

      iii. Therapeutic levels range from 200 to 400 ng/mL and are maintained until day +60 (patients at high risk of relapse) to day +90 posttransplant, with intent to taper off by day +180 in the absence of active GvHD, at a rate of 20–25% per month [13, 14].

   c. Trough levels should be monitored at least weekly until dose tapering is initiated.

   d. Adjustment of taper schedules should be made for high-risk disease, relapse, or GvHD activity.

   e. Notable adverse effects include, but are not limited to, renal dysfunction, hypomagnesemia, hyperkalemia, hyperglycemia, hypertension, and neurotoxicity (altered mentation and tremors).

   Author's note: We must acknowledge that the American Society for Transplantation and Cellular Therapy (ASTCT) does not publish a specific guideline for IST tapering, and practices vary among institutions [15].

4. Antimetabolites

   a. MMF (Cellcept®, MMF)

      i. Initial dose is 1 g or 15 mg/kg, three times per day (IV and oral).

      ii. The duration of MMF exposure varies across publications and treatment protocols. It is sometimes stopped at day +30 posttransplant, whereas in some protocols it is given for longer periods, up to day +180.

b. MTX

   i.   Administered 10–15 mg/m^2 IV on days +1, 3, and 6, +/− day +11 based on regimen-related toxicities, in particular mucositis.

   ii.   Alternative dosing is "mini-MTX": 5 mg/m^2 IV on days +1, 3, 6, and 11.

c. Notable adverse effects of MMF and MTX include, but are not limited to, cytopenias, mucosal ulceration, and pulmonary fibrosis. Of note, MMF's mucosal and intestinal toxicity may mimic GvHD on histologic analysis.

5. All IST agents increase infection risk.
6. The most common GvHD prophylaxis backbone for patients receiving intensive conditioning is a calcineurin inhibitor plus MTX.

   a. Substitution of MTX with MMF has been the subject of two retrospective studies and a Cochrane Database review.

      i.   The Cochrane review, which included three trials involving 177 patients, showed no difference in overall survival (OS), GvHD, neutrophil engraftment, or relapse; the use of MMF favored faster platelet engraftment and decreased mucositis [16].

      ii.   Both retrospective studies with MMF showed faster neutrophil engraftment, faster platelet engraftment, and less mucositis in patients who received MMF.

      iii. There were conflicting results regarding cGvHD incidence, with one study showing a possible increased incidence with the MMF and cyclosporine prophylaxis regimen [17, 18]. Thus, MMF may provide similar GvHD protection but with reduced toxicity.

7. The use of ATG for GvHD prophylaxis is the subject of an ongoing debate in the allo-HCT community.

   a. The three most recent large, randomized phase 3 studies studied different populations, utilized different designs, and came to somewhat discordant conclusions.

      i.   An open-label study conducted in Canada and Australia among patients receiving myeloablative and non-myeloablative conditioning and grafts from unrelated donors utilized an end point of freedom from immunosuppressive drugs without resumption up to 1 year after transplant.

   b. Thirty-seven percent of ATG recipients compared with 16% of non-ATG recipients met the primary end point.

   c. Epstein-Barr virus reactivation was more frequent with ATG, 20% versus 2% [19].

      i.   An open-label study conducted in Europe among patients receiving myeloablative conditioning and peripheral blood stem cell grafts from HLA-matched siblings showed reduced incidence of cGvHD at 2 years, 32% versus 69%, favoring ATG. Two-year OS and relapse-free survival were not different [20].

ii. A double-blind study of myeloablative peripheral blood transplant recipients from HLA-matched unrelated donors utilized a primary end point of moderate-severe cGvHD-free survival, which was not met.
- There was a reduction in moderate-to-severe cGvHD, 12% versus 33%, favoring ATG.
- However, this outcome came at the cost of lower PFS and OS in the ATG arm [21].

d. The three studies had different designs and utilized different rabbit-based formulations of ATG, which possibly accounts for the conflicting results.

e. Meta-analyses of ATG use in allo-HCT demonstrated reductions in aGvHD and cGvHD, without changes in OS or NRM [22, 23].

8. Posttransplant high-dose cyclophosphamide (PT-Cy), administered on days 3 and 4 posttransplant, may reduce rates of cGvHD.

a. The mechanism of action is thought to be cyclophosphamide's ability to favor survival of Treg cells in the posttransplant period due to their higher expression of ALDH.

b. A retrospective study of 209 consecutive patients transplanted for a hematologic malignancy, who received HLA-matched related and unrelated allografts with PT-Cy as sole prophylaxis showed a cGvHD rate of 13% at 2 years. The 3-year OS and survival free of disease and cGvHD were 58% and 39%, respectively [24].

c. A prospective phase 2 study of 43 patients with hematologic malignancies who received myeloablative conditioning and peripheral blood HLA-matched allografts with PT-Cy and cyclosporine prophylaxis showed a 1-year incidence of NIH-defined cGvHD of 16% [25].

d. A multicenter analysis of PT-Cy GvHD prophylaxis suggests that patients experienced a lower immunosuppressive burden posttransplant, with median IST durations of 4.5–5 months [26].

e. Similarly, a European Group for Blood and Marrow Transplantation (EBMT) study of PT-Cy showed a reduced incidence of severe cGvHD in patients who received additional IST agents with their PT-Cy [27].

f. PT-Cy appears to be a promising approach, although data and regimens are still maturing.

Treatment

1. Severity assessment

a. Therapy for cGvHD is tailored to global severity assessment.

b. Patients with mild cGvHD can be managed with organ-specific topical therapies alone, with the goal of minimizing systemic IST, especially corticosteroids. Topical therapy may be most beneficial in treating cGvHD of the oral mucosa, eyes, and genital tract.

    c. Strongly consider systemic therapy in patients with moderate-to-severe cGvHD, which is involvement of three or more organs or a score ≥2 in any single organ using the 2014 NIH criteria [3].

2. Primary systemic therapy

    a. Prednisone 0.5–1 mg/kg/day for at least 1–2 weeks, but up to 30 days if needed, followed by a gradual taper over several months to 1 year.

       i. Every-other-day dosing during the taper maintains adrenal function, reduces corticosteroid toxicity, and provides immunosuppression, though in higher dose ranges is sometimes poorly tolerated by patients [4].

      ii. Steroid-based therapy has a 50% response rate (RR) as a first-line regimen [28].

     iii. Steroid-refractory disease is defined as no response or progression on prednisone dose equivalent of more than 0.5 mg/kg/day or 1 mg/kg every other day for 30 days at any time within the previous year.

    b. Tacrolimus or cyclosporine

       i. CNI prophylaxis is generally maintained or resumed in addition to corticosteroid therapy.

      ii. Target troughs are in the lower end of the therapeutic range (5–10 ng/mL for tacrolimus and 120–180 ng/mL for cyclosporine) due to the anticipated prolonged duration of therapy and the need to minimize adverse effects, especially nephrotoxicity.

3. Secondary systemic therapy

    a. Ibrutinib (Imbruvica®) is a tyrosine kinase inhibitor that targets Bruton tyrosine kinase (BTK) in B cells and interleukin-2-inducible T-cell kinase (ITK) in T cells.

       i. The United States Food and Drug Administration (FDA) approved ibrutinib for treatment of steroid-refractory cGvHD in August 2017; ibrutinib was the first drug to be approved for GvHD.

      ii. The starting dose is 420 mg by mouth daily.

     iii. A multicenter phase 2 trial demonstrated a 67% response rate (RR) and efficacy in multi-organ disease.

     iv. Adverse effects include fatigue, diarrhea, and increased bleeding risk [29], and patients should be monitored clinically for invasive aspergillosis and other fungal infections.

    b. Ruxolitinib (Jakafi®) is a Janus kinase 1/2 inhibitor that has shown efficacy in steroid-refractory cGvHD, with RR reported from 44% to 85%.

       i. The starting dose is 5 mg by mouth twice a day, with increase to 10 mg twice a day if tolerated.

      ii. Adverse effects include cytopenias, diarrhea, hyperlipidemia, and elevations in the liver enzymes [30].

    iii. At the time of publication, data from a phase 3 randomized clinical trial are pending.

    iv. The FDA approved ruxolitinib for steroid-refractory aGvHD in May 2019.

c. Extracorporeal photopheresis (ECP)

    i. While the precise mechanism of ECP against cGvHD is unknown, the procedure is thought to expand Treg populations and suppress the allo-reactive T-cell population.

    ii. ECP requires placement of apheresis-capable central venous catheter or port and is accompanied by line-associated risks of infection and thrombosis.

    iii. Therapy is usually initiated with two consecutive sessions/week, weekly for 4 weeks, then every 2 weeks for 8 weeks, followed by less frequent sessions. Six to twelve months of therapy may be required for responses.

    iv. A multicenter prospective study of 83 patients demonstrated a RR of 44% based on the NIH criteria [31].

d. Mycophenolate (Cellcept®), a reversible inhibitor of inosine monophosphate dehydrogenase, has been used for treatment of cGvHD with varying responses reported.

    i. Dosing is 750–1000 mg by mouth twice daily.

    ii. In a randomized trial comparing MMF, prednisone, and CNI therapy versus prednisone and CNI, the cGvHD resolution rate at 2 years was 23%, but the MMF arm had a twofold increase in mortality with an increased incidence of relapsed malignancy [32]. Therefore, MMF should be used with caution in patients with cGvHD.

e. Sirolimus (Rapamune®) targets the mammalian target of rapamycin (mTOR) pathway.

    i. The loading dose is 4–6 mg by mouth, followed by 1–2 mg by mouth once daily.

    ii. Target trough levels are 6–12 ng/mL.

    iii. Caution must be used if administering sirolimus in combination with a CNI due to increased risk of thrombotic microangiopathy/hemolytic uremic syndrome [33].

    iv. There are significant interactions between sirolimus and azole-class antifungals; concomitant use of posaconazole (Noxafil®) or voriconazole (VFend®) with sirolimus is generally contraindicated. If concomitant use is absolutely necessary, sirolimus dose reductions are required.

f. Rituximab (Rituxan®) depletes donor-derived B cells that may contribute to clinical cGvHD.

    i. The antibody is administered at 375 mg/m^2 intravenously for 4 consecutive weeks, with a second course administered 8 weeks later if the initial response is suboptimal.

    ii. Rituximab has a 40–70% RR with major benefit in cutaneous and musculoskeletal manifestations [34].

   g. Bortezomib (Velcade®), a proteasome inhibitor that suppresses lymphocytes and plasma cells, may have activity in cGvHD.

      i. The dosing schedule is 1.3 mg/m^2 on days 1, 8, 15, and 22 of 35-day cycles.
      ii. A small translational study of six patients suggested single-agent efficacy for refractory cGvHD, and a phase 2 study of 22 patients that combined bortezomib and prednisone suggested efficacy for the combination [35, 36].
      iii. Subcutaneous administration is recommended to minimize neuropathy.

   h. Other agents with reported responses in case series or small studies are as follows: imatinib (Gleevec®), hydroxychloroquine (Plaquenil®), thalidomide (Thalomid®), etanercept (Enbrel®), cyclophosphamide, vedolizumab (Entyvio®), infliximab (Remicade®), daclizumab (Zenapax®), basiliximab (Simulect®), and total lymphoid irradiation.

4. Pulmonary cGvHD-directed therapy

   a. cGvHD of the lung takes the form of bronchiolitis obliterans (BO) and is characterized by its chronic progressive course and generally poor treatment response. This results in irreversible airflow obstruction and high mortality.
   b. In addition to systemic IST, the contemporary treatment standard includes fluticasone (Flovent®) inhaled twice daily, azithromycin (Zithromax®) 250 mg orally three times per week, and montelukast (Singulair®) 10 mg daily (FAM), established by a multicenter phase 2 study of 36 patients [37].

      i. In this study, patients took prednisone 1 mg/kg/day for 2 weeks, followed by taper of 0.25 mg/kg/day per week as tolerated.
      ii. Laboratory evidence in murine models suggests that azithromycin may have a preventive benefit as well; putative mechanisms are Treg expansion and decreased pulmonary cytokine and chemokine expression [38].
      iii. Of note, preventive usage of azithromycin in patients after allogeneic HCT prior to onset of cGvHD has been associated with increased relapse rates of myeloid malignancies, whereas the use of FAM therapy in the context of cGvHD has not been shown to increase disease recurrence [39]. FAM does not increase risk.

5. Organ-specific and topical therapies (see Table 28.3):

   a. Skin

      i. Steroid creams/ointments
      ii. CNI creams/ointments
      iii. Massage and active range of motion (ROM) exercises
      iv. Narrowband UVB or PUVA

   b. Musculoskeletal
      i. Exercise.
      ii. Yoga or Pilates for core building.

Table 28.3 Topical agents and organ-specific treatment considerations

Cutaneous	Topical corticosteroids Topical CNI UVA/UVB	Referral to dermatology for moderate-to-severe disease is recommended Nonhealing lesions should be referred to dermatology Annual skin examination due to increased risk of cutaneous malignancy Massage and physical therapy for sclerodermoid manifestations
Ocular	Artificial tears Topical corticosteroids Topical CNI Autologous serum eye drops Topical antibiotics Scleral lenses	Referral to ophthalmology is recommended Severe cases may require corneal transplantation in cases of refractory corneal ulceration
Oral	Steroid mouthwashes Artificial saliva Sialagogues Topical steroid or CNI ointment	Referral to oral medicine is recommended Annual oral examination due to increased risk of oral malignancy Fluoride toothpaste/rinse to decrease risk of dental caries in setting of xerostomia
Pulmonary	Systemic treatment Inhaled corticosteroids Bronchodilators Azithromycin	All patients with chronic GvHD should be screened for pulmonary manifestations with PFTs regardless of symptoms Supportive care, including vaccinations, and appropriate antimicrobial prophylaxis encouraged
Liver	Ursodiol (Actigall®) 12 mg/kg/day in divided doses	All patients should be assessed for iron overload contributing to hepatic dysfunction
Gastrointestinal	Nonabsorbable steroids (i.e., beclomethasone 1 mg po QID, budesonide 9 mg po daily)	Referral to gastroenterologist should be considered
	Pancreatic enzymes	Referral to dietician with experience in managing patients with GvHD should be considered
Genital	Topical steroids, especially mucoadherent formulations Topical CNI	Referral to gynecology should be considered Consideration of hormone supplementation for those with premature menopause or signs/symptoms of hypogonadism
Infections	Prophylaxis against encapsulated bacteria, viruses (HSV/VZV), fungal infections, and PJP should be considered	Vaccinations against influenza, pneumococcus, and *Haemophilus influenzae* should be provided Monitor for CMV viremia Live virus vaccines should not be administered IVIG can be supplemented if significant hypogammaglobulinemia and recurrent infections

UVA ultraviolet A, *UVB* ultraviolet B, *CNI* calcineurin inhibitor, *GvHD* graft-versus-host disease, *PFTs* pulmonary function tests, *HSV* herpes simplex virus, *VZV* varicella zoster virus, *PJP* *Pneumocystis jirovecii* pneumonia

    iii. Stretching and active ROM exercises.
    iv. Calcium and vitamin D supplements.
    v. Bisphosphonates if indicated.
    vi. Inflammatory myopathy: Myositis or dermatomyositis may occur as a cGvHD manifestation. Unexplained fatigue or weakness should prompt evaluation, including biopsy of the skin or muscle and laboratory testing for muscle breakdown with initiation of treatment if cGvHD is confirmed [40, 41].

c. Eyes
    i. Preservative-free natural tears.
    ii. Immunosuppressive eye drops (e.g., cyclosporine [Restasis®]).
    iii. Ocular ointment (Lacri-Lube®) at bedtime.
    iv. Autologous serum eye drops.
    v. Scleral lenses [42].
    vi. Barrier glasses.
    vii. Lacrimal plugs/ablation.
    viii. Flaxseed oil/fish oil.
    ix. Severe cases may require corneal transplantation in cases of refractory corneal ulceration.

d. Oral mucosa
    i. Steroid rinses (e.g., dexamethasone 0.01%, clobetasol 0.05%)
    ii. CNI rinses
    iii. Steroid ointment with occlusion
    iv. Depot steroids injected directly into ulcerations
    v. Cholinergic sialagogues (cevimeline [Evoxac®], pilocarpine [Salagen®])

e. Liver
    i. Ursodiol (Actigall®) 12 mg/kg/day in divided doses.
    ii. Avoid toxins such as acetaminophen (Tylenol®) and alcohol.

f. GI tract
    i. Nonabsorbable steroids
      • Beclomethasone (orBec®) 1–2 mg po QID
      • Budesonide (Entocort®) 9 mg po daily in one or divided doses
    ii. Pancreatic enzymes
    iii. Restricted diet (e.g., see Appendix 7)

g. Vulvovaginal
    i. Topical hydrocortisone (e.g., high vaginal application of hydrocortisone acetate 100 mg/g mucoadherent rectal foam 1 g daily for 4–6 weeks, followed by serial reduction in dose frequency according to response).
    ii. Topical cyclosporine (e.g., cyclosporine oral solution 100 mg/ml, 1 ml in 20 ml normal saline high vaginal installation for 15 min daily for 4–6 weeks, followed by serial reduction in dose frequency according to response).

    iii.   Vaginal dilatation once to twice daily for established vaginal stenosis, and then when adequate vaginal capacity is achieved, it can continue 2x weekly. Dilatation can be achieved with commercially available dilators, intercourse, or digital examination.

    iv.   Hormone therapy, either systemic or topical.

Concurrent Supportive Therapy for cGvHD (See Also Chap. 10)

1. cGvHD patients are profoundly immunosuppressed due to incomplete immune reconstitution and IST. Ongoing infection surveillance and prophylaxis is indicated as follows:

   a. Antiviral

       i.   CMV: Regular viremia testing by PCR should be performed for patients receiving ongoing IST due to the risk of reactivation and organ infection. Viral testing should be included in all evaluations for cGvHD (e.g., endoscopy).

       ii.   Herpes simplex and varicella zoster: Patients should continue prophylaxis with acyclovir (Zovirax®) or valacyclovir (Valtrex®) until 6 months after withdrawal of IST.

       iii.   Antifungal: Prophylaxis with fluconazole (Diflucan®) or posaconazole (Noxafil®) (preferred) is indicated for patients receiving corticosteroids. In a phase 3 randomized trial of patients taking prednisone equivalent of ≥0.8 mg/kg every other day, posaconazole was superior to fluconazole for preventing aspergillosis and death from fungal infection [43].

       iv.   *Pneumocystis jiroveci*: Patients should receive prophylaxis until 6 months after withdrawal of IST. The preferred agent is trimethoprim-sulfamethoxazole (Bactrim®). For those who cannot receive sulfa drugs, consider sulfa desensitization or use of dapsone, atovaquone (Mepron®), or pentamidine (IV or inhaled).

       v.   Pneumococcus and encapsulated bacterial organisms: Patients should receive prophylaxis until 6 months after withdrawal of IST. Preferred agents include trimethoprim-sulfamethoxazole (Bactrim®), penicillin VK, or azithromycin (Zithromax®).

2. Conduct surveillance for complications of corticosteroid therapy, including but not limited to hypertension, hyperglycemia and insulin resistance, cataracts, and bone loss.

3. Debilitation and muscle loss are frequent in patients with cGvHD. To combat the negative impact of IST, especially glucocorticoid agents, patients should participate in weight-bearing exercise for 30 minutes daily at least 5 days per week. Daily stretching, physical therapy, and deep tissue massage are helpful adjunctive measures [4].

Research Areas and Potential Therapeutic Targets

1. Progress in the classification of cGvHD manifestations and estimation of prognosis is ongoing.
2. Computational analysis of 339 patients identified seven clinical patterns of cGvHD, based on the organ manifestation phenotypes and severity scores that clustered into three survival prognostic risk groups. These patients fell into high-risk clusters with the shortest median OS [44]; however, pulmonary cGvHD was not included in this matrix.

   a. Patients with severe liver involvement
   b. Moderate oral, ocular, and liver involvement, as well as mild gut involvement
   c. Diffuse erythrodermatous changes but no liver involvement

3. Development of serum biomarkers that predict outcomes has proven to be more challenging in cGvHD than in aGvHD. However, pooled plasma proteins from a training cohort of 35 cGvHD patients and 18 allo-HCT patients without cGvHD revealed that four proteins (ST2, CXCL9, MMP3, and OPN) could predict the occurrence of cGvHD within 3 months in a second verification cohort [45].
4. Several classes of agents are under study in cGvHD and are reviewed in detail elsewhere [46]:

   a. IL-1 antagonists
   b. IFN-alpha antagonists
   c. T-cell costimulation blockers
   d. Mesenchymal stromal cells
   e. Spleen tyrosine kinase (SYK) inhibitors
   f. Antifibrotics
   g. Hedgehog inhibitors
   h. Rho kinase inhibitors

Prognosis

1. Nearly all patients with moderate-to-severe cGvHD will require systemic therapy for at least 1 year.
2. In addition, 50–60% of patients require secondary treatment within 2 years of starting systemic therapy.
3. Among all patients with cGvHD, approximately 50% are cured within 7 years of starting systemic treatment, and 10% require treatment beyond 7 years.
4. Unfortunately, the remaining 40% will experience relapse of their malignancy or die during treatment of cGvHD [4, 47].

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Chapter 29
Immune Reconstitution

Sarah J. Nagle and Richard T. Maziarz

Introduction: The Human Immune System

The most important function of the immune system is to identify and eradicate foreign pathogens. It accomplishes this through recognition and non-reactivity to self and response to non-self-target antigens. To accomplish this evolutionary goal, the human immune system has two components: the innate immune system and the adaptive immune system.

1. Innate Immune System

   a. The innate immune system is the body's first line of defense and is characterized by a rapid and non-specific response to foreign pathogens. Key components include:

      i. Intact surface epithelial barriers (skin and mucosa)
      ii. Soluble proteins such as cytokines, chemokines, and defensins
      iii. The complement system
      iv. Multiple unique immune effector cell populations

   b. The effector cells of the innate immune system include natural killer (NK) cells, dendritic cells (DCs), macrophages, monocytes, and polymorphonuclear cells (PMNs).

   c. Cells of the innate immune system express toll-like receptors (TLRs).

      i. These transmembrane receptors recognize various molecules, e.g., lipopolysaccharide, glycolipids, and unmethylated CpG oligoDNA, generally shared by various classes of microbes not present on normal host cells

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[pathogen-associated molecular patterns (PAMPs)], although some host molecules also can trigger activation of the TLR (e.g., heat shock proteins, extracellular matrix molecules) [1].
ii. Upon engagement, TLRs induce the production of cytokines and other inflammatory mediators that lead to a robust and immediate inflammatory response and activation of the adaptive immune system.

2. Adaptive Immune System

a. While innate immunity represents the early and non-specific host defense, the adaptive immune system is characterized by a slower and more specific response to foreign pathogens.
b. The adaptive immune system is divided into two major general sections, including components of both humoral and cell-mediated immunity.

   i. Humoral immunity mediated by B cells and the antibodies they produce.
   ii. Cell-mediated immunity mediated primarily by T lymphocytes.
   iii. Both function through the surface expression of molecules with antigen-binding regions with unique specificity for each target antigen.

c. For B cells, the antibody can recognize antigenic epitopes directly, while T cells recognize their antigenic peptide in the context of self-major histocompatibility complex (MHC) molecules.

   i. Upon stimulation after antigen recognition, the lymphocytes undergo clonal expansion to mount a robust response and differentiate into effector cells as well as memory B and T lymphocytes.
   ii. Memory cells persist and provide immunologic memory, allowing for a more rapid and more robust proliferative secondary immune response upon re-exposure to the same antigen.

d. In humoral immunity, antibodies are secreted by the clonal B cells and plasma cells and enter the circulation where they can bind and eliminate foreign microbes present outside the cell, providing defense against extracellular pathogens.

   i. The humoral immunity system achieves these goals by selective antibody subclass complement binding to lead to direct target lysis or by opsonization, which is via the constant region of the immune globulin molecule (Fc) binding to Fc receptors expressed by cellular constituents of the reticuloendothelial system, particularly in the spleen.

e. Within the adaptive immune system, functional cell-mediated immunity is generated and provided by various T-cell subsets including CD4+ helper T cells, CD8+ cytotoxic T cells, and regulatory T cells (Treg). These cellular components are the main defense against intracellular microbial pathogens.

   i. CD4+ effector cells produce cytokines, which signal and activate B cells, macrophages, and other cells of the immune system.

ii. CD8+ CTLs have cellular machinery to kill infected host cells, by directly adhering to target cells and releasing a number of intracellular molecules, including perforins and granzymes [2–5].

Assays for Monitoring Immune Reconstitution

1. Commonly used assays for monitoring immune reconstitution are listed within Table 29.1. The most frequently utilized assay to measure recovery of immune effector cells is surface antigen expression analysis using multiparameter flow cytometry.

   a. This laboratory analytic tool allows users to:

      i. Quantify the recovery of the unique immune effector cell populations of interest
      ii. Determine the surface phenotypes present recognizing that resting cells differ in multiple surface antigen expression than activated cells
      iii. Allow detection and measurement of production of various intracellular cytokines

2. Additionally, there are diagnostic tools that can detect qualitative differences and independently measure the function of the B and T lymphocyte subpopulations.

   a. The most effective way to measure the functional status of B lymphocytes is with measurement of total immune globulin (or subsets, i.e., IgA, IgM, or IgG, or even IgG subclasses: IgG1, IgG2, IgG3, IgG4) production in primary response to antigen or after secondary challenge.
   b. A significant increase in antibody production in response to infection or vaccination serves as a reliable assessment of reconstitution of the humoral immune system.

Table 29.1 Immune reconstitution assays

Assay	Cell population	Interpretation
Flow cytometry	T cells, B cells, NK cells	Quantify IEC population
	T cells	Production of intracellular cytokines
TRECs	T cells	Thymic output
Proliferative responses to mitogens, recall antigens, viral antigens	T cells	T-cell functional recovery
Antibody response to recall antigens or vaccine	B cells	B-cell functional recovery
Spectratyping	T cells, B cells	T- and B-cell repertoire
Next-generation sequencing	T cells, B cells	T- and B-cell repertoire

TRECs T-cell receptor excision circles, *IEC* immune effector cell

   i. Challenges with unique antigens such as ǾX174 or even diphtheria/teta-
      nus toxoid (DT) have been used in the past by clinical immunology labo-
      ratories to examine B-cell recovery.
   ii. If responses to exogenous antigen were identified, these observations were
       then used as a signal for revaccination, post-HCT [6].

3. T lymphocyte function can be measured via target cell cytotoxic assays, delayed-
   type hypersensitivity assays, class I or II HLA-peptide tetramer labeling, cyto-
   kine secretion analysis, lymphoproliferation assays, and immunoscope/
   spectratyping. Through deep sequencing of the T-cell receptor, one can identify,
   quantify, and follow specific T-cell clones and measure T-cell immune repertoire
   expansion.
4. Finally, recent thymic T-cell production and antigen specific T-cell proliferation
   can be measured through the signal joint T-cell receptor excision circles (TREC)
   and the size distribution of the T-cell receptor complementary determining
   region 3 [7].

Reconstitution of the Innate Immune System

1. Physical barriers

   a. The first lines of defense to recover after HCT are the physical epithelial sur-
      face barriers (skin and mucosa). These non-hematopoietic, immune system
      components can experience damage by administration of pre-transplant che-
      motherapy and radiation and contribute to the origin of the inflammatory
      response. The integrity of the surface epithelial barriers is generally rapidly
      restored in patients, particularly in the allogeneic HCT recipients who do not
      develop graft-versus-host disease (GvHD), yet in patients with acute or
      chronic GvHD can be significantly altered and allow for increased transloca-
      tion from infectious agents across the mucosal barrier into the blood and
      lymph system [6].

2. Antigen presenting cells (APCs)

   a. APCs physiologically present non-self-antigens to T cells and can be divided
      into professional (dendritic cells, macrophages, B cells) and nonprofessional
      APCs [8, 9].

      i. Professional APCs present internalized and then processed antigens on
         their surface as small peptides embedded in MHC class II molecules to
         CD4+ T cells.
      ii. Nonprofessional APCs theoretically include all nucleated cells in the
          body, as they present endogenous peptides in MHC class I molecules to
          CD8+ T cells. Some of those cells, such as endothelial cells, epithelial
          cells, mast cells, and granulocyte, under certain conditions can also pres-

ent MHC class II on their surface, yet their capacity to elicit a rigorous T-cell response is limited.

b. APCs are tissue resident cells which during allogeneic HCT are exposed to chemotherapy or radiation conditioning. There is evidence that recipient APCs can survive conditioning longer than most other hematopoietic cells which is critical to the inflammatory response after HCT.

c. Donor monocytes are the first immune effector cell population to engraft and are followed soon thereafter, by granulocytes and NK cells.

   i. Monocytes traffic to tissues and, when established, contribute to restitution of two unique subsets of DCs:

- Type 1 DCs are myeloid DCs (CD11c+, CD123−) which can induce a Th1 response and produce proinflammatory cytokines.
- Type 2 DCs are of lymphoid origin (CD11−, CD123+), induce a Th2 response, produce anti-inflammatory cytokines, and are thought to facilitate engraftment by decreasing anti-donor cytotoxicity [6, 10–12].

d. Recipient DCs will die off secondary to the conditioning effects on their viability as well as they will be progressively eliminated by alloreactive donor T cells. DCs present the main interface between the innate and the adaptive immune system.

3. Granulocytes

a. During the pre-engraftment period, patients experience absolute neutropenia putting them at significant risk for life-threatening fungal and bacterial infections. Neutrophils then recover 2–4 weeks post-transplant depending on the stem cell source and whether exogenous cytokine exposure to G-CSF (e.g., Neupogen®) is utilized to facilitate recovery.

b. Despite the early recovery, many patients experience neutrophil dysfunction after transplant which may persist for months.

   i. After autologous HCT, neutrophils have been shown to have impaired respiratory burst and phagocytosis.

   ii. After allogeneic HCT, neutrophils have decreased respiratory burst, phagocytosis, and chemotaxis.

   iii. The causes of neutrophil dysfunction after transplant are multifactorial and may be due to the underlying hematologic malignancy, pre-transplant chemotherapy, immunosuppression (particularly moderate- to high-dose corticosteroids which induce a functional neutropenia), or GvHD [13].

4. NK cells

a. NK cells are the first lymphoid cell type to reconstitute after transplant, and given the slow recovery of the adaptive immune system, they remain the predominant lymphoid population for the first 3 months post-transplant. NK cells recover in the first 2–3 weeks after transplant, but may remain functionally abnormal for up to a year.

b. The phenotype of early NK cells post-transplant differs from NK cells in the general population. There is an increase in cells that express surface antigen phenotype of CD56^{high}CD16$^-$, an immature NK surface phenotype, of which the NK can produce IFN-γ and are less cytotoxic than those seen in the healthy individual.

c. Notably, NK cell activity after transplant remains normal even in the presence of severe GvHD. Additionally, cytomegalovirus (CMV) reactivation or infection after transplant can further augment NK cell activity [2–6, 10–12].

Reconstitution of the Adaptive Immune System

1. B Cells

    a. The recovery of the adaptive immune system is much slower than the innate immune system.

        i. B cells are undetectable or low during the first 3 months after transplant.
        ii. Different graft sources impact the rate of B-cell recovery. For example, the total B cells are 10- to 20-fold higher in peripheral blood stem cell (PBSC) grafts compared with bone marrow (BM) grafts. The mature B-cell subsets are adoptively transferred in the PBSC graft, and therefore initial numbers of B cells are higher in the recipient.

    b. The reconstitution of B cells recapitulates normal B-cell development, recognizing that both T-cell-independent and T-cell-dependent B-cell maturation occurs with the T-cell-dependent development particularly driven by CD4 T helper populations. Therefore, the initial observed B-cell surface phenotypes are most similar as those seen on B-cell precursors.

    c. Naive B cells undergo antigen-mediated activation and clonal expansion and differentiate into antibody-secreting plasma cells or memory B cells. However, given the scarcity of CD4+ T cells, patients experience impairment in antibody isotype switching and somatic hypermutation after transplant, which contributes to defective humoral immunity. Therefore, most B cells in the first 1–2 years post-transplant are naive B cells (membrane IgD^{high}, membrane IgM^{high}) that lack somatically mutated VDJ genes and produce IgM. For this reason, IgM production normalizes between 3 and 6 months post-transplant, but other immunoglobulin production takes longer.

        i. Isotype-switched memory B cells that produce IgG can be detected between 3 and 6 months post-transplant, and their ability to secrete specific IgG in response to antigen is acquired 1–2 years after transplant.
        ii. IgA is the last immunoglobulin to recover and may be undetectable for several years. This delay in recovery places patients at risk for recurrent sinopulmonary and gastrointestinal infections even years after transplant.
        iii. In general, responses to protein antigens recover in the first 1–2 years, whereas responses to polysaccharide antigens take more than 2 years

after transplant. During this time, the ability to detect carbohydrate anti-
gens on the bacterial capsules, not just the bacterial cell walls, is impaired,
resulting in decreased opsonization and destruction of encapsulated bac-
teria, such as pneumococcus, *Haemophilus*, and *Klebsiella* by the reticu-
loendothelial system (RES) and increased risk of severe and potentially
life-threatening infections [2–5].

2. T Cells

    a. T-cell reconstitution occurs in two stages: thymus-independent and
    thymus-dependent.

        i. Expansion of the thymus-independent cells occurs early from mature,
        donor-derived peripheral T cells adoptively transferred from the
        allograft [14].

- In normal individuals, T cells compete for available "immunologic
  space" through competition for homeostatic cytokines such as IL7
  and IL15.
- After transplant, IL7 and IL15 are produced in the amounts to maintain
  a complete naive and memory T-cell compartment, but there are few T
  cells so the cytokine amounts are not immediately depleted.
- Therefore, donor-derived T cells that are present will expand until they
  reach a number that is in the range of that memory pool in normal indi-
  viduals. The T cells produced in this manner are most commonly CD8+
  cytotoxic T cells with a well-recognized delay in CD4 recovery and
  expansion. As a consequence, the CD4:CD8 ratio (a normal CD4:CD8
  ratio is approximately 2:1 and remains an accepted measure of immune
  reconstitution) is reversed and may persist for years.
- Practically, measurement of CD4 count recovery is used as predictive
  of restoration of immune competence, but with no clear unity of what
  level constitutes threshold for recovery, although many clinicians use
  target levels of 200 or 300/uL. PBSC grafts have greater numbers of
  CD4+ and CD8+ T cells as compared with BM grafts and, therefore,
  initial T-cell recovery is faster in patients who receive PBSC grafts.
  Likewise, the thymus-independent pathway is absent in T-cell-
  depleted grafts.

        ii. In thymus-dependent T-cell reconstitution, T cells develop in the typical
        developmental pathway.

- Donor-derived stem cells seed the bone marrow and differentiate into
  CD4⁻CD8⁻ lymphoid progenitor cells. These cells migrate to the thy-
  mus where they undergo positive and negative selection to become
  naive CD4+ and CD8+ T cells.
- Naive T cells then encounter foreign antigen in secondary lymphoid
  tissues where they are stimulated and proliferate to form activated
  effector cells or memory cells.

- Naive CD4+ T cells start to appear at 6 months post-transplant once thymus-dependent T-cell reconstitution begins. The generation and maintenance of a diverse TCR repertoire is critical for control of infections and is restored by 6–12 months post-transplant [6, 10–12].
- Notably, compared with children, adults whose thymus has atrophied due to age are significantly impaired in their lymphocyte reconstitution following HCT [15]. Even in the normal lifespan of an individual, there is marked diminution of new thymic T-cell emigrants over age, as determined by T-cell receptor excision circle (TREC) analysis. After allogeneic HCT, this thymic dysfunction in the adult can be potentiated by the intensive conditioning regimen and particularly if GvHD is experienced by the recipient [16]. This deleterious effect on the thymus can be profound with complete absence of thymic education and generation of new T-cell emigrants, although studies suggest that this can be reversed with exposure to exogenous IL7 [17].

Factors Affecting Immune Reconstitution

1. Immune reconstitution can be affected by factors related to the stem cell graft, recipient, and post-transplant events [18].

    a. Recipient-related factors include age, thymic function, underlying disease, previous therapy, conditioning regimen, and past infectious exposure.
    b. Graft-related factors include stem cell source, degree of histocompatibility, graft manipulation, transplanted cell dose, and donor herpesvirus serologic status.
    c. Post-transplant factors that influence immune reconstitution include the development of GvHD, immunosuppressive medications, and donor lymphocyte infusion (Table 29.2).

2. Stem Cell Source and Histocompatibility

    a. HLA-matched donor transplants are associated with a better chance of successful immune recovery as compared with alternative donors [10].

Table 29.2 Factors that influence immune reconstitution

Graft	Recipient	Post-transplant
Stem cell source	Age	GvHD
Degree of histocompatibility	Thymic function	Immunosuppression
Graft manipulation	Malignancy	Donor lymphocyte infusion
Transplanted cell dose	Prior therapy	
Donor herpesvirus serologic status	Conditioning regimen	

b. PBSC grafts contain significantly more T cells than BM grafts. This numerical difference results in significantly faster early immune recovery in patients who receive PBSC allografts. These patients also have more rapid thymic recovery that results in earlier reconstitution of the adaptive immune system. However, PBSC grafts are also associated with increased rates of GvHD which has long-term implications for immune function.

c. Umbilical cord blood (UCB) HCT is associated with a longer median duration of neutropenia (30 vs. 14 days) and delayed acquired immune reconstitution when compared with BM or PBSC grafts. Notably, in this unique setting, the stem cell product is collected before any environmental exposure; thus, the T-cell repertoire is extremely immature due to limited antigen exposure. As a result, one of the greatest limitations of UCB procedures remains treatment-related mortality with associated infections, far greater than seen with BM or PBSC allografts [19].

d. Significant improvements in HLA-haploidentical HCT have occurred over the past decade, and the use of haploidentical family donors is increasing. There are varying approaches to haploidentical HCT with designs aimed to limit the intense bi-directional alloreactivity that can lead to severe GvHD, associated with the major mismatched HLA antigen recognition [20]. The degree and rate of recovery of immune reconstitution is related to the technique employed.

  i. T-cell depletion with mega-dose infusion of donor CD34+ cells has been performed with the greatest depletion of donor T cells. As a result, patients experience slow immune reconstitution with some reports of infectious mortality approaching 40%.

  ii. An alternative approach is the use of post-transplant cyclophosphamide which is able to deplete in vivo the alloreactive, rapidly proliferating, high affinity T cells. This approach substantially decreases infectious mortality. When compared with a HLA-matched sibling HCT, haploidentical HCT with post-transplant cyclophosphamide is associated with lower T-cell (particularly naive T cells) and DC counts in the first 90 days after transplant, which contributes to the observed increased rate of CMV reactivation. Conversely, B-cell and monocyte reconstitution is unchanged.

3. Donor and Recipient Characteristics

  a. The age of the donor and recipient can both affect outcome [21].

    i. Donor age >35 years is associated with delayed engraftment and immune reconstitution.

    ii. Increasing recipient age is associated with delayed immune reconstitution, particularly of CD4+ T cells due to thymic evolution with aging [15, 16].

  b. CMV-positive recipients are at risk for CMV reactivation. CMV reactivation causes the expansion of CMV-specific CD8+ T effector cells and delays reconstitution of a more diverse T-cell repertoire [22].

4. Graft Manipulation and Cell Dose

    a. The dose of hematopoietic stem cells infused affects the rate of recovery. Exact numbers depend on the stem cell source, but in general, immune reconstitution is faster with higher transplanted doses of CD34+, NK, and T cells in the graft [10].

    b. T-cell depletion is used in an attempt to decrease the rates of GvHD. However, the removal of T cells from the product leads to significant delay in immune reconstitution. The early thymus-independent T-cell expansion cannot occur which results in fewer memory and naive T cells and a more limited T-cell repertoire. Ultimately, patients have increased risk of morbidity and mortality from infection [10].

Patterns of Immune Reconstitution

1. Autologous HCT

    a. The innate immune system recovers early post-transplant, with NK cells recovering in normal number and function as early as 14 days post-transplant. In G-CSF-mobilized peripheral blood stem cell transplant, lymphocytes and mononuclear cells are contained in the graft. These may contribute to the rapid immune recovery.

    b. The numbers of circulating mature B cells are low for 3 months after transplant and then gradually increase. However, they can remain low for up to 18 months post-HCT due to decreased T-cell help and intrinsic B-cell defects.

    c. The production of immunoglobulins at normal levels is as follows:

        i. IgM at 6 months
        ii. IgG at 12–18 months
        iii. IgA by 36 months

    d. B-cell function is also abnormal after transplant. In vitro B-cell responses to a polyclonal stimulator and in vivo antibody responses are diminished for months to years.

    e. The number of CD3+ cells remains significantly decreased for 3–5 months post-HCT.

    f. Patients have persistently low levels of CD4+ cells lasting 1 year or longer.

    g. CD8+ T cells recover between 3 and 18 months; they return earlier than CD4+ cells resulting in an inverted CD4:CD8 ratio that can last years after the transplant.

    h. T-cell functions including proliferation, cytokine production, response to exogenous IL-2, and cytotoxic activity remain depressed for up to 5 years post-transplant.

     i. Autologous HCT is not generally associated with GvHD and its associated immunosuppression, and therefore the recovery of the immune system is not anticipated to be impaired by either of these factors.

     j. Additionally, autologous HCT is not considered to have a graft-versus-tumor benefit because of pre-existing, endogenous T-cell tolerance to the tumor antigen. However, changes during immune recovery may unmask endogenous antitumor activity that was previously ineffective, therefore resulting in antitumor beneficial effects [23].

     k. Of historical interest, multiple studies in the past attempted to generate an autologous GvHD syndrome in subjects undergoing autologous HCT by co-administration of cyclosporine A to disrupt normal immune recovery [24].

2. Allogeneic HCT

    a. Immune reconstitution in allogeneic HCT recipients differs based on stem cell source, immunosuppression, and presence of GvHD. Despite this, recovery of the innate and adaptive immune systems tends to occur in a predictable manner.

       i. Post-transplant, neutrophil count normalizes within weeks, and neutrophil function recovers several months later.

      ii. NK cells return to normal numbers relatively early. However, particularly after haploidentical HCT, NK cells have an immature phenotype, and their cytotoxic activities are reduced.

    b. Full recovery of the adaptive immune system takes years.

       i. Absolute T-cell counts gradually recover over the first year to nearly normal by 9 months post-transplant.

      ii. Before the production of naive T cells in the thymus starts, cytokines and alloreactive antigens drive the peripheral expansion of memory T cells.

     iii. CD4+ T cells rely more heavily on thymic production of naive T cells and therefore recover more slowly than CD8+ T cells resulting in a delay in CD4 recovery and a reversed CD4:CD8 ratio that may last years.

    c. Absolute B-cell counts are decreased during the first 100 days, but thereafter start to recover to normal numbers; yet full B-cell reconstitution may take years. Patients remain vulnerable to bacterial infections for a prolonged time period due to lack of memory B cells, decreased levels of circulating immunoglobulins, impaired immunoglobulin class switching, and loss of complexity in immunoglobulin gene rearrangement patterns.

    d. Serum IgM levels normalize by 3–6 months, IgG by 9–12 months, and IgA by 2–3 years post-transplant [25].

3. Umbilical Cord Blood HCT

    a. UCB HCT is associated with delayed engraftment, poor immune reconstitution, and increased risk of infection. Delayed immune reconstitution is likely multifactorial and due to:

      i. A lower cell dose as compared with bone marrow or peripheral blood stem cell grafts

      ii. A predominance of naive T cells in UCB grafts

      iii. Frequent HLA disparity

b. There are no major differences in the recovery of innate immune effector cells including PMNs, NK cells, and DCs which all recover within weeks post-transplant.

c. B cells start to recover around 3 months and reach normal numbers by 6 months. However, functionally the B cells can be abnormal with decreased capability to produce immunoglobulin upon stimulation and increased susceptibility to apoptosis.

d. T-cell reconstitution is much slower in patients who undergo UCB HCT as compared with peripheral blood or bone marrow HCT. While PBSC and BM grafts contain memory T cells that will expand in response to antigen, UBC grafts contain antigen-inexperienced naive T cells, given the immune sanctuary status of development within the placenta. During the first 6 months post-UCB HCT, the adoptively transferred T naive T cells undergo proliferation, immunophenotype changes, and gradual loss of the original naive phenotype. However, functionally, these UCB-derived T cells are significantly impaired for the first 6 months post-transplant. Additionally, there is impaired thymopoiesis in adults who undergo UCB HCT which further delays T-cell reconstitution [26].

Immune Enhancement Therapy

1. Multiple strategies have been attempted to enhance immune reconstitution after HCT. Many of these strategies have been studied in preclinical settings, but some approaches have progressed to clinical trials. The thymus is clearly vital for T-cell recovery, and therefore many strategies have focused on thymic manipulation. However, given the extensive cross-talk between the thymic stromal compartment and developing hematopoietic stem cells, it is likely that a combination of strategies that target different pathways could offer more success than individual therapies alone.

2. Exogenous administration of cytokines in model systems has shown the ability to regenerate lymphopoiesis.

a. IL-7 is a pro-lymphocytic cytokine that acts directly on T-cell precursors to enhance T-cell proliferation, T-cell expansion, and TCR diversity. In a phase I trial of recombinant IL-7 in adults undergoing T-cell-depleted allogeneic HCT, patients experienced improved T-cell recovery and TCR diversity without significant toxicity [27].

b. IL-22 is a mediator of thymic regeneration. Administration of recombinant IL-22 improves thymopoiesis after damage and can promote thymic regeneration despite GvHD [28].

c. Other cytokines under investigation include IL-2, IL-12, IL-15, and Flt3L.

3. Hormones and growth factors offer an alternative method to enhance immune reconstitution following HCT.

   a. Keratinocyte growth factor (KGF) enhances thymic regeneration in acute thymic atrophy [17]. However, when administered post-HCT in a phase I/II study, it did not promote early T-cell recovery.
   b. Growth hormone (GH) receptor is expressed on thymocytes and thymic epithelial cells. GH modulates intrathymic hormone secretion as well as T-cell import, migration adhesion to stromal cells, and export. GH is therefore an attractive method to enhance immune reconstitution.
   c. Additional hormones and growth factors that are being investigated include IGF-1 and BMP4 [29].

4. Sex steroids have been implicated in the degeneration of thymopoiesis, B lymphopoiesis, and early lymphoid precursors [17]. Therefore, sex steroid ablation (SSA) via castration or pharmacological methods has been investigated to improve immune reconstitution after HCT. In preliminary studies, SSA has been shown to increase thymic cellularity and weight as well as alleviate irradiation-induced atrophy of the thymus.

5. Cellular therapies offer a novel approach to augmenting immune reconstitution after HCT.

   a. The ex vivo system for generating T cells using Notch-1 stimulation has allowed the development of large numbers of T lineage precursors that could be used for adoptive therapy.
   b. The adoptive transfer of T lineage precursors into allogeneic HCT recipients enhances peripheral T-cell reconstitution.
   c. In vitro generated pre-T cells can also be genetically engineered for tumor specificity and used for targeted tumor immunotherapy [30].
   d. Additionally, given the deterioration of the thymus with age, there have been attempts to build a new thymus using endogenous thymic epithelial progenitor cells on which one can assist T-cell reconstitution [28].

Clinical Evaluation for Immune Reconstitution

1. A robust and ordered immune reconstitution after autologous or allogeneic HCT is associated with better clinical outcomes with less risk of relapse and/or non-relapse mortality of the recipient. However, practical aspects of immune reconstitution analysis remain a consideration and management of the HCT recipient.
2. A simple measure of immune reconstitution, which was associated with improved overall survival of the transplant recipient, was the early recovery of the absolute lymphocyte count. Clearly, extensive detailed analysis of the transplant recipient's immune system can also be performed, recognizing that the more detailed analyses can be costly.

3. Hospital immunology laboratories offer multiple analytic panels to assess the qualitative defects in immune function, and these extremely detailed studies have been very effective at analyzing newborn immune deficiency. Current emerging technology offers even greater analytic opportunities for deeper investigations into effector populations with cytokine profiling, RNA sequencing (RNAseq), and multicolor cytometry by time-of-flight (CYTOF) technologies allowing further dissection of the immune repertoire.

4. What remains unclear are the central and necessary elements that will prove to be most predictive of improved overall survival.

   a. The Center for International Blood and Marrow Transplant Research (CIBMTR) Infection and Immune Reconstitution Working committee recently launched a study, CIBMTR IN19-01, with the goal of assessing transplant outcomes of both adult and pediatric patients to undergo allogeneic HCT based on immune recovery.

      i. What is most notable are the minimal elements being assessed: immunoglobulin subset recovery as well as CD4, CD8, CD19/20, and CD56 populations, when compared to more complex immune recovery flow cytometric panels which investigate T-cell subpopulations, NK subpopulations, surface activation markers, presence or absence of checkpoint inhibition molecules, as well as naive vs. memory subsets.

      ii. Data obtained provide in-depth insights from which investigators can glean important information for determining immune monitoring essentials for future patients and improving patient outcomes.

5. Currently, in the absence of validated, prospectively collected data on immune reconstitution, it often remains difficult to obtain reimbursement for these immune reconstitution studies as they still are considered investigational in the absence of linkage to improvements in patient outcome.

Conclusion

Prompt immune reconstitution remains a challenge following HCT. The innate immune system recovers early, but the adaptive immune system can take years to return to normal numbers and function. The full recovery of the immune system may be affected by GvHD and its associated immunosuppression. Methods to enhance immune reconstitution following HCT remain an area of active investigation. Ultimately, the goal is rapid recovery of the immune system in the recipient to decrease risk for infections and improve outcomes following HCT.

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Chapter 30
Infectious Complications

Lynne Strasfeld and Marcie Riches

Introduction

Infections remain a cause of significant morbidity and mortality following hematopoietic cell transplantation (HCT) and are reported to be the primary cause of death in 7% of autologous and up to 21% of allogeneic transplant recipients [6]. The conditioning regimen (chemotherapy, radiation therapy), mucosal damage, type of transplant, immune suppressive therapy, and graft-versus-host disease (GvHD) all predispose the HCT recipient to infection. Abnormal B- and T lymphocyte function results in impaired humoral and cellular immunity, respectively. Humoral defects can predispose to infection with pyogenic organisms and other bacteria as well as viral infections. Neutrophil function is impaired by the use of corticosteroids and other medications. Hypogammaglobulinemia and functional asplenia are common. The occurrence of infections in an individual patient varies according to the phase of the transplant process and reflect the type(s) of immune defect(s), underlying disease, endogenous host flora, exposure history, and pretransplant infections (see Fig. 30.1).

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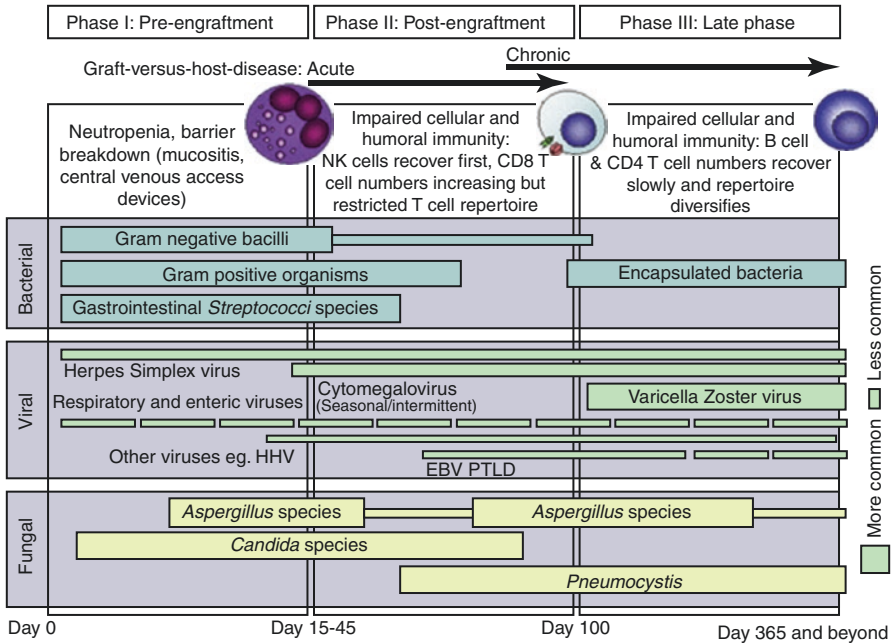
Fig. 30.1 Phases of opportunistic infections among allogeneic HCT recipients. Abbreviations: *EBV* Epstein-Barr virus, *HHV6* human herpesvirus 6, *PTLD* posttransplant lymphoproliferative disease [34]. (© Granted by Elsevier)

Empiric Antimicrobial Therapy and Evaluation of Neutropenic Fever [33]

1. For the first neutropenic fever (T ≥38°C):

   a. Comprehensive fever workup includes the following, with additional testing as prompted by localizing signs/symptoms:

      i. Blood cultures drawn from the central venous catheter and ideally from at least one peripheral site

      ii. Chest X-ray (CXR)

      iii. Urine analysis and urine cultures per institutional practice or if symptoms present

      iv. Sputum culture, if productive cough is present

   b. Discontinue prophylactic antibiotic and begin empiric parenteral antibiotic therapy as soon as possible and always *within 1 hour* of the initial fever.

      i. Empiric antibiotic therapy should be sufficiently broad, providing coverage of *Pseudomonas aeruginosa*, Enterobacteriaceae, and oral streptococci.

     ii. Options include cefepime, piperacillin/tazobactam (Zosyn®), or an antipseudomonal carbapenem (e.g., meropenem [Merrem®] or imipenem [Primaxin®]) [9].

    iii. Consideration of the local institutional antibiogram as well as any patient-specific history of prior drug-resistant bacteria is critically important in determining empiric antibiotic selection.

    iv. For septic/clinically unstable patients, consider broadening empiric regimen to include extended gram-positive coverage (see below, "Indications for the use of empiric extended gram-positive coverage for neutropenic fever") as well as an aminoglycoside (once-daily dosing is preferred).

c. For subsequent fevers

    i. Frequent (at least daily), thorough clinical evaluation for signs or symptoms of new or emergent infection is imperative.

    ii. For T ≥38°C, obtain blood cultures.

       a. Every 24–72 hours if clinically stable; or
       b. If clinical worsening; or
       c. Prior to change in empiric antibiotic therapy

    iii. After initial defervescence, recrudescent fever should be reevaluated with blood cultures and careful clinical assessment.

d. Adjustment of empiric antibiotic regimen for neutropenic fever

    i. Tailor antibiotic regimen based upon identified pathogens and susceptibility data.

    ii. Discontinue empiric antibiotic therapy once ANC ≥500 cells/mm^3, provided patient remains afebrile and there is no documented infection.

    iii. Currently, there are limited data to support de-escalation of empiric antimicrobial therapy for neutropenic HCT recipients who have defervesced, have negative cultures, and have no signs and symptoms of infection. De-escalation is an evolving area of investigation [6].

2. Indications for the use of empiric extended gram-positive coverage for neutropenic fever:

a. Add vancomycin for any patient with:

    i. Sepsis/unstable clinical condition, particularly for those patients with an established history of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization or infection

    ii. Documented infection with a gram-positive organism while awaiting results of identification and susceptibility testing (e.g., gram-positive cocci in clusters or pairs/chains for patient *not* previously known to be colonized/infected with vancomycin-resistant enterococcus (VRE))

    iii. Skin/soft tissue infection

    iv. Suspected/documented catheter-related infection, pending culture data

    v. Healthcare-associated pneumonia, while awaiting data from respiratory samples

b. For patients known to be colonized/infected with VRE, use daptomycin*
for extended gram-positive coverage in the setting of sepsis and/or gram-positive bacteremia (gram-positive cocci in pairs and/or chains) while awaiting results of identification and susceptibility testing. Given the potential for myelosuppression with extended linezolid use, daptomycin is the preferred agent in this setting.

  *Note, daptomycin should *not* be used for treatment of pneumonia due to lack of efficacy for this indication. In the setting of possible/proven MRSA pneumonia, consider the use of vancomycin or linezolid.

c. Blood cultures, as well as wound and sputum cultures when applicable, should be obtained prior to adding vancomycin, daptomycin or linezolid.

d. Irrespective of persistent fevers, discontinue vancomycin, daptomycin, or linezolid after 72 hours if no gram-positive organisms have been cultured and there are no other indications as noted above.

3. Criteria necessitating removal of central venous catheters include [21]:

  a. Clinical criteria:

    i. Septic patient with suspected line source

    ii. Tunnel tract infection

    iii. Persistent bacteremia with positive blood cultures after 48 hours of appropriate antibiotic therapy

  b. Microbiologic criteria:

    i. *Staphylococcus aureus*

    ii. *Pseudomonas aeruginosa*

    iii. *Candida* species

    iv. Multidrug resistant gram-negative bacteria

    v. Mycobacterial species

4. Management of persistent neutropenic fevers (>72 hours after initiation of empiric antibacterial therapy):

  a. Frequent (at least daily), thorough clinical evaluation for signs or symptoms of new or emergent infection

  b. Strong consideration for CT chest to evaluate for opportunistic pulmonary infection

  c. Broaden empirical antifungal coverage:

    i. For patients who are receiving fluconazole prophylaxis, change to voriconazole (see Chap. 10 for dosing guidelines) or to an echinocandin (e.g., micafungin 100 mg IV q24 hours; caspofungin 70 mg IV × 1, then 50 mg

IV q24 hours; or anidulafungin 200 mg IV × 1, then 100 mg IV q24 hours) if azole-resistant candidiasis is suspected/documented.

   ii. Posaconazole is an acceptable alternative to voriconazole, for patients who have voriconazole-specific intolerance.

  iii. If the use of an extended-spectrum azole is contraindicated (e.g., liver enzyme abnormalities, drug-drug interactions), alternatives include:

- Lipid-based amphotericin product (3–5 mg/kg IV q24 hours)
- Echinocandin, though recognizing the inferiority of these agents for prophylaxis/treatment of mold infections

  iv. For patients already on voriconazole or posaconazole (prophylaxis or empirical therapy), check antifungal trough drug level (see Table 10.4) to ensure adequate dosing.

   v. If CT chest is concerning for invasive fungal infection, consider the role for diagnostic evaluation (e.g., bronchoscopy with BAL or lung biopsy) and consult with infectious diseases service for input regarding best empiric antifungal therapy.

Treatment of Common Specific Infections

Of paramount importance in the treatment of infections in the HCT recipient is the ability to obtain an accurate diagnosis. Symptoms of infection may be nonspecific or even attenuated in the heavily immune suppressed HCT recipient. Diagnosis of infection may require culture of blood or other body fluid, molecular diagnostic testing (e.g., polymerase chain reaction [PCR]), radiographic study, or invasive diagnostics to obtain tissue or other material. It is imperative to consider the possibility of drug-drug interaction(s) and/or organ toxicity when considering the initiation of a new antimicrobial(s). Optimization of the immunosuppressive regimen should be considered in the setting of severe or life-threatening infection, with careful consideration of risks and benefits. Furthermore, once treatment for established infection has begun, monitoring for clinical response as well as antimicrobial-related side effect or toxicity is critical.

1. Herpes zoster (VZV) infection

  a. Acyclovir (or related congener) prophylaxis decreases occurrence.

  b. Dermatomal localization or dissemination may occur (see Fig. 30.2). A thorough skin examination is recommended to evaluate for disseminated disease.

  c. Visceral and/or CNS disease should be considered in patients with appropriate clinical findings.

  d. Oral antiviral therapy (7- to 10-day course) is a reasonable approach for dermatomal zoster. Valacyclovir (Valtrex®) and famciclovir (Famvir®) achieve better therapeutic plasma levels than oral acyclovir (Zovirax®) against VZV and require less frequent dosing. Valacyclovir (1000 mg po TID, renal
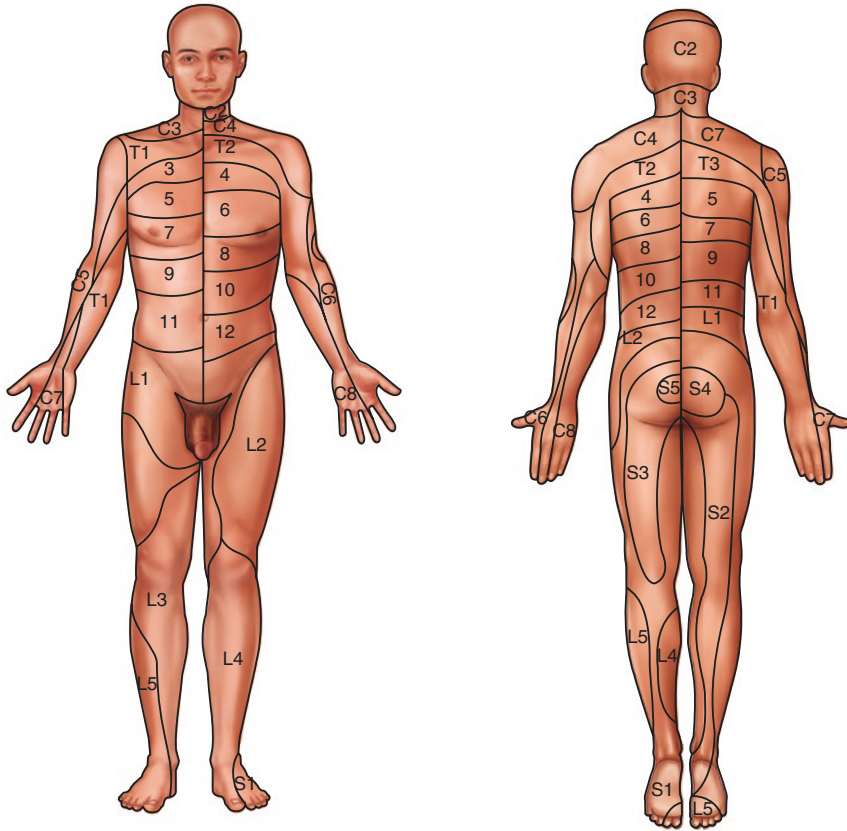
Fig. 30.2 Dermatome map for the determination of the extent of herpes zoster infections

dose adjustment as indicated) or famciclovir (500 mg po TID, renal dose adjustment as indicated) may be used as an alternative to oral acyclovir (800 mg five times daily, renal dose adjustment as indicated).

e. For severe herpes zoster infections (>1 dermatome, trigeminal nerve involvement, visceral or disseminated disease), patients should be hospitalized and treated with intravenous acyclovir (10 mg/kg IV every 8 hours, renal dose adjustment as indicated) until lesions have crusted and no new lesions are evident and then transitioned to an oral compound to complete the treatment course. Monitor for acute kidney injury and encephalopathy as possible adverse effects of high-dose IV acyclovir.

f. Acyclovir-resistant VZV occurs infrequently; if suspected, a viral culture should be obtained for phenotypic resistance testing and consult infectious disease. Consider treatment with foscarnet (Foscavir®; 40 mg/kg IV every 8 hours, renal dose adjustment as indicated) if resistance is documented or in the context of life-threatening infection while awaiting results of resistance testing.

2. Herpes simplex virus (HSV) infection

   a. Infection is largely related to reactivation in the posttransplant setting, and absent prophylaxis occurs early (within the first month post-transplant).
   b. Acyclovir (or a related congener) prophylaxis decreases risk for infection.
   c. HSV-1 infections most often present as severe mucositis, occasionally as esophagitis, and less often as with secondary infection of various organs in the context of viremia. HSV-2 infections are less common and typically affect the genital/perineal/buttocks region.
   d. For non-severe infection limited to the mucous membranes, oral antiviral therapy is usually adequate: acyclovir 400 mg po 5 times daily for 7 days, valacyclovir 1000 mg po BID, or famciclovir 500 mg po TID (renal dose adjustment as indicated). If unable to tolerate oral medications, then use acyclovir 5 mg/kg IV every 8 hours (renal dose adjustment as indicated) for 7 days or until able to tolerate oral therapy.
   e. In the case of suspected/proven visceral dissemination (e.g., encephalitis, hepatitis, pneumonitis), acyclovir 10 mg/kg IV every 8 hours (renal dose adjustment as indicated) should be used as initial therapy for 14–21 days, depending on clinical syndrome and course.
   f. Select patients with frequently recurring outbreaks may require chronic suppression. Any of the following regimens is acceptable: acyclovir 400–800 mg po BID–TID or valacyclovir 500 mg po BID (renal dose adjustment as indicated).

3. Human herpes virus type 6 (HHV-6) infection

   a. Infection is nearly universally related to reactivation and occurs in 30–50% of allogeneic recipients in the early post-HCT period (2–4 weeks).
   b. Viremia is often asymptomatic. A causal association with encephalitis is supported by a number of case reports and case series. Patients who received T-cell depleted cord blood or haplo-identical stem cell products or who have been exposed to ATG are at higher risk for HHV-6 encephalitis [1, 25].
   c. When encephalitis is suspected, HHV-6 PCR testing (CSF, blood) should be performed; MRI of the brain may reveal abnormalities, often involving the medial temporal lobes.
   d. Treatment is controversial, but for established encephalitis, foscarnet or ganciclovir (Cytovene®) should be used in therapeutic doses. Treatment decisions should be made on a case-by-case basis in consultation with the infectious diseases service [13].

4. Cytomegalovirus (CMV) infection (DNAemia [viremia] and/or organ disease)

   a. CMV infection is most often due to reactivation of latent virus, and risks of reactivation are dependent upon donor and recipient CMV serostatus. CMV monitoring and preemptive therapy for isolated viremia is covered in Chap. 10.
   b. CMV can lead to end-organ disease in the HCT recipient, manifesting as pneumonia, colitis, gastroenteritis, hepatitis, retinitis, encephalitis, etc. [14].

    c. While detection of CMV by PCR in blood in the context of clinical signs/symptoms consistent with CMV end-organ disease is suggestive, PCR is not fully sensitive for detection of end-organ disease, particularly gastrointestinal disease. If CMV disease is suspected, procedures to obtain diagnostic certainty (i.e., bronchoscopy and/or tissue biopsy for histopathology and viral culture and/or PCR) should be obtained when feasible.

    d. For suspected/proven end-organ disease, consultation with the infectious diseases service for patient-specific treatment recommendations is advised.

    e. First-line therapy for CMV end-organ disease is generally IV ganciclovir, with switch to oral valganciclovir (Valcyte®) for continuation therapy after stabilization and presuming there are no barriers to enteral absorption.

    f. Ganciclovir-resistant virus is an unusual occurrence in the HCT population and most often occurs in patients who have had prolonged exposure to ganciclovir or valganciclovir. Foscarnet can be used for patients with intolerance to ganciclovir (e.g., refractory cytopenias) or if ganciclovir-resistance is suspected (e.g., if CMV viral load increases while on therapy for more than 2 weeks despite treatment) or documented.

    g. Treatment duration should be determined on a case-by-case basis, taking into consideration the severity of CMV disease and the immune status of the host. Generally, induction dosing (see Tables 10.2 and 10.3) should be given for at least 2 weeks and until the CMV viral load is undetectable and symptoms of end-organ disease have resolved. Some centers transition to maintenance (or prophylactic) dosing of oral valganciclovir or IV ganciclovir after completion of induction dosing, particularly for heavily immune suppressed patients.

    h. For CMV pneumonia, adjuvant immune globulin has historically been recommended based on small uncontrolled studies. More recent analyses, however, have raised question about the value of this intervention [7].

        i. CMV-specific immune globulin has not been shown to be more effective than IVIG and is more costly

        ii. The dose, frequency, and duration of IVIG for CMV pneumonia have not been well studied. Historically, IVIG dosing has been 500 mg/kg IV every other day for up to 10 doses.

5. Adenovirus and BK virus infections of the genitourinary tract

    a. Both adenovirus and BK virus can result in posttransplant hemorrhagic cystitis.

    b. For patients who develop BK viral cystitis, the initial approach should consist of supportive care.

        i. Begin with antispasmotics (e.g., oxybutynin [Ditropan®]) or urinary tract analgesics (e.g., phenazopyridine [Pyridium®]).

        ii. If symptoms are not controlled with antispasmotics and/or analgesics, pursue hydration and bladder irrigation, particularly if there is frank hematuria with attendant risk for clot retention.

    iii. Retrospective uncontrolled studies and series describe success with cidofovir in various dosing regimens and administration schemas for BK hemorrhagic cystitis, though toxicities (nephrotoxicity and myelosuppression) are not insignificant [30]. Prospective controlled data is not available at this time. For patients who develop fulminant hemorrhagic cystitis and fail to respond to bladder irrigation, intravenous or intravesical cidofovir can be considered, with close monitoring for toxicity. Various dosing schema have been proposed (e.g., 1 mg/kg weekly to 3 times weekly without probenecid [Benemid®]), though there is no agreement on the optimal dose, frequency, or route of administration.

    iv. Other approaches that have been proposed but with limited data to support efficacy include bladder application of fibrin glue by cystoscopy and hyperbaric oxygen therapy [4].

    v. Consider reducing immune suppression, if feasible.

c. Adenovirus infection can manifest as hemorrhagic cystitis but is significantly more likely than BK virus to result in disseminated and potentially life-threatening disease.

    i. Adenovirus can affect the lungs, gastrointestinal tract, liver, genitourinary system, and/or the central nervous system.

    ii. Patients who have a positive culture or PCR for adenovirus from their urine should have blood sent for quantitative adenovirus PCR.

    iii. For patients with adenovirus viremia and/or in the setting of fulminant hemorrhagic cystitis, strong consideration should be given to systemic treatment with cidofovir (5 mg/kg IV once weekly for 2 weeks and then every other week or 1 mg/kg three times weekly, renal dose adjustment as indicated). If systemic or disseminated disease (e.g., disease outside the GU tract) is suspected, add probenecid 2 g PO 3 hours prior to cidofovir dose and then 1 g PO at 2 and 8 hours after dose [24].

6. Community respiratory virus infections

    Community respiratory virus infections are common in HCT recipients and can result in a wide spectrum of illness, from upper respiratory tract infection (URI) to lower respiratory tract infection (LRTI), often with serious associated morbidity and even mortality [5]. In addition to the "direct effects" of viral infection, there is increased risk for coinfection (e.g., with bacteria or fungi) as well as risk for bronchiolitis obliterans syndrome (BOS) or late airflow obstruction. There are some data to suggest that azithromycin, by way of its immunomodulatory effects, can decrease risk for development of BOS following respiratory virus infection in this patient population [27].

    While some of the community respiratory viruses have a distinct seasonality [e.g., influenza and respiratory syncytial virus (RSV)], others occur year-round (e.g., rhinovirus). Testing for community respiratory virus infections should be by molecular methods/multiplex PCR from nasopharyngeal sample or lower respiratory tract sample, as this offers the highest sensitivity for diagnosis. Evaluation of suspected LRTI should include chest imaging (CXR and/or CT chest). Isolation

precautions (droplet and contact) should be initiated for hospitalized patients with suspicion for community respiratory virus infection and then modified based on local hospital infection control protocol once a specific diagnosis is made. Airborne precautions are advised in the context of aerosol-generating procedures (e.g., BiPAP and suctioning). Effective antiviral therapy is available for influenza and perhaps for RSV and adenovirus as well [36]. For the other community respiratory virus infections, care is supportive. For patients with severe illness, tapering of immune suppression, especially corticosteroid dosing, should be considered if/when able.

a. Influenza A and B

   i. Initiate therapy with an appropriate antiviral agent as soon as possible and regardless of time from symptom onset to diagnosis.
   ii. Neuraminidase inhibitors (oral oseltamivir [Tamiflu®], inhaled zanamivir [Relenza®], intravenous peramivir [Rapivab®]) are the first-line agents for treatment of influenza A or B. The standard dose of oseltamivir for treatment is 75 mg po BID (renal dose adjustment as indicated).
   iii. Duration of therapy with neuraminidase inhibitors is typically 5 days, though a longer duration of therapy (≥10 days) may be considered in hospitalized patients with severe influenza infection.
   iv. Chemoprophylaxis (e.g., oseltamivir for 7–14 days after the last exposure) as soon as possible and ideally within 48 hours of the exposure should be considered for unvaccinated and/or severely immunocompromised transplant recipients who had close contact with an active influenza case.
   v. In the context of an outbreak or transmission on the transplant unit/transplant clinic, broad chemoprophylaxis should be discussed and considered with the infectious diseases service/infection prevention and control team, along with control measures to decrease the risk for ongoing transmission.

b. RSV

   i. Historically, inhaled ribavirin 20 mg/mL (2 g over 6 hours every 8 hours) × 7 days using a Viratek small particle generator (SPAG 2) with or without adjuvant IVIG (500 mg/kg QOD × 5 doses) has been the approach to treatment of RSV LRTI and, in some instances, URI, with the goal of preventing progression to LRTI [10]. These interventions are largely based on single-center retrospective reviews [31].
   ii. There is an emerging body of data to support the use of oral ribavirin (off-label indication) for treatment of RSV LRTI and URI, as a less toxic, less costly, and easier to administer alternative to inhaled ribavirin [8, 35]. Optimal dosing for oral ribavirin has not been established – studies reporting on use cite 600–800 mg 2–3 times daily or a single 10 mg/kg loading dose followed by 20 mg/kg/day in 3 divided doses. With oral ribavirin, close monitoring of hemoglobin (e.g., CBC at least twice weekly) is advised to monitor for hemolytic anemia.
   iii. While prospective and controlled data are lacking, some centers use combination therapy with ribavirin and passive immunotherapy (palivizumab 15 mg/kg as a single dose or IVIG) for select patients [31, 36].

    c. Adenovirus

        i. Systemic cidofovir should be strongly considered for patients with invasive adenovirus infection [12]. While data on optimal dosing of cidofovir are not available, the usual practice is to use 5 mg/kg IV once weekly (renal dose adjustment as indicated) for 2 weeks and then every other week in the setting of life-threatening or disseminated disease, along with probenecid (2 g po 3 hours prior to cidofovir dose and then 1 g PO at 2 and 8 hours after dose). Important adverse drug effects associated with cidofovir administration include nephrotoxicity as well as hematologic and ocular toxicity, and so careful monitoring is recommended.

       ii. When possible, immune suppression should be reduced in the setting of life-threatening or disseminated adenovirus disease.

    d. Parainfluenza virus 1–4

        i. Supportive care

    e. Rhinovirus

        i. Supportive care

    f. Human coronavirus

        i. Supportive care

    g. Metapneumovirus

        i. Supportive care

7. Epstein-Barr virus (EBV)

    a. EBV can result in posttransplant lymphoproliferative disease (PTLD), manifesting as fever, adenopathy, and/or extranodal disease.

    b. Quantitative EBV PCR from blood and/or other body fluids (e.g., CSF) may support the diagnosis, though diagnostic confirmation of PTLD requires tissue biopsy with immunohistochemistry.

    c. EBV viral load monitoring has been recommended by some for certain high-risk HCT recipients. Patients who received T-cell depleted cord blood or haplo-identical stem cell products or who have been exposed to antithymocyte globulin (ATG) should be considered for preemptive monitoring with quantitative EBV viral load monitoring.

    d. Although the threshold for preemptive intervention (e.g., with rituximab [Rituxan®]) is not clear, it is commonly undertaken by centers [39].

    e. First-line therapy for CD20-positive PTLD is the administration of rituximab [32].

    f. Infusion of EBV-specific cytotoxic T lymphocytes has been used with success in various study protocols, though this requires significant time for in vitro generation.

    g. There is little evidence at this time to support the contribution of antiviral therapy for this indication.

8. *Pneumocystis jiroveci* pneumonia (PJP)

   a. Infection is unusual in patients compliant with first-line PJP prophylaxis (e.g., trimethoprim-sulfamethoxazole [Bactrim®]), but breakthrough infections are possible, in particular in patients on other than first-line agents [38].

   b. Radiographic studies of the chest (CT and CXR) typically reveal diffuse interstitial infiltrates with ground glass appearance, though appearance can be quite varied.

   c. Diagnosis is typically by visualization of the organisms by microscopy in respiratory specimens (induced sputum or bronchoalveolar lavage (BAL) fluid). While still considered investigational, PCR of induced sputum or BAL fluid can increase the diagnostic yield over the conventional microscopy. At times, lung biopsy is required to make the diagnosis.

   d. First-line treatment is trimethoprim-sulfamethoxazole, dosed at 15–20 mg per kg per day (renal dose adjustment as indicated) of trimethoprim equivalent divided into 3–4 daily doses for 21 days.

   e. In the case of significant sulfa allergy or intolerance, alternative therapies include:

      i. Mild disease:

         • Atovaquone (Mepron®; 750 mg po twice daily)
         • Clindamycin (Cleocin®; 450 mg po every 6 hours or 900 mg IV every 8 hours) with primaquine (30 mg base po daily)
         • Trimethoprim (Proloprim®; 5 mg per kg every 8 hours, renal dose adjustment as indicated) with dapsone (100 mg po daily); check G-6PD level prior to initiation of dapsone and monitor for methemoglobinemia if long-term use is required

      ii. Moderate disease:

         • Clindamycin with primaquine
         • Trimethoprim with dapsone

      iii. Severe disease:

         • Clindamycin with primaquine
         • Pentamidine (4 mg per kg IV daily, renal dose adjustment as indicated)

            – Unique side effects associated with daily pentamidine therapy include hypotension, hypo- or hyperglycemia, pancreatitis, and/or cardiac arrhythmias.

   f. In the context of moderate to severe disease, adjunctive corticosteroids should be considered, though recognizing that direct data for this intervention in the HIV-negative population is lacking.

     i. For patients with PaO2 < 70 mmHg and/or an alveolar-arterial oxygen gradient > 35 mmHg and/or hypoxemia on pulse oximetry, prednisone 40 mg po BID days 1–5, then 40 mg po daily on days 6–10, and then 20 mg po daily on days 11–21 can be considered in combination with antimicrobial therapy if the patient is not already receiving steroids in comparable dosages.

    ii. Patients who are on corticosteroids at the time of PJP diagnosis (e.g., for GvHD) should continue on their current regimen.

9. *Toxoplasma gondii*

  a. The risk of toxoplasmosis following allogeneic HCT depends on recipient and donor serostatus and on the degree of immune suppression. Seroprevalence studies indicate that 15–30% of the US population has been previously infected with toxoplasmosis. Most toxoplasmosis in transplant HCT recipients is reactivation disease. Prophylaxis is recommended in seropositive patients (see Chap. 10, section "Toxoplasma gondii")

  b. Toxoplasmosis often affects the central nervous system but can also present as disseminated infection in HCT recipients [17]. A CT or MRI of the brain may reveal focal mass lesion(s) or less commonly, diffuse encephalitis.

  c. If toxoplasmosis is suspected, a *Toxoplasma* PCR (CSF and/or blood) should be obtained. Tissue biopsy is sometimes necessary to establish a certain diagnosis. Given the often nonspecific presentation of disseminated toxoplasmosis, a high index of suspicion for this diagnosis should be maintained, particularly in seropositive individuals not on appropriate prophylaxis.

  d. Treatment of established disease due to toxoplasmosis includes:

     i. Pyrimethamine (Daraprim®; 200 mg loading dose on day 1 and then 75 mg po daily for patients >60 kg or 50 mg po daily for patients <60 kg) *and* sulfadiazine (1500 mg po four times daily for patients >60 kg or 1000 mg po four times daily for patients <60 kg) *and* folinic acid (10–25 mg po daily).

    ii. For patients who cannot tolerate sulfadiazine due to significant allergy or other contraindication, pyrimethamine, *and* folinic acid *plus* clindamycin (600 mg po/IV QID) *or* azithromycin (Zithromax®; 900–1200 mg po daily) can be used.

    iii. For patients who cannot tolerate pyrimethamine, sulfadiazine *plus* atovaquone (1500 mg po BID) can be used.

    iv. For patients who cannot tolerate both sulfadiazine and pyrimethamine, salvage single-agent atovaquone can be considered.

  e. Duration of therapy is typically 6 weeks followed by chronic maintenance therapy (i.e., secondary prophylaxis), though this should be individualized based on clinical/radiographic response

10. *Clostridioides difficile*

    a. *C. difficile* is a frequent cause of infectious diarrhea among hospitalized patients, particularly for HCT recipients owing to often long hospitalizations, receipt of broad spectrum antibiotics, and chemotherapy-induced gut disruption.

    b. There is a suggestion of an interaction between gastrointestinal GvHD and *C. difficile* [3].

    c. *C. difficile* should be considered in HCT recipients with new/worsening diarrhea, with the caveat that diarrhea is common posttransplant, with a broad list of differential diagnoses. Many centers have protocolized *C. difficile* testing algorithms, so as to avoid overdiagnosis or detection of colonization.

    d. Laboratory diagnosis of *C. difficile* is typically by demonstration of *C. difficile* toxin(s). A number of tests are available for broad clinical use: PCR for toxins A and B, enzyme immunoassay (EIA) for *C. difficile* toxins A and B, and EIA for *C. difficile* glutamate dehydrogenase (GDH, an enzyme produced by toxigenic and nontoxigenic *C. difficile* strains).

       i. PCR is more sensitive than EIA for toxins A and B but has potential for false positive results.

      ii. EIA for GDH is sensitive but not specific.

     iii. Some labs favor the use of tiered screening, with EIA for GDH the first test, and then reflexing to EIA and/or PCR for toxins A and B if the GDH test is positive.

    e. In addition to specific antimicrobial therapy for *C. difficile*, the general principles of management include discontinuation or narrowing of other antibiotics as able, fluid and electrolye support, avoidance of antiperistaltic agents until on appropriate treatment for *C. difficile* infection, and institution of appropriate infection control measures (contact precautions, hand hygiene with antibacterial soap and water, environmental cleaning with bleach, etc.).”

    f. For treatment of non-severe and severe *C. difficile* infection, oral vancomycin (125 mg po QID) and oral fidaxomicin (Dificid®; 200 mg po BID) are first-line options [20]. Fidaxomicin is significantly more costly than oral vancomycin but has been associated with a lower recurrence rate [22].

    g. For first recurrence of *C. difficile* infection, oral vancomycin pulsed-taper* or fidaxomicin can be used if vancomycin was used for treatment of the initial episode or vancomycin if fidaxomicin was used.
       *Vancomycin pulsed-taper: 125 mg po QID × 10–14 days, then 125 mg po BID × 7 days, then 125 mg po QD × 7 days, and 125 mg po every 2 or 3 days for 2–8 weeks

    h. For second and subsequent recurrences, vancomycin pulsed-taper, fidaxomicin, vancomycin followed by rifaximin (Xifaxan®; 400 mg every 8 hours × 20 days), or fecal microbiota transplant (FMT) can be considered. Candidacy for FMT should be carefully considered with input from infectious diseases and/or gastroenterology colleagues.

    i. For fulminant (severe, complicated) disease characterized by ileus, megacolon, and/or shock, a combination of high-dose vancomycin (500 mg po, via nasogastric tube or via retention enema every 6 hours) and metronidazole (Flagyl®; 500 mg IV every 8 hours) should be used, along with early surgical evaluation to consider the role for colectomy.

    j. Duration of therapy is at least 14 days, and for patients who have an indication for other antibiotic therapy, providers often choose to extend the course of *C. difficile*-active therapy for a fixed period following the discontinuation of other antibiotics (e.g., 1 week).

11. Candidiasis [26]

Infections with *Candida* species can be classified as primarily invasive (e.g., candidemia, hepatosplenic candidiasis, etc.) or superficial (e.g., mucosal). In the era of the widespread use of azole prophylaxis, candidiasis occurs with relative infrequency in the HCT population; however, fluconazole-resistant *Candida* species (*C. krusei* and *C. glabrata*) and emergence of echinocandin-resistant species (*C. glabrata*) are of particular concern.

    a. Candidemia

        i. An echinocandin (micafungin [Mycamine®] 100 mg IV daily or caspofungin [Cancidas®] 70 mg IV load then 50 mg IV daily, or anidulafungin [Eraxis®] 200 mg IV load then 100 mg IV daily) is recommended for empiric treatment of candidemia in neutropenic hosts while awaiting species-level identification, which can guide further therapy.

       ii. For patients who develop candidemia while on or who have recently been on an echinocandin, an amphotericin B lipid-based product (AmBisome® or Abelcet®, dose 3–5 mg/kg IV daily) should be considered while species-level identification and susceptibility testing are pending.

     iii. For non-critically ill patients with no prior azole exposure, an unlikely scenario in the HCT population, fluconazole (Diflucan®) can be considered as initial therapy.

     iv. Antifungal treatment should be adjusted once species-level identification and susceptibility testing are available and with input from the infectious diseases service. Azole antifungals can be used as step-down treatment of candidemia, provided there is demonstrated susceptibility to these agents.

      v. Duration of therapy for candidemia is 2 weeks from documented clearance of blood cultures and until resolution of neutropenia, provided there is no concern for deep-seated foci or persistent positive blood cultures.

     vi. Removal of vascular catheter(s) is advised in the setting of candidemia, though acknowledging that gut translocation is a potential source of infection.

vii. A dilated retinal exam, ideally by an ophthalmologist, should be performed to evaluate for Candida endophthalmitis. The optimal time to perform this examination is following neutrophil recovery, unless symptoms dictate otherwise.

viii. With high-grade and persistent candidemia, an echocardiogram should be obtained to evaluate for endocarditis.

b. Chronic disseminated candidiasis

i. This syndrome, also referred to as hepatosplenic candidiasis, is most often seen following recovery from neutropenia.

ii. C. albicans is most often the causative organism, with other species seen far less often.

iii. Presenting signs/symptoms are often vague, with malaise, fever, and/or non-specific gastrointestinal complaints.

iv. Diagnosis is suggested by an elevation of the serum alkaline phosphatase and/or multiple hepatic hypodensities seen on CT or MRI. While some patients have an antecedent blood culture with Candida species, cultures are often negative.

v. Definitive diagnosis is established by liver biopsy which classically demonstrates multiple granulomas with visualization of yeast and hyphal elements on special stains. More often than not, culture of tissue from liver biopsy is negative, particularly if the patient has received antifungal therapy.

vi. Molecular diagnostic studies (e.g., fungal PCR) can offer additional sensitivity and provide species-level information.

vii. Treatment considerations include an echinocandin, a lipid-based amphotericin product or azole therapy (frequently fluconazole, as C. albicans is the most common species implicated), with input from the infectious diseases service. Treatment decisions should be based on the previous antifungal therapy and, when available, microbiologic data.

viii. Duration of therapy is typically prolonged (many months) and is guided by clinical response and radiographic resolution or calcification.

c. Esophageal candidiasis

i. Fluconazole 200–400 mg po/IV daily for 14–21 days is the first line in azole-inexperienced individuals.

• In patients with significant antecedent azole exposure, for infection with culture-documented fluconazole-resistant *Candida species*, or for fluconazole-refractory disease, an echinocandin (e.g., micafungin 150 mg IV daily) or an extended spectrum azole (e.g., posaconazole [Noxafil®] 400 mg po BID or voriconazole [VFend®] 200 mg po BID) can be used.

• Low-dose amphotericin B lipid-based product is an alternative for patients refractory to other agents.

    d. Vulvovaginal candidiasis

        i. Fluconazole 100–200 mg po/IV daily for 7–10 days or topical antifungal treatment (e.g., clotrimazole, miconazole, or nystatin) for 7–10 days can be used.

       ii. If refractory or recurrent vulvovaginal candidiasis (≥4 symptomatic episodes within a year) occurs, consultation with the infectious diseases service should be obtained.

12. Invasive aspergillosis

    a. *Aspergillus fumigatus* is the most common *Aspergillus* species implicated as a cause of infection in immune compromised hosts, though other species can also result in invasive infection.

    b. Pulmonary infection is the most common clinical presentation; however, sinus disease and/or hematogenous dissemination with other organ involvement (e.g., central nervous system, skin, etc.) is occasionally seen.

    c. The key to successful management is early consideration of this process with diagnostic evaluation and prompt initiation of antifungal therapy [29].

    d. Chest imaging can be suggestive in the appropriate context, but proven or probable diagnosis requires a mycologic diagnosis, either by culture or fungal biomarker (galactomannan from serum or BAL fluid [23]).

    e. When a diagnosis cannot be obtained by less invasive means, surgical biopsy should be considered.

    f. Voriconazole (VFend®) is first-line therapy for invasive aspergillosis [11].

    g. Posaconazole (Noxafil®) and isavuconazole (Cresemba®) are reasonable alternatives [15, 37], if side effects or toxicity preclude the use of voriconazole.

        i. Therapeutic drug monitoring (TDM) should be performed for voriconazole [28], posaconazole, and perhaps for isavuconazole (see Table 10.4 for dosing guidelines).

       ii. If a significant increase in serum transaminase levels is noted while on azole therapy (≥5 times the upper limit of normal), check a trough antifungal drug level and consider change to an alternative class. If the antifungal drug level is supratherapeutic, reintroduction at a lower dose can be considered after normalization of serum transaminase levels.

    h. Echinocandins are considered inferior to voriconazole for monotherapy of invasive aspergillosis.

    i. Data from a phase 4 clinical trial of combination therapy (voriconazole + anidulafungin vs. placebo) for invasive aspergillosis demonstrated a trend toward improved outcome but did not meet the statistical significance [16]. Combination therapy can be considered, particularly in patients with a high burden of disease.

    j. Reduction of immunosuppression is advised if and when possible.

    k. Surgical resection can be considered for fungal sinusitis and other scenarios, based on the site of involvement, the risks of surgery, and the patient's immune status.

l. Patients with a history of invasive aspergillosis prior to transplant should receive at least 6 weeks of antifungal therapy and have a documented partial or complete response to therapy before proceeding to conditioning [18]. Ideally, these patients should undergo a non-myeloablative HCT.

    i. Secondary prophylaxis with an *Aspergillus*-active azole antifungal (voriconazole, posaconazole, or isavuconazole) should be given to patients in the posttransplant setting.

    ii. If significant drug-drug interaction or drug toxicity limits azole use, a lipid-based amphotericin product or an echinocandin can be used as a second-line approach in this setting.

13. Mucormycosis

a. Clinical presentation can include angioinvasive infection of the lungs, skin, brain, and/or disseminated disease with widespread visceral involvement.

b. Diagnosis often requires tissue biopsy, although bronchoscopy with BAL can sometimes be informative in the setting of pulmonary infection.

c. Management of this infection should include antifungal therapy, reversal of underlying defects in host defense (e.g., tapering immune suppression when possible, growth factor support for neutropenia, restoration of euglycemia), and surgical resection or debridement whenever feasible.

d. An amphotericin B lipid-based product (AmBisome® or Abelcet®) dosed at 5 mg per kg IV daily is first-line antifungal therapy.

e. Isavuconazole or posaconazole can be considered for patients intolerant to amphotericin, for continuation therapy after a course of amphotericin, or for secondary prophylaxis [19].

f. Voriconazole does not have activity against mucormycosis.

g. Despite aggressive management of this infection, mortality rates remain very high.

h. Consultation with the infectious diseases service is suggested.

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Chapter 31
Oral Complications

Erin Combs, Joel B. Epstein, and Kimberly Brennan Tyler

Introduction

Oral complications following hematopoietic cell transplantation have been reported to be among the most distressing treatment-related side effects and can have a significant negative impact on the quality of life (QoL) in hematopoietic cell transplant (HCT) recipients. In the peri-transplant period, mucositis and infectious complications are common causes of increased morbidity and sometimes mortality in transplant recipients. Neutropenia, disrupted mucosal barrier, immune suppression, and delayed immune reconstitution increase the risk of viral, fungal, or bacterial infections in transplant recipients. Mucocutaneous chronic graft-versus-host disease (cGvHD) is a common posttransplant complication, that may affect oral tissues which often warrants a multimodal treatment approach. Transplant survivors also experience saliva change that impacts oral health, taste change, and neuropathy-related symptoms.

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Oral Mucositis

Oral mucositis (OM) is a consequence of chemotherapy and/or radiation that results in tissue damage manifested by erythema, edema, and ulceration of the gastrointestinal mucosa that disrupt the protective epithelial barrier. It has been reported to affect between 47% and 100% of HCT recipients, depending on multiple factors, including nature and intensity of conditioning regimen, recipient age, GvHD prophylaxis, comorbidities, and prior chemotherapy [1]. The breakdown of the mucosal barrier represents an increased infection risk, results in pain that in turn leads to decreased alimentation, and is associated with increased use of opiates, increased total hospital days, and a significantly decreased QoL. The pathophysiology is due to chemotherapeutic effect on epithelial and connective tissues, which can result in a significant delay in the repair of the damaged tissues, further potentiating the effects of the inflammatory process. The epithelial lining is then at an increased risk for colonization of and invasion by various microorganisms. The most commonly used tools to score the severity of mucositis are the World Health Organization (WHO) and National Cancer Institute (NCI) scales (see Table 31.1). An overwhelming majority of HCT recipients receiving myeloablative conditioning regimens (>70%) experience grades 2–4 mucositis [2]. Current treatment strategies focus on minimizing infectious risks, controlling pain, and supplementing alimentation as needed [1, 2]. Mucositis typically peaks during theneutropenic nadir and resolves

Table 31.1 Stomatitis evaluation scales

Grade	WHO[a]	NCI-CTC[b]	Bearman
Grade 0	No oral abnormalities	No oral abnormalities	No oral abnormalities
Grade 1	Oral soreness +/− erythema without; able to tolerate regular diet	Erythema	Pain and/or ulceration not requiring a continuous IV narcotic drug
Grade 2	Oral soreness with erythema and ulcerations; able to tolerate solid food	Patchy ulcerations or pseudomembranes	Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)
Grade 3	Oral soreness with erythema and ulcerations; able to tolerate liquids only	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Severe ulceration and/or mucositis requiring preventative intubation; or resulting in documented aspiration pneumonia with or without intubation
Grade 4	Oral soreness with erythema and ulcerations; unable to tolerate anything by mouth	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
Grade 5	None	Death	None

[a]World Health Organization
[b]National Cancer Institute-Common Toxicity Criteria

concurrent with neutrophil engraftment, related to epithelial and connective tissue repair associated with recovery of the regenerating innate immune system.

1. Risk factors

    a. Conditioning regimen (e.g., total body irradiation (TBI), melphalan, thiotepa)
    b. Medications that result in xerostomia and decreased saliva production (e.g., opiates, diuretics, antiemetics, etc.)
    c. Prolonged antimicrobial usage
    d. Prolonged hospitalization
    e. Prolonged myelosuppression
    f. History of OM with previous treatment cycles
    g. Body mass index (>25 increases risk of OM)
    h. Medical comorbidities (e.g., diabetes)
    i. GvHD prophylaxis (calcineurin inhibitor, methotrexate)
    j. Emesis
    k. Poor oral health and hygiene
    l. Poor nutritional status
    m. Tobacco and alcohol use
    n. Infectious disease exposures (e.g., herpes simplex)
    o. GvHD
    p. Mouth breathing

2. Prophylaxis

    a. Oral hygiene prior to admission

        i. Brushing with fluoride toothpaste BID and daily interdental cleaning (e.g., flossing).
        ii. Use foam toothbrush with chlorhexidine if painful mucositis precludes the use of a regular soft toothbrush or platelet count falls below 50,000/μl. Daily interdental cleaning if atraumatic and platelet count is >50,000/μl.
        iii. Chlorhexidine gluconate 0.12% (Peridex®) which contains alcohol could be used to minimize bacterial colonization but may not prevent OM. Patients should be warned about the potential for tooth discoloration with its use. In patients with mucositis, chlorhexidine 0.12% aqueous alcohol-free solution (GUM® Paroex™) is available by prescription.
        iv. Pretransplant dental evaluation and cleaning by a dentist with experience working with HCT patients is recommended.

            • All sources of dental infection should be preferentially corrected prior to conditioning. Badly decayed teeth and broken roots/teeth with advanced periodontal involvement may require extraction.
            • Patients receiving IV bisphosphonates (i.e., Zometa®, Aredia®) and RANK-ligand inhibitors (i.e., Xgeva®) require special consideration

  and conservative management of dental problems to reduce the risk
  of osteonecrosis of the jaw.
- Conditioning regimen may begin 7–14 days after surgical wound
  coverage with mucosa.
- Patients should be educated on the importance of good oral care dur-
  ing HCT with ongoing reinforcement throughout the HCT admission
  and survivorship.

 v. Photobiomodulation therapy [PBM] (low-level laser therapy; red/infra-
 red light) to reduce plaques before HCT (if available).

 vi. Orthodontic bands should be removed and rough/irregular dental sur-
 faces smoothed or removed.

 vii. Avoid the use of other dental appliances unless they have been evaluated
 and approved prior to HCT.

 viii. Avoid alcohol and tobacco.

b. Oral hygiene during transplant

 i. Ongoing oral assessment using validated evaluation scales (Table 31.2).

 ii. Ongoing oral assessment from a specialized oral management group if
 available.

 iii. Encourage the patient to communicate symptoms in a timely manner for
 prompt initiation of therapy.

 iv. Palifermin (Kepivance®) 60 mcg/kg/day IV on 3 consecutive days, with
 the last dose given not less than 24 hours prior to initiation of the condi-
 tioning regimen, then on days +1, +2, and +3 post HCT. This growth
 factor has been approved for use in autologous HCT recipients only and
 is used primarily with TBI-based regimens.

Table 31.2 Oral mucosa rating scale (OMRS)

Location	Ulceration[a]	Erythema[b]
Lip Upper Lower	0, 1, 2, or 3 (score separately for upper and lower)	0, 1, or 2 (score separately for upper and lower)
Buccal mucosa Right Left	0, 1, 2, or 3 (score separately for right and left)	0, 1, or 2 (score separately for right and left)
Ventrolateral tongue Right Left	0, 1, 2, or 3 (score separately for right and left)	0, 1, or 2 (score separately for right and left)
Floor of mouth	0, 1, 2, or 3	0, 1, or 2
Palate Hard Soft	0, 1, 2, or 3 (score separately for hard and soft)	0, 1, or 2 (score separately for hard and soft)
		Total score:

[a]0 = none; 1 = <1 cm; 2 = 1–3 cm; 3 = >3 cm
[b]0 = none; 1 = not severe; 2 = severe

      v. Photobiomodulation (previously known as low-energy laser or low-level laser therapy), if available, may be used for recipients receiving high-dose chemotherapy and/or radiation therapy to prevent OM (use with a wavelength at 640–820 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 4–6 J/cm^2) [1].

     vi. Oral cryotherapy during and for 1 hour after the administration of high-dose melphalan.

    vii. Frequent rinsing with bland solution (normal saline or sodium bicarbonate) between 4 and 10 times daily or mouth wetting agent (e.g., Caphosol®) oral rinse solutions. Caphosol® is a combination of 1 ampule of sodium phosphate and an equal volume of calcium chloride. For dosing, patients are instructed to rinse with ½ of the solution for 1 full minute and spit, then repeat with the remaining ½ of the solution. Patients should refrain from oral intake for 15 minutes after each dose.

   viii. Denture use should be minimized; dentures should be immersed in antimicrobial solution when stored and the solution should be changed daily. Avoid use if dentures are ill fitting, abrasive to mucosa, or if there is active mucositis.

    ix. Avoid hot, abrasive, sharp, or hard foods. Moisten food with sauces or gravies. Avoid hot, acidic, or carbonated liquids. Avoid artificial flavoring especially pungent compounds, such as mint and cinnamon.

     x. Maintain adequate hydration.

    xi. Keep lips moist using ointment and lip moisturizers containing lanolin, wax, or aloe. Avoid products containing petrolatum.

    xii. Sucralfate (Carafate®) 1 gm dissolved in solution, swish, and swallow every 6 hours beginning on admission has been used in some centers as a soothing/coating product, although there is no preventive effect on OM.

   xiii. Maintain and promote saliva production.

3. Treatment

   a. See Table 31.3 for common treatment approaches. neutropenic nadir and resolves concurrent with neutrophil engraftment, related to epithelial and connective tissue repair associated with recovery of the regenerating innate immune system.

Infections

1. The most common pathogens causing infection in patients with OM undergoing HCT include:

   a. *Streptococcus viridans*
   b. Coagulase-negative staphylococci
   c. Gram-negative bacteria
   d. Herpes simplex (HSV)
   e. *Candida* species
   f. Cytomegalovirus

Table 31.3 Management of oral complications

Symptom	Severity	Treatment

Pain	Mild	Use of bland oral rinses to maintain moisture
		   Normal saline swish and spit every 2 hours
		   Sodium bicarbonate solution every 2 hours
		   Sodium chloride rinses
		   Sponge swab
		   Ice chips
		Use of sialagogues
		   Artificial saliva
		   Sugarless hard candies or sugarless gum
		   Pilocarpine (Salagen®) 5–10 mg po TID
		   Cevimeline (Evoxac®)30 mg po TID
		   Bethanechol (Urecholine®) 25 mg po TID
		   Topical fluoride treatments
		   Biotene® mouthwash or toothpaste
		Reduce oral challenges such as converting all applicable medications to IV formula, providing IV fluid and/or parenteral nutrition

	Moderate	Topical analgesia
		   Compounded mouthwashes (Maalox®: diphenhydramine elixir:viscous lidocaine 1:1:1) 10–15 mL swish and spit every hour PRN
		   Benzocaine gel apply topically to oral lesions QID PRN
		   Doxepin (Sinequan®, Adapin®) 5 mg/mL 5 mL po held in the mouth for 5 minutes PRN
		Systemic opiates
		   Scheduled opiate administration
		   Consider narcotic patches
		   Consider pain management consult (ketamine oral compound, bupivacaine lozenges, if available)

	Severe	Parenteral narcotics
		   Use of narcotic patches and IV administration
		   Patient-controlled analgesia (PCA)
		   Consider pain management consult (ketamine oral compound, bupivacaine lozenges, if available)

Xerostomia and hyposalivation		Use of bland oral rinses to maintain moisture
		   Normal saline swish and spit PRN
		   Sodium bicarbonate solution every 2 hours
		   Sponge swab
		   Half-strength hydrogen peroxide swish and spit PRN
		Use of sialagogues
		   Artificial saliva
		   Sugarless hard candies or sugarless gum
		   Pilocarpine (Salagen®) 5–10 mg po TID
		   Cevimeline (Evoxac®) 30 mg po TID
		   Bethanechol 25 mg po TID
		   Topical fluoride treatments
		   Biotene® mouthwash or toothpaste
		   Caphosol® swish and spit 4–10 times daily PRN

Table 31.3 (continued)

Symptom	Severity	Treatment
Thick secretions		Use of mucolytic agents (guaifenasin, n-acetyl cysteine (Mucomyst (r)
		Use of drying agents
		Scopolamine patch (Transderm Scop®) TD behind ear apply every 72 hours
		Dimenhydrinate (Dramamine®) 25–50 mg po every 4 hours PRN
		Diphenhydramine 25–50 mg po or 12.5–25 mg IV every 6 hours PRN
		Amitriptyline 10-25 mg. tid
		Lorazepam 0.5–1 mg po/IV every 6 hours PRN (gag reflex)
		Utilize suction to alleviate secretions
		Utilize blowby by humidified air
Emesis		Antiemetics scheduled around the clock
Bleeding		Transfuse to maintain platelets >20,000 for mild gingival bleeding
		Transfuse to maintain platelets >50,000 for severe gingival bleeding
Airway protection		Utilize blowby humidified air
		Short course of IV steroids
		ENT consult for preemptive intubation for airway protection

Fig. 31.1 Oral candidiasis

2. Swab and culture all oral lesions
3. *Candida* infections (see Figs. 31.1 and 31.2)

   a. Topical treatments

      i. Cautious use of nystatin liquid 10 mL, swish and spit/swallow q6 hours (may cause nausea and is highly sugar sweetened, increasing dental demineralization and caries)

     ii. Clotrimazole (Mycelex®) troches 1 by mouth 5 times daily

    iii. Amphotericin mouthwash: 50 mg amphotericin B mixed in 200 mL sterile water 5–10 mL, swish and spit/swallow every 6 hours

Fig. 31.2 Oral candidiasis

Fig. 31.3 HSV lesions to the hard palate

    b. Systemic antifungals

        i. Fluconazole (Diflucan®) 400 mg po or IV daily if oral involvement

       ii. Voriconazole (VFend®) 6 mg/kg po/IV q12h × 2 doses, then weight-based maintenance (see Chap. 10)

      iii. Micafungin (Mycamine®) 150 mg IV once daily if esophageal involvement and fluconazole intolerance

4. Viral infections (see Figs. 31.3 and 31.4)

    a. HSV

        i. Prophylaxis: Acyclovir (Zovirax®) 800 mg po daily or BID or 250 mg/m^2 IV twice daily (assuming CrCl >50 mL/minute/1.73 m^2; refer to renal dosing otherwise) or valacyclovir (Valtrex®) 500 mg po daily.

Fig. 31.4 HSV lesion to the lower lip

ii. Treatment: Acyclovir 400 mg po 5 times daily for 14–21 days or 5 mg/kg IV every 8 hours for 7- to 14-day treatment course (renally adjust if CrCl <50 mL/minute/1.73 m^2) or valacyclovir 1000 mg po twice daily for 10 days.

iii. Consider sending for HSV sensitivity/resistance testing if no improvement in oral lesions within 72 hours of treatment initiation or empirically switching.

5. Bacterial (based upon bacterial culture and sensitivity)

   a. Systemic antibacterials

      i. Fluoroquinolone through engraftment or for periods of neutropenia >7 days

         • Ciprofloxacin (Cipro®) 500 mg po BID (assuming CrCl >50 mL/minute/1.73 m^2; refer to renal dosing otherwise)
         • Levofloxacin (Levaquin®) 500 mg po daily (assuming CrCl >50 mL/minute/1.73 m^2; refer to renal dosing otherwise)

      ii. Consider addition of penicillin, penicillin + clavulanic acid (Augmentin®) +/− metronidazole based on allergies and need for anaerobic coverage.

Predental Procedures

The American Dental Association (ADA) does not recommend prophylaxis for dental procedures for immunocompromised hosts; however, it continues to be used at some institutions, particularly in the setting of indwelling catheters (i.e., port-a-cath, Groshong, etc.). Common regimens include the following:

1. Amoxicillin 2 gm po once, 1 hour prior to procedure
2. Clindamycin (Cleocin®) 600 mg po once, 1 hour prior to procedure or QID for 10 days post procedure
3. Azithromycin (Zithromax®) 500 mg po once, 1 hour prior to procedure or once daily for 10 days post procedure

Taste Alterations

1. Dysgeusia (distorted taste), hypogeusia (loss of taste), or ageusia (absence of taste)

   a. Most affected are sweet and salty tastes with loss of umami taste and sensitivity to spicy/acidic foods; bland taste is commonly observed by patients.
   b. Maintain good oral hygiene.
   c. Sialagogues in patients with residual gland function.
   d. Season foods.
   e. Eat small portions.

Discharge Instructions

1. Patients should resume interdental cleaning once platelet count is > 50,000/μl.
2. Patients should be encouraged to use saline rinses for 3–6 months post HCT if dry mouth persists as recommended by their care team.
3. Patients with GvHD should:

   a. Undergo oral evaluation every 3–6 months
   b. Practice meticulous dental hygiene with the use of toothbrush TID, flossing daily providing platelets are >50,000/μl, dental fluoride treatments, and use of sialagogues as needed
   c. Prevent dental demineralization if dry mouth is present

4. Sugar-free candy or gum should be encouraged particularly in patients with xerostomia.
5. Return to routine professional dental care in 6–12 months if blood counts are normal. Delay elective oral surgical procedures for 12 months posttransplant.

Chronic Graft-Versus-Host Disease (See Also Chap. 28)

1. Pathophysiology: Chronic GvHD has a complex and incompletely understood pathogenesis. There are two prominent theories: the first focuses on the role of donor Th2 cells in association with activated donor B cells, which drive tissue destruction. The second theory postulates that an impaired immune tolerance

leads to differentiation of autoreactive T cells, which release cytokines and subsequently result in an immune response in which host tissues are damaged, activating a cycle of inflammation and further tissue destruction. The rate of cGvHD is reported to be between 35% and 80% with the skin, eyes, and oral tissue being the most commonly afflicted. Oral cGvHD can manifest with a variety of presentations [3–5].

2. Risk factors.

    a. Prior acute GvHD
    b. Peripheral blood stem cell products
    c. TBI-based or other myeloablative conditioning regimens
    d. Recipient age (>60)
    e. Female donor for male recipient
    f. Donor lymphocyte infusions (DLI)

3. Presentation.

    a. Increased sensitivity to spicy/acidic/salty foods or hot or cold foods/beverages; intolerance of hard/rough/crunchy foods
    b. Oral pain
    c. Oral ulcerations and/or blisters
    d. Xerostomia (dry mouth)
    e. Difficulty chewing/speaking
    f. Dysgeusia (taste alterations)
    g. Sclerotic changes/limited mouth opening, fibrosis in cheeks, and limited jaw movement

4. Physical exam findings (see Figs. 31.5–31.10).

    a. Generalized erythema of buccal mucosa, soft palate, and tongue
    b. Lichenoid changes to the buccal mucosa, tongue, gingiva, and/or hard palate
    c. Hyperkeratotic plaques primarily on dorsal surface of tongue
    d. Ulcerations with pseudomembranes

Fig. 31.5   Oral GvHD

Fig. 31.6 Oral GvHD with
gingival changes and
lichenoid-type changes to
the lower lip

Fig. 31.7 Oral GvHD with
ulcerations along
ventrolateral tongue and
diffuse buccal erythema

Fig. 31.8 Oral GvHD

Fig. 31.9 Oral GvHD

Fig. 31.10 Oral GvHD
affecting the lips

    e. Atrophic glossitis
    f. Superficial mucoceles
    g. Restriction in mouth opening due to sclerosis

5. Chronic GvHD is graded according to the revised NIH criteria and includes individual measurements for overall performance status, the skin, mouth, eyes, GI tract, liver, lungs, joints/fascia, and GU. Severity is based on a scale of 0–3, with 0 being the absence of disease and 3 being severe, symptomatic, and potentially life-altering/limiting cGvHD. Additionally, there is an overall score for the patient, which differentiates between mild, moderate, and severe disease. There are several other scales to assess either physical findings or oral symptoms, such as the Lee Symptom Scale, NIH Mouth cGvHD Activity Assessment Scale, and the Oral Mucositis Rating Scale (OMRS), among others. Please see Table 31.4 for NIH grading criteria [3, 6, 7].

Table 31.4 NIH oral assessment scale of chronic GvHD

Mucosal change	No evidence of cGvHD		Mild		Moderate		Severe
Erythema	None	0	Mild erythema of moderate erythema (<25%)	1	Moderate (≥25%) or severe erythema (<25%)	2	Severe erythema (≥25%) 3
Lichenoid	None	0	Hyperkeratotic changes (<25%)	1	Hyperkeratotic changes (25–50%)	2	Hyperkeratotic changes (>50%) 3
Ulcers	None	0	None	0	Ulcers involving ≤20%	3	Severe ulcerations (>20%) 6
Mucoceles*	None	0	1–5 mucoceles	1	6–10 scattered mucoceles	2	Over 10 mucoceles 3
			*Mucoceles scored for lower labial and soft palate only				*Total score for all mucosal changes*
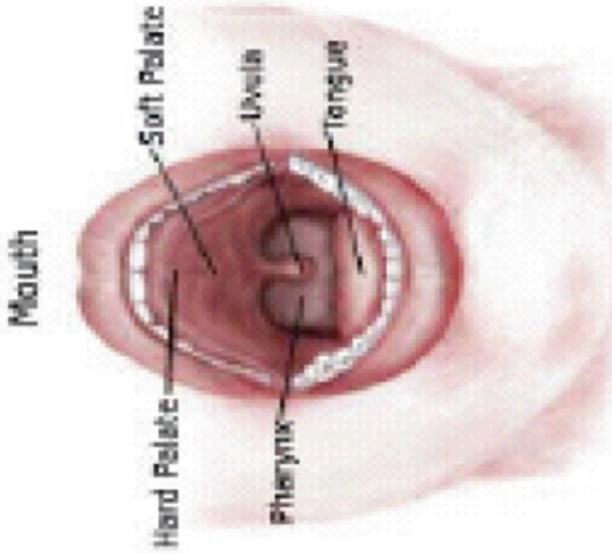
6. Diagnosis of cGvHD is largely based on symptom presentation, clinical exam findings, and clinical context (i.e., the onset of symptoms in relationship to time from HCT, other signs/symptoms of cGvHD, tapering of immune suppression therapy, etc.). When possible, other confounding factors, such as infections, should be evaluated and treated before arriving at a diagnosis of cGvHD. Culturing ulcerations or obtaining oral culture to exclude other diagnosis, such as HSV infection or oral candidiasis, should be undertaken before starting treatment. Biopsy of oral lesions may be indicated and best interpreted by an experienced pathologist and read as "consistent with" or "unequivocal for" GvHD. Biopsy with immunofluorescence may be needed [3].

7. Treatment: Depending on the extent and severity of presentation, cGvHD of the mouth is generally treated with local or topical therapies. The goal of treatment is to reduce oral symptoms, correct underlying physical abnormalities (i.e., resolution of lesions, physical exam findings), and screen for/minimize secondary complications (i.e., infections, dental caries, etc.) [3, 8].

    a. Oral mucosal disease

        i. Dexamethasone solution (0.5 mg/mL) 5 mL swish/rinse for 3–5 minutes 2–4 times daily. Instruct patients not to eat/drink anything for 15 minutes following rinse. This is generally considered the first-line therapy. Allow 2–4 weeks prior to escalating to higher-potency steroids, such as clobetasol or budesonide; the latter has the advantage of limited systemic absorption.

        ii. Clobetasol 0.05% solution.

        iii. Budesonide mouthwash: Dissolve 3 mg tablet in 10 mL sterile water and rinse for 3–5 minutes twice daily.

        iv. Tacrolimus 0.1% solution: This is usually added in addition to higher-potency steroid rinses, such as clobetasol and budesonide if they have been ineffective in alleviating symptoms within 2–4 weeks of starting. Tacrolimus can be added to clobetasol rinse in equal parts as a single rinse.

        v. Fluocinonide 0.05% gel or clobetasol 0.05% gel and protopic ointment (0.03–0.1%) can be applied with a Q-tip or gauze directly to any painful lesions, hard palate, etc., 2–4 times daily.

        vi. PUVA therapy or PBM if available.

        vii. For patients with oral pain, the following solutions can be used to alleviate painful oral symptoms:

           • Compounded mouthwashes (magnesium hydroxide [Maalox®], diphenhydramine elixir, and viscous lidocaine in a 1:1:1 ratio)

           • Benzocaine gel topically to discrete ulcerations

           • Doxepin (5 mg/mL) 5 mL swish/rinse for up to 5 minutes

           • Liquid dyclonine (Sucrets®) PRN prior to meals

           • Depending on symptom severity, long-acting or short-acting narcotics prior to meals

b. Lips

   i. Tacrolimus (Protopic®) ointment applied 2–4 times/day
   ii. Fluocinonide (Lidex®) or hydrocortisone 0.1% ointment applied 2–4 times/day
   iii. PBM

c. Salivary gland (i.e., xerostomia)

   i. Salivary stimulants (sugar-free gum/candy)
   ii. Oral moisturizing agents
   iii. Sialagogue therapy

   • Pilocarpine (Salagen®) 5–7.5 mg po TID
   • Cevimeline (Evoxac®) 30 mg po TID
   • Bethanechol (Urecholine®) 10–50 mg TID

d. Sclerotic cGvHD

   i. Physical therapy
   ii. Intralesional steroid therapy
   iii. PBM
   iv. Rarely, surgical intervention to disrupt mucosal bands due to fibrosis risk

e. Additional considerations

   i. Patients should be monitored for oral candidiasis and should receive prophylaxis either with a systemic antifungal, such as fluconazole, or with topical agents, such as clotrimazole or nystatin (the latter with caution due to sucrose content).
   ii. Systemic absorption of high-potency steroids and topical tacrolimus may occur (i.e., dexamethasone, clobetasol) due to disruption of mucosal barrier, despite not ingesting either solution. Systemic dosing is reduced with the use of budesonide. Patients may need to be screened for signs of adrenal suppression, hyperglycemia, and Cushingoid presentation, if using these therapies.
   iii. For patients with symptomatic xerostomia, sialagogue therapy can take between 8 and 12 weeks for full efficacy. Additionally, these medications should be avoided in patients with underlying pulmonary disease.
   iv. In situations where disease is severe and potentially life-limiting/impairing, systemic therapy may need to be considered. Please refer to Chap. 28 for a more in-depth review on systemic therapy.
   v. Routine dental screening for caries should be done frequently in this patient population.

8. Additional considerations

   a. Late complications of treatment

      i. Oral squamous cell carcinomas account for 50% of reported non-cutaneous secondary malignancies posttransplant. Oral cGvHD represents a major

risk factor for development (increase in relative risk of 6.0) and may complicate detection and diagnosis [3] (see Figs. 31.11 and 31.12).

b. Nutritional considerations

   i. Patients may need to be referred to dietician if persistent weight loss (> 5%) occurs due to inability to tolerate oral nutrition.

   ii. In severe cases (>10% weight loss and severe oral impairment), supplemental nutrition (i.e., nasogastric or percutaneous endoscopy tube) may need to be considered.

c. Taste function, appetite stimulation affected by prior therapy, ongoing medications, xerostomia, cGvHD, and oral infection require consideration for management for best outcomes.

Fig. 31.11 Squamous cell carcinoma

Fig. 31.12 Squamous cell carcinoma

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Chapter 32
Gastrointestinal Complications

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Introduction

Gastrointestinal and hepatic complications are common in the hematopoietic cell transplant (HCT) patient. The agents used in the conditioning regimen induce direct disruption of the intestinal barrier as well as indirect damage from cytokine release and a generalized inflammatory state. These events lead to permeation of bacteria and endotoxins through the bowel wall with subsequent organ damage and increased risk for infection. Similarly, HCT conditioning can directly affect the hepatic parenchyma or hepatic sinusoids. The immunosuppressed state of the HCT patient also increases the risk for opportunistic infections of the gastrointestinal tract and liver. This chapter includes information describing potential gastrointestinal and hepatic complications that may arise in the HCT patient and provides guidelines for their management.

Upper Gastrointestinal

1. Anorexia

    a. Etiology and pathogenesis
        Usual onset during conditioning and first week posttransplant; may last longer in patients with mucositis, infection, or graft-versus-host disease (GvHD). May result from:

        i. Direct emetogenic effect from conditioning therapy
        ii. Delayed gastric emptying or gastroparesis

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      iii. Circulating inflammatory cytokines directly affecting appetite centers [1]
      iv. Mucositis-related pain and dysphagia
       v. GvHD
      vi. Infection
      vii. Medications

  b. Diagnosis

     Most cases are identified by clinical presentation and do not require additional workup. Endoscopic evaluation (i.e., esophagogastroduodenoscopy) with biopsies to identify potential underlying causes is recommended for cases of protracted or prolonged nausea, vomiting, or anorexia after mucositis has resolved.

  c. Treatment

       i. Conditioning regimens for HCT include highly emetogenic therapy. Antiemetic prophylaxis during conditioning therapy (see also Chap. 6) should aim at minimizing nausea and vomiting and preserving enteral nutrition for as long as possible.
      ii. Daily calorie count to determine:

         • If adequate nutritional goals are achieved
         • If there is a need for enteral or parenteral supplementation (see also Chap. 7)

     iii. The efficacy of appetite stimulants in the transplant setting has not been studied.

2. Esophagitis/gastritis

  a. Etiology and pathogenesis

     Usually presents during conditioning and period of mucositis but may last longer in patients with GvHD [2]. Potential etiologies include the following:

       i. Mucositis
      ii. Medications
     iii. Poor oral intake
     iv. Altered gastric pH
      v. Peptic ulcer disease

  b. Diagnosis

     Diagnosis is clinical. Symptoms typically include heartburn and/or epigastric pain.

  c. Treatment

       i. First line of therapy is elevation of the head of bed and administration of antacids (calcium carbonate, magnesium, or aluminum hydroxide).
      ii. H_2 blockers (ranitidine [Zantac®], cimetidine [Tagamet®], famotidine [Pepcid®]) should be avoided in the first 100 days post HCT due to the potential risk for myelosuppression [3].

iii. Proton-pump inhibitors may be of utility in patients with gastritis symptoms. However, their use should be reserved for patients failing first-line treatment and for limited time only, as prolonged use may inhibit the natural antimicrobial barrier and increase the risk for infections.

- Lansoprazole (Prevacid®) 30–60 mg po daily to BID
- Omeprazole (Prilosec®) 20–40 mg po daily to BID
- Pantoprazole (Protonix®) 40–80 mg po daily

iv. Gastric acid blockade therapy can impact the absorption of concurrent oral azole antifungal therapy and several immunosuppressive therapies [4].

3. Nausea

a. Etiology and pathogenesis

Usually presents during conditioning [5]. Also observed in conjunction with mucositis, during the recovery period, and as a consequence of GvHD. Potential individual and overlapping etiologies include:

i. Chemotherapy effect
ii. Side effects of other medications
iii. Mucositis
iv. Gastroparesis

b. Treatment

i. Patients with persistent nausea despite prn antiemetics should receive scheduled antiemetics.
ii. Schedule a dopamine antagonist + a short-acting benzodiazepine, e.g., lorazepam (Ativan®) +/− diphenhydramine (Benadryl®).
iii. Examples of dopamine antagonists include:

- Prochlorperazine (Compazine®) 5–10 mg po/IV q6hr
- Metoclopramide (Reglan®) 20–30 mg po/IV or qAC and HS
- Haloperidol (Haldol®) 0.5–2 mg po/IV q4–6 hour
- Promethazine (Phenergan®) 12.5 mg po/IV q4–6 hour

iv. Lorazepam should not be used alone as a scheduled antiemetic unless for anticipatory nausea.
v. Motion-induced nausea should be treated with either a scopolamine (Transderm Scop®) patch 1.5 mg changes every 3 days or meclizine (Bonine®, Antivert®) 12.5–25 mg po q8hr. These medications have been proven effective for acute nausea, however, not in the setting of delayed nausea.
vi. Serotonin 5-HT3 inhibitors (ondansetron [Zofran®], granisetron [Kytril®]) are best used during administration of the conditioning therapy. Prolonged use after completion of the conditioning regimen is discouraged due to the risk for prolongation of QT interval and arrhythmias [6].
vii. See Chap. 6 for additional information about management of nausea.

Lower Gastrointestinal

1. Diarrhea (see Table 32.1)

    a. Etiology and pathogenesis
        May present any time during conditioning or post HCT. The time of onset may assist in identifying potential etiologies including [7]:

        i. Direct side effect from conditioning and other medications.
        ii. Mucositis and intestinal epithelial sloughing.
        iii. Infection.
        iv. GvHD.
        v. Pancreatic insufficiency.
        vi. Brush-border disaccharidase deficiency.
        vii. Malabsorption.
        viii. Intestinal thrombotic microangiopathy.
        ix. Mycophenolate mofetil (Cellcept®) is a very common inciting agent (through direct mucosal toxicity) and may be very difficult to distinguish from GvHD.

    b. Diagnosis

        i. Rule out infection with stool cultures for enteric pathogens.
        ii. For patients in which diarrhea does not improve after resolution of oral mucositis, consider rectosigmoidoscopy to perform visual inspection and obtain tissue biopsies.

    c. Treatment

        i. Identify and treat the underlying cause.
        ii. Supportive care should focus on hydration and prevention/treatment of electrolyte imbalances.
        iii. Bowel rest/restricted diet (low roughage, low residue; low or no lactose [see Appendix 5]).
        iv. Calculate and replace enteral volume losses with isotonic fluid.
        v. Monitor and replace protein losses if severe (albumin).

Table 32.1 Grading of non-GvHD diarrhea

Grade	Diarrhea
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4–6 stools per day over baseline; IV fluid indicated <24 hours; moderate increase in ostomy output compared to baseline; not interfering with ADL
3	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hours; severe increase in ostomy output compared to baseline; interfering with ADLs
4	Life-threatening consequences (i.e., hemodynamic collapse)
5	Death

      vi. Vitamin K depletion associated with chronic diarrhea is common. If the prothrombin time is elevated, vitamin K should be replaced. The dose is 2.5–25 mg IV or SQ (max 10 mg for children); if prothrombin time is not satisfactory within 6–8 hour, the dose may be repeated.

     vii. Antidiarrheal agents that could be used include:

- Loperamide (Imodium®) 2–4 mg po every 6 hours.
- Diphenoxylate hydrochloride with atropine sulfate (Lomotil®) 2.5–5 mg, 3 or 4 times daily (maximum of 20 mg/24 hr).
- Downward adjustment should be made as soon as initial control of symptoms is accomplished.
- Octreotide (Sandostatin®) may be effective to treat or relieve diarrhea associated with conditioning regimen and GvHD. The recommended octreotide regimen varies. A fixed dose of 500 mcg IV every 8 hours for 7 days or 50 mcg (2 mcg/kg) IV TID escalated to continuous infusion at 15 mcg/hour (1 mcg/kg/hour) has been reported to have some success in control of diarrhea in the HCT setting.

   viii. Antidiarrheal agents should not be used in patients with ileus or infectious diarrhea.

     ix. Grading of non-GvHD diarrhea should be done at the time of presentation and at intervals to monitor response to therapy (Table 32.1).

2. Gastrointestinal bleeding

  a. Etiology and pathogenesis

     Most cases have diffuse or multiple areas of bleeding as opposed to a localized ulceration site. Causes of GI bleeding include [8]:

      i. Thrombocytopenia
     ii. Esophageal trauma (from retching)
    iii. Esophagitis
    iv. Colitis
     v. Anal fissures or hemorrhoids
    vi. Viral infections
   vii. GvHD
  viii. Transplant-associated thrombotic microangiopathy [9]

  b. Diagnosis

     Diagnosis is clinical. An esophagogastroduodenoscopy with rectosigmoidoscopy/colonoscopy may aid in identifying the cause of and controlling localized bleeding if present.

  c. Treatment

     When available, treatment of the underlying disorder should be initiated. Symptom control may be achieved with:

     i. Platelet support to maintain platelets ≥50,000/mm^3.
    ii. Octreotide (Sandostatin®) may provide short-term control [10].
   iii. Control of localized bleeding with endoscopic cautery or embolization.

     iv. There is no evidence base for the use of desmopressin (DDAVP®), amino-caproic acid, tranexamic acid, or recombinant factor VII (NovoSeven®) in lower GI bleeding post-HCT.

     v. If localized bleeding is suspected, consider radiologic assessment with angiography or a red cell nuclear scan to identify area(s) of active bleeding.

3. Pneumatosis intestinalis

  a. Etiology and pathogenesis

     Characterized by the accumulation of gas in the intestinal wall. Causes include:

     i. Mucositis/enteritis
     ii. Infection
     iii. GvHD
     iv. Prolonged treatment with systemic steroids or budesonide

  b. Diagnosis

     i. Clinical picture varies from asymptomatic to abdominal pain and distention.
     ii. Diagnosis is usually established by radiographic findings (CT scan or plain films).

  c. Treatment [11]

     i. Treatment of pneumatosis intestinalis in HCT patients is primarily nonsurgical with gut rest and parenteral nutrition +/− antibiotics.
     ii. Surgical intervention carries a high risk of mortality and should be avoided.

4. Ileus

  a. Etiology and pathogenesis

     i. Mucositis/enteritis/colitis
     ii. Infection/sepsis
     iii. Severe gut GvHD
     iv. Medications (particularly opioids)

  b. Diagnosis

     i. Clinical presentation: bilious vomiting, abdominal distention, abdominal pain, decreased or absent bowel sounds, and decreased or absent stool output.
     ii. Confirmation by imaging (plain films, CT scan, or ultrasound). Administration of oral contrast should be avoided if ileus is suspected.

  c. Treatment

     i. Conservative medical management with gut rest, nasogastric tube with or without suction for gastric decompression, and parenteral nutrition +/− antibiotics if infectious cause is suspected.
     ii. Surgical management is not recommended unless peritonitis or perforation is suspected or confirmed.

Hepatobiliary Diseases

1. Sinusoidal obstruction syndrome or veno-occlusive disease of the liver (SOS/VOD)

   a. Epidemiology

      Incidence is reported at approximately 5–10%. Severe SOS/VOD frequently leads to multi-organ failure and is associated with day 100 mortality of >90%.

   b. Etiology and pathogenesis [12]

      Usually presents during the first weeks following conditioning, prior to engraftment, and results from direct injury to sinusoidal endothelial cells and hepatocytes. Pretransplant risk factors include:

      i. Infants and older adults (>50 years)
      ii. Poor performance status
      iii. Advanced malignancy, patients with inborn errors of metabolism or hemoglobinopathies
      iv. Reduced pulmonary diffusion capacity (DLCO)
      v. Prior hepatic disease (elevated bilirubin or AST, preexisting cirrhosis, iron overload)
      vi. Prior abdominal radiation
      vii. Use of gemtuzumab (Mylotarg®) or inotuzumab ozogamicin (Besponsa®) prior to transplant

   c. Transplant risk factors include:

      i. Myeloablative conditioning
      ii. Second HCT
      iii. Use of high-dose alkylating chemotherapy (busulfan) or total body irradiation (TBI)
      iv. Use of methotrexate for GvHD prophylaxis

   d. Diagnosis

      i. Diagnosis is made on clinical basis. See Table 32.2 for diagnostic criteria. Features include:

         • Total bilirubin >2 mg/dL
         • Weight gain >5% from baseline
         • Right upper quadrant tenderness (tender hepatomegaly) ± ascites

Table 32.2 Criteria for diagnosis of SOS/VOD

Modified Seattle criteria	Baltimore criteria
At least two of the following, occurring within 20 days of HCT:	Serum bilirubin >2 mg/dL within 21 days of HCT and at least two of the following:
Serum bilirubin >2 mg/dL	Hepatomegaly
Hepatomegaly with RUQ pain	>5% weight gain from baseline
>2% weight gain from baseline due to fluid retention	Ascites

ii. Abdominal ultrasound with liver Doppler usually shows hepatomegaly, ascites, and, in more advanced cases, reversal of portal flow.

iii. Liver biopsy is not necessary for diagnosis. If needed to rule out other causes, a transvenous liver biopsy with measurement of hepatic venous pressure gradient should be obtained. More invasive procedures (percutaneous or open biopsy) carry higher risk due to high pressures and coexisting coagulopathy associated with hepatic synthetic dysfunction.

iv. Differential diagnoses include sepsis-related cholestasis, other cholestatic liver disease, and GvHD.

e. Treatment

i. Prevention of SOS/VOD is the best "treatment" by recognizing patients who are at risk and, when possible, avoiding exposure to known risk factors (i.e., selection of transplant conditioning regimen).

ii. Ursodeoxycholic acid (Ursodiol®) 12 mg/kg/day divided in 2 doses from the start of conditioning has been shown in small randomized studies of prophylaxis to provide benefit in decreasing the severity of SOS/VOD and hepatic complications of transplant. Duration of prophylaxis varied from 1 to 3 months posttransplant [13].

iii. Prompt diagnosis and management are crucial, as the severe form of this disease results in very high rates of mortality.

iv. Supportive care is the treatment of choice, including:

- Maintaining careful fluid (water and sodium) balance
- Providing aggressive diuresis
- Discontinuing/avoiding agents that may exacerbate hepatotoxicity when possible
- Preserving renal blood flow
- In severe cases, use of continuous renal replacement therapy until fluid balance is improved

v. Defibrotide (Defitelio®) is a potent antithrombotic and profibrinolytic agent [14].

- A historical-controlled phase III study demonstrated a survival advantage for patients with severe SOS/VOD who receive this drug early in their course.
- This drug is indicated for severe SOS/VOD with renal or pulmonary dysfunction, dosed at 6.25 mg/kg every 6 hours IV for a minimum of 21 days.
- The most common side effects of defibrotide are hypotension and increased risk for bleeding. Concomitant administration of other anticoagulants is contraindicated.
- If invasive surgical procedures are planned, the drug should be held at least 6 hours prior to the procedure.

2. Acute hepatitis (also see Chap. 30)

   a. Etiology and pathogenesis [15]

      May present anytime during conditioning or post-HCT. The time of onset may assist in identifying potential etiologies which includes the following:

     i. Infection/sepsis
     ii. Acute biliary obstruction
     iii. Drug-induced toxicity
     iv. GvHD

   b. Diagnosis

     i. Sudden elevation of serum transaminases (AST, ALT).
     ii. Blood tests for viral DNA (herpes viruses, adenovirus, hepatitis B, hepatitis C).
     iii. Imaging (CT or ultrasound) may be used to identify fungal abscesses in the setting of disseminated infection.
     iv. Liver biopsy may aid in identifying a cause.

   c. Treatment

      Supportive care, removal of inciting agents when possible (if drug related), and treatment of infection.

     i. A prolonged course of antibiotics or antifungals may be required for bacterial or fungal infections.
     ii. Acute viral hepatitis may lead to fulminant hepatic failure if not treated promptly. Possible viruses include herpes simplex, varicella zoster, cytomegalovirus, and human herpesviruses (HHV-6 and HHV-8). If the patient is not receiving acyclovir prophylaxis, initiation of empiric treatment is recommended.
     iii. Hepatitis B can also present with fulminant hepatic failure. Patients with a previous history of hepatitis B or exposure to a donor with a previous history of hepatitis B are at higher risk. Antiviral therapy should be initiated promptly (lamivudine [Epivir®], tenofovir [Viread®], entecavir [Baraclude®], or similar). The initiation and further dosing for these agents should be determined with the assistance of a gastroenterology/hepatology specialist.

3. Gall bladder disease and pancreatitis

   a. Etiology and pathogenesis [16]

      Biliary sludging is very common in transplant patients and is usually asymptomatic but may also cause acute acalculous cholecystitis, pancreatitis, or cholangitis. Sludging may result from:

     i. Chemotherapy.
     ii. Parenteral alimentation with prolonged absence of oral intake.
     iii. Antibiotics.

    iv. Hyperlipidemia.

    v. GvHD.

    vi. Infection/sepsis. Consider adenoviral infection, especially in children.

b. Diagnosis

Abdominal ultrasound may reveal gall bladder disease (thickening of gallbladder wall, stones, etc.). Hepatobiliary iminodiacetic acid (HIDA scan) may reveal gall bladder obstruction.

c. Treatment

    i. Bowel rest.

    ii. Discontinuation of parenteral alimentation if inciting agent.

    iii. Cholecystectomy is infrequently needed.

    iv. Endoscopic retrograde cholangiopancreatography (ERCP) is only needed in the case of obstructive cholangitis.

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Chapter 33
Pulmonary Complications

Gregory A. Yanik and Adam S. DuVall

Introduction

Lung injury is a significant complication after hematopoietic cell transplant (HCT) and can lead to significant morbidity and mortality. As infection and non-infectious etiologies are common and have, at times, indistinguishable features, diagnosis is often difficult. Additional early intervention is critical to patient management and delays lead to negative outcomes. This chapter will describe the most common pulmonary syndromes post HCT in addition to reviewing their evaluation and management.

Pulmonary Function Tests

1. Spirometry is used to aid in the diagnosis of obstructive versus restrictive lung disease. Two-year mortality after hematopoietic cell transplant (HCT) has been estimated using a Pre-transplantation Assessment of Mortality (PAM) score which incorporates a spirometry variable in combination with age, donor type and match, disease risk, and cytomegalovirus (CMV) status (Table 33.1) [1].

    a. Obstructive lung disease is diagnosed with a forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio <70% and FEV1 <80%. If plethysmography (measurement of changes in lung volumes) is performed,

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Table 33.1 Selected acronyms of interstitial lung disease

Acronym	Interstitial lung disease
UIP/IPF	Usual interstitial pneumonitis/Idiopathic pulmonary fibrosis
HSP	Hypersensitivity pneumonitis (often due to an aeroallergen such as thermophilic fungi)
NSIP	Non-specific interstitial pneumonitis
IPS	Idiopathic pneumonia syndrome
BOS	Bronchiolitis obliterans syndrome
BOOP/ COP	Bronchiolitis obliterans organizing pneumonia/Cryptogenic organizing pneumonia
AIP	Acute interstitial pneumonia

the presence of increased residual volume (RV) indicates air trapping, common with bronchiolitis obliterans syndrome (BOS).

b. Low FVC and/or low total lung capacity (TLC) with normal FEV_1/FVC ratio indicates restrictive lung disease.

2. DLCO

a. DLCO corrected for hemoglobin should be used [DLCOadj].
b. >80% normal, 60–80% mild, 40–60% moderate, <40% severe.

Bronchoscopy

1. Broncho-alveolar lavage (BAL) via bronchoscopy should be pursued if an infectious pneumonia is being considered, though yield can be highly variable [2, 3].
2. Pre-procedure stabilization with supplemental oxygen is key.

a. Depressed mental status may increase procedural risk.
b. The presence of severe hypoxia and a depressed mental status may require endotracheal intubation to safely perform the procedure.
c. Conscious sedation with fentanyl and/or midazolam is often used for comfort and amnesia.

3. Unless there is active bleeding, correction of coagulopathy is not required and there is no absolute platelet level required for performing a BAL alone.

a. However, if a transbronchial biopsy (TBBx) will be attempted, a pre-procedure platelet count of $\geq$30,000–50,000/mm^3 and INR of <1.5 are recommended.

4. Complications of a BAL, though <5%, may include worsening hypoxemia, hemorrhage, hypotension, arrhythmia, and respiratory failure requiring mechanical ventilation.

5. Risks associated with TBBx including pneumothorax, refractory hypoxia, and hemorrhage. TBBxs have not been shown to increase diagnostic yield for pathogen identification [4].
6. Appropriately stained BAL smears may suggest a pathogen in a matter of hours while cytology, culture, and genetic results are pending. BAL fluid should routinely be sent for:

    a. Cytology including stains for organisms (fungi, *Pneumocystis jiroveci* pneumonia [PCP]) and potentially hemosiderin laden macrophages
    b. Bacterial cultures (including *Nocardia*) and sensitivity
    c. Fungal smear and culture
    d. Mycobacterium smear and culture
    e. Cell count and differential
    f. Galactomannan antigen
    g. PCR for respiratory viral panels
    h. PCR for legionella
    i. Direct fluorescent antibody (DFA) stain or PCR for PCP

Idiopathic Pneumonia Syndrome (IPS)

IPS is an acute, severe lung injury that develops after allogeneic HCT in the absence of an infectious process. It encompasses a spectrum of disorders including acute interstitial pneumonitis, diffuse alveolar hemorrhage (DAH), periengraftment respiratory distress syndrome (PERDS), and chemotherapy-related lung injury or delayed pulmonary toxicity syndrome (DPTS). DPTS and DAH are considered separate entities by some groups. The incidence ranges between 2% and 10% with mortality rates ranging from 50% to 80% within 28 days of diagnosis. If mechanical ventilation becomes necessary, mortality rates are even higher. Median time to onset of IPS is 14–42 days post-HCT; however, later onset forms of IPS have been reported [5–7].

1. Risk Factors [5]

    a. Grade 3–4 acute graft-versus-host disease (GvHD)
    b. Donor cytomegalovirus (CMV) positivity
    c. Conditioning regimens containing total body irradiation (TBI)
    d. Older age (older than 40 years of age)
    e. Certain malignancies (acute leukemia, myelodysplastic syndrome)
    f. Certain chemotherapeutic agents (methotrexate, busulfan)

2. Clinical Findings
   Clinical findings are often indistinguishable from infectious pneumonia which include fever, cough usually productive of scant or no phlegm, shortness of breath, and hypoxia.
3. Diagnostic tests
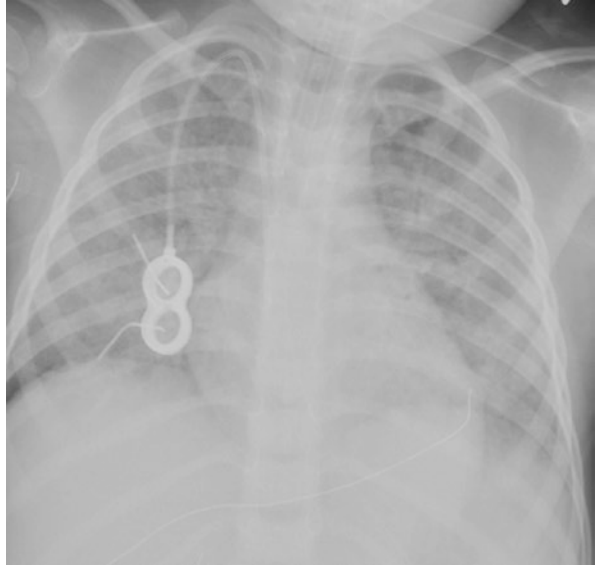
All patients with suspected IPS should undergo chest imaging and bronchoscopy with BAL to rule out infection. Occasionally, CXR does not show obvious infiltrates and CT scan of the chest is warranted. The criteria for diagnosis of IPS were initially proposed in 1993 and updated by the American Thoracic Society in 2010 to include [5]:

a. Evidence of widespread alveolar injury

   i. Radiologic imaging evidence of multi-lobar, diffuse infiltrates (Fig. 33.1).
   ii. Signs and/or symptoms of pneumonia.
   iii. Hypoxia or elevated alveolar-arterial gradient.
   iv. Restrictive pattern on PFTs

b. Absence of lower respiratory tract infection

   i. Negative BAL fluid cultures for bacterial, fungal, mycobacteria, and viral pathogens.
   ii. Negative viral PCRs (CMV, HSV, VZV, RSV, influenza, adenovirus, parainfluenza, and other pathogens)
   iii. Negative serum and BAL fluid galactomannan ELISA for Aspergillus species
   iv. Though not mandatory for diagnosis, a negative TBBx for infectious etiologies supports the diagnosis.

c. Absence of cardiac dysfunction, renal failure, or fluid overload as etiology of pulmonary dysfunction

4. Pathogenesis of IPS

   IPS is a complex cytotoxic and immune-mediated attack of the lung associated with activation of cytokine/chemokine signal transduction pathways that lead to lung inflammation and injury [8]. It is believed to be initiated by conditioning chemotherapy and radiation or potentially infection that results in endothelial injury and oxidative stress [9]. This can lead to innate immune activation and damage to lung parenchyma which initiates the positive feedback loop of GvHD-donor T-cell activation, further tissue injury, and then additional T-cell activation [10].

5. Management

   a. Corticosteroids should be started early in the disease course. A common starting dose is 2 mg/kg daily of methylprednisolone-equivalent for the first week of therapy, followed by a slow taper over 2–3 months.
   b. PCP and fungal prophylaxis are recommended.
   c. Etanercept (Enbrel®) 0.4 mg/kg (max 25 mg) SQ twice weekly for 8 doses used in conjunction with corticosteroids should be strongly considered [11, 12]. A phase II trial through the Children's Oncology Group (COG) and Pediatric Blood and Marrow Transplant Consortium (PBMTC) identified patients that responded dramatically to combination therapy, though this was not replicated in a phase III trial in adults as the trial closed early due to poor enrollment [3].

Diffuse Alveolar Hemorrhage (DAH)

DAH is a subset of IPS that can develop in up to 10% of allogeneic HCT recipients with mortality rates ranging between 50% and 100%. DAH exhibits a similar median time to onset and risk factors as seen with IPS [10]. Though the pathogenesis of DAH appears distinct from other forms of IPS, the epidemiology, clinical presentation, and outcomes are very similar.

1. Risk factors [10]

   a. Myeloablative conditioning
   b. Conditioning regimens containing TBI
   c. Increased age
   d. Coagulopathy

2. Clinical findings

   a. Subjective findings

      i. Shortness of breath
      ii. Cough
      iii. Rarely hemoptysis

   b. Objective findings

     i. Fever
    ii. Tachypnea
   iii. Acrocyanosis
   iv. Crackles heard on lung auscultation

3. Diagnostic Tests

   a. CXR classically shows bilateral diffuse alveolar opacities which could be confirmed by CT scan imaging (see Fig. 33.1) as ground glass opacities. These findings, however, are not specific and may be seen in many other conditions.
   b. Bronchoscopy with BAL is the confirmatory diagnostic method demonstrating any of the following

     i. Progressive bloody return on serial lavages.
    ii. Cytology with Prussian blue staining with ≥20% hemosiderin laden macrophages. This test is of limited diagnostic value if alveolar hemorrhage occurred <48–72 hours before the procedure, as duration of time may be too short for RBC phagocytosis by pulmonary macrophages.
   iii. Blood in ≥30% of alveolar surfaces.

4. Pathogenesis of DAH
   DAH post-HCT is thought to result from a similar pathogenesis as IPS leading to epithelial and endothelial injury, resulting in hemorrhage [8–10].
5. Management
   Patients with suspected DAH are routinely transferred to a medical-intensive care unit, given that respiratory failure may develop acutely in this clinical setting. Many patients with DAH require high flow oxygen and subsequent mechanical ventilation for management. Supportive management and high dose systemic steroids are the key elements of DAH treatment.

   a. Mechanical ventilation should be tailored to each individual, reflecting the acute respiratory distress syndrome (ARDS) mechanical ventilation protocol/low tidal volume for management of acute lung injury. This practice has not been validated in DAH, but the pathological pattern of DAH is similar to acute lung injury/ARDS. Similarly, prone positioning may be of benefit in refractory cases.
   b. Immunosuppressive therapy with high dose corticosteroids is the mainstay of therapy, based on case reports and retrospective series. Doses of up to 1 gm of methylprednisolone divided into 2–4 doses should be given daily for 3–5 days, followed by a slow taper over 1–3 months. Alternate dosing schedules have been suggested, beginning at 2 mg/kg daily in divided doses, tapering over a 2-month period.
   c. Correction of underlying coagulopathy by maintaining a platelet count >50,000/mm^3 and INR <2.

    d. BAL to rule out a concomitant infectious pathogens.

    e. Recombinant factor VIIa (NovoSeven®) and/or aminocaproic acid (Amicar®) have been used; however, no benefit has been demonstrated with limited supporting data.

Bronchiolitis Obliterans Syndrome (BOS)

The most common late-onset, non-infectious pulmonary complication following allogeneic HCT is BOS. The reported incidence ranges between 2% and 20%, with varying estimates likely related to the different diagnostic criteria used in studies over time [13]. BOS is usually diagnosed between the third month and first 2 years following HCT [13]. Most investigators consider BOS to be a manifestation of chronic GvHD of the lung. It is also important to recognize BOS as a separate clinical entity from cryptogenic organizing pneumonia (COP).

1. Risk factors [13–15]

    a. Extrathoracic chronic GvHD is the only associated finding that is consistent across all studies

    b. Use of peripheral stem cells

    c. Busulfan-based conditioning regimen

    d. Degree of HLA mismatch

    e. Prior interstitial pneumonitis

    f. An episode of grade 3–4 acute GvHD

    g. Personal tobacco use

    h. Age $\geq$20 years

    i. Pre-existing airflow obstruction

    j. Previous respiratory viral infection (CMV, RSV, or Parainfluenzae)

    k. IgG level <350

2. Definition

The NIH diagnosis and staging working group prepared a consensus definition for BOS to provide uniform inclusion criteria for future studies. To make the diagnosis of BOS, these criteria must be present along with active chronic GvHD in at least one organ other than the lung [16]:

    a. PFTs: FEV_1 <75% of predicted normal, a ratio of FEV_1/FVC ratio <0.7 and RV >120% of predicted normal

    b. Imaging: Expiratory high-resolution chest CT that reveals air trapping, small airway thickening, or bronchiectasis

    c. Absence of active infection

    d. Or pathologic confirmation of constrictive bronchiolitis

        i. Lung biopsy typically shows cicatricial bronchial obliterans (i.e., obliteration of airways by dense fibrous scar tissues)
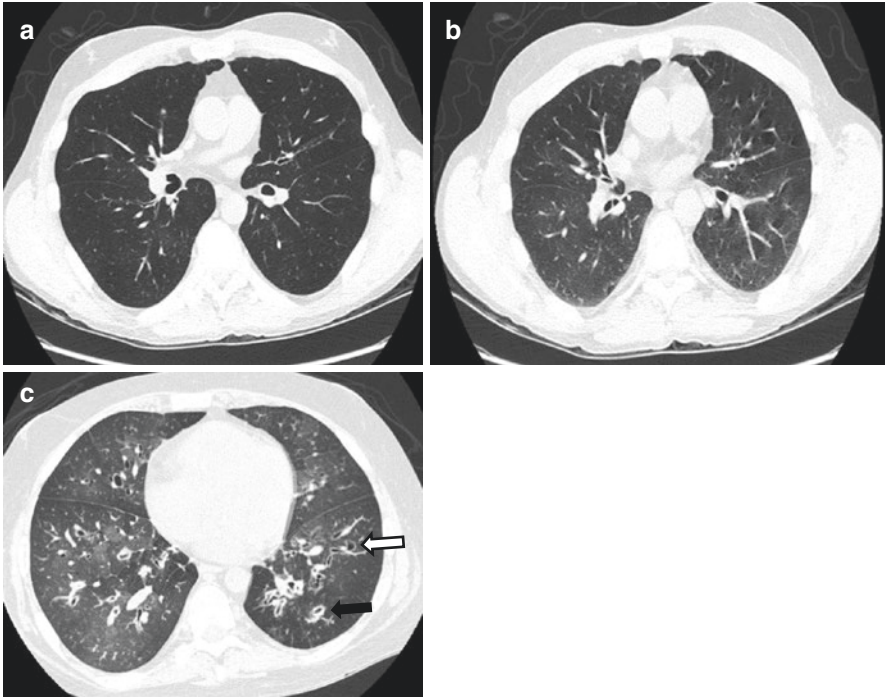
Fig. 33.2 a, **b**. High-resolution computed tomography. Bronchiolitis obliterans syndrome with mosaic (heterogeneous) attenuation pattern on expiratory imaging, with air trapping present. **a**. Inspiration. **b**. Expiration. **c**. Severe bronchiolitis obliterans syndrome (expiratory image). Extensive air trapping, with moderate to severe bronchiectasis (white arrow). Note markedly dilated and thickened airways (black arrow)

3. Clinical Findings [13]

   BOS has an insidious course, manifested by non-productive cough, wheezing, and dyspnea. Recurrent lung infections may also occur throughout the course. Early in the course of BOS, the patient's pulmonary exam may be normal; however, later stages of BOS are manifested by wheezing, prolonged expiratory phase, and inspiratory crackles.

4. Diagnostic tests [13]

   a. Chest imaging should be carried out in all patients suspected to have BOS. CXR may be normal in the early stages of the disorder with hyperinflation seen as BOS progresses.
   b. High-resolution CT of the chest is more specific (Fig. 33.2a–c). Inspiratory and expiratory phases should be included to evaluate for air trapping or "mosaic lung appearance" which indicates regional airflow obstruction during the expiratory phase.

   c. PFTs are obtained as part of every patient's pre-HCT baseline evaluation and should be repeated if BOS is suspected.

   d. Bronchoscopy is not routinely performed during the work up of BOS unless imaging is suspicious for an infectious process.

   e. TBBx is often non-diagnostic as the disease process is patchy.

   f. Surgical lung biopsy has higher chance of demonstrating constrictive bronchiolitis, the pathology seen in BOS.

      i. With the introduction of high-resolution CT, surgical lung biopsy is often not required to confirm a diagnosis of BOS.

5. Pathogenesis of BOS

BOS is postulated to be a form of chronic GvHD with the etiology related to recognition of disparate antigens present in the context of HLA class I and class II MHC molecules. It is thought to be initiated by damage to small airway epithelium caused by infections or other epithelial insults [13, 17]. This leads to activation and proliferation of allo-reactive T cells, which then lead to further damage of small (or terminal) airways. However, B cells are also thought to play a role in BOS, as demonstrated through animal models and circulating biomarkers in affected patients [18, 19]. Pathologically, BOS begins as a fibro-proliferative disease of the small airways, which results in inflammation, epithelial metaplasia, and denudification [13, 17]. Submucosal/mucosal fibrosis then develops resulting in obliteration of the airways [13, 17].

6. Management

Management of BOS mainly involves intensifying immunosuppressive therapy and supportive care. There are no specific recommendations associated with treatment of BOS. The management of BOS mimics that of chronic GvHD with the goal of preventing the further decline of lung function. Recommendations are mostly based on prospective case series or retrospective reviews [13]:

   a. Response to bronchodilators is often minimal but nevertheless may be considered because of presence of airflow obstruction.

   b. Corticosteroids 1 mg/kg prednisone per day for 2 weeks, then tapered by approximately 0.25 mg/kg/day per week as tolerated to goal dose of approximately 0.25 mg/kg/day by 5 weeks [20].

   c. Other immunosuppressive medications may be effective as steroid sparing agents, including calcineurin inhibitors.

   d. FAM (fluticasone, azithromycin, montelukast) is often given as first-line therapy based on a phase II, single-arm, open-label study [20]. In this trial, fluticasone (Flovent®) was given at 440 mcg twice daily for patients ≥12 years in age, and 220 mcg twice daily for patients 6–<12 years. Azithromycin (Zithromax®) is given three times weekly at 250 mg for those >18 years old and 5 mg/kg (max 250 mg) for those ≤18 years old. Montelukast (Singulair®)

is given at 10 mg nightly for those ≥14 years old and 5 mg nightly for those 6 to <14 years old. *Of note, increased rates of hematologic relapse (for patients with primary hematologic malignancies) have been reported when azithromycin has been given as BOS prophylaxis at onset of conditioning for HCT* [31].

e. Patients should be assessed for oxygen needs using a 6-minute walk test and/or nocturnal O2 monitor study.

f. Echocardiogram can be used to screen for pulmonary hypertension and left ventricular dysfunction, both accompanied by dyspnea.

g. Lung transplant may be considered for selected patients with severe respiratory impairment; however, many centers require patients to be at least 5 years post-HCT before they can be listed for lung transplant.

h. Progressive disease: The majority of studies have been small retrospective cases series, with few randomized clinical trials.

   i. Extracorporeal photopheresis (ECP) has demonstrated efficacy post-lung transplant with similar results in post-HCT patients [22].

   ii. Etanercept (Enbrel®) in patients with subacute lung injury has shown improvement in lung function with a 5-year overall survival of 61%, 90% in patients who responded to therapy [23]. However, clinical benefits were most pronounced when the agent was started early in the course of BOS.

   iii. Kinase inhibitors, such as ruxolitinib (Jakafi®) and ibrutinib (Imbruvica®), are becoming more widely used for steroid refractory or progressive disease; however, there are limited data of their effectiveness in BOS [24]

The management of BOS is complicated and requires a multi-specialty approach (stem cell transplant, pulmonary, and radiology specialists). BOS has been historically associated with a very poor prognosis [13]. However, more recent studies have demonstrated plateauing of lung function after diagnosis and the initiation of treatment with survival between 70% and 80% [25]. Attention to dyspnea and early and frequent PFTs may allow for earlier identification of BOS before permanent (fibrotic) airway changes, respiratory insufficiency, and pneumonia occur allowing for further improvement in outcomes.

Cryptogenic Organizing Pneumonia (COP)

COP, also known as bronchiolitis obliterans organizing pneumonia (BOOP), is a disease process of unknown etiology that differs from BOS in clinical findings, response to treatment, and prognosis [3, 13, 26]. It develops in 1–2% of HCT recipients though there are no consensus diagnostic criteria [26, 27].

1. Risk factors [27, 28]

   a. Acute or chronic GvHD is the strongest, most reproducible association
   b. TBI-containing conditioning regimen
   c. HLA mismatch
   d. Stem cell source (peripheral blood stem cells > bone marrow)

2. Clinical findings
   The presentation of COP is similar to many respiratory disorders; most commonly dyspnea is accompanied by non-productive cough and fever. Physical exam is primarily notable for the presence of crackles and the absence of wheezing.

3. Diagnostic tests

   a. CXR may show patchy consolidation with ground glass or nodular infiltrates.
   b. CT scan of the chest is typically required to demonstrate areas of bilateral organizing pneumonia and consolidation in subpleural or peri-bronchial distribution associated with areas of ground glass opacities [29]. Migratory opacities on CT scan have been described in patients with COP though predominantly in immunocompetent patients [21, 30].
   c. PFTs typically show a restrictive pattern with decreased FVC, decreased TLC, and decreased DLCOadj; airflow obstruction (decreased FEV_1) is generally absent [21, 29, 30].
   d. Bronchoscopy with BAL may be helpful in determining the diagnosis.
   e. Lung biopsy, either by TBBx or video-assisted thoracic surgery (VATS), is occasionally required to confirm the diagnosis.

      i. Typical pathology shows granulation tissue plugs in the bronchioles and alveolar ducts associated with surrounding chronic interstitial inflammation [26].

4. Management

   a. Bronchoscopy with BAL is often required to rule out infectious processes that may confound the diagnosis of COP.
   b. Systemic corticosteroids have been used, though relapses may occur if steroids are tapered too rapidly [26].
   c. Overall, the prognosis of COP is favorable with 80% of patients expected to recover lung function [26].

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Chapter 34
Cardiovascular Complications

Michael E. Layoun and Maros Ferencik

Introduction

The assessment of cardiovascular risk and attention to the cardiovascular system of patients undergoing hematopoietic cell transplant (HCT), as well as an awareness of the treatment's potential long-term cardiac effects are critical in the overall care of these complex and vulnerable patients. The issues facing patients and their treating clinicians are primarily centered in three arenas: (1) cardiovascular comorbidities and the overall cardiovascular reserve, (2) chemotherapy and radiation–associated cardiovascular toxicities, and (3) long-term effects of HCT.

As it stands, there are well over 160,000 HCT survivors living in the United States today, and that number is expected to exceed 500,000 by 2030 [1, 2]. HCT survivors carry increased risk of future cardiovascular disease compared to the general population, with pre-transplant comorbidities playing a major role (Fig. 34.1) [3]. Heart failure risk is close to 5% at 5 years and almost 10% at 15 years [4]. Arrhythmias make up the largest risk in this population, being notable in about a quarter of the population [5]. Cardiotoxic side effects from various chemotherapeutic agents and chest wall radiation pose specific cardiovascular risks that are outlined in this chapter. With this information in mind, early recognition and treatment of cardiotoxicities, as well as the potential identification of at-risk patients, allows treating providers to optimize care of patients undergoing HCT, ensuring the best treatment of the underlying hematologic malignancy while mitigating cardiovascular risk. Lastly, monitoring of patients for long-term cardiovascular effects of HCT may prevent the success of cancer therapy from being overshadowed by cardiovascular morbidity and mortality.

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Fig. 34.1 Decline in cardiovascular reserve following HCT

Development of cardiovascular disease
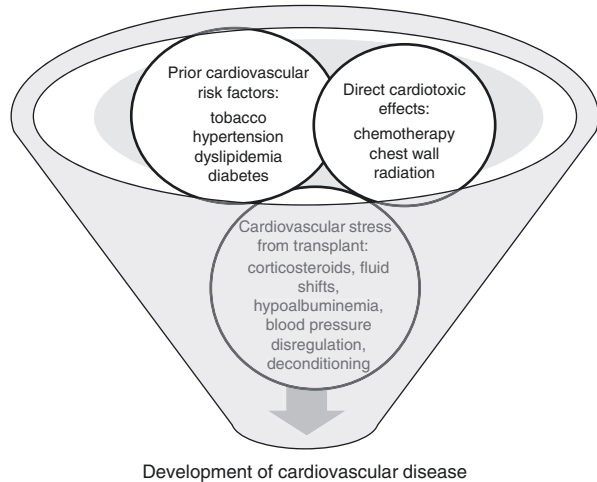
Baseline Cardiac Evaluation

1. History and Physical Exam

    a. Assess for any prior history of cardiovascular disease:

        i. Adequate blood pressure control in hypertensive patients is important as post-transplant immunosuppressive medications (cyclosporine, tacrolimus) can worsen hypertension (HTN) [6–9].

        ii. If there is known history of atrial fibrillation, ensure there is adequate rate (or rhythm) control and the patient is on thromboembolic protection, as indicated per American Heart Association/American College of Cardiology (AHA/ACC) guidelines (see section "Cardiac Arrhythmias" Arrhythmia) [10].

        iii. If there is known stable ischemic heart disease, ensure it is appropriately controlled with adequate anti-anginal therapy prior to initiation of HCT.

    b. Establish a functional baseline based on Eastern Cooperative Oncology Group (ECOG) performance status (see Chap. 4) and/or New York Heart Association (NYHA) score (see Table 34.1).

    c. Risk factors for post-transplant cardiac complications include advanced age, prior anthracycline use, cyclophosphamide-based conditioning regimens, 5-fluorouracil (5-FU), capecitabine (Xeloda®), prior trastuzumab-mediated cardiotoxicity, and chest wall radiation [11–14].

    d. In addition to standard cardiac and pulmonary examination, physical exam findings should include assessment of possible increased intravascular and extravascular fluid accumulation with elevated jugular venous pressure (JVP), presence of a positive hepatojugular reflux (1 cm increase in JVP >15 seconds with RUQ abdominal pressure), inspiratory crackles on lung exam, and pitting edema of the lower extremities or sacrum.

Table 34.1 NYHA score

NYHA class	Symptoms
I	No limitation of physical activity Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath)
III	Marked limitation of physical activity. Comfortable at rest Less than ordinary activity causes fatigue, palpitation, or dyspnea
IV	Unable to carry out any physical activity without discomfort Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

2. Assessment of Left Ventricular Function

   a. All patients should undergo assessment of left ventricular systolic function prior to planned HCT with special attention to patients with known history of heart disease or risk factors.

   b. Left ventricular ejection fraction (LVEF) of ≥45–50% is commonly chosen as an eligibility criterion for conventional myeloablative HCT by most centers, with reduction to >35% for reduced-intensity conditioning regimens; however a formal consensus is not available.

   c. Imaging modalities for LVEF include transthoracic echocardiography (TTE), multi-gated radionuclide angiography (MUGA), cardiac-gated computed tomography angiography (cardiac CTA), and cardiac magnetic resonance imaging (CMR):

      i. MUGA when compared to TTE has higher specificity and less inter-observer variability but caries the burden of radiation exposure [15].

      ii. TTE and CMR provide additional information such as valvular function when compared to MUGA [16].

      iii. With the added benefit of objective measurement of global longitudinal strain (early indicator of myocardial dysfunction with the potential to predict future systolic dysfunction), TTE has become a more attractive method to assess LV function at experienced centers [16–18].

         • Global longitudinal strain is a measure of the percentage of ventricular muscle shortening.

      iv. Cardiac CTA provides a noninvasive method to assess for the presence of coronary atherosclerosis and significant stenosis with high sensitivity and negative predictive value compared to other noninvasive imaging modalities [19, 20].

3. Indications for Noninvasive Stress Testing

   a. There is a paucity of literature to suggest stress testing improves the ability to predict risk of peri-transplant cardiovascular complications. However, some

centers routinely perform noninvasive stress testing as part of the pre-transplant evaluation.

b. If pre-transplant baseline cardiovascular evaluation reveals an indication to obtain noninvasive stress testing independent of the HCT, such as a new diagnosis of stable ischemic heart disease (SIHD), stress testing should be performed based on AHA/ACC guideline recommendations [21].

   i. Current indications for stress testing include, but are not limited to, patients with history and/or physical examination findings suggestive of stable ischemic heart disease, newly diagnosed cardiomyopathy, valvular heart disease, history of ventricular arrhythmia, and significant risks for coronary artery disease (CAD) who are undergoing non-cardiac surgery.
   ii. Further cardiac evaluation and management should be pursued if indicated based on the results of the stress test with cardiology consultation (Fig. 34.1).

Congestive Heart Failure (CHF)

1. CHF is a clinical diagnosis, independent of LVEF, which is made on the basis of history and physical exam findings suggestive of intravascular and/or extravascular fluid accumulation related to increased intracardiac pressures.
2. Heart failure etiologic considerations in HCT patients include ischemic cardiomyopathy, non-ischemic cardiomyopathies, and heart failure with preserved ejection fraction.

   a. Ischemic cardiomyopathy:

      i. Heart failure with reduced LVEF (typically <50%) in the setting of known obstructive CAD [22]
      ii. May either be diagnosed at the time of acute coronary syndrome (ACS) or SIHD in an ambulatory setting
      iii. Ischemic cardiomyopathy may be a comorbidity in those patients with known CAD who present for HCT
      iv. Revascularization in patients with ischemic cardiomyopathy may lead to improvement of LVEF and heart failure symptoms

   b. Nonischemic cardiomyopathy:

      i. This label covers a wide range of cardiomyopathies (LVEF typically <50%) without obstructive CAD, confirmed either by a noninvasive assessment or by invasive coronary angiography.
      ii. Etiologies are numerous and in an HCT population are focused on chemotherapy-induced mechanisms as well as prior chest wall radiation:

         • Cyclophosphamide cardiotoxicity: Heart failure associated with cyclophosphamide therapy may occur in up to 28% of patients, has a dose-related risk (>150 mg/kg and 1.5 g/m^2/day), and occurs within 1–10 days

after administration of the first dose [23, 24]. Dose schedules where cyclophosphamide dosing is administered based on ideal body weight, as opposed to actual body weight, will reduce this risk (see Chap. 6).

- Anthracycline cardiotoxicity: Dose-related risk, typically seen with cumulative lifetime doses exceeding doxorubicin equivalent dose of 400 mg/m^2. Risk for systolic heart failure below this dose is less than 1%. However, acute toxicity can be seen at lower doses, especially when combined with other risks (e.g., prior cardiovascular disease, volume overload in the setting of treatment, arrhythmia, etc.). Heart failure symptoms and/or decrease in LVEF are seen weeks to months after exposure, typically within the first 12 months after the completion of treatment [15, 17, 18, 25, 26].

c. Heart failure with preserved ejection fraction (HFpEF):

i. A category of diseases that present with heart failure symptoms (NYHA symptoms and evidence of intravascular and/or extravascular fluid accumulation, as listed above) in the setting of a preserved LVEF (LVEF > 50%).

ii. The unifying etiology for these findings is related to increased intracardiac pressures, specifically left ventricular end-diastolic pressures that manifest with symptomatic dyspnea on exertion or at rest and fluid accumulation.

iii. While there are various etiologies for HFpEF, the typical ambulatory presentation is seen in patients with risk factors including essential HTN, diabetes mellitus, obesity, impaired renal function, and sleep apnea [27].

iv. Other etiologic considerations include valvular heart disease and infiltrative cardiomyopathies (e.g., cardiac amyloidosis). Cardiology consultation for co-management is recommended if there is concern for these etiologies.

v. A specific subgroup of HFpEF that may be seen in the HCT population includes patients previously exposed to chest wall and mediastinal radiation. This treatment predisposes patients to structural heart disease and CAD including stenosis of the coronary ostia (see section "Congestive Heart Failure (CHF)" 2.a) and microvascular disease. Structural heart disease includes constrictive pericarditis and predominantly left-sided heart valve pathologies (stenosis and/or regurgitation of the mitral and aortic valves) [28–30].

d. Hypoalbuminemia, fluid shifts, tachyarrhythmias, ischemia, and renal failure may exacerbate an acute decompensated heart failure presentation in patients with risk factors or known heart failure.

3. Cardiogenic shock is due to inadequate cardiac output (cardiac index <2.2 L/min/m^2) from impaired ventricular function, resulting in end-organ hypoperfusion. Findings to be cognizant of include low urine output (<30 mL/hour), cool extremities, and altered mental status. This life-threatening condition necessitates urgent cardiology consultation and transfer to the intensive care unit.

4. Symptoms and physical exam:

  a. Dependent on the extent of cardiac output, or stroke volume, from the ventricles as well as congestion associated with increased intracardiac pressures [31]

    i. Low cardiac output (cardiac index <2.2 L/min/m^2)

      • Symptoms: Fatigue, decreased exercise tolerance, and altered mental status
      • Physical exam: Weakened peripheral pulses, narrow pulse pressure, and cool extremities

    ii. Congestion (increased intracardiac pressures)

      • Symptoms: Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and fluid accumulation
      • Physical exam:

        – Intravascular fluid accumulation: elevated JVP, positive hepatojugular reflux, S3 on cardiac auscultation, pulmonary crackles, bendopnea (shortness of breath triggered by bending over)
        – Extravascular fluid accumulation: decreased basilar breath sounds (pleural effusion), shifting dullness of the abdomen and/or flank fullness (ascites), peripheral edema of the lower extremities or other parts of the body exposed to higher hydrostatic pressure (important in patients laying for prolonged periods of time)

5. Management of CHF:

  a. Goals of acute heart failure management are focused on alleviating congestion and improving cardiac output through decreasing preload, augmenting cardiac contractility, and decreasing afterload. Management should be collaborative with consultative assistance from a cardiologist:

    i. Acute pulmonary edema treatment includes intravenous diuretics, nitrates (if blood pressure is elevated), oxygen, and sitting the patient upright.
    ii. In those with cardiogenic shock, consideration for pulmonary artery catheter placement in an intensive care unit setting may be warranted. Pulmonary artery catheter-guided therapy can assist with the initiation and titration of vasoactive medications (inotropes, vasodilators) as well as consideration for advanced mechanical circulatory support in consultation with cardiology.

  b. Chronic heart failure management in HCT patients is generally consistent with treatment of heart failure in the general population as outlined in the AHA/ACC/Heart Failure Society of America Guidelines [32]:

    i. Use of an angiotensin-converting enzyme inhibitor (ACE inhibitor) or angiotensin receptor blocker (ARB), beta-blocker (carvedilol [Coreg®] or metoprolol succinate [Lopressor®]), and aldosterone antagonists (spironolactone [Aldactone®]) all have proven mortality benefits and are considered staples of chronic heart failure management [32].

    ii. Newer heart failure therapies including sacubitril/valsartan [Entresto®] should be discussed with the cardiology team [33].

    iii. Prophylactic use of combination therapy with ACE inhibitor and carvedilol may also help reduce the risk of chemotherapy-induced cardiomyopathy in select populations [34–38].

c. Medication titration constitutes a fundamental element of CHF management:

    i. Renin-angiotensin-aldosterone system inhibition

- Start with captopril (Capoten®) 6.25 mg PO and then increase to 12.5 mg PO after 8 hours. If tolerated (systolic BP >80 mmHg), give 25 mg PO after an additional 8 hours. Increase by 25 mg PO every 8 hours until the daily dose of 100 mg PO is reached or the patient does not tolerate higher doses.
- There is a roughly 5:1 conversion from daily total captopril to lisinopril dosing.
- Spironolactone is typically started at 12.5 mg PO daily, uptitrated to 25 mg PO daily with careful monitoring of kidney function and serum potassium levels.

    ii. Long-acting nitrates and alpha inhibitors

- In those with impaired renal function, consider initiation of these therapies for preload and afterload reduction.
- Isosorbide dinitrate can be started at 5 mg PO TID and uptitrated as tolerated.
- Hydralazine can be started at 12.5 mg PO TID and uptitrated as tolerated.

    iii. Beta-blocker therapies

- Heart failure-specific beta blockers include carvedilol and metoprolol succinate.
- If blood pressure is low at baseline, consider metoprolol succinate starting at 12.5 mg PO daily and uptitrate as tolerated (assessing heart rate and BP closely). It is common to start low-dose metoprolol tartrate TID with transition to dose equivalent metoprolol succinate daily closer to discharge.
- Carvedilol can be initiated at 3.125 mg PO BID and uptitrated to 25 mg PO BID with similar careful monitoring.

Cardiac Arrhythmias

1. Cardiac arrhythmias are among the most common cardiovascular complications following HCT with a reported incidence as high as 9–27%. Patients who suffer from arrhythmia during HCT period have longer hospital stays, are more often transferred to the intensive unit care, and carry overall long-term poor outcomes (~3.5-fold increased risk of death in the first year after HCT) [12, 13].

2. Initial assessment should be focused on obtaining a complete set of vital signs, thorough cardiopulmonary examination, and a 12-lead electrocardiogram (ECG).

   a. Often, HCT patients will be on telemetry monitoring, which may provide insight into the etiology, onset, and burden of arrhythmia.
   b. Management of all unstable arrhythmias (hypotension, mental status changes, signs of CHF) should be focused on immediate implementation of advanced cardiac life support initiatives (ACLS guidelines).

3. The most common post-transplant arrhythmias observed in descending order are atrial fibrillation, atrial flutter, and supraventricular tachycardias. Rarely, post-transplant patients may develop ventricular arrhythmias (<1% of tachyarrhythmias) that often are life threatening and are typically related to underlying cardiac disease. Arrhythmias are associated with significant in-hospital morbidity and mortality and warrant urgent intervention [12, 39]. For the diagnosis of any new arrhythmia, cardiology consultation is indicated.

   a. Atrial fibrillation

      i. May either be a new diagnosis or exacerbation of known atrial fibrillation with poor rate control (heart rate >110 BPM). However, in patients undergoing HCT, comparison to baseline heart rate may be helpful, as heart rate is often elevated due to other medical conditions (e.g., anemia, fever, volume loses).
      ii. Possible precipitants include, but are not limited to, CHF, high catecholamine states, electrolyte disturbances, as well as a direct effect from certain chemotherapy agents (e.g., 5-FU/capecitabine) [40–42].
      iii. Among drugs used for HCT conditioning, melphalan (typically ≥140 mg/m^2) is strongly associated with the development of atrial fibrillation. Careful electrocardiographic monitoring during administration of this medication is warranted [43, 44].
      iv. Management includes rate versus rhythm control along with initiation of anticoagulation when appropriate from a hematologic perspective to lower the risk of thromboembolic complications per AHA/ACC guidelines [10].

         • Rate controlling agents (all can cause hypotension and bradycardia and should be administered in a monitored setting) include AV-nodal blocking such as beta-blockers, non-dihydropyridine calcium channel blockers, and digoxin (caution in renal failure patients).

            – Metoprolol 5 mg IV every 5 minutes × 3, and then 25–200 mg/day PO in divided doses.
            – Diltiazem (Cardia®, Diltzac®) 0.25 mg/kg IV; may repeat after 15 minutes, and then 120–360 mg/day PO in divided doses.
            – Beta-blockers and non-dihydropyridine calcium channel blockers have negative inotropic effects and should be used with caution in patients with heart failure and reduced systolic function (low LVEF).
            – Digoxin (Lanoxin®) 1 mg IV or PO load in three divided doses every 4–8 hours given as 50% initially and then 25% × 2, and then
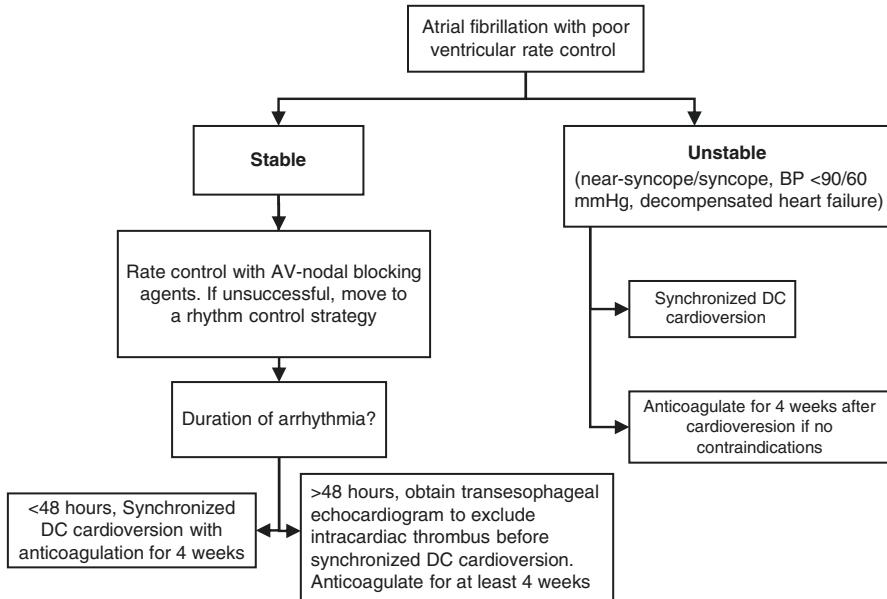
Fig. 34.2 Standard approaches to acute atrial fibrillation

 0.125–0.375 mg PO daily (need to adjust for creatinine clearance); therapeutic serum digoxin levels are typically around 0.8–1.0 ng/dL.

- Rhythm control can be obtained either pharmacologically or with direct current (DC) cardioversion. The most common rhythm control agent is amiodarone. Ensuring the patient is appropriately anticoagulated before initiation is warranted to decrease thromboembolic risk.

  - Amiodarone (Cordarone®) 150 mg IV over 10 minutes, and then 0.5–1 mg/min IV.
  - Alternatively, one can give an oral amiodarone load to achieve a total load dose of 12 g (e.g., amiodarone 400 mg PO TID × 7 days, then 400 mg PO BID × 7 days, then 200 mg PO daily).
  - DC cardioversion typically requires 150–200 J.

- See Fig. 34.2 for further details of acute atrial fibrillation management.

b. Atrial flutter

  i. Similar to atrial fibrillation, atrial flutter may be newly diagnosed or exacerbated following HCT.
  ii. Unlike atrial fibrillation, however, atrial flutter is often more challenging to rate control and often requires rhythm control strategies, typical with DC cardioversion in the setting of appropriate anticoagulation.
  iii. Success rates for atrial flutter ablation are high and, with cardiology consultation, may be considered in select population [45].

Fig. 34.3 How to measure QT correction based on the RR interval
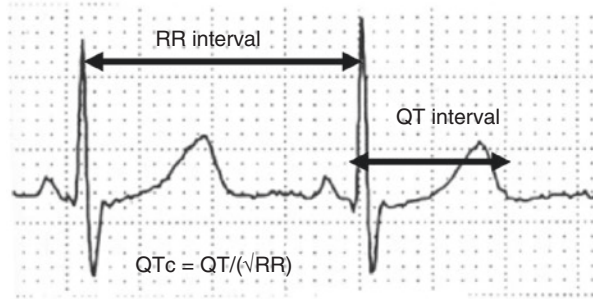
c. Supraventricular tachycardia (SVT)

  i. Includes a vast array of tachyarrhythmias involving the atria, AV node, or macro-reentrant (involving the atria and ventricle).
  ii. Often self-limited and can be terminated with vagal maneuvers (Valsalva maneuver, carotid sinus massage, cough, immersion of face into ice-cold water). Success rates increase with leg elevation in the supine position [46].
  iii. For SVTs that do not respond to AV-nodal blocking agents and vagal maneuvers, cardiology consultation is indicated.

d. QT interval monitoring

  i. A marker of depolarization and repolarization of the sum of the cardiomyocytes.
  ii. Measured from the initial Q wave to the end of the T wave. The corrected QT is normalized to the heart rate (Fig. 34.3):

    • Several formulas exist and are in clinical use today (Bazett, Fridericia).
    • Long QTc is >470 msec (men), >480 msec (women).
    • Highly abnormal QTC is >500 msec [47].

  iii. Long QT intervals are associated with a specific type of polymorphic ventricular tachycardia, termed *Torsades de pointes* [48].
  iv. QT prolongation may result from various chemotherapy agents, electrolyte derangements, concomitant medications, or underlying heart disease [26].
  v. QT prolongation requires a search for possible offending medications and assessment of interactions. Reduction of doses or discontinuation of offended doses may be necessary.

Myocardial Ischemia and Coronary Artery Disease

1. Preexisting CAD is a frequently encountered medical comorbidity in patients undergoing HCT [49]:

   a. Management of SIHD in HCT patients is similar to that of an ambulatory population with a focus on maximally tolerated anti-anginal agents as well as secondary risk reduction with antiplatelet and statin therapies [21].

   b. Assessment for appropriate anginal control with exertion should be assessed prior to undergoing HCT and noninvasive stress testing and/or coronary angiography be considered in those patients with poorly controlled angina despite anti-anginal therapy (see section "Baseline Cardiac Evaluation" for details).

   c. Treatment of angina with revascularization can be considered in selected patients. However, cardiologists and oncologists have to balance the need for antiplatelet therapy (typically dual antiplatelet therapy for at least 3 months) in patients with treatment- or disease-related thrombocytopenia.

2. Acute coronary syndrome (ACS) is a relatively uncommon complication following HCT.

   a. ACS is the result of unstable coronary artery plaque and/or rupture resulting in myocardial ischemia and progression to infarction.

   b. Risk factors for ACS include preexisting HTN, tobacco abuse, age, gender, hyperlipidemia, diabetes/impaired glucose tolerance, and a family history of premature CAD (<50 years).

     i. Specific etiologic considerations in an HCT population include administration of etoposide, cisplatin, 5-FU, capecitabine, and certain small molecule inhibitors (e.g., nilotinib [Tasigna®], ponatinib [Iclusig®]) [50–53]. ACS may still occur in these patients with normal coronary arteries [26, 40, 54–58].

     ii. Patients with CAD are at increased risk for ACS due to physiologic stresses associated with transplantation [26]. In those patients with known CAD who will receive 5-FU or capecitabine, consultation with cardiology should be considered for medical optimization [40].

   c. Differential diagnosis of this presentation includes acute myopericarditis, myocardial toxicity from chemotherapy, and CHF.

   d. Management of ACS:

     i. Management of cardiac ischemia and ACS is often complicated by limitations in the use of antithrombotic and anticoagulant therapies due to thrombocytopenia resulting from HCT conditioning therapy or from the underlying hematologic disease.

     ii. Development of chest pain with ischemic ECG ST segment and T wave changes and elevated troponin should prompt immediate cardiology consultation.

     iii. Given the profound hematologic derangements in this population, coronary intervention may be limited given the need for uninterrupted antiplatelet and antithrombic therapies. A detailed multidisciplinary discussion among the oncologist, cardiologist, and patient should include the risks and benefits of a coronary intervention. In selected populations, conservative management with close observation may be reasonable [59].

Fig. 34.4
Revascularization
strategies for acute
coronary syndrome
presentation. *TIMI Risk
Score for ACS per AHA/
ACC guidelines. (Adapted
from the MD Anderson
Cancer Center)
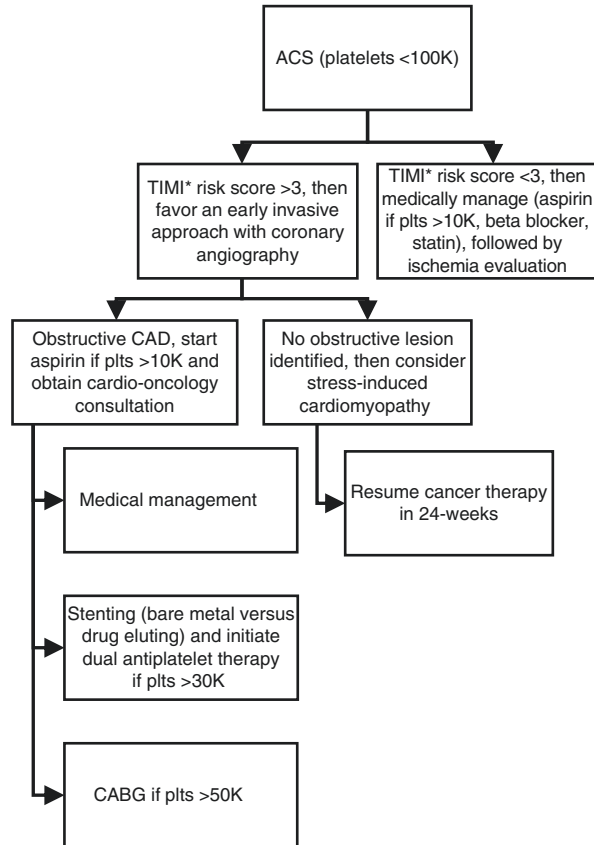
*TIMI Risk Score for ACS per AHA/ACC guidelines

- Society for Cardiovascular Angiography and Interventions (SCAI) guidelines suggest the use of thromboelastography (TEG) in those patients with thrombocytopenia (typically <30,000/mL) and the need for revascularization. An abnormal TEG may suggest the need for platelet transfusion prior to coronary intervention [60].
- For patients with expected survival less than 1 year, coronary angiography should be reserved for those patients with ST-elevation myocardial infarction or high-risk non-ST-elevation myocardial infarction. Uptitration of anti-anginal medications should be the initial strategy for stable ischemic heart disease.
- If coronary artery bypass grafting (CABG) is considered, a compromised immune system should be considered when assessing postoperative recovery.
- See Fig. 34.4 for details on revascularization strategies adapted from the MD Anderson Cancer Center.

Systemic Arterial Hypertension

1. The most common presentation of high blood pressure (>140/90 mmHg) in the HCT population is preexisting benign essential HTN [61].

    a. Blood pressure control in this population should be similar to that of an ambulatory setting per current societal guidelines prevent future cardiovascular complications [26, 62].
    b. Home antihypertensive medications should be continued unless contraindications are present.

2. Medication-induced HTN is a unique circumstance seen in this population. Chronic immunosuppression with calcineurin inhibitors (CNIs [cyclosporine, tacrolimus]) is the mainstay of therapy for prevention and treatment of graft-versus-host disease (GvHD).

    a. CNI-associated HTN occurs in 15–50% of patients and typically develops within a month of starting therapy [7–9].
    b. The treatment of choice is calcium channel blockade:

        i. The mechanism is decreased peripheral vascular resistance (including the renal arteriolar constriction associated with CNIs) and lowering blood pressure by causing direct vasodilation in the peripheral arteries of the vascular smooth muscle.
        ii. Of note, exercise cautious use of this medication class in those with known reduced LVEF.

3. Posterior reversible encephalopathy syndrome (PRES) is a neurologic complication seen occasionally in patients with CNI-associated HTN [6, 63].

    a. The clinical syndrome includes headache, mental status changes, and seizures with specific radiologic features.
    b. Management includes withdrawal of the drug and aggressive blood pressure control.

Pericardial Disease

1. Acute and chronic disease processes involving the pericardium have been associated with several chemotherapy agents, chest wall radiation, and GvHD [26, 64–66].
2. Manifestations of pericardial disease include pericardial effusion, cardiac tamponade, constrictive pericarditis, and effusive-constrictive pericarditis.
3. Cardiac tamponade is a life-threatening condition that requires emergent attention.

    a. Increased intrapericardial pressures result in cardiac chamber compression and decreased venous return, ultimately reducing cardiac stroke volume.

b. Clinical presentation is similar to that of cardiogenic shock, although usually without pulmonary edema.

c. Certain physical exam findings are pathognomonic for cardiac tamponade:

   i. Beck's triad: distant heart sounds, elevated JVP, and hypotension
   ii. Pulsus paradoxus is present with a decrease in systolic pressure ≥10–12 mmHg with inspiration:

   - The mechanism for this is an exaggeration of normal physiology with inspiration causing a decrease in intrapericardial and right atrial pressures, increasing right-sided venous return, and right ventricular size.
   - Due to increased ventricular interdependence, increased right-sided filling is at the expense of decreased left ventricular filling, resulting in decreased left ventricular stroke volume and blood pressure (respirophasic interventricular dependence).

d. Diagnosis is made by clinical manifestations and presence of pulsus paradoxus

e. Echocardiographic findings include pericardial effusion, dilated inferior vena cava (IVC), diastolic collapse of the right-sided cardiac chambers, and respirophasic changes in transvalvular velocities.

f. Treatment is aimed at initial intravascular volume resuscitation to provide sufficient preload and vasoactive medications. Ultimate treatment is pericardial fluid removal, typically by pericardiocentesis:

   i. It should be noted that malignant pericardial effusions often reaccumulate after 24–48 hours.
   ii. Placement of a pericardial drain, balloon pericardiotomy, and/or consultation with cardiothoracic surgery for surgical pericardial window should be considered.
   iii. In some patients, removal of fluid does not alleviate symptoms. This is likely related to effusive-constrictive pericarditis and requires surgical evaluation for pericardiectomy [67].

4. Constrictive pericarditis is a condition caused by a stiffened, inflexible pericardium that limits diastolic filling.

   a. Etiologies for constrictive pericarditis specific to the HCT population include certain chemotherapeutic agents (such as anthracyclines), prior chest wall radiation, malignancy, or GvHD.

   b. Physical exam findings demonstrate elevated JVP (prominent *y* descent), a pericardial knock, and Kussmaul's sign (increased JVP with inspiration).

      i. The mechanism for this is related to respirophasic interventricular dependence from a fixed pericardial space.

   c. Diagnosis is suggested by clinical manifestations and echocardiographic findings of a "septal bounce" and other signs of ventricular interdependence (respirophasic changes in transvalvular velocities). Thickened pericardium can also be seen on TTE, CT, or MRI. Definitive diagnosis may require cardiac catheterization [68].

    d. Primary treatment is with diuretics to manage volume status

      i. Surgical pericardiectomy is reserved for cases that have failed conservative management, although outcomes are generally poor.

      ii. Effusive-constrictive pericarditis is a pericardial syndrome with features of both pericardial effusion with cardiac tamponade and constrictive pericarditis (as described above). May be seen following pericardiocentesis in those patients with long-standing pericardial effusions.

Effect of Chest Wall Radiation

1. Patients exposed to mediastinal or chest wall radiation for prior hematologic malignancy or breast cancer treatments are predisposed to a variety of structural cardiovascular diseases.
2. Radiation therapy can lead to the accelerated development of obstructive CAD [28, 69–72].

    a. Both endovascular proliferation and accelerated atherosclerosis appear to be involved in the disease process.

    b. Ostial lesions are common, with the left anterior descending artery most frequently involved due to its location relative to the radiation field.

    c. Microvascular disease can lead to ischemia even the absence of epicardial (large vessel) CAD.

    d. Management of radiation-associated CAD is similar to conventional treatment for ischemic heart disease, although coronary artery bypass surgery may be more difficult because of prior radiation to the surgical field.

3. Radiation therapy can lead to fibrosis and calcification of cardiac valves, manifesting as either regurgitation and/or stenosis.

    a. Left-sided valves are more commonly affected with aortic stenosis and mitral regurgitation being two of the more common disease entities associated with radiation-induced valvulopathy [60].

    b. It is not entirely clear why the pulmonic and tricuspid valves are often spared but may be due to lower pressures in the right heart and hence lower shear across these valves [19].

4. Pericardial sequelae include acute pericarditis, pericardial effusions, constrictive pericarditis, and rarely cardiac tamponade (see section "Pericardial Disease", above).
5. Radiation therapy can cause myocardial fibrosis and small-vessel ischemic disease, leading to a spectrum ranging from diastolic dysfunction to restrictive cardiomyopathy.

    a. Clinically, restrictive cardiomyopathy presents as right-sided > left-sided heart failure with more peripheral edema and less dyspnea. Patients may be "refractory" to diuresis based on their preload-dependent state [68].

    b. Physical exam findings can include increased JVP, Kussmaul's sign, presence of an S3 and/or S4, hepatomegaly, ascites, and peripheral edema.

    c. Echocardiography findings of biatrial enlargement and abnormal diastolic parameters are suggestive of restrictive physiology. A definitive diagnosis is established by hemodynamics on invasive cardiac catheterization.

    d. Management is focused on maintaining a euvolemic state and appropriate heart rate control. Tachyarrhythmias are poorly tolerated and typically require rhythm control strategies for atrial fibrillation/flutter.

Survivorship (See Also Chap. 51)

1. Cardiovascular disease is among the most debilitating and lethal complications in HCT survivors. Compared to the general population, HCT survivors are at increased risk for development of future cardiovascular events [73–76].

2. While rates of atherosclerotic disease are higher, cancer survivors may be asymptomatic or have atypical chest pain presentations [75, 77–80].

3. Cardiotoxicity may develop from select chemotherapy agents, especially anthracyclines, cyclophosphamide-based conditioning regimens, trastuzumab (Herceptin*) and 5-FU/capecitabine (as discussed elsewhere).

    a. National Comprehensive Cancer Network (NCCN) and the MD Anderson Practices in Cardio-oncology recommend routine assessment of LVEF in those patients receiving anthracycline-based regimens as well as trastuzumab.

        i. If LVEF is >50%, patients can proceed with usual chemotherapy.

        ii. If LVEF is <50%, patients should be started on low doses of carvedilol and lisinopril, which are uptitrated to maximally tolerated doses.

        iii. The use of dexrazoxane (Zinecard®) or slow infusion of anthracycline can also decrease the risk of cardiotoxicity.

        iv. Typically, if LVEF drops by >10–15% on subsequent echocardiograms, medical therapy is initiated and chemotherapy is held with reevaluation in 1 month.

    b. Global longitudinal strain has also been used by some practices given its function as an early indicator of myocardial dysfunction. The decrease of mean global longitudinal strain below −17% and/or decrease of >15% from baseline can be seen in patients with subclinical cardiotoxicity [18, 81].

    c. TTE is recommended prior to the start of potentially cardiotoxic therapy, immediately after completion of cardiotoxic therapy, and at 1 year after completion. Further follow-up in 2–5-year intervals is recommended by some groups.

4. Radiation to the chest wall predisposes to a multitude of structural heart disease complications including stenosis of the coronary artery ostia, various pericardial diseases, and left-sided valvulopathies.

    a. In cancer survivors with NYHA symptoms and prior mediastinal radiation, the European Association of Cardiovascular Imaging and the American

Society of Echocardiography (EACVI/ASE) recommends a screening TTE at 10 years after radiation exposure, followed by serial exams every 5 years [14].

b. For suboptimal echo windows or challenging echo quantification, multimodality imaging may be considered (CMR, and less commonly cardiac CTA).

5. Optimization of cardiovascular risk factors plays a crucial role in the prevention of future cardiovascular events following HCT.

a. Tobacco cessation as well as lipid and diabetes management provides a significantly lower medical expenditure among cancer patients [82].

b. Survivors should be encouraged to participate in low-intensity and supervised group exercise programs. These interventions have shown improvement in lean muscle mass, cardiorespiratory fitness, and overall health [83, 84].

c. Coronary artery calcium scoring for risk stratification in those with intermediate cardiovascular risk (5–20%) can help to reclassify risk and guide initiation of statin therapy [85].

6. The growing field of cardio-oncology serves to manage patients undergoing HCT and HCT survivors to help prevent and manage cardiovascular disease.

a. This is a multidisciplinary movement assembled to promote training and study in the fields of clinical cardiovascular and oncologic morbidities as well as advance basic science research in mechanics of cardiotoxicities, pericardial disease, and interactions of cardiovascular health and malignancy.

b. Cardio-oncology is a rapidly growing subspecialty across the United States, accounting for one of the fastest growing clinical network programs nationally.

c. There is an exponential surge in cardio-oncology research over the last 10 years [86].

d. Establishment of cardio-oncology clinics/program and early referral may be beneficial for patients undergoing HCT or after HCT.

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Chapter 35
Kidney Disease in Hematopoietic Cell Transplantation

Tonja Dirkx

Introduction

Kidney damage is a common complication of hematopoietic cell transplantation (HCT); its severity may range from a transient and reversible rise in creatinine to a complete loss of kidney function with need for hemodialytic support. Acute kidney injury (AKI) requiring dialysis in critically ill HCT recipients is associated with greater than 80% mortality [1]. Additionally, AKI of any degree of severity confers risk for the development of chronic kidney disease (CKD) [1–3]. Even in the absence of AKI in the immediate post-transplant period, HCT recipients are at high risk for CKD over the long term, and this complication is associated with decreased life expectancy. Nephroprotective measures during the HCT process are thus of utmost importance. Early diagnosis and treatment of AKI, and early nephrology consultation should likewise be considered. Long-term follow-up of HCT patients should include routine surveillance for the development of CKD.

Definitions of AKI and CKD

1. *AKI:* AKI is defined by an acute rise in serum creatinine or a fall in urine output, or both. There are several expert guidelines describing staging of AKI severity; the most recent is summarized in Table 35.1 [2–4]. Patients who are cachectic and have low muscle mass may have a baseline creatinine below the reference

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Table 35.1 Stages of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline *or* >/= 0.3mg/dL increase	<0.5 mL/kg/hr × 6–12 hr
2	2.0–2.9 × baseline	<0.5 mL/kg/hr for >12 hr
3	3.0 × baseline *or* increase to >/+ 4.0 mg/dL *or* need for dialytic support	<0.3 mL/kg/hr for >/= 24 hr or anuria for >/= 12 hr

Table 35.2 Stages of CKD

Stage	GFR
1	>90 mL/min/1.73 m^2 and proteinuria or structural abnormality
2	60–89 mL/min/1.73 m^2
3	30–59 mL/min/1.73 m^2
3a	45–59 mL/min/1.73 m^2
3b	30–44 mL/min/1.73 m^2
4	15–29 mL/min/1.73 m^2
5	<15 mL/min/1.73 m^2

range for normal; in these patients, a rise in the serum creatinine to a normal level may indicate AKI.

2. *CKD:* CKD is a structural or functional renal abnormality that persists for at least 3 months. Reduced glomerular filtration rate (GFR) and persistent albuminuria (proteinuria) are the most common manifestations of chronic kidney injury. Five stages of CKD are defined based on GFR (Table 35.2).

Kidney Disease in HCT: Incidence and Risk

1. AKI:

    a. The incidence of AKI in the first 100 days following HCT is likely > 50%, though estimates in the literature range from 15% to 80% [1–4]. It is likely that AKI which occurs prior to engraftment confers a greater risk of mortality than that which occurs beyond engraftment [1].

    b. Risk factors for AKI after HCT include:

        i. Pre-transplant complications

            • CKD
            • Hypertension
            • Diabetes

    ii. Post-HCT complications

- Sepsis
- Amphotericin product exposure
- Hepatic sinusoidal obstructive syndrome (SOS)
- Acute graft versus host disease (GvHD)

    iii. The type of HCT performed influences the risk for SOS and GvHD, and the need for calcineurin inhibitor (CNI) therapy, and therefore the risk of severe AKI.

- Myeloablative regimens confer a higher risk for SOS compared with nonmyeloablative regimen and are associated with a higher incidence of AKI. Myeloablative allogeneic HCT bestows the additional risk of acute GvHD, and thus the highest risk of the most severe AKI (estimates range from 36% to 78%; 20–33% may require dialysis).
- Autologous HCT patients enjoy the lowest risk for severe AKI given lack of need for CNIs and minimal risk of GVHD (incidence of AKI approximately 20%, with roughly 7% requiring dialysis).

2. CKD: Survivorship has improved among HCT recipients; as a result, long-term complications are becoming more widely recognized.

    a. CKD occurs in about 20% of patients post-HCT, a rate more than double that in the general population [1, 5, 6].

    b. Risk factors

      i. Older age at the time of transplant
      ii. AKI at the time of HCT, especially more severe
      iii. Total body irradiation as a part of the conditioning regimen
      iv. Certain chemotherapeutic agents (see Table 35.3)
      v. Chronic GvHD
      vi. Long-term CNI exposure

General Classification of Causes of AKI and Basic Evaluation

It is useful to consider causes as *prerenal* (or reduced blood flow to the kidneys), *intrinsic* renal, and *postrenal* in order to have a systematic approach to evaluating a patient with AKI [1–4].

1. Prerenal

    a. Causes

      i. Hypotension
      ii. Volume depletion secondary to vomiting, diarrhea, poor fluid intake, etc.
      iii. Hypercalcemia

Table 35.3 HCST-related AKI

Mechanism of injury	Causes	Typical clinical findings
Prerenal state	Volume depletion, hypotension, medications (ACE inhibitors, angiotensin receptor blockers, NSAIDs, diuretics, calcineurin inhibitors, IV contrast), hypercalcemia, hepatic sinusoidal obstructive syndrome (SOS)	Urine Na < 10 mmol/L; FeNa < 1% Urine sediment w/ hyaline casts
ATN	*Ischemic*: prolonged prerenal state *Nephrotoxic:* vancomycin, aminoglycosides, IVIG, platins, IV contrast, amphotericin products, BK or adenovirus *Sepsis:* cytokines	Urine Na >20 mmol/L; FeNa >1% Urine sediment w/ granular or "muddy brown" casts
AIN	Penicillins, cephalosporins, quinolones, sulfa drugs, furosemide, allopurinol, NSAIDs, rifampin, proton-pump inhibitors	Peripheral eosinophilia possible Eosinophiluria possible Sterile pyuria and proteinuria common; classic triad of fever, rash; AKI may be present
Thrombotic microangiopathy	Calcineurin inhibitors, infections (parvo B19, CMV, BK virus, adenovirus, other systemic), GvHD, TBI, complement abnormalities	Signs of intravascular hemolysis (may not be present if due to CNI) Hematuria, proteinuria likely HTN often present, may be first sign
Crystal formation/ obstruction	TLS (uric acid and calcium phosphate crystals) Medications (high-dose IV acyclovir, methotrexate, foscarnet, ganciclovir)	Crystalluria present
Hemorrhagic cystitis	BK and adenovirus	Hematuria; clots may cause lower tract obstruction

ACE angiotensin-converting enzyme, *NSAIDs* non-steroidal anti-inflammatory drugs, *Na* sodium, *FeNa* fractional excretion of sodium, *IVIG* intravenous immunoglobulin, *AKI* acute kidney injury, *CMV* cytomegalovirus, *GvHD* graft-vs-host disease, *TBI* total body irradiation, *CNI* calcineurin inhibitors, *HTN* hypertension, *TLS* tumor lysis syndrome

    iv. Hepatic sinusoidal obstructive syndrome (SOS)
    v. Medications (CNIs, non-steroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, diuretics)
    vi. Hypoalbuminemia

b. If the kidney is otherwise functioning normally, reduced renal blood flow will result in a sodium-avid state. The laboratory hallmark is a low spot urine sodium value (<10–20 mmol/L) or a FeNa of <1%. Patients exposed to diuretics, however, may have a high urine sodium concentration in the setting of volume depletion.

2. Intrinsic renal

   a. Causes

      i. Acute tubular necrosis (ATN) due to:

- Prolonged prerenal state (see above)
- Sepsis
- Drug toxicity
- IV contrast-induced nephropathy

      ii. Thrombotic microangiopathy (TM)

      iii. Allergic interstitial nephritis (AIN, drug reaction)

   b. Urinalysis is often abnormal when there is intrinsic renal damage.

      i. Muddy brown casts are seen in ATN.

      ii. Sterile pyuria with or without WBC casts and proteinuria is typical for AIN.

      iii. Hematuria and proteinuria can be seen with TM.

3. Postrenal

   a. Causes

      i. Intrarenal obstruction from uric acid, phosphate, or drug crystals

      ii. Extrarenal obstruction from bladder outlet obstruction (prostatic hypertrophy or clot from hemorrhagic cystitis)

4. Initial evaluation

   a. History including potential nephrotoxin exposures, and careful physical examination with attention to trends in the vital signs, urine output, and estimated intravascular volume status

   b. Basic chemistries including calcium, phosphate, and uric acid

   c. Complete blood count (CBC)

   d. Urinalysis and urine microscopy

   e. Spot urine for sodium, creatinine, and protein

   f. Bladder scan for post-void residual

   g. Renal ultrasound

Timing and Cause of Renal Injury

1. Conditioning regimen (AKI)

   a. Tumor lysis syndrome

   b. Stem cell infusion toxicity

2. Days-weeks post-HCT (AKI)

    a. Volume depletion
    b. ATN
    c. SOS
    d. Medications (e.g., CNIs, antibiotics, antivirals, amphotericin products)
    e. Hemorrhagic cystitis with urinary obstruction
    f. TM

3. Months post-HCT (CKD)

    a. CNI toxicity
    b. TM
    c. Chronic GVHD

Evaluation and Management of Common Causes of AKI

1. General recommendations

    It is important to prevent renal injury given the high rate of mortality associated with severe AKI and the risk for the development of CKD over the long term. Close monitoring of renal function, avoidance of nephrotoxic agents when feasible (e.g., unnecessary intravenous contrast agents), maintenance of adequate intravascular volume, and avoidance of hypotension and of medications which impair renal vascular autoregulation (NSAIDs, ACE inhibitors, angiotensin receptor blockers) are all important nephroprotective strategies [2, 3]. Nephrology consultation early in the course of AKI, rather than waiting until dialysis is imminent, is recommended. When AKI is diagnosed, the following points should be considered in management:

    a. Diagnosis and treatment of the underlying cause (see section "Systemic Arterial Hypertension") [1, 7–12].
    b. Maintenance of intravascular euvolemia.
    c. Adjustment of dietary intake to limit potassium and phosphorus.
    d. Sodium and fluid restriction should also be instituted if hypervolemia is present (a typical hospital "renal diet" includes sodium, potassium, and phosphorus restrictions).
    e. Avoidance of nephrotoxins as possible (including IV contrast, ACE inhibitors, angiotensin receptor blockers, CNIs, and NSAIDs).
    f. Adjustment in medication dosing for estimated GFR

        i. Accurate assessment of GFR is not possible when creatinine is not at steady state.
        ii. A rise in creatinine of 0.5–1.0 over 24 hr may correlate with a GFR of <10 mL/min.

2. Tumor lysis syndrome (TLS)

   a. TLS is caused by rapid massive tumor cell necrosis with release of intracellular contents into the blood. High lactate dehydrogenase (LDH), hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia are hallmark signs [3, 7].

   b. Elevated urinary levels of uric acid and phosphate lead to formation of uric acid and calcium phosphate crystals, which are both directly toxic to kidney tubule cells and can cause intrarenal obstruction. Calcium precipitates with phosphorus in alkaline environment; for this reason, urinary alkalization is contraindicated in TLS.

   c. Hyperkalemia, often the earliest sign, may be life threatening via induction of cardiac dysrhythmias.

   d. Prophylaxis

      i. Intravenous fluids: Aggressive IV hydration (up to 3 L/m^2/d for up to 2 days prior to therapy) establishes high urine output and helps prevent precipitation of uric acid and phosphorus in the renal tubules and should be given to those patients at intermediate and high risk for the development of TLS.

      ii. Allopurinol (Zyloprim®) or Febuxostat (Uloric®): Both of these medications decrease formation of new uric acid by blocking the metabolism of xanthine to uric acid. Either drug may be used starting 1–2 days prior to induction chemotherapy and continuing on for 7–14 days after chemotherapy to prevent hyperuricemia.

         • The usual dose for allopurinol in adults is 100 mg/m^2 every 8 hr with dose adjustment for renal function; maximum daily dose is 800 mg per day

         • Febuxostat has been dosed at 120 mg daily to prevent TLS. Maximum daily dose should be limited to 40 mg/day in patients with creatinine clearance of 15–30 mL/min.

      iii. Recombinant urate oxidase (Rasburicase®): Lowers uric acid by increasing the conversion of uric acid to water-soluble allantoin. It can be used for both prevention and treatment of hyperuricemia.

         • FDA-labeled dose is 0.15–0.2 mg/kg in 50 mL of isotonic saline over 30 min daily for 5 days, but a single fixed dose of 3 or 6 mg with a repeated dose as needed may be as effective and less expensive.

   e. Management

      i. Hyperuricemia

         • Administer Rasburicase if not already given.

      ii. Hyperkalemia

         • If the plasma potassium level is >5.5:

- Obtain an EKG; if there are changes consistent with hyperkalemia, give 1 ampule of calcium gluconate IV to (transiently) decrease risk of dysrhythmia
- Give insulin 10 units IV and D_{50} 1 ampule IV to (transiently) shift potassium into the intracellular compartment
- Remove potassium from the body by giving a loop diuretic (e.g., furosemide IV bolus) as long as there is no hypovolemia, or by giving an oral potassium binding resin such as Kayexalate®, Patiromir, Lokelma, or via dialysis.
- For all patients with hyperkalemia, ensure the patient is on a low-potassium diet, IV fluids are potassium-free, and medications do not include potassium supplements or drugs that impair the renal excretion of potassium (e.g., ACE inhibitors, angiotensin receptor blockers, or NSAIDs).

iii. Hyperphosphatemia

- Initiate a low-phosphate diet, and add an oral phosphate binder with meals. Examples of phosphate binders:

  - Aluminum hydroxide (Amphogel®, etc.) 300–600 mg po, or 5–15 mL po with each meal; well-tolerated and most efficacious binder; however, due to risk for aluminum toxicity with long-term exposure, use is limited to 1–2 weeks.
  - Calcium-containing formulations (calcium carbonate and calcium acetate, 1–3 tabs/capsules po with each meal); use should be avoided until plasma phosphorus level is <7 mg/dL to avoid calcium-phosphate precipitation and urinary crystal formation.
  - Sevelamer hydroxide (Renagel®) 800–2400 mg po with each meal
  - Lanthanum carbonate (Fosrenol®) 500–1000 mg po with each meal. Must be chewed, so not appropriate choice for edentulous patients unless crushed and sprinkled on food

iv. Hypocalcemia

- In the presence of concomitant hyperphosphatemia (>7 mg/dL), avoid repletion of calcium unless symptoms or EKG signs of hypocalcemia are present.

v. AKI

- Supportive care is described in section "Systemic Arterial Hypertension" (1).
- Nephrology should be consulted for persistent AKI and/or electrolyte abnormalities (especially hyperkalemia), hyperuricemia unresponsive to medical management, or oliguria.
- Hemodialysis or continuous renal replacement therapy may be required for uric acid, phosphate, potassium, and volume removal.

3. Hematopoietic stem cell product infusional toxicity

    a. May occur in patients undergoing autologous HCT [2].
    b. DMSO, a cryopreservative, can cause hemolysis, leading to pigment nephropathy and AKI.
    c. Because of changes in stem cell preservation and thawing/washing techniques, this complication is now uncommon.
    d. Treatment is alkalization of the urine and mannitol-induced diuresis.

4. Volume depletion

    a. Results from vomiting, diarrhea, increased insensible losses (e.g., with fever), poor oral intake, or excessive diuretic use.
    b. May cause a transient prerenal state with reversible rise in creatinine upon rehydration.
    c. Because this is a very sodium-avid state, a spot urine sodium (or FeNa) will be low, as described in section "Cardiac Arrhythmias" (1.b).
    d. Prolonged prerenal state may result in necrosis of highly metabolic renal tubular cells and the development of ATN.
    e. Concomitant use of certain medications (ACE inhibitors, angiotensin receptor blockers, NSAIDs) interferes with autoregulation of renal blood flow and increases risk of conversion of prerenal azotemia to ischemic ATN.

5. Sepsis

    a. Common cause of AKI, particularly in neutropenic patients.
    b. Systemic cytokine release results in renal hypoperfusion via vasodilation and capillary leak, as well as local renal vasoconstriction; cytokines may also be directly toxic to renal tubular cells.
    c. ATN is the usual renal pattern of injury due to sepsis, and muddy brown casts are commonly seen in the urine sediment.
    d. Antibiotics may also cause AKI, either via direct renal tubular toxicity (e.g., aminoglycosides or amphotericin products), or via an idiosyncratic hypersensitivity reaction (AIN).
    e. Supportive care is required if AKI develops, along with treatment of the underlying infection.
    f. Consult to the Transplant Infectious Disease service can be helpful in choosing appropriate drugs that may be less nephrotoxic.

6. Sinusoidal obstruction syndrome (SOS), aka veno-occlusive disease (see also Chap. 32) [3]

    a. SOS occurs in approximately 5–10% of allogeneic HCT recipients.
    b. Myeloablative conditioning therapy may cause injury to the endothelial cells of hepatic venules resulting in thrombosis of small vessels and subsequent sinusoidal and portal hypertension.
    c. The clinical triad of painful hepatomegaly, anasarca, and jaundice usually occurs in the first weeks following conditioning.

    d. There is intense vasoconstriction in the kidney which results in a prerenal, sodium-avid state.

        i. Weight gain, peripheral edema, and very low urinary sodium concentrations (<10 mmol/L) result.
        ii. These features may be observed even with the use of diuretics.
        iii. Hemodialysis may be required to manage volume overload in these diuretic-resistant patients.

    e. Severe SOS is associated with ~90% mortality at 100 days.

        i. Tissue plasminogen activator (TPA) and defibrotide (Defitelio®) have been used with variable success to treat this condition.

7. Drug-induced AKI

    a. A common occurrence, as many drugs used in HCT are nephrotoxic.
    b. AIN, a drug-induced renal hypersensitivity reaction may also occur, particularly with antibiotics.
    c. Typical drugs that are associated with AKI include chemotherapy agents (methotrexate), antimicrobial agents (amphotericin products, aminoglycosides, high-dose IV acyclovir), and immunosuppressants (CNIs).

        i. Some liposomal formulations of amphotericin are less nephrotoxic.
        ii. Aminoglycoside and vancomycin trough levels should be monitored to reduce toxicity.
        iii. CNIs are vasoconstricting and nephrotoxic; high levels may contribute to development of a prerenal AKI.

            • Trough drug levels should be monitored, and doses should be reduced or drug temporarily held if a patient develops AKI.

8. Thrombotic microangiopathy (see also Chap. 38)

    a. May occur early (within 3 months) or late (6–12 months) after HCT and may result in AKI, CKD, or both; see also section "Pericardial Disease" (2b) [11, 13].
    b. Early TM with AKI is often caused by drugs (especially CNIs), complement deficiency, total body irradiation (TBI), GvHD, or infection.
    c. Treatment should be directed towards the underlying etiology; eculizumab may be a treatment option.

9. BK virus

    a. Immunosuppression can allow for reactivation of dormant infection; this may result in renal tubular injury and hemorrhagic cystitis [2, 3].
    b. Treatment is the reduction of immunosuppression intensity along with supportive care for cystitis. Intra-vesicular and intravenous cidofovir have been used to treat BK-induced hemorrhagic cystitis; however, this medication may be nephrotoxic in some patients [10].

Evaluation and Management of Common Causes of CKD

1. General considerations:

   a. Risk for CKD after HCT include history of AKI, acute and chronic GvHD, HTN, survival >1 year after transplant, TBI, and age > 45 years at the time of transplant [4–6].

   b. CKD may develop 3 months to 10 years after transplantation with a cumulative incidence of 10–50%. Given the high prevalence of CKD in the post-HCT population, annual surveillance of renal function, including estimated GFR and urinalysis with evaluation for proteinuria, is recommended.

   c. When CKD is diagnosed, referral to nephrology should be considered for management of complications, for help in slowing progression, and for preparation for end-stage kidney disease, which occurs in about 5%.

   d. CKD is an independent risk factor for cardiovascular disease and mortality; therefore, aggressive management of modifiable cardiovascular risks should be considered as well.

2. Causes of CKD in HCT patients

   a. Chronic CNI toxicity

      i. Common cause of CKD in HCT patients, even in the setting of therapeutic levels.

      ii. Chronic vasoconstriction and ischemia is the likely mechanism.

      iii. CNIs are nearly always continued even when chronic nephrotoxicity is suspected.

      iv. CNIs are also implicated in both acute and chronic TM as an idiosyncratic reaction [13].

      - CNI-associated TM may solely involve the kidneys with lack of usual systemic signs.
      - Withdrawal of CNI should strongly be considered for any patient who develops TM.

   b. Thrombotic microangiopathy (see also Chap. 38)

      i. TM that develops 6–12 months after HCT is usually the result of the myeloablative process, GvHD, or infection, any of which cause endothelial cell damage [11, 13]. CNIs may also be causative, as above.

      ii. Pre-HCT TBI is strongly associated with the later development of TM; concomitant use of conditioning chemotherapeutic agents such as high-dose cyclophosphamide, busulfan, carmustine, or cisplatin further increase risk.

      iii. Presentation includes new-onset or refractory hypertension (may be the earliest sign), hematuria, proteinuria, and renal dysfunction. Patients

have microangiopathic anemia with elevated LDH, decreased haptoglobin, and thrombocytopenia.
iv. Both the thrombotic microangiopathy and resultant hemoglobinuria cause ATN.
v. Investigation into etiology may require serologic testing for infection (herpes virus, parvovirus B19, adenovirus, cytomegalovirus, blood cultures) as indicated; ADAMTS-13 level and antibody should be tested to rule out thrombotic thrombocytopenia purpura (TTP), and genetic tests for alternative complement pathway abnormalities should be considered.
vi. TM-related kidney injury requires supportive therapy as well as treatment of any potentially causative infection, escalation of immunosuppression to treat GvHD if present, and withdrawal of CNI.

- HCT-related TM may be less responsive to plasma exchange than TMs unrelated to HCT.
- Other agents have been used with variable success, including rituximab (Rituxan®) and defibrotide (Defitelio®).
- Eculizumab (Soliris®) may be helpful, particularly in those with alternate pathway abnormalities.

vii. Prognosis is very poor and mortality rates may be close to 50%.

c. Nephrotic syndrome

i. Defined by heavy proteinuria (>3 g/24 hr), hypoalbuminemia and edema.
ii. This is a rare, late complication of HCT (median onset ~20 months posttransplant) and most commonly associated with chronic GvHD of the kidney after myeloablative or reduced-intensity allogeneic HCT [8, 14].
iii. Renal biopsy is essential for diagnosis; the usual pattern of injury is membranous nephropathy; however minimal change disease, IgA nephropathy, focal segmental glomerulosclerosis (FSGS), and anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis have also been reported.
iv. Treatment includes high-dose steroids, cyclosporine, and other immunosuppressive agents such as rituximab to achieve resolution of the nephrotic syndrome.

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Chapter 36
Neurological Complications

Kester A. Phillips and David Schiff

Introduction

Neurological complications after hematopoietic cell transplantation (HCT) represent a significant cause of morbidity and mortality in transplant recipients. The reported incidence of transplant-related neurotoxicity varies widely from 3% to 70% [1–6]. These neurological issues can be mild and self-limiting; however, therapy-related neurotoxicity can lead to life-threatening adverse events. Neurotoxic events may be classified according to the latency period between HCT and symptom onset, clinical manifestation, as well as the underlying etiology. The spectrum of neurological complications may be related to the type of HCT (autologous versus allogeneic), tumoricidal and supportive medications, radiotherapy, infectious pathogens, metabolic disarray, central nervous system (CNS) vasculopathy, and immune-mediated toxicity (Table 36.1). Both the central and peripheral nervous system can incur collateral damage during therapy. Neurological sequelae may emerge: (1) during the first month of treatment (early phase), (2) two to six months post-transplantation (intermediate phase), and (3) beyond 6 months after transplantation (late stage). In general, the risk of neurologic complications is higher in patients undergoing allogeneic HCT; however, the incidence is similar in autologous and allogeneic HCT recipients [7]. The neurotoxic side effects of conventional cytotoxic agents are widely recognized (Table 36.2). Currently, however, there are emerging data regarding the neurotoxic adverse events associated with several immunotherapy-based platforms.

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Table 36.1 Noninfectious treatment-related neurological complications

Drug	Complication	Presentation	Onset	Imaging	Treatment
Cytarabine	Cerebellar syndrome	Nystagmus, dysarthria, ataxia, oculomotor impairment, cerebral dysfunction	Early	MRI normal early or cerebellar atrophy later	Discontinue drug, steroids
	Chemical meningitis	Headache, seizure	Early	MRI normal	Discontinue drug, prophylactic steroids
	Chemical arachnoiditis	Cauda equina syndrome	Early	MRI lumbar spine with nerve root thickening	Discontinue drug, prophylactic steroids, analgesics for pain
Fludarabine	Encephalopathy	Confusion, somnolence, seizure, headache, blurred vision, cortical blindness, cognitive dysfunction, PRES	Early, intermediate, or late	Non-enhancing periventricular white matter changes with restricted diffusion	None
CNI	Encephalopathy, neuropathy	PRES, seizures, tremors, akinetic mutism, opisthotonus, rigidity, psychosis, pseudotumor cerebri, brachial plexopathy, optic neuropathy, hearing loss, CIDP, and Parkinsonism [105]	Early, intermediate, or late	T2/FLAIR hyperintensity in the subcortical and cortical regions of the bilateral parieto-occipital lobes	Discontinue drug, reduce drug dose
Busulfan		Generalized seizures	Early	Neuroimaging normal	Anticonvulsants
Ifosfamide	Encephalopathy	Confusion, disorientation, somnolence, agitation, hallucinations, lethargy, seizures, and coma	Early	Neuroimaging normal	Discontinue drug, methylene blue 50 mg q4 IV
Methotrexate	Chemical meningitis	Fever, meningeal signs, headache, altered sensorium, nausea, vomiting, and lethargy	Early	MRI normal	Spontaneous recovery in 2–3 days
	Chemical arachnoiditis	Cauda equina syndrome	Early or intermediate	Lumbar spine MRI may reveal enhancing nerve roots adherent to each other or the thecal sac	Discontinue drug, prophylactic steroids, analgesics for pain
	Transverse myelopathy	Paraparesis, impaired deep sensation, sphincter dysfunction, paresthesia, and back pain	Early	Longitudinal T2-weighted hyperintensity in the lateral and dorsal, may enhancement	Steroids, IVIG, FA, aminophylline, DXM, and CPG rescue

			Late	Subcortical white matter T2/FLAIR hyperintensity and cerebral atrophy	Supportive
	Chronic leukoencephalopathy	Bradyphrenia, poor memory, and concentration, behavioral abnormalities, dementia, seizures, long tract signs, and incontinence			
Vincristine	Peripheral neuropathy	Symmetrical length-dependent sensory loss, paresthesia, rarely cranial nerve palsies, acute motor neuropathy, and autonomic dysfunction	Early, intermediate, or late		No approved drugs. Consider antidepressant, anticonvulsant, physical therapy
Platinum compounds	Peripheral neuropathy, myasthenic-type syndrome	Symmetrical length-dependent sensory loss, paresthesia, rarely ototoxicity, encephalopathy, and cerebrovascular infarcts	Early, intermediate, or late		No approved drugs. Consider antidepressant, anticonvulsant, physical therapy for neuropathy
Immunomodulatory drug	Peripheral neuropathy	Hypoesthesia, paresthesia, neuropathic pain, or weakness, tremor, dizziness, and sedation	Early, intermediate, or late		No approved drugs. Consider antidepressant, anticonvulsant, physical therapy
Proteasome inhibitors	Peripheral neuropathy	Symmetrical length-dependent sensory loss, and paresthesia	Intermediate or late		Discontinue drug. Consider once weekly dosing or SQ dosing
Brentuximab vedotin	Peripheral neuropathy	Symmetrical length-dependent sensory loss, and paresthesia	Intermediate or late		Discontinue drug
Rituximab	Infusion reaction	Headaches, fatigue, cognitive impairment, rarely cerebrovascular infarction, convulsion, epilepsy, and PRES	Early		Discontinue drug
Alemtuzumab	Myelitis and progressive peripheral neuropathy	Progressive peripheral sensorimotor polyneuropathy and Guillain–Barre Syndrome	Early, intermediate, or late		IVIG, plasmapheresis, steroids
Blinatumomab	Encephalopathy	Tremor, aphasia, encephalopathy, and seizure	Early	Leukoencephalopathy on MRI	Discontinue drug, steroids, anticonvulsants

(continued)

Table 36.1 (continued)

Drug	Complication	Presentation	Onset	Imaging	Treatment
CAR-T Cell Therapy	ICANS	Aphasia, confusion, depressed level of consciousness, cognitive slowing, myoclonus, motor weakness, seizures, brain hemorrhage, and cerebral edema	Early	T2/FLAIR changes, leptomeningeal enhancement, or multifocal microhemorrhages on MRI	Steroids, interleukin-6-targeted therapies, and supportive care
Imipenem		Seizure	Early		Discontinue drug
Amphotericin B	Encephalopathy	Parkinsonism, confusion	Early		Discontinue drug
TPN	Wernicke's encephalopathy	Gait ataxia, bilateral ophthalmoparesis, confusion	Early	Symmetrical T2/FLAIR hyperintensity in the hypothalamic region, mammillary bodies, walls of the 3rd ventricle, and medial region of the thalamus	IV thiamine
Haloperidol	Malignant neuroleptic syndrome	Rigidity, somnolence, hyperthermia, elevated CK	Early		Bromocriptine
Posaconazole	Encephalopathy	Altered mental status	Early		Discontinue drug
Voriconazole		Visual hallucinations	Early		Discontinue drug
Metronidazole		Dysarthria, ataxia	Early	T2/FLAIR bilateral symmetric hyperintensities within the dentate nuclei of the cerebellum	Discontinue drug
Acyclovir	Encephalopathy	Tremors, disorientation, agitation, hallucinations, delirium, and seizures	Early	T2/FLAIR hyperintensity in the subcortical and cortical regions of the bilateral parietooccipital lobes, pons, cerebellum	Discontinue drug
Corticosteroids	Neuropsychiatric syndrome	Mood changes, mania, psychosis, depression, cognitive changes, delirium, confusion	Early		Discontinue drug. Antipsychotics, mood stabilizers can be considered in severe cases

MRI magnetic resonance imaging, *PRES* posterior reversible encephalopathy syndrome, *CIDP* chronic inflammatory demyelinating polyneuropathy, *IVIG* intravenous immunoglobulin, *FA* folinic acid, *DXM* dextromethorphan, *CPG* carboxypeptidase G2, *ICANS* immune effector cell-associated neurotoxicity syndrome, *TPN* total parenteral nutrition, *CK* creatine kinase

Table 36.2 Causes of neurological complications during HCT

Pharmacotherapy related	Adoptive cell transfer therapy
	Alkylating agents
	Antibiotics
	Antimetabolites
	Bispecific T-cell engagers
	Calcineurin inhibitors
	Immunomodulatory drugs
	Monoclonal antibodies
	Platinum compounds
	Proteasome inhibitors
	Supportive Medications
	Vinca alkaloids
Infectious pathogens	Bacteria
	Viruses
	Fungi
	Parasites
Vasculopathy	Hemorrhage cerebrovascular infarct
	Ischemic cerebrovascular infarct
	Posterior reversible encephalopathy syndrome (PRES)
Metabolic	Hepatic encephalopathy
	Uremic encephalopathy
	Wernicke encephalopathy
Immune mediated	Myositis
	Myasthenia gravis
	Immune-mediated neuropathies
	Immune effector cell-associated neurotoxicity syndrome (ICANS)
Radiation related	Cranial nerve neuropathy
	Stroke-like migraine attacks after radiation therapy (SMART syndrome)
	Vasculopathy
	Secondary malignancies

Notably, monoclonal antibodies, bispecific T-cell engagers (BiTE®), and chimeric antigen receptor T cell (CAR-T) therapy have emerged as effective therapies in this burgeoning field of medicine but have ushered in a broad spectrum of off-target neurotoxic events. Accordingly, it is of paramount importance that treating providers maintain a high index of suspicion for treatment-related neurotoxicity so these issues can be remedied at the outset to prevent irreversible damage. In some cases, the etiology may be readily identifiable, but diagnostic enigmas often require a thorough history, neurological evaluation, and diagnostic workup for appropriate treatment.

Noninfectious Treatment-Related Neurotoxicity

1. Cytarabine Arabinoside (Ara-C)

    Ara-C is a nucleotide analog commonly used in the treatment of leukemia and lymphoma, particularly in cases with CNS dissemination. The drug is typi-

cally administered intravenously or intrathecally and undergoes rapid metabolism by cytidine deaminases in the liver and kidneys [8]. Cerebrospinal fluid (CSF) has deficient cytidine deaminase activity; therefore, clearance occurs primarily by CSF bulk flow and diffusion into plasma [9]. Neurologic toxicity of high-dose Ara-C ranges from a mild peripheral neuropathy to, more commonly, an acute cerebral and cerebellar syndrome. The precise mechanism of Ara-C-induced cerebellar syndrome is unknown, but autopsy reports reveal the loss of Purkinje cells in the cerebellum [10]. The reported incidence of neurotoxicity approaches 60% and is more prevalent in patients with renal insufficiency [11]. Other risk factors include the elderly patient population, patients with coexisting neurological conditions, and patients receiving cumulative doses greater than 48 g/m². Symptoms are readily discernible and include cerebellar signs such as nystagmus, dysarthria, dysdiadochokinesia, appendicular ataxia, and oculomotor impairment with concurrent encephalopathy [12]. Fortunately, these warning signs are short-lived when treatment stops but up to 17% of patients may experience irreversible ataxia [11]. In the acute setting, the clinical syndrome is usually discordant with MRI findings (typically absent); however, imaging later in the course may reveal cerebellar atrophy and cerebral leukoencephalopathy. Daily monitoring of cerebellar signs is necessary to minimize the risk of neurologic sequelae during therapy. Although there are no validated effective treatment options, corticosteroids may be beneficial [13, 14].

2. Fludarabine

Fludarabine is a purine analog mainly used to treat chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and non-Hodgkin lymphoma (NHL). The drug also has application in reduced intensity and myeloablative conditioning regimens before allogeneic HCT and as lymphodepleting chemotherapy prior to CAR-T therapy. Dose-limiting neurotoxicity is unique and varies from very high incidence (30–40%) when the dose exceeds 100 mg/m2/day for 5–7 days to 0.2% with the standard low dose [15]. Moreover, sporadic fatal neurotoxicity can occur at doses greater than 40 mg/m2/day [16]. Fludarabine elimination is dependent on renal excretion (60% during the first 24 hours); therefore, transplant recipients with reduced creatinine clearance are prone to therapy-related neurotoxicity [17]. Furthermore, prior CNS toxic exposure and older age may also influence neurologic compromise. Interestingly, clinical manifestations usually emerge several weeks to months post-treatment. Patients may present with confusion, somnolence, generalized seizure, severe persisting headache, blurred vision, cortical blindness, cognitive dysfunction, and posterior reversible encephalopathy syndrome (PRES). Toxicity is sometimes irreversible and can potentially evolve to coma and death. Published autopsy reports have demonstrated gliosis, macrophage infiltrate, and demyelination of white matter [15]. MRI usually shows non-enhancing periventricular white matter changes with restricted diffusion. Unfortunately, there are no known effective treatment options.

3. Calcineurin Inhibitors (CNIs)

CNIs such as cyclosporine and tacrolimus have been the cornerstone of immunosuppressive therapy for graft-versus-host-disease (GvHD) prophy-

laxis in allogeneic HCT recipients and are notorious for some of the most menacing adverse events. Cyclosporine and tacrolimus are the classic offenders with a reported incidence of treatment-induced neurotoxicity ranging from 25% to 59% [18]. Generalized seizures and PRES are the most severe and dramatic consequence of CNI-induced neurotoxicity and typically occur immediately after infusion. Treatment is also associated with early onset tremors, akinetic mutism, opisthotonus with severe rigidity, pseudotumor cerebri, and psychosis. Patients may also experience early or delayed chronic inflammatory demyelinating polyneuropathy (CIDP), brachial plexopathy, optic neuropathy, and hearing loss. The underlying pathophysiology remains undefined; however, CNI-related neurotoxicity appears to be associated with genetic polymorphisms in CYP3A5 and P-glycoprotein encoded by the ABCB1 gene [19]. Moreover, several authors have substantiated prior reports of the stimulatory effect of CNI on sympathetic outflow, which appears to be the critical driver of cerebrovascular vasoconstriction during hypertensive adverse events [20, 21]. Interestingly, CNI-related neurotoxic effects occur irrespective of drug dose, but side effects are more frequent with elevated serum levels. Furthermore, hypertension and electrolyte imbalances, including hypomagnesemia, hyponatremia/hypernatremia, hepatic dysfunction, and dyslipidemia are other putative factors for neurotoxicity [21]. Fortunately, deleterious events can be mitigated by drastically reducing the dose of immunosuppressive therapy or by aborting treatment altogether. In some patients, neurotoxicity may be permanent and lethal [21, 22]. Neurotoxicity is less common with newer-generation CNIs.

4. Busulfan

Busulfan is an alkylating agent administered as part of many reduced intensity and myeloablative conditioning regimens before HCT. The drug has a low molecular weight and high lipophilicity that permit excellent blood-brain barrier (BBB) penetration. This property often leads to a cascade of events that provoke generalized seizures. The estimated incidence of neurotoxicity is approximately 10% in the absence of primary seizure prophylaxis and only 1.3% with preemptive anticonvulsants [23]. Historically, phenytoin has been the drug of choice during high-dose therapy. However, the concomitant administration of enzyme-inducing antiepileptic drugs (AEDs) has been shown to increase the hepatic metabolism of busulfan and thereby decreases the myelosuppressive effects of busulfan during conditioning treatment [24]. Presently, second-generation AEDs, such as levetiracetam (Keppra®), with fewer drug interactions are first line. The general approach to seizure prophylaxis includes the combination of levetiracetam 500 mg oral tablets b.i.d. and clonazepam 0.5 mg oral tablets b.i.d., beginning 12 hours before the first dose of busulfan and continuing for 24 hours after the last treatment.

5. Ifosfamide

Ifosfamide is an alkylating agent with well-demonstrated efficacy against a wide range of tumors including ovarian, testicular, cervical, head, and neck cancers, lymphomas, and soft tissue sarcomas. Approximately 10–40% of

patients experience treatment-related toxicity [25–27]. Neurological sequelae are typically self-limiting and generally resolve in 7 days. Well-acknowledged risk factors include cisplatin exposure, concomitant opioids or CYP2B6 inhibitors, hepatic impairment, and hypoalbuminemia. Interestingly, age and infusion dose do not influence toxicity [27]. Symptoms typically include confusion, disorientation, somnolence, agitation, hallucinations, lethargy, seizures, and coma. Death is rare but reported [28, 29]. The mainstay of treatment includes discontinuation of ifosfamide, but the use of methylene blue 50 mg q4 hours IV is anecdotally reported to be beneficial.

6. Methotrexate (MTX)

MTX has been a staple in immunosuppressive and cancer therapy for generations. The drug is a folate analog that inhibits the enzyme dihydrofolate reductase resulting in the depletion of intracellular pools of reduced folate necessary for the de novo synthesis of nucleotides. The net effect of intracellular MTX metabolism is a marked attenuation of serum folate levels as well as increased levels of adenosine and homocysteine (all of these are associated with neurotoxicity). Additionally, polymorphisms of methylenetetrahydrofolate reductase (MTHFR) gene are the most common cause of toxicity in high-dose MTX therapy as these mutations have been shown to delay drug clearance [30]. Moreover, oligodendrocytes are highly vulnerable to the cytotoxic effects of MTX and thus may lead to dysregulation of CNS myelination [31]. The drug is not lipophilic; therefore, high intravenous doses (>1 g/m2) or direct administration into the subarachnoid space is required to achieve CNS penetration. Both intravenous and, more commonly, intrathecal administration have been implicated in acute, subacute, and chronic neurotoxicity syndromes. Neurotoxicity may be fleeting and reversible, but severe neurological disorders leading to coma or even death may also occur [32, 33].

a. Acute MTX-induced neurotoxicity

Rarely, intrathecal MTX may lead to chemical meningitis within hours of administration. The reported incidence is ~7% but increases threefold after the second dose [34]. The frequency of complications is much lower in patients without CNS disease due to unobstructed CSF outflow pathways. Invariably, patients present with fever, meningeal signs, headache, altered sensorium, nausea, vomiting, and lethargy. CSF analysis usually demonstrates high protein with sterile monocytic or lymphocytic pleocytosis. While infectious etiologies should be ruled out, the timing of symptom onset often suggests an iatrogenic origin. Symptoms are typically self-limiting with spontaneous recovery in 2–6 days after symptomatic management. Finally, adhesive arachnoiditis is also common among patients treated via lumbar puncture. Patients may present with radicular pain, urinary retention and incontinence, and flaccid paralysis. MRI may reveal enhancing nerve roots adherent to each other or the thecal sac [35]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids may arrest pain symptoms.

b. Subacute MTX-induced neurotoxicity

Occurs within days to weeks of intrathecal or intravenous treatment. Patients may develop symptoms akin to cerebrovascular infarcts including acute hemiparesis, hemisensory deficits, aphasia, dysarthria, dysphagia, ataxia, and diplopia. In this scenario, diffusion-weighted MRI demonstrates well-demarcated hyperintense lesions within the subcortical white matter corresponding to areas of restricted diffusion on apparent diffusion coefficient (ADC) maps [36]. In contrast to typical stroke, MTX-induced restricted diffusion patterns do not conform to vascular territories and clinical symptoms and ADC abnormalities usually resolve within 1–4 days [37]. Transverse myelopathy is also a rare neurological sequela of MTX use and has a reported incidence of ~3% [38]. High-dose intrathecal MTX, repeated injections within 1 week, cranial radiotherapy, and active CNS disease are common risk factors for the development of transverse myelopathy [39, 40]. Patients may develop myelopathic changes including paraparesis, impaired deep sensation, sphincter dysfunction, paresthesia, or back pain within days to weeks after therapy. Spinal MRI typically shows a longitudinal diffuse increase in signal intensity on T2-weighted imaging in the lateral and dorsal columns as well as enhancement on post-contrast imaging. CSF analysis may reveal albuminocytologic dissociation, hypoglycorrhachia, elevated myelin basic protein and homocysteine levels, with negative cytopathology. The pathogenesis of MTX-induced myelopathy remains unelucidated, but postmortem studies have demonstrated vacuolar degeneration in the white matter. It is possible that toxicity is related to diminutive synthesis and maintenance of myelin sheaths as a result of disarray in folic acid metabolism [41]. Furthermore, small vessel vasculopathy as a direct toxic effect of the drug on the endothelial cells of the venules and capillaries remains another leading theory [42]. There are no clearly effective treatment options; clinical recovery is variable after the administration of corticosteroids, IVIG, or radiotherapy. There are, however, anecdotal reports of improvement with systemic folinic acid, aminophylline (competitive antagonist adenosine), dextromethorphan (a noncompetitive antagonist of the N-methyl-1-aspartate receptor), and carboxypeptidase G2 rescue [43–46].

c. Chronic MTX-induced neurotoxicity

A delayed complication of recurrent cycles of both intrathecal and intravenous administration most commonly occurring in association with antecedent cranial irradiation. Symptoms may develop after months or even years from treatment. MTX-related leukoencephalopathy may lead to progressive bradyphrenia, behavioral abnormalities, dementia, seizures, long tract signs, and incontinence. The clinical trajectory is variable and can be very severe, leading to coma and death [47]. The pathognomonic MRI findings include diffuse subcortical white matter T2/FLAIR (fluid-attenuated inversion recovery) hyperintensity and cerebral atrophy.

7. Vincristine

Vincristine is an antineoplastic agent used in treatment regimens for hematologic malignancies. Vincristine induces cell cycle arrest of tumor cells by

binding to the β-subunit of tubulin and thereby inhibits microtubule polymerization. The drug primarily effects sensory and motor neurons, but it can also damage autonomic and cranial nerves. Research has shown that vincristine-induced microtubule disarray contributes to impaired axonal transport of essential cellular components leading to neuropathy [48]. The severity of vincristine-induced peripheral neuropathy is dose-dependent and usually develops at a cumulative dose of >2–6 mg/m^2. Symptoms develop initially in the distal extremities leading to a functional disability with impaired fine motor skills and ambulation [49, 50]. Less commonly, patients may suffer from ocular palsies, vocal cord paralysis, acute motor neuropathy (characterized as wrist or foot drop), sphincter disturbance, constipation, orthostatic hypotension, and anhidrosis [51, 52]. Vincristine-induced neuropathy is generally reversible after discontinuation of the drug, but some patients may experience persistent distressing, and sometimes disabling neuropathy that negatively impacts their quality of life.

8. Cisplatin, Oxaliplatin, Carboplatin

   Platinum-based antineoplastics have played a role in some high-dose preparatory regimens used in HCT. Peripheral neuropathy is a common neurological sequela of treatment with members of this drug class. Patients receiving cisplatin- and oxaliplatin-based therapies may experience unbearable neuropathic symptoms that often prevent administration at the optimal effective doses and duration. Large-diameter sensory nerve fibers appear to take the brunt of the toxic effects of these agents, leading to a symmetrical glove and stocking type of sensory loss, numbness, tingling, pain, and burning sensation [53]. For the most part, early symptoms emerge during treatment but may progress several months after completion of therapy. Cisplatin-related peripheral neuropathy occurs after a cumulative dose in the range of 250–500 mg/m^2, whereas patients treated with oxaliplatin-based therapy often report symptoms at a cumulative dose of 750–850 mg/m^2. Neurological examination classically reveals diminished vibration and proprioception with reduced or absent deep tendon reflexes; other sensory modalities (pain, light touch, and temperature) are less likely involved but can be compromised. In patients with fulminant sensory peripheral neuropathy, sensory ataxia, Lhermitte's sign, and Rombergism may be present. Cisplatin therapy may also lead to ototoxicity, encephalopathy, and cerebrovascular infarcts [54–56]. On the contrary, carboplatin-related peripheral neuropathy is infrequent and less severe. There is no standard clinical method for early detection. Electrophysiological assessment remains the gold standard technique for detecting, localizing, and grading the severity of the damage.

9. Thalidomide (Thalomid®), Lenalidomide (Revlimid®), Pomalidomide (Pomalyst®)

   The immunomodulatory drug thalidomide and its derivatives lenalidomide and pomalidomide are often incorporated into treatment protocols for transplant-eligible patients with multiple myeloma. Neurotoxic adverse effects

of thalidomide include peripheral neuropathy, tremor, dizziness, and sedation. A length-dependent (primarily sensory) axonal neuropathy affecting both large and small fibers neurons is the most common manifestation and has an estimated incidence ranging from 1% to 70% [57, 58]. Patients characteristically present with sensorimotor symptoms, such as hypoesthesia, paresthesia, neuropathic pain, or weakness that usually surface after prolonged administration. Symptoms are reversible with dose reductions or discontinuation of therapy. Furthermore, mild somnolence and fatigue are very common during treatment. As such, taking a single dose at bedtime is an effective strategy for mitigating daytime somnolence and fatigue. On the other hand, lenalidomide and pomalidomide are less neurotoxic [59, 60]. Unlike thalidomide, lenalidomide-related peripheral neuropathy can be mild or subclinical and seems to occur independently of cumulative dose [61]. However, a minority of patients may experience amnesia, expressive aphasia, and dysarthria during lenalidomide and pomalidomide therapy [62].

10. Bortezomib (Velcade®), Carfilzomib (Kyprolis®), Ixazomib (Ninlaro®)

Dose-limiting neuropathy (mainly sensory) is a well-recognized adverse effect of bortezomib therapy and has a reported incidence of roughly 30–60% [63]. Several risk factors for neuropathy include preexisting neuropathy, age, and comorbidities. Symptoms may abate 3–4 months following discontinuation of treatment. In a phase III study, 64% of patients with at least grade 2 bortezomib-related peripheral neuropathy achieved symptomatic improvement or resolution of symptoms at a median of 110 days after the termination of treatment [64]. Moreover, once weekly dosing (rather than the standard twice-weekly dosing) has been shown to reduce the frequency and severity of symptoms [65]. Interestingly, Arnulf et al. reported significantly lower rates of peripheral neuropathy and increased rates of improvement/resolution with subcutaneous administration [66]. The pathogenesis of neuropathy is not fully understood, although it appears to involve direct toxic injury to the dorsal root ganglion [67]. Fortunately, second-generation proteasome inhibitors carfilzomib and ixazomib are less neurotoxic than bortezomib and can be considered. Likewise, the monoclonal antibodies daratumumab (Darzalex®) and elotuzumab (Empliciti®) have emerged as promising agents for the treatment of multiple myeloma, although the former has been linked to higher rates of peripheral neuropathy [72].

11. Brentuximab Vedotin (Adcetris®)

Brentuximab vedotin is an anti-CD30 monoclonal antibody used in conjunction with monomethyl auristatin E (an anti-tubulin agent) for the treatment of relapsed or refractory Hodgkin lymphoma and anaplastic large cell lymphoma [73]. Peripheral neuropathy is relatively common during therapy and has an estimated incidence of 57% [74]. Patients may develop pure sensory neuropathy or pure motor neuropathy. The median time to the onset of peripheral neuropathy is approximately 15 weeks. In general, symptoms resolve or improve, on average, around 14.1 weeks after discontinuation of treatment [75].

12. Managing Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Regrettably, CIPN, regardless of the culprit, is stubbornly responsive to conventional therapies, and to date, there are no approved treatment options. There are several agents with purported chemoprotective properties such as acetylcysteine (Mucomyst®), amifostine, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, retinoic acid, and vitamin E; however, a Cochrane review found insufficient data to validate the neuroprotective properties of these drugs [68]. On the contrary, some antidepressants can ameliorate neuropathic pain. A randomized controlled trial evaluated the efficacy of the antidepressant duloxetine (Cymbalta®) in 231 patients taking oxaliplatin, paclitaxel, or other taxanes and found that those receiving duloxetine were significantly more likely to experience a 30% or 50% reduction in neuropathic pain than those in the placebo group [69]. Additionally, there are reports of a modest benefit of venlafaxine (Effexor®), topical amitriptyline (Elavil®), and oxcarbazepine (Oxtellar XR®, Trileptal®) [70]. It is worth pointing out that negative symptoms such as numbness and motor weakness do not respond to pharmacotherapy. Moreover, non-pharmacological interventions may be useful in reducing CIPN symptoms [71].

13. Rituximab (Rituxan®)

Rituximab is a human monoclonal antibody directed against CD20-positive B cells and is used to treat a broad variety of B-cell NHLs. The agent is used in several myeloablative conditioning regimens and as maintenance therapy post-HCT. Rituximab has an excellent safety profile. Neurologic side effects are commonly related to neurotropic infections; however, there are rare occurrences of headaches, fatigue, cognitive impairment, cerebrovascular infarction, convulsion, epilepsy, serotonin syndrome, and PRES [76–79].

14. Alemtuzumab (Campath®, Lemtrada®)

Alemtuzumab is a humanized anti-CD52 monoclonal antibody that successfully depletes B and T-cells. The drug has a myriad of applications for use in a wide variety of hematologic malignancies and autoimmune diseases and in abrogating the risk of GvHD. In addition to the increased risk of opportunistic infections, a few case reports have illustrated a rare development of Guillain-Barre syndrome after treatment [80, 81]. The immunopathogenesis of this is unknown, but it appears that an acute inflammatory demyelinating neuropathy may arise as a result of viral infection/reactivation or as a result of the iatrogenic immune dysregulation.

15. Blinatumomab (Blincyto®)

Bispecific T-cell engagers (BiTEs; see also Chap. 57) are novel molecules containing antigen-binding domains of two independent antibodies that create cross-links between T lymphocytes and tumor cells. BiTEs contain an antigen-binding motif of monoclonal antibodies in the form of two single-chain variable fragments on the N- and C-terminal ends. This immune construct deliberately engages tumor-associated surface antigens and the CD3 receptor on T lymphocytes triggering an exaggerated inflammatory response with potent cell-mediated immune cytotoxicity. Blinatumomab is the first BiTE molecule that has gained US Food and Drug Administration (FDA) approval for relapsed/refractory Philadelphia-negative B-cell acute lymphoblastic leukemia. Blinatumomab

has a short serum half-life and targets the CD19 cell surface receptor expressed on B cells. The initial trials that tested the drug yielded dramatic response rates, albeit with clinically significant neurologic events that necessitated frequent treatment interruptions and drug discontinuation. In a landmark phase I study that evaluated blinatumomab in relapsed/refractory B-cell NHL, the most clinically relevant adverse events were neurologic with an overall incidence of 71%, including National Cancer Institute Common Toxicity Criteria (NCI CTC) grade 3 events that occurred in 22% of patients [82]. The neurotoxic threshold is 60 μg/m2/day. CNS toxicities may manifest as tremor, aphasia, encephalopathy, and seizure but appear reversible with drug discontinuation and corticosteroid use [83, 84]. The genesis and development of neurotoxicity are obscure; however, the presence of active CNS disease seems unlikely related since those patients with coexisting CNS pathology were excluded from clinical trials. As a precautionary measure, preemptive dexamethasone is standard before commencing therapy when the dose is escalated or following interruptions of more than 4 hours. Seizure naïve patients do not need prophylactic anticonvulsants; however, for patients who experience a seizure, secondary seizure prophylaxis is obligatory before blinatumomab therapy. Additionally, further drug administration is contraindicated if more than one seizure occurs [85].

16. Chimeric Antigen Receptor T cell (CAR-T) Therapy (see also Chaps. 52 and 58)

Advances in cancer immunotherapy have skyrocketed over the past decade, and seemingly, the field has reached a tipping point with rapid progress in and growth of CAR-T therapy. Recently, two autologous CAR-T cell therapies, tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) were approved by the FDA for personalized treatment of refractory or relapsed B-cell malignancies. While toxicities may be similar, each product has a unique side effect profile. The novel genetically engineered autologous T-cells express a CD19-specific CAR that recognize and kill CD19+ cells, indiscriminately, with potent antitumor activity [86, 87]. Nonetheless, as CAR-T cell therapy continues to gain exponential momentum in clinical practice, these new therapies are fraught with toxicity profiles that present new challenges in immuno-oncology. CAR-T cell therapy may lead to cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which are two of the most vexing toxicity concerns. In the former, a supraphysiologic systemic inflammatory response generated by T-cell activation induces constitutional symptoms such as hyperpyrexia and malaise which may progress to hemodynamic instability with elevated plasma interleukins within the first 2 weeks after CAR-T cell infusion [88]. The hallmark clinical manifestations of ICANS may overlap with or emerge after the resolution of CRS and may include aphasia, confusion, depressed level of consciousness, cognitive slowing, myoclonus, motor weakness, seizures, brain hemorrhage, and cerebral edema. The median time for onset of ICANS is 4 days after infusion, and the median duration is 5 days [89]. In a recent retrospective study of patients receiving CD19-directed CAR-T therapy, 48% experienced grade 1/2 neurotoxicity, while 52% experienced grade 3/4 that correlated with poor survival [90]. ICANS presents with varying degrees of severity and duration. Neurological toxicities can be mild and paroxysmal, lasting seconds or

minutes. Conversely, life-threatening calamitous events may fulminantly progress in hours or days to coma and death [89]. Generally, spontaneous recovery usually occurs over days without long-term sequelae; however, in a minority of cases, neurotoxicity may be irreversible [89, 91]. An understanding of the pathogenesis of neurotoxicity is of paramount importance for gauging risk factors and determining optimal management. There are conflicting data regarding CD19 expression levels in the brain substance, but the pendulum seems to be swinging towards an absence of this antigen in the CNS [92–94]. Several authors have proposed that endotheliotoxic proinflammatory cytokines may create BBB disruption leading to the influx of systemic cytokine and lymphocytes [89]. Risk factors for neurologic adverse events include acute lymphoblastic leukemia, high CD19+ cells in bone marrow, high CAR-T cell dose, cytokine release syndrome, and preexisting neurologic comorbidities [89]. Moreover, the identification of potential biomarkers to help forecast neurotoxicity has recently garnered widespread research attention. Notably, thrombocytopenia (platelet < 60,000 μL), marked elevations in ferritin, C-reactive protein, mean corpuscular hemoglobin concentration >33.2%, morphologic disease (>5% blasts), and serum interleukin-6 ≥ 16 pg/mL in the first 36 hours after CAR-T cell infusion may be prerequisites for severe neurological toxicity [89, 90, 95]. CSF analysis may reveal markedly elevated protein, lymphocytes, and interleukins. Electroencephalography (EEG) patterns can be normal, but diffuse and focal slowing, as well as clinical and subclinical seizures, can be observed [89]. MRI imaging phenotypes such as T2/FLAIR changes, leptomeningeal enhancement, or multifocal microhemorrhages may portend poor clinical outcome. Options for remedying ICANS include corticosteroids, interleukin-6-targeted therapies, and supportive care, but high-quality evidence of their efficacy is lacking. In 2018, a unified grading system for CRS and ICANS was implemented for use in both clinical trials and daily clinical practice [96].

17. Antimicrobials and Supportive Medications

Systemic antimicrobial and supportive medications are associated with neurotoxicity. The temporal association between the onset of symptoms and drug administration usually pinpoints the exact cause. Several reports have linked acyclovir (Zovirax®), amphotericin B, cephalosporine, quinolone, and posaconazole (Noxafil®) to acute encephalopathy [97–101]. Metronidazole (Flagyl®) and voriconazole (VFend®) are associated with cerebellar syndrome and visual hallucinations, respectively. Finally, supportive medications such as neuroleptics, parenteral nutrition, and corticosteroids administration may also cause neurological complications [102–104].

Neuro-infectious Complications

Immunosuppression during HCT predisposes patients to infection with a wide variety of bacteria, fungi, viruses, and parasites (see Table 36.3). The reported incidence of CNS infections ranges from 0.8% to 15% [106–113]. The most common

Table 36.3 Neuro-infectious complications

Pathogen	Timing	Signs and symptoms	MRI findings	Diagnosis	Treatment
Fungal					
Aspergillus	Any time	Seizure, altered sensorium, with either focal neurological deficits or meningeal irritation	Multiple lesions with subtle mass effect, shift, and minimal to no enhancement. Restricted diffusion on DWI	Serum and BAL GM, beta-(1,3)-D-glucan, biopsy definitive	Voriconazole
Candida	Early or intermediate	Meningeal signs, encephalopathy	Numerous microabscesses at the corticomedullary junction, basal ganglia, or cerebellum. Often with enhancement	Serum Beta-(1,3)-D-glucan	Fluconazole Voriconazole L-AmB plus 5-FC
Mucorales	Late	Headache, low-grade fever, facial swelling, orbital or paranasal sinus syndrome, cranial nerve neuropathy	Nonspecific; may include an irregular abscess cavity wall, intracavitary projections, and abscess cavity with avid diffusion restriction (almost always involves the frontal lobes)	Biopsy	L-AmB Posaconazole isavuconazole
Parasitic					
Toxoplasma gondii	Intermediate or late	Altered sensorium, focal neurologic deficits	Multiple abscesses in the white or gray matter of the cerebral hemispheres, associated with ring enhancement	Toxoplasma DNA in CSF by PCR	Trimethoprim-sulfamethoxazole with clindamycin or pyrimethamine
NCC	Late	Seizure, headache, vomiting, diplopia, bilateral ophthalmoparesis, bilateral horizontal and vertical nystagmus, gait ataxia, truncal ataxia, and somnolence	Vesicular stage: cystic lesions within the brain parenchyma Colloidal stage: ill-defined enhancing lesions surrounded by edema on FLAIR Granular cysticerci: nodular hyperdense lesions surrounded by edema or a rim of gliosis after contrast (usually not visible by MRI)	ETIB to detect antibodies specific for *T. solium* antigens	Praziquantel and albendazole. Anticonvulsants for seizures

Table 36.3 (continued)

Pathogen	Timing	Signs and symptoms	MRI findings	Diagnosis	Treatment
Viral					
HHV-6	Intermediate	Altered sensorium, headache, seizure	Bilateral medial temporal lobe T2 prolongation	HHV6 DNA in CSF by PCR	Ganciclovir, foscarnet
CMV	Intermediate or late	Ventriculo-encephalitis, seizure, polyradiculopathy, myelitis	Nonspecific, increased T2/FLAIR signal in the white matter. Enhancement of the ependymal surface and hydrocephalus may be present in cases with ventriculitis	CMV DNA in CSF by PCR	Ganciclovir or foscarnet
VZV	Late	Postherpetic neuralgia, meningoencephalitis, facial nerve palsy, hearing loss, large- and small-vessel strokes, myelopathy	MRI may be normal or may show areas of high signal intensity on T2-weighted sequence at the gray-white matter junction and in the deep white matter, or abnormal enhancement	VZV DNA in CSF by PCR or detection of VZV IgG antibodies in CSF	Acyclovir or ganciclovir
HSV1-2	Early	Fever, confusion, aphasia, and seizures	T2/FLAIR signal hyperintensity involving cortex and underlying white matter with a predilection for the mesial temporal and inferior frontal lobes, as well as the insular and cingulate cortexes	HSV DNA in CSF by PCR or detection of HSV antigens and antibodies in CSF	Acyclovir, foscarnet valacyclovir
PML	Late	Sensorimotor changes, visual impairment, altered mentation, ataxia, dysmetria, dysarthria, headache, vertigo, seizures, aphasia, and neglect syndromes	Multifocal, asymmetric periventricular and subcortical T2/FLAIR hyperintensity with minimal or no mass effect or enhancement (U-fibers are commonly involved). A high predilection for the parieto-occipital regions. Posterior fossa may be involved	JCV DNA in CSF by PCR. Biopsy definitive	Reduction of immunosuppression. Cidofovir may be beneficial in some patients

Epstein–Barr virus	Intermediate or late	Altered sensorium, meningeal signs, bulbar signs, cerebellar signs, cranial nerve palsy, dysmetropsia	Bilateral and symmetric increased T2-weighted signal in the caudate nuclei, putamen (tropism for the basal ganglia), and thalami. The cortex may be involved but rarely the white matter, brainstem, and splenium	EBV DNA in CSF by PCR. Biopsy definitive	Reduction of immunosuppression, ganciclovir, valganciclovir, foscarnet
West Nile virus	Anytime	Fever, confusion, obtundation, focal weakness, headache, visual changes, flaccid paralysis	T2/FLAIR hyperintense signal in the midbrain. May show enhancement of the leptomeninges, the periventricular area, or both	West Nile virus-specific IgM antibodies in CSF	Supportive therapy. Antivirals not efficacious
Bacterial					
Nocardiosis	Late	Fever, altered sensorium, fever, headache, seizure, focal deficits	Multiple or singular localized ring-enhancing lesions on T1-weighted post-contrast imaging (often mimic high-grade glioma, stroke, lymphoma, vasculitis, mycotic infection, miliary *Tuberculosis*, or metastatic disease)	Needle aspirate, culture, and gram stain	Trimethoprim/sulfamethoxazole. Surgical drainage

BAL bronchoalveolar lavage, *GM* galactomannan, *L-amb* liposomal amphotericin B, *5-FC* 5-fluorocytosine, *DNA* deoxyribonucleic acid, *CSF* cerebrospinal fluid, *PCR* polymerase chain reaction, *NCC* neurocysticercosis, *ETIB* electroimmunotransfer blot, *HHV6* human herpesvirus 6, *CMV* cytomegalovirus, *VZV* varicella zoster virus, *IgG* immunoglobulin, *HSV* herpes simplex virus, *PML* progressive multifocal leukoencephalopathy, *JCV* John Cunningham virus, *EBV* Epstein-Barr virus

neurotropic organisms in patients with malignancies are *Toxoplasma gondii* and fungi, particularly *Aspergillus*. In general, neuro-infectious complications are higher in allogeneic HCT recipients. Neutropenia before engraftment predisposes patients to developing opportunistic infections such as *Aspergillus*, herpes simplex virus (HSV), and *Candida*. In the early post-engraftment period (30–100 days), *Nocardiosis, Candidiasis*, *Aspergillus*, cytomegalovirus (CMV), and human herpesvirus 6 (HH6) infections (see Fig. 36.1) are the most common pathogens. Moreover, immunosuppressive therapy to prevent chronic GvHD may predispose patients to disease by encapsulated bacteria, along with reactivation of latent pathogens such as HSV and *Toxoplasma gondii*. Furthermore, lymphocyte deletion by novel antibody-based therapies has led to severe neuro-infectious complications. Notably, alemtuzumab (Campath®), brentuximab (Adcetris®), and rituximab (Rituxan®) can cause reactivation of latent John Cunningham virus (JCV) leading to progressive multifocal leukoencephalopathy (PML) [114–116]. The clinical manifestations of neuro-infectious disorders are nonspecific; thus, a high index of suspicion for CNS infection should be maintained in all cases presenting with altered level of consciousness with either focal signs of neurologic or meningeal irritation. Regarding the choice of neuro-imaging, gadolinium-enhanced MRI is more sensitive than CT and remains the gold standard. However, it is essential to recognize that in immunosuppressed hosts, CNS lesions may be associated with subtle mass effect and minimal to no pathological enhancement due to a blunted inflammatory response. CSF analysis can potentially establish the diagnosis; however, seronegative cases warrant tissue diagnosis.
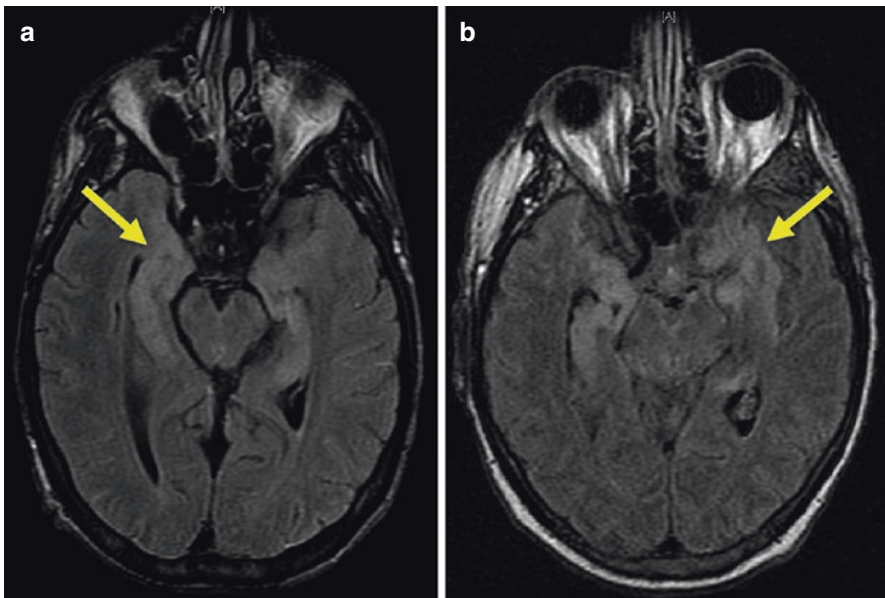
Fig. 36.1 Axial MRI images from two patients (**a** and **b**) with HHV-6 limbic encephalitis demonstrating T2/FLAIR signal hyperintensities of the bilateral medial temporal lobes (arrows)

Cerebrovascular Complications

1. Hemorrhagic and Thrombotic Events

   HCT recipients are at increased risk for life-threatening cerebrovascular hemorrhagic and thrombotic complications. In a retrospective review of 1000 HCT recipients, cerebrovascular insults (31.4%) were the most common neurological sequelae of treatment [102]. In that cohort, 29% of patients experienced intracranial hemorrhage, while cerebrovascular infarct occurred in 2.4%. Intraparenchymal bleed (see Fig. 36.2) was most frequent, and rarely, patients experienced subarachnoid, subdural, and epidural hemorrhages. In another study of 657 patients undergoing allogeneic or autologous HCT, 2.6% suffered subdural hematoma [117]. In addition to thrombocytopenia and coagulopathy, the authors also noted a relationship with the inclusion of intrathecal methotrexate in the conditioning regimen. The standard guidelines for emergent management of intracranial hemorrhage include neurosurgical assessment for craniotomy, ventriculostomy, or placement of an intracranial pressure monitor. Platelet transfusions to maintain platelets > 50,000/μL and reversal of coagulopathic defect are essential in early hemostatic therapy. Though the data are limited, in some life-threatening cases recombinant factor VII and antifibrinolytic amino acids such as aminocaproic acid (Amicar®) and tranexamic acid (Lysteda®), or 1-deamino-8-D-arginine vasopressin (DDAVP, Desmopressin®) can be considered.

   Furthermore, specific fungal pathogens, particularly *Aspergillus*, have a high degree of cerebral angioinvasion that may lead to a mycotic aneurysm. The
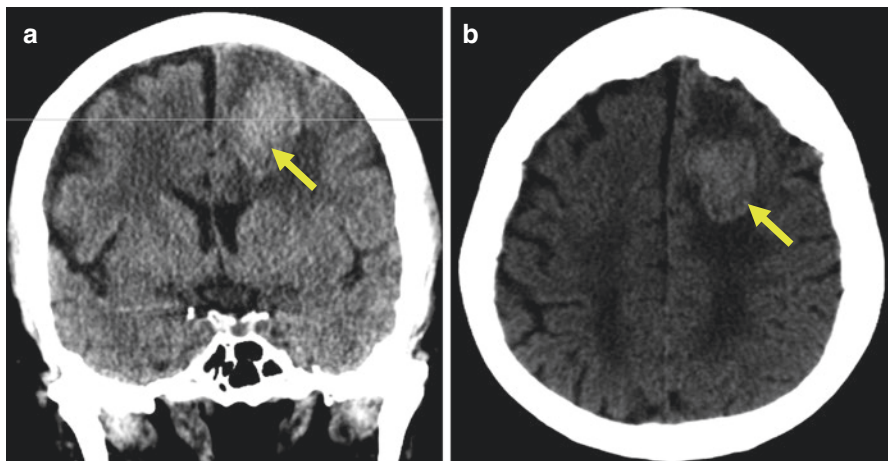
Fig. 36.2 Coronal (**a**) and axial (**b**) non-contrast CT illustrating a left frontal intraparenchymal hemorrhage *(arrow)* in a 52-year-old woman with confusion and inability to follow directions, 22 days after matched-unrelated HCT for acute lymphoblastic leukemia with platelets 18,000/micro/L

respiratory tract is the primary site for *Aspergillus,* but dissemination to the CNS is quite common. In a retrospective analysis of a large cohort of patients undergoing allogeneic HCT, 55% of patients with pulmonary disease developed CNS involvement [118]. The prognosis of CNS aspergillosis is grave with an overall fatality rate of around 70% but approaches 100% in patients with hematologic malignancies [119]. Establishing the diagnosis can be quite challenging, and in most cases the diagnosis is made postmortem. MRI may show ring-enhancing lesions (see Fig. 36.3), infarction, or vascular infiltration on MR angiography. In patients presenting with focal neurological deficits due to thrombotic or hemorrhagic stroke, cerebral aspergillosis should remain high among the differential considerations. The detection of fungal cell wall antigens by the galactomannan test (Platelia™ Antigen EIA) is well established for the use in serum but may be useful in CSF. Regardless of the situation, ischemic infarcts should prompt an evaluation for a source of septic emboli, which are most often fungal.

Additionally, antineoplastic agents, such as L-asparaginase, 5-fluorouracil monotherapy, or in combination with cisplatin, methotrexate, and cyclophosphamide can incite a hypercoagulable state in cancer patients that may lead to arterial and venous thrombosis [120]. L-asparaginase-related strokes may manifest

Fig. 36.3 Axial MRI image of CNS aspergillosis depicted by two T1 post-contrast ring-enhancing lesions (arrows) in a 39-year-old man with headaches after an unrelated donor allogeneic HCT and found to have disseminated aspergillosis
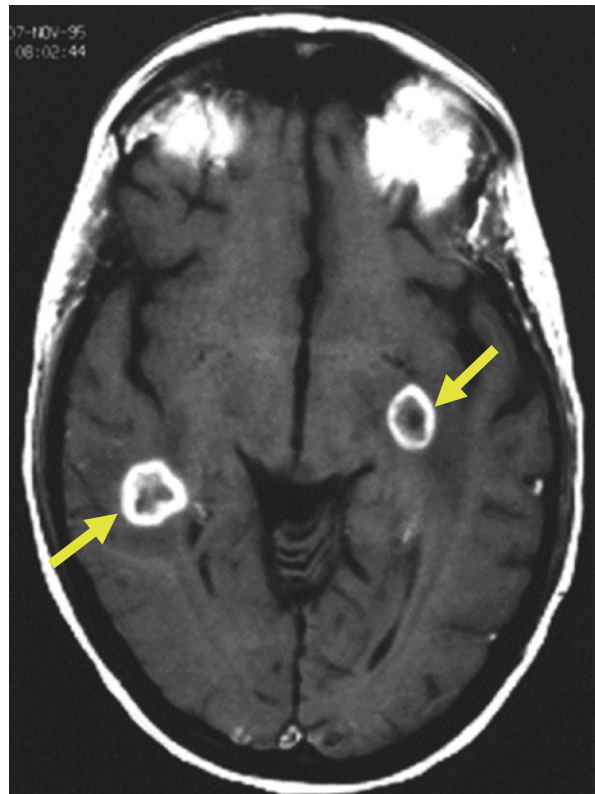
as cerebral venous sinus thrombosis, cortical or capsular infarction, and intracerebral hemorrhage. It is a widely held view that a reduction in the synthesis of proteins such as antithrombin III and fibrinogen trigger thrombotic events. Thrombotic events typically occur during or shortly after induction of treatment. When suspected, termination of the drug is recommended; therapeutic low molecular weight heparin (LMWH) is the mainstay of treatment. In select cases of venous thromboembolism (VTE), L-asparaginase therapy can continue; however, therapeutic LMWH should remain throughout the treatment course. Accordingly, careful monitoring of anti-Xa levels (to confirm optimal anticoagulation with LMWH) and antithrombin levels (to maintain level >60%) is essential [121]. Direct thrombin or factor Xa inhibitors do not require monitoring of antithrombin level and in theory may lower the risk of recurrent VTE; however, large-scale studies are needed to confirm this.

2. Posterior Reversible Encephalopathy Syndrome (PRES)

Several chemotherapeutic agents and monoclonal antibodies utilized during HCT can cause PRES. Patients typically present with a constellation of signs and symptoms including headache, impaired consciousness, visual disturbances, seizures, and focal neurological signs. PRES is thought to be triggered by impaired autoregulation of cerebral blood pressure and local CNS inflammation and is commonly seen in patients receiving calcineurin inhibitors (CNIs) for GvHD prophylaxis. The risk is highest in the first months after HCT when doses are higher and varies by CNI. The incidence of neurotoxicity is higher with cyclosporine than with tacrolimus. Less frequently, patients receiving cisplatin, cytarabine, ifosfamide, vincristine, and rituximab experience PRES.

Once suspected, immediate discontinuation of the offending agent is crucial, and treatment involves blood pressure management, restoring fluid/electrolyte balance, and seizure control with anticonvulsants. MRI is the gold standard diagnostic imaging modality and classically demonstrates hyperintensities on T2-weighted sequences involving the bilateral white matter, particularly in the posterior circulation (see Fig. 36.4). These imaging findings are usually reversible on follow-up exams within days or several months. Unfortunately, PRES is not always reversible. In patients with hematologic malignancies, PRES confers worse prognosis [122].

Radiation-Induced Complications

Total body irradiation (TBI)-containing regimen predisposes HCT recipients to acute and delayed neurotoxicity. Myeloablative TBI typically consists of 12–15 Gy given in 8–12 fractions over 4 days, with 2–3 treatments daily. Headache and fatigue are common in the acute setting [123]. Delayed effects including neurocognitive deficits, mineralizing microangiopathy, cavernoma, and panhypopituitarism requiring hormonal replacement are pervasive in pediatric patients with hematologic
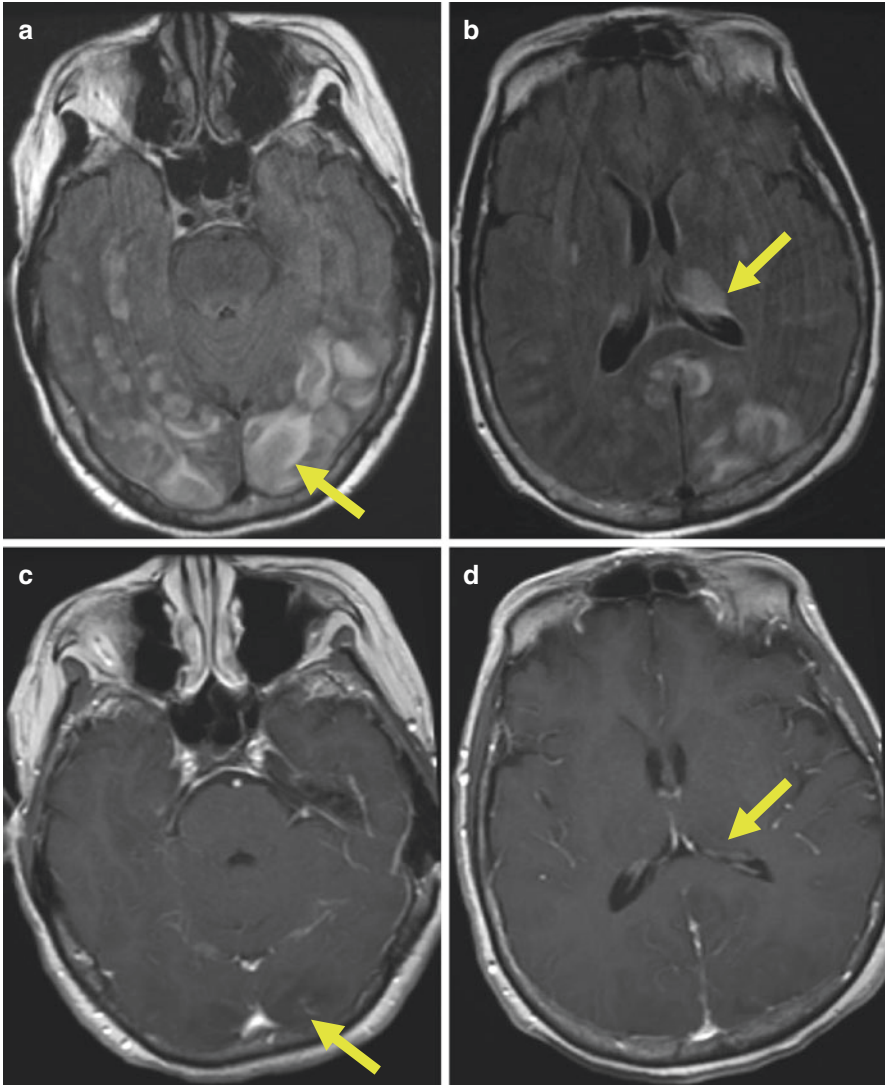
Fig. 36.4 Axial MRI images of PRES with multiple areas of T2/FLAIR (**a**, **b**) hyperintensity involving the white matter of the occipital lobes and thalamus (arrows) and correlating minimal T1-contrast-enhancing *(arrows)* (**c**, **d**) in a 60-year-old woman with depressed consciousness, hypertension, fever, day 216 after reduced intensity allogeneic HCT

malignancies. Furthermore, many years after treatment, patients may develop secondary malignancies including meningiomas, gliomas, or malignant schwannomas.

In patients who receive cranial irradiation as part of TBI, retinopathy may occur. Moreover, Schwartz et al. reported an unexpected case of radiation-induced myelopathy following a conditioning regimen of cyclophosphamide and TBI [124]. Additionally, the literature highlights a rare case of intraspinal irradiation-induced

cavernous hemangioma with spontaneous symptomatic hemorrhage years after TBI [125]. Finally, stroke-like migraine attacks after radiotherapy (SMART syndrome) is a rare complication of cranial irradiation and may occur within 1–35 years after brain radiation [126]. Patients present with recurrent episodes of complicated migraine symptoms consisting of transient sensorimotor deficits, aphasia, visual disturbances, and seizures. MRI classically demonstrates reversible, short-lived, unilateral cortical gadolinium enhancement as well as correlative hyperintense T2/FLAIR signal abnormality, predominantly in the posterior brain region. The syndrome somewhat mimics PRES, but patients spontaneously recover with time.

Post-Transplant Lymphoproliferative Disorder

Immunosuppressive therapy poses a significant risk for isolated CNS post-transplant lymphoproliferative disorder (PTLD) in HCT recipients. Most CNS PTLD cases (90%) are driven by EBV reactivation [127]. Under normal circumstances, EBV-specific T lymphocytes can control the primary infection and thwart EBV reactivation. However, delays in the reconstitution of EBV-specific T lymphocyte activity can promote a fulminant viremia and consequential life-threatening EBV-driven PTLD.

Apart from T-cell depletion, major risk factors for EBV-viremia and PTLD include donor-recipient mismatch and the extent of immunosuppression used for preemptive therapy and to treat GvHD [128]. PTLD after HCT is predominantly derived from donor B cells and typically occurs within the first 6 months post-transplant, before reconstitution of the EBV-specific T lymphocyte response [129]. Clinical manifestations are nonspecific and are related to the anatomical location of the lesions. More commonly, patients present with focal neurologic deficits, neuropsychiatric symptoms, signs of raised intracranial pressure, and visual disturbances. Unlike other lymphoid malignancies, pyrexia and other constitutional symptoms are uncommon. In contrast to primary diffuse large B-cell lymphoma, MRI lesions in PTLD often reveal hemorrhage, necrosis, and peripheral or ringlike enhancement with extensive edema and marked expansion of the perivascular spaces. Most cases show a solitary mass that typically affects the periventricular region [130]. Tissue acquisition via biopsy establishes the diagnosis; several protocols incorporating high-dose systemic chemotherapy with or without anti-CD20 monoclonal antibody have been utilized. Among patients with PTLD, CNS involvement confers poor survival [131].

Metabolic Complications

Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially lethal complication of HCT and occurs in approximately 50–60% of transplant recipients [132]. The syndrome usually develops within 30 days after HCT and is characterized by symptoms of liver failure, including encephalopathy,

coagulopathy, and severe renal failure. Risk factors for VOD/SOS include preexisting hepatic damage, abdominal irradiation, donor-recipient human leukocyte antigen disparity, and previous high-dose chemotherapy. Notably, cyclophosphamide and busulfan are the most common offenders.

Uremic encephalopathy is also common during HCT and is seen in conjunction with CNI nephrotoxicity and thrombotic microangiopathy/hemolytic-uremic syndrome. Early signs of encephalopathy can be nonspecific and may include fatigue, apathy, irritability, and poor concentration. Clinical signs may later progress to clouded sensorium accompanied by tremor, fasciculations, asterixis, and seizures. Thereafter, patients may present with severe confusion, disorientation, delirium, hallucinations, and a depressed level of consciousness.

Finally, a few case reports have illustrated the development of Wernicke's encephalopathy during prolonged total parenteral nutrition (TPN) use in severely malnourished patients with inadequate oral intake [133–135]. Though rare, the risk is high in commercialized TPN, which often lacks thiamine. The syndrome is easily recognized based on history and clinical findings (acute mental confusion, ataxia, and ophthalmoplegia); however, symmetric hyperintensity on T2/FLAIR images or symmetric areas of contrast enhancement in the thalamus, periventricular region of the third ventricle, mammillary bodies, periaqueductal region, and tectal region can help clinch the diagnosis. When suspected, intravenous thiamine 500 mg, infused over 30 minutes, three times daily for two consecutive days is standard. Recovery is variable; about 20% recover completely [136, 137].

Conclusion

Neurologic complications of HCT are common, difficult to identify early in the treatment course, often missed, and portend a worse outcome. Clinicians caring for this population should have a low clinical suspicion for thoroughly investigating any neurologic symptoms even up to a year after transplant and regardless of risk factors. Though deficits are often reversible, early detection and discontinuing the offending agent (if drug-induced) and appropriate treatment are critical.

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Chapter 37
Endocrine Complications Following Hematopoietic Cell Transplantation

Malinda West

Introduction

As the numbers of hematopoietic cell transplants (HCT) performed around the world increase, so does the number of transplant survivors [1, 2]. Endocrine complications are under recognized and estimated to affect up to 50% of transplant recipients [3, 4]. Knowledge of current and past therapies is critical in understanding overall risk. Risk factors for developing endocrine complications include exposure to radiation therapy, alkylating agents, or antimetabolites, prolonged immunosuppressive treatment with corticosteroids, and chronic graft-versus-host disease (GvHD) [5, 6]. Risks are primarily related to allogeneic transplantation, although autologous transplantation carries risk of complication as well. Such treatments can lead to development of (1) metabolic syndrome which encompasses hypertension, dyslipidemia, abdominal obesity, and insulin resistance, (2) diabetes mellitus, (3) adrenal insufficiency, (4) thyroid dysfunction, (5) decreased bone mineral density, and (6) hypogonadism. Many treatment options exist. Appropriate diagnostic testing and treatment can alleviate symptoms, improve quality of life (QOL), and decrease later mortality.

Primary factors associated with endocrine complications are treatment related, not disease specific [26]:

1. Chemotherapy: type and dose
2. Radiotherapy: involved field, cumulative dose, duration of exposure
3. Surgery: degree and number of surgeries

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Transplant-related agents associated with endocrine complications [2, 5]:

1. Alkylating agents

   a. Cyclophosphamide, melphalan, busulfan, thiotepa, cisplatin, ifosfamide, mechlorethamine, nitrosoureas, carmustine, lomustine, procarbazine

2. Antimetabolites

   a. Methotrexate, cytarabine, fludarabine

3. Corticosteroids
4. Total body irradiation (TBI)

   Non-transplant-related risk factors for endocrine complications include [5, 7]:

1. Age: older age associated with increased risk.
2. Gender: females are at slightly higher risk for many of these endocrine disorders.
3. Genetics: hereditary predisposition, family history.
4. Social: health and lifestyle practices, e.g., smoking, alcohol intake, diet, obesity, and sedentary lifestyle.

   See Table 37.1 for summary of recommendations

Metabolic Syndrome

Metabolic syndrome is the combination of hypertension, dyslipidemia, obesity with visceral adiposity, and insulin resistance. It is estimated nearly half of HCT recipients develop metabolic syndrome; this complication confers a two- to threefold increased risk of having a serious cardiovascular event [3, 6, 10]. Older individuals are increasingly undergoing HCT, and survivors are living longer. Advanced age in combination with post-HCT metabolic syndrome confers additive cardiovascular risk.

1. Hypertension (HTN) [8, 9]

   a. Most common within first 2 years after transplant.
   b. Two- to threefold increased risk post-HCT.
   c. Transplant-related risk factors include:

      i. TBI
      ii. Medications: glucocorticoids and calcineurin inhibitors (CNIs), especially cyclosporine [11–13]

         • Cyclosporine-induced HTN is mediated initially via systemic vasoconstriction with increased endothelin and decreased nitric oxide and prostacyclines. Later physiologic events include elevated renin levels and activation [8] of renin angiotensin aldosterone system and sodium retention.
         • Glucocorticoids primarily contribute to the development of HTN via salt and water retention from mineralocorticoid excess.

Table 37.1 Summary of recommendations for endocrine complication monitoring and management

Endocrine complication	Screening	Diagnosis	Management
Metabolic syndrome	See below for each component recommendations	Combination of hypertension, dyslipidemia, obesity with visceral adiposity and insulin resistance	See below for each component recommendations
Hypertension	- Baseline: pre-HCT measurements - BP at every visit - Home BP log if borderline	- ≥ 60 years old: if > 150/90 mmHg on multiple occasions - < 60 years old: if > 140/90 mmHg on multiple occasions, targeting a diastolic goal of < 90 mmHg - Any age and have diabetes mellitus or chronic kidney disease: > 140/90 mmHg on multiple occasions	- Lifestyle changes - Limit glucocorticoids and CNI if able - First line for non-black patients: ACEI, ARB, dihydropyridine CCB, or thiazide diuretic - First line for black patients: thiazide diuretics, dihydropyridine CCB - ACEI or ARB in patients with CKD - CSA-related HTN: dihydropyridine CCB - Glucocorticoid related HTN: first line (low-salt diet and aldosterone antagonists), second line (dihydropyridine CCB)
Dyslipidemia	- Baseline: pre-transplant fasting lipid panel - Day +100 post-HCT, then annually if stable on or off therapy, or without risk factors - If presence of transplant-related risk factors, screen 3 months post-HCT, then q3–6 months - If not at goal or adjusting medications, check q6–8 weeks until goal reached, then q4–6 months	- Total cholesterol >200 mg/dL - LDL > 100 mg/dL - Non-fasting triglycerides > 150 mg/dL - HDL < 40 mg/dL in men and < 50 mg/dL in women	- Lifestyle changes - Consider immunosuppression changes for less dyslipidemia effect and/or to minimize statin interaction - Initiate statin if ASCVD risk 7.5%+ according to AHA guidelines - To minimize drug-drug interactions with many HCT medications, recommend pravastatin for low intensity statin and rosuvastatin for high intensity statin - If statin intolerant, try other agents as indicated

(continued)

Table 37.1 (continued)

Endocrine complication	Screening	Diagnosis	Management
Obesity	- Baseline: pre-HCT BMI, waist circumference. Consider baseline fat composition analysis with dual-x-ray absorptiometry - If BMI > 25 kg/m2, presence of central or sarcopenic obesity, presence of risk factors or actively undergoing weight loss strategy, measure q3–6 months - If none of the above, screen annually	- BMI ≥ 30 kg/m², ethnic variations (see AACE/ACE guidelines) - Central obesity: waist circumference > 102 cm in men, > 88 cm in women - Sarcopenic obesity: body fat > 27% in men, > 38% in women	- Reduced calorie diet - Resistance exercises for sarcopenic obesity - Goal of 150 min/week of aerobic exercise over at least 3 days per week and resistance training at least 2–3 days per week - Limited role for pharmacotherapy; however consider if obesity refractory to diet/exercise
Diabetes mellitus	- Baseline: pre-transplant fasting blood glucose - Post-HCT: monitor fasting blood glucose weekly, then at 3, 6 and 12 months - If no additional risk factors: screen yearly - If risk factors and ongoing steroid use, continue screening every 3 months post-HCT	- Fasting plasma glucose ≥ 126 mg/dL - HgbA1c ≥ 6.5% - 2 hours 75 gm oral glucose tolerance test ≥ 200 mg/dL - Random plasma glucose ≥ 200 mg/dL in patient with hyperglycemia symptoms	- Insulin basal-bolus regimen is the safest strategy with the least interactions - Consider oral agent if consistent oral intake, stable renal/liver function, in outpatient setting. Recommend classes include sulfonylureas, meglitinide analogues, DPP4 analogues
Adrenal insufficiency	- Recommended screening if symptoms develop after prolonged steroid course totaling > 7.5 mg/day for > 3 weeks, or in setting of acute illness/trauma/trigger	- ACTH stimulation test: measure baseline plasma cortisol levels, then administer cosyntropin and measure plasma cortisol again 30 and 60 min after administration. Plasma cortisol < 20 mcg/dL is diagnostic for adrenal insufficiency	- Hydrocortisone 15–25 mg total per day divided 2/3 in the morning and 1/3 in the evening - Consider DHEA supplementation in women - If illness, surgery or stressor: supplement to 100–150 mg/day total of hydrocortisone - If hospitalized and parenteral administration required, give 100 mg IV/IM hydrocortisone once, then 200 mg IV q24 hours via continuous infusion or 50 mg IV q6hr

Endocrine complication	Screening	Diagnosis	Management
Thyroid dysfunction and neoplasm	- Check yearly TSH and free thyroxine levels or sooner if symptoms develop - If evidence for subclinical hypothyroidism, repeat screening in 2 months. - Hyperthyroid symptoms: additional anti-thyroglobulin antibody, anti-thyroid peroxidase antibody, TSH receptor antibodies - Thyroid exam at each visit	- Hypothyroidism: low free T4 and elevated TSH - Subclinical hypothyroidism: normal free T4 and elevated TSH - Hyperthyroidism: high free T4 and low TSH - Autoimmune thyroiditis: presence of anti-thyroglobulin antibody, anti-thyroid peroxidase antibody, or TSH receptor antibodies	*Subclinical hypothyroidism:* - Monitor *Hypothyroidism:* - Initiate levothyroxine at 1.6 mcg of levothyroxine/kg of body weight per day taken without food or other medications to facilitate absorption - Use lower dose initially 25–50 mcg daily until response - Reassess 6 weeks post initiation - Goal to get TSH within normal limits of lab test *Hyperthyroidism:* - Symptom control with beta blocker - Endocrinology evaluation for thionamide, radioiodine ablation and/or surgery evaluation *Thyroid nodule:* - If mass palpated, a thyroid ultrasound should follow with biopsy of mass >1 cm or with concerning features otherwise
Decreased bone mineral density	- DEXA scan within 1 year post-HCT - If normal bone mineral density, repeat every 2 years - If abnormal, yearly screen with treatment - Check serum 25-hydroxy vitamin D level yearly	- Osteopenia T score −1 to −2.5 - Osteoporosis T score < −2.5	- Lifestyle approaches: weight-bearing exercises, smoking cessation, alcohol avoidance - If on chronic steroids or osteoporosis, supplemental calcium 1200 mg/day and vitamin D 1000 IU per day - Pharmacologic intervention if indicated - Duration of treatment unclear, consider drug holiday after 5 years of bisphosphonate

HCT hematopoietic cell transplant, *BP* blood pressure, *CNI* calcineurin inhibitor, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker, *CSA* cyclosporine, *HTN* hypertension, *ASCVD* atherosclerotic cardiovascular disease, *AHA* American Heart Association, *BMI* body mass index, *AACE/ACE* American Association of Clinical Endocrinologists/American College of Endocrinology, *DPP4* dipeptidyl-peptidast-4 inhibitor, *ACTH* adrenocorticotropic hormone, *DHEA* dehydroepiandrosterone, *TSH* thyroid-stimulating hormone, *DEXA* dual-energy x-ray absorptiometry

   d. Non-HCT-related risk factors:

      i. Pre-transplant HTN
      ii. Obesity
      iii. Chronic kidney disease
      iv. Smoking
      v. Diabetes

   e. Screening:

      i. Obtain baseline [8] pre-HCT blood pressure (BP) measurements.
      ii. BP screening at every visit. If borderline clinic recordings, use home BP log to interpret if confounding "white coat" effect present.

   f. Guidelines for initiation of treatment [13, 14]:

      i. 60+ years old: if BP > 150/90 mmHg on multiple occasions.
      ii. < 60 years old: if BP > 140/90 mmHg on multiple occasions, targeting a diastolic goal of < 90 mmHg.
      iii. Any age and have diabetes mellitus or chronic kidney disease: BP > 140/90 mmHg on multiple occasions

   g. Antihypertensive management [14]:

      i. Lowest possible [8] glucocorticoid dose and taper of immunosuppressive medications as able.
      ii. Unless otherwise indicated, first line in non-black patients: angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), dihydropyridine calcium channel blocker (CCB), or thiazide diuretics.
      iii. Thiazide diuretics [8], CCBs as first line in black patients.
      iv. ACE inhibitor or ARBs are beneficial in patients with chronic kidney disease; however if using in combination with cyclosporine, monitor creatinine and potassium values closely [8, 11].
      v. Specific considerations [11, 12]:

         • Cyclosporine-related hypertension: CCBs are recommended initially given benefit of smooth muscle relaxation within arterial vasculature and reduced interactions with other antihypertensive agents.
         • Glucocorticoid-induced hypertension: aldosterone antagonists recommended [8] for preferential salt and water wasting in combination with reduced dietary sodium intake, adding CCBs second line if needed.

2. Dyslipidemia [3, 13, 15]

   a. Target lipid panel results:

      i. Total cholesterol < 200 mg/dL
      ii. Low-density lipoproteins (LDL) < 100 mg/dL
      iii. Non-fasting triglycerides < 150 mg/dL

    iv. High-density lipoproteins (HDL) > 40 mg/dL in men and > 50 mg/dL in women

b. Most often presents 8–11 months post-HCT

c. Estimated incidence in 60–70% HCT survivors

d. HCT-related risk factors [16, 17]

    i. TBI

    ii. Hyperalimentation post-HCT, high in glucose and lipid content [14]

    iii. Chronic GvHD: Etiology is multifactorial via liver involvement causing impaired bile salt and cholesterol clearance and from immunosuppressive medication side effects

    iv. Coexisting hypothyroidism, hypogonadism

    v. Immunosuppressive agents [8, 17–20]

- Sirolimus (Rapamycin®)

    – Associated with elevated hyperlipidemia and hypertriglyceridemia

    – Mechanism: multifactorial via increased free fatty acids and hepatic very-low-density lipoprotein (VLDL) synthesis, increased lipase activity and lipolysis, decreased triglyceride storage

- Cyclosporine (Neoral®, Sandimmune®)

    – Associated with elevated total cholesterol and LDL

    – Mechanism: multifactorial via enzymatic inhibition preventing cholesterol conversion into bile acids, blocks LDL receptors so more remains in circulation, and impairs VLDL and LDL clearance

- Tacrolimus (Prograf®)

    – Similar to cyclosporine but possibly associated with less dyslipidemia [18]

- Mycophenolate mofetil (Cellcept®)

    – Not associated with dyslipidemia in solid organ transplantation, although hyperlipidemia is listed as side effect on package insert when in combination with cyclosporine and steroids

- Glucocorticoids

    – Mechanism: multifactorial via increased lipase activity, increased lipogenesis, increased VLDL export, downregulated LDL receptor

e. Non-HCT-related risk factors: pre-transplant hyperlipidemia, family history, obesity, tobacco use, alcohol intake [1, 3, 8]

f. Screening: [9, 13]

    i. Baseline pre-transplant fasting lipid panel, day +100, then annually if stable on or off therapy, or without risk factors.

    ii. If transplant-related risk factors are present, screen at day +100, then every 3–6 months thereafter. If not high risk for dyslipidemia, follow

standard American Heart Association (AHA) recommendations of screening every 5 years in men $\geq$ 35 years and women $\geq$ 45 years of age.

   iii. If not at goal or adjusting medications, check every 6–8 weeks until goal achieved, then every 4–6 months.

g. Treatment approach [9, 13, 16]:

   i. Dietary modification, exercise, and smoking and alcohol cessation.

   ii. Adjust immunosuppression for less dyslipidemia effect, based on individual patient condition and side effect profile of each immunosuppressive agent (see section "Introduction" (2.d.*v*)).

   iii. Initiate statin therapy based on 10-year atherosclerotic cardiovascular disease risk (ASCVD) risk and other risk factors:

- ASCVD risk of $\geq$ 7.5%, initiate statin therapy according to AHA guidelines.
- For side effect mitigation and less transplant-related drug interactions, recommend pravastatin (Pravachol®) for low-intensity statin and rosuvastatin (Crestor®) for high-intensity statin.
- Consider non-statin therapy for those who are intolerant or due to side effect or interaction profile:
    - Omega 3-polyunsaturated fish oils
    - Fibrates: gemfibrozil (Lopid®), fenofibrate (Tricor®, Lofibra®)
    - Ezetimibe (Zetia®)
    - Niacin
    - Bile acid sequestrants: cholestyramine (Questran®), colestipol (Colestid®)
    - PCSK9 inhibitors: evolocumab (Repatha®), alirocumab (Praluent®)
- Consider adjusting immunosuppression to minimize interactions.
- Caution combining fibrates and statins due to increased side effect profile.

   iv. Special considerations:

- Statin therapy interactions with transplant-related medications [1, 16, 20]:
    - Statins are effective in lowering LDL and triglycerides.
    - Caution in use of atorvastatin, lovastatin, and simvastatin which are metabolized via the CYP3A4 system.

        Potentiated by CYP3A4 strong or moderate inhibitors like azole antifungals, sirolimus, cyclosporine, macrolide antibiotics, proteasome inhibitors, amiodarone (Pacerone®), amlodipine (Norvasc®), verapamil (Calan®, Isoptin®), diltiazem (Cardiazem®), nicotinic acid.

        - If combined usage needed, recommend using lower statin dosage and monitoring for statin-associated adverse effects.

Tacrolimus has minimal to no effect on pharmacokinetics of statins [22].

Fluvastatin (Lescol®), rosuvastatin (Crestor®), and pravastatin (Pravachol®) are not metabolized via CYP3A4 system and therefore have less interactions.

- Statins and hyperlipidemia control as beneficial or protective [18]:

  – Statin use may limit effector T cell expansion involved in GvHD by limiting available lipid for fatty oxidation fuel source.
  – Shifts T cell differentiation into non-inflammatory TH2 phenotypes, protective against GvHD.
  – Lovastatin (Mevacor®) and simvastatin (Zocor®) have been shown to inhibit T cell migration to lymph nodes and decreased T cell proliferation.

3. Obesity [3, 13, 17, 21]

   a. Definition: Body mass index (BMI) ≥ 30. Exceptions exist for normal BMI obesity, as in sarcopenic obesity or isolated central adiposity, and ethnic variations, e.g., South Asian populations where a BMI > 25 is defined as obese
   b. In the United States, central adiposity is defined as a waist circumference > 102 cm in men and > 88 cm in women:

      i. May have normal BMI.
      ii. Carries a greater risk for metabolic syndrome and cardiovascular disease.
      iii. If normal BMI, use waist circumference for predictive cardiovascular risk.

   c. Sarcopenic obesity refers to the loss of muscle mass in the setting of normal or elevated BMI, generally associated with aging; however it has been shown to be a complication of HCT:

      i. Defined as body fat composition > 27% in men, > 38% in women.
      ii. HCT-related risk factors include GvHD, corticosteroid use, and advanced age.
      iii. Non-HCT-related risk factors include pre-transplant obesity, inactivity, and poor diet.

   d. Screening:

      i. Baseline: pre-transplant BMI, waist circumference. Consider baseline fat composition analysis with dual-x-ray absorptiometry.
      ii. Weight at every visit. Consider measuring waist circumference or a fat composition if concern for isolated central adiposity or sarcopenic obesity.
      iii. Goal BMI < 30 kg/m2. If normal BMI, measure waist circumference for goal < 102 cm in men and < 88 cm in women [8].

   e. Treatment approach:

i. Exercise and reduced calorie diet modifications with pharmacotherapy as indicated

- Diet and exercise modifications can be challenging in HCT patients who experience frequent/chronic symptoms of fatigue, nausea, reduced appetite, gastrointestinal discomfort, and/or diarrhea.
- Resistance exercises in addition to endurance cardiovascular-based activities are important for patients with sarcopenic obesity to prevent loss of lean muscle mass otherwise associated with weight loss.
- Goal of 150 min/week of aerobic exercise over at least 3 days per week and resistance training at least 2–3 days per week.
- If obesity remains refractory despite lifestyle changes, consider adjunctive pharmacotherapy such as drugs that impair fat digestion, GLP1 receptor agonists, and sympathomimetic agents; however these medications have not been studied in the post-HCT recipient.

4. Insulin Resistance: see section "Metabolic Syndrome".

Diabetes Mellitus [3, 15, 22, 23]

1. Incidence: up to 40% post-allogeneic HCT recipients, 3% reported post-autologous HCT recipients
2. Insulin resistance and pre-diabetes definition:

   a. Fasting plasma glucose 100–126 mg/dL
   b. HgbA1c 5.7–6.4%
   c. 2-hour 75 gm oral glucose tolerance test: plasma glucose 140–199 mg/dL

3. Diabetes mellitus definition:

   a. Fasting plasma glucose ≥ 126 mg/dL
   b. HgbA1c ≥ 6.5%
   c. 2-hour 75 gm oral glucose tolerance test ≥ 200 mg/dL
   d. Random plasma glucose ≥ 200 mg/dL in patient with hyperglycemia symptoms

4. HCT-related risk factors [6, 10, 19, 22]:

   a. TBI conditioning: leads to decreased pancreatic volume, islet cells, and neurons involved in hypothalamic axis
   b. Medications:

      i. Corticosteroids

      - Cumulative prednisone dose of > 0.25 mg/kg/d: mechanism of insulin resistance is mainly via decreased expression of glucose transporter 4 on skeletal muscle, required for glucose to enter the myocyte for glycogen synthesis.

    ii. CNIs

- Tacrolimus > cyclosporine
- Impairs insulin secretion from islet cells

    iii. Mycophenolate mofetil (Cellcept®): limited data, appears to impair insulin secretion

    iv. Sirolimus (Rapamune®): inconclusive data, unclear glucose effects

  c. Chronic GvHD: disrupted gut mucosa can lead to increased systemic absorption of oral steroids resulting in increased side effects

  d. Associated risks with hypogonadism, hypothyroidism

5. Non-HCT risk factors

  a. Age > 45 years
  b. Non-Caucasian race
  c. Increased BMI
  d. Family history of diabetes mellitus
  e. History of hepatitis C

6. Screening [3, 9]

  a. Post-transplant fasting blood glucose: at 3, 6, and 12 months:

    i. If no additional risk factors: screen yearly.
    ii. If risk factors and ongoing steroid use, continue screening every 3 months post-HCT.

  b. Caution in using HgbA1c for monitoring given inaccuracy in patients receiving red blood cell transfusions or who have chronic kidney or liver diseases.

7. Treatment [22, 24]

  a. Non-pharmacological: modifiable weight loss, exercise, dietary changes as able.

  b. Adjust immunosuppressive regimen as appropriate: consider reduced use of glucocorticoids, changing tacrolimus to cyclosporine.

  c. Medications: [10, 17, 21, 22]

    i. Insulin is the safest medication with the least interactions, especially for patients who remain on high steroids. A basal bolus regimen based on carbohydrate count given variable intake for many patients.

    ii. Oral agents:

- These agents can be considered if the patient is clinically stable with consistent oral intake, has no signs of severe GvHD, has stable renal and liver function, and remains in the outpatient setting.
- Preferred oral agents:

- Sulfonylureas: glimepiride (Amaryl®), glipizide (Glucotrol®).

   Risk for hypoglycemia if variable oral intake.
   Few interactions with immunosuppressive regimens.
   Avoid glyburide (DiaBeta®) which increases hypoglycemia when used in combination with immunosuppression.

- Meglitinide analogues: repaglinide (Prandin®), nateglinide (Starlix®).

   Short acting
   Should be taken with meals, advantage in variable intake.
   Metabolized with p450 system and potentiated with cyclosporine, voriconazole (VFend®), fluconazole (Diflucan®), and other p450 inhibitors

- Dipeptidyl-peptidast-4 inhibitors: sitagliptin (Januvia®), linagliptin (Tradjenta®), alogliptin (Nesina®).

   Less risk of hypoglycemia than with other oral agents
   Can be used in patients with chronic kidney disease
   Minimal interaction with other immunosuppressants.
   Unclear clinical significance of interaction with mycophenolate mofetil by competing for excretion at renal tubule

- Caution with other agents:

  - Metformin (Glucophage®)

     Cyclosporine interaction causing increased metformin levels
     Caution in patients with post-transplant AKI, diarrhea, or anticipated need for imaging with contrast given risk for higher renal toxicity, lactic acidosis, and diarrhea exacerbation

  - Glucagon-like peptide 1 agonists: liraglutide (Victoza®), exenatide (Byetta®), dulaglutide (Trulicity®), semaglutide (Ozempic®)

     Use with caution given these medications are long acting with side effects of nausea and delayed gastric emptying.

  - Sodium glucose cotransporter 2 inhibitors: dapagliflozin (Jardiance®), canagliflozin (Invokana®)

     Avoid given increased risk for urinary tract infections.

  - Thiazolidinediones: rosiglitazone (Avandia®), pioglitazone (Actos®)

     Not recommended due to long half-lives

  - Amylin analogs: pramlintide (SymlinPen 60®)

     Concern for impaired gastric emptying resulting in increased absorption of other medications

Adrenal Insufficiency [5, 8, 15, 17]

1. Incidence 13% post-allogeneic HCT, 1% post-autologous HCT.
2. Chronic glucocorticoid use is the major risk factor, resulting in secondary hypoadrenalism via suppression of hypothalamic-pituitary-adrenal axis:

   a. Low adrenocorticotropic hormone (ACTH) causes decreased levels of cortisol and dehydroepiandrosterone (DHEA).
   b. Risk for suppression increases with doses of exogenous steroid dosing > 7.5 mg/d and/or duration > 3 weeks.
   c. Reversible over time once exogenous steroids discontinued.

3. Other risk factors: TBI
4. Signs/symptoms:

   a. Anorexia, nausea, vomiting, abdominal pain
   b. Fatigue
   c. Postural dizziness
   d. Limb and back pain
   e. Impaired consciousness
   f. Laboratory abnormalities of hyponatremia, hyperkalemia, hypoglycemia

5. Adrenal crisis definition [25]:

   a. Includes more profound symptoms of delirium, obtundation, pyrexia.
   b. Absolute hypotension with systolic blood pressure < 100 mmHg or relative hypotension with a 20+ mmHg systolic decrease from baseline with features that resolve within 1–2 hours of steroid administration.
   c. Triggered by infection, sepsis, surgery, non-adherence to replacement therapy, addition of a CYP3A4 inducer while on glucocorticoids, hyperthyroidism or initiation of thyroid replacement:

      i. Glucocorticoids are metabolized via CYP3A4 pathway and inducers can increase steroid metabolism, lowering levels and contribute to adrenal crisis.
      ii. Examples of CYP3A4 inducers include carbamazepine (Tegretol®), phenytoin (Dilantin®), rifampin (Rifadin®), phenobarbital (Luminal®), St. John's wort, nafcillin, enzalutamide (Xtandi®), and others.

6. Diagnosis

   a. ACTH stimulation test. Peak plasma cortisol levels < 20 mcg/dL after stimulation is diagnostic for adrenal insufficiency.
   b. Critical illness, stress, or surgery may impact cortisol level and test interpretation.

7. Treatment [8, 15, 24, 25]

   a. Cortisol steroid replacement

      i. Hydrocortisone 15–25 mg/day po divided 2/3 in the morning and 1/3 in the evening

  b. Consider supplementation of DHEA, especially in women where this is primary source of testosterone which is protective for bone density and muscle mass.

  c. If significant illness or surgery, administer stress dose steroids of 100–150 mg/day total of hydrocortisone:

      i. If hospitalized and parenteral administration is required, administer 100 mg IV/IM hydrocortisone once, then 200 mg IV q24 hours via continuous infusion or 50 mg IV q6hr.

      ii. Can titrate back to oral at 2–3× usual dose then taper down to usual dose over 2–3 days.

8. Prevention of adrenal crisis [17, 25]

  a. Every other day steroid dosing, when appropriate, may reduce the risk of developing adrenal insufficiency.

  b. Taper steroids over months rather than weeks.

  c. Counsel patients regarding signs/symptoms to be aware of, especially during decreased titrations.

  d. Medical bracelet.

Thyroid Dysfunction [7, 8, 15, 24]

1. Therapy-induced primary hypothyroidism is the most frequently observed thyroid disorder:

  a. Incidence of 30–50% hypothyroid post-HCT [10, 12, 19].

  b. Typically diagnosed 4–7 years post-transplant.

  c. Risk factors include:

      i. Radiation exposure:

- Single dose ablative > fractionated TBI
- Total radiation dose correlates with greater degree of secondary hypothyroidism
- Previous thyroid gland or neck mantle radiation

     ii. Exposure to alkylating agents, busulfan, and cyclophosphamide

    iii. Female gender

    iv. Caucasian race

     v. Older age

  d. Symptom, recognizing these are common post-HCT symptoms:

      i. Fatigue, increased sleep

    ii. Constipation
    iii. Weight gain
    iv. Dry skin
    v. Irregular menses
    vi. Depression
    vii. Cold intolerance
    viii. Edema
    ix. Loss of lateral third of eyebrows

e. Subclinical hypothyroidism occurs in up to 15% of transplant survivors [8–10, 24]:

    i. Typically presents within first year post-HCT
    ii. Mildly elevated thyroid stimulating hormone (TSH) to < 10 IU/mL but normal free T4
    iii. May resolve without intervention

f. Screening:

    i. TSH and free thyroxine levels annually or as needed if symptoms develop.
    ii. If evidence for subclinical hypothyroidism, repeat screening in 2 months.

g. Treatment:

    i. Thyroid replacement

- Levothyroxine 1.6 mcg/kg/day [19], taken without food or other medications to facilitate absorption.
- Begin with lower doses of 25–50 mcg po daily until response is seen.
- Reassess 6 weeks post initiation.
- Goal to get TSH within normal limits of lab test, improve symptoms.

2. Therapy-induced primary hyperthyroidism [7, 8, 17]:

a. Less frequent; if present, consider autoimmune induced.
b. Symptoms:

    i. Insomnia
    ii. Diarrhea
    iii. Weight loss
    iv. Tremor
    v. Diaphoresis
    vi. Palpitations

c. Risk factors:

    i. Neck or mantle irradiation
    ii. TBI
    iii. Busulfan/cyclophosphamide conditioning
    iv. Hematologic malignancy

  d. Screening:

    i. TSH and free thyroxine levels annually or as needed if symptoms develop.
    ii. Consider autoimmune etiology and antibody screening if hyperthyroidism identified.

  e. Treatment approach:

    i. Symptom control with beta blocker
    ii. Endocrinology evaluation for thioamides (methimazole [Tapazole®], carbimazole [Neomercazole®], propylthiouracil [Mercazole®, Thyrozole®]), radioiodine ablation, and/or surgery evaluation

3. Therapy-induced autoimmune thyroiditis [7, 9, 17]:

  a. Incidence up to 3% post-HCT
  b. Risk factors:

    i. Radiation to neck or TBI
    ii. May be HLA linked with transfer of abnormal clones of T or B cells from donor to recipient

  c. Screening:

    i. TSH and free T4
    ii. Anti-thyroglobulin antibody
    iii. Anti-thyroid peroxidase antibody
    iv. TSH receptor antibodies

4. Thyroid neoplasms:

  a. Increased risk of thyroid tumors with radiation exposure
  b. Long latent period; may present years after radiation exposure
  c. Screening

    i. Thyroid exam at each visit
    ii. If mass is palpated, a thyroid ultrasound should follow with biopsy of mass > 1 cm or with concerning features

Skeletal Complications [8, 9, 12, 15, 27, 28]

1. Osteopenia/Osteoporosis

  a. Best measurement tool is a dual energy x-ray absorptiometry (DEXA) scan to determine bone density:

    i. Results are reported as a T-score which is a comparison between the patient's bone density and that of a same sex, same race 30-year-old:

      • T-scores ≥ -1.0 are considered within the normal range.

- T-scores between −1.0 and −2.5 are consistent with osteopenia or reduced bone mass.
- T-scores ≤ −2.5 are consistent with osteoporosis.

ii. Additionally, the Fracture Risk Assessment Tool (FRAX®) is a calculation of a patient's 10-year probability of a major osteoporosis-associated fracture. This assessment includes fractures of the spine, hip, forearm, and proximal humerus.

- This measure has been shown to have a modest ability to predict osteoporosis-associated fractures in HCT recipients.

b. Post HCT incidence: 50% of patients develop osteopenia while 20% of patients develop osteoporosis by 2 years post-HCT

c. Occurs in part due to rapid bone loss within 3–12 months post-transplant secondary to direct damage to osteoprogenitor cells and bone marrow stroma, worsened by high prevalence of vitamin D deficiency in up to 90% HCT recipients. Immune-mediated factors are also implicated.

d. Pre-transplant risk factors

  i. Advanced age
  ii. Female gender
  iii. Low body mass index
  iv. History of tobacco use
  v. Caucasian race
  vi. Chemotherapy
  vii. Hypogonadism

e. Post-transplant risk factors

  i. Glucocorticoid use is the strongest risk factor. Total body cumulative steroid dose of 5 mg prednisone equivalent per day for > 3 months necessitates initiation of early screening.
  ii. Hypogonadism.
  iii. Use of calcineurin inhibitors.
  iv. Renal dysfunction and/or renal wasting of calcium or magnesium with decreased vitamin D production.
  v. Presence of chronic GvHD.
  vi. Hyperthyroidism.
  vii. Calcium and vitamin D deficiency leading to secondary hyperparathyroidism:

f. Recommended screening

  i. Consider pre-HCT DEXA scan to identify patients at higher risk for skeletal complications:

- If osteopenia/osteoporosis is identified and patient did not receive bone resorption inhibitor therapy, consider repeat DEXA scan at 3 months post-HCT due to rapid bone loss associated with the HCT procedure.

 ii. All patients should undergo a DEXA scan within 1 year post-HCT.

- If normal bone mineral density is present, repeat every 2 years.
- If abnormal, repeat screen annually with consideration for treatment.

g. If a patient requires chronic steroids, a preventative approach should be implemented.

 i. Supplemental calcium 1200 mg/day in divided doses with vitamin D 1000 IU/day:

- Note that GvHD of gut can impair absorption.
- Calcium carbonate supplements should be given with food while calcium citrate supplements are not dependent on food for absorption but may result in constipation.
- Calcium citrate is recommended to increase absorption if patients are also taking antacids or a proton-pump inhibitor.

 ii. Check serum 25-hydroxy vitamin D level yearly with high-dose replacement therapy if a deficiency is identified.

iii. Consider hormone replacement therapy, especially in younger patients who have experience premature menopause.

iv. Lifestyle approaches:

- Weight-bearing and muscle-strengthening exercises
- Smoking cessation
- Avoidance of alcohol
- Fall prevention

h. Treatment of osteoporosis

 i. There are no consensus guidelines regarding optimal timing of initiation of pharmacologic agents post-HCT for patient with evidence of decreased bone density.

- National Osteoporosis Foundation recommends initiation of therapy for patients with the following [29]:
  - Vertebral or hip fracture
  - T-scores of ≤ −2.5 at the femoral neck, total hip, or lumbar spine
  - Osteopenia and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of any major osteoporosis-associated fracture ≥ 20%

- Recommendations from HCT experts including intervention earlier than in patients with post-menopausal or idiopathic osteoporosis:
  - Consider intervention for patients with a pre-HCT T-score ≤ −1.5.
  - Additionally, intervention could be considered for patients with a T-score > −1.5 in the setting of glucocorticoid therapy or GvHD.

ii. Medications

- There is no consensus on a preferred agent for treatment of osteoporosis.
- Duration of treatment is unclear; however efficacy beyond 5 years is limited.
- Bisphosphonates are associated with increased risk of osteonecrosis of the jaw and acute kidney injury.
- Oral bisphosphonates must be taken on an empty stomach with a full glass of water; patients must remain upright for at least 30 min after administration.
- FDA-approved agents.

  – Bisphosphonates

    Alendronate (Binosto®, Fosamax®) 5–10 mg po daily for glucocorticoid-induced osteoporosis; 70 mg po weekly for postmenopausal osteoporosis
    Ibandronate (Boniva®) 150 mg po monthly or 3 mg IV every 3 months
    Risedronate +/− calcium (Actonel®) 5 mg po daily *OR* 35 mg po weekly *OR* 75 mg po taken on two consecutive days once a month *OR* 150 mg po monthly
    Zoledronic acid (Reclast®) 5 mg IV annually

  – Estrogen therapy or hormone replacement therapy
  – Estrogen agonist/antagonist

    Raloxifene (Evista®) 60 mg by mouth once daily

  – Parathyroid hormone

    Teriparatide (Forteo®) 20 mcg SQ daily. *This medication *should not* be used in patients with a history of bone metastases, hypercalcemia and skeletal malignancy or any history of prior radiation therapy to skeleton.

  – Monoclonal antibodies

    Denosumab (Prolia®) 60 mg SQ every 6 months
    Romosozumab (Evenity®) 210 mg SQ monthly × 12 months

2. Avascular Necrosis

   a. Occurs in 4–19% of HCT recipients.
   b. Most typically affects the ends of long bones such as the femur or humerus but may also occur in the shoulders, wrists, knees, and ankles.
   c. Risk factors include:

      i. GvHD
      ii. Corticosteroid therapy
      iii. TBI

d. Joint pain is the most frequent presenting symptom.

e. MRI is the preferred imaging tool as standard x-rays may not detect abnormalities until late in the disease course.

f. Surgical intervention may be required.

 i. Core decompression: Pressure is relieved by drilling into the area of necrosis, allowing for increased blood flow. A bone graft may then be inserted to stimulate recovery of bone growth. This strategy may prevent collapse of the femoral head and delay hip replacement surgery.

 ii. Total hip arthroplasty: Major disadvantage is a short life span of the implanted joint. Younger patients may require a second replacement surgery later in life.

Hypogonadism (See Chaps. 39 and 40)

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Chapter 38
Thrombotic Microangiopathies

Joseph J. Shatzel and Thomas G. DeLoughery

Introduction

The thrombotic microangiopathies (TM) are a group of diseases which share the characteristic clinical features of thrombocytopenia and microangiopathic hemolytic anemia resulting in microvascular occlusion and end organ damage. The "classic" TMs are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Since the early days of hematopoietic cell transplantation (HCT), many patients have developed a TM-type disease that was often fulminant and fatal [1, 2]. Research has been difficult due to lack of standardized diagnostic criteria, and much controversy remains about optimal therapies.

Clinical Presentation

The fundamental problem in all TMs is occlusion of the vasculature by platelet aggregates. This event restricts blood flow which leads to areas of high shear that damage red cells resulting in fragmentation. This is the origin of the "helmet cells" or "schistocytes" component of the diagnostic criteria (microangiopathic hemolytic anemia). This vascular occlusion leads to tissue ischemia and end organ damage. In classic HUS, the predominant pathophysiologic finding involves the kidney leading to renal failure, while in TTP, damage can occur in any organ. The high serum lactate dehydrogenase levels (LDH) seen in TM is due both to red cell destruction and tissue ischemia [3].

In HCT patients, the onset of the TM is often gradual with slowly rising LDH and deteriorating renal function. Often hypertension develops and can be an early clue to the diagnosis. In TM associated with agents such as calcineurin inhibitors

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(CNI), the onset can be more rapid. As the TM progresses, renal insufficiency and neurological symptoms are the most common findings in many patients running a relentless course until the patient expires [1].

Risk Factors

Many risk factors for TM have been proposed. One difficulty with these factors is that any widespread disease process such as severe infection or graft-versus-host disease (GvHD) can lead to a clinical syndrome similar to TM. This lack of clarity in identification of etiologic events results in the extreme variations in reported post-transplant incidence rates ranging from 0% to 93% of patients [4, 5]!

Risk factors include:

1. Older age
2. Female gender
3. Advanced disease
4. Unrelated donor transplant
5. Radiation-containing conditioning regimens
6. Calcineurin inhibitors
7. Infection
8. GvHD

Classification

Pettit and Clark in 1994 proposed a classification which still provides a useful schema for thinking about transplant-related TM [2].

1. One group is the "multi-organ fulminant" which occurs early (day +20–60), has multi-organ system involvement, and is often fatal.
2. A second type of TTP/HUS is similar to CNI-associated HUS.
3. A third type described as "conditioning" TTP/HUS occurs 6 months or more after total body irradiation and is associated with primary renal involvement.
4. Finally, patients with systemic cytomegaloviral (CMV) infections may present with a TTP/HUS syndrome related to vascular endothelial cell CMV infection.

Etiology

1. In classic TTP, autoimmune destruction leads most patients to have very low levels of ADAMTS-13 (<5%) which is thought to lead to spontaneous platelet aggregation via the failure to cleave the ultrahigh molecular weight multimers of von Willebrand protein.

2. In patients with HCT-related TM:

    a. Most reports show reduced but not extremely low levels of ADAMTS-13.

    b. The underlying precipitant is thought to be endothelial damage, either by GvHD, medications, radiation, or infection.

        i. This endothelial damage leads to platelet aggregation, microangiopathic hemolytic anemia, and end organ damage.

    c. Over-activation of complement has been reported, similar to genetic variants of atypical HUS, suggesting inhibition of complement to be a reasonable therapeutic target [6].

        i. The fact that many patient will have mutations in genes associated with complement regulation and that clinically patients often quickly respond to anticomplement therapy provides evidence for this concept [7].

    d. This premise that endothelial injury is the main trigger for HCT-related TM would explain why vascular damage is a shared component of many of the risk factors for TM [8].

Diagnosis

Given that the diagnosis of any TM is a clinical one and that HCT patients are prone to have many complications that can mimic a TM, it is easy to appreciate and understand the great center-to-center variation in describing the incidence. Recently two groups have proposed diagnostic consensus criteria that share the common features of evidence of a microangiopathic hemolytic anemia and elevated LDH.

1. Blood and Marrow Transplant Clinical Trial Network (BMT-CTN) Criteria [5]

    a. RBC fragmentation and ≥ 2 schistocytes per high-powered field
    b. Concurrent increase in LDH from institutional baseline
    c. Concurrent renal and/or neurological dysfunction with no other explanation
    d. Negative Coombs test

2. International Working Group Criteria [4]

    a. Increased percentage (>4%) of schistocytes in the blood
    b. New, prolonged, or progressive thrombocytopenia (<50,000/uL or >50% decrease from previous counts)
    c. Sudden and persistent increase in LDH
    d. Decreased hemoglobin or increased transfusion requirements
    e. Decrease in serum haptoglobin

More recently, it has been observed that many patients will have rising LDH and signs of renal damage (proteinuria, severe hypotension) before the onset of overt TM. There is also increasing use of sC5-9 to detect complement activation [9].

Treatment

1. *CNI-associated TM*: This disorder often occurs within days after the introduction of these medications or with a significant increase in blood levels of these agents. The renal and neurological manifestation can be rapid and severe including malignant hypertension, seizures, and cortical blindness. Therapy is discontinuation of the medications and to manage the closely associated hypertension. In patients with mild TM and high serum levels, one can lower the dose to see if the symptoms abate [7].
2. *Conditioning-associated TM*: This subtype is rare and may be a manifestation of radiation damage to the vasculature. Usually the course is progressive with no specific therapy available [7, 10].
3. *Systemic CMV-associated TM*: CMV is trophic to the endothelium and aggressive therapy of CMV is the cornerstone of therapy [7, 9].
4. *Multi-organ fulminant TM*: Therapy remains unsatisfactory. The first step is to maximize treatment of any process that may be aggravating the TM (GvHD, infection, etc.). Unlike classic TTP, the role of plasma exchange remains controversial. Most series report very poor response rates with poor outcomes and high rates of complications [11]. Increasingly utilized for these patients, prompt initiation of the complement inhibitor eculizumab (Soliris®) has been reported to improve outcomes. A reasonable approach would be for a patient with signs of TM (rising LDH, signs of renal dysfunction [hypertension, proteinuria]) is to initiate eculizumab at a HUS dosing (900 mg IV once weekly × 4 doses then 1200 mg IV every other week). If the patient responds, there is uncertainly how long therapy should be continued, but many will continue for 6 months minimum prior to reevaluation [8, 9, 12]. Narsoplimab is another antibody therapy, targeting the mannan-binding lectin-associated serine protease-2 (MASP-2) in the lectin pathway for complement activation that is in advanced clinical trials and could emerge as another therapeutic option for advanced TM.

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Chapter 39
Women's Health Care

Lisa Egan

Introduction

Unique issues arise in women's health care before, during, and after hematopoietic cell transplant (HCT). Women can face both short- and long-term consequences of treatment including ovarian insufficiency, infertility, higher risk of HPV-mediated dysplasia, genital tract graft versus host disease (GvHD), and changes to sexual function and well-being. This chapter provides an overview of the evaluation and management strategies for women's health care issues in the female HCT recipient.

Amenorrhea

Amenorrhea occurs frequently following HCT. This finding is most commonly due to primary ovarian insufficiency (see section "Primary Ovarian Insufficiency (POI)"), however, alternate causes need to be considered. In women who have menstruated previously, *secondary amenorrhea* is defined as the absence of menses for more than 3 months in women who previously had regular menstrual cycles or 6 months in those who had irregular menses.

1. Amenorrhea does not necessarily indicate lack of ovarian function; further evaluation should be performed.

    a. Diagnostic procedures

        i. Women with secondary amenorrhea are evaluated with physical exam including a pelvic exam, a serum human chorionic gonadotropin (hCG)

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test to rule out pregnancy, and a follicle-stimulating hormone (FSH) serum level. An elevated FSH is consistent with ovarian insufficiency.

ii. Screening for sex hormone levels including FSH and serum estradiol (E2) is recommended no later than 1 year after HCT [1].

iii. A pelvic exam is important in the HCT recipient with secondary amenorrhea to assess for outflow obstruction. The particular concern in this patient population is genital tract graft versus host disease (GvHD) causing vaginal agglutination and subsequent hematocolpos.

iv. Other potential causes for secondary amenorrhea, not related to HCT conditioning, include hyperprolactinemia and hypo- or hyperthyroidism. In select patients, it is reasonable to test for these alternate explanations by measuring a serum prolactin level (PRL) and a thyroid stimulating hormone (TSH), respectively.

b. Clinical management

i. Clinical management is based on the cause of amenorrhea. For management of primary ovarian insufficiency, see sections "Primary Ovarian Insufficiency (POI)" and "Hormone Therapy" on hormone therapy.

Primary Ovarian Insufficiency (POI)

Primary ovarian insufficiency (POI) is defined as the development of primary hypogonadism before the age of 40 years in women who have a normal karyotype. POI has replaced the terminology of "premature menopause" and "premature ovarian failure." Restoration of ovarian function is improbable but not impossible in young women posttransplant [2].

The presence of amenorrhea is not required for a diagnosis of POI as women can have intermittent ovarian function and subsequent menstrual bleeding. POI following HCT is usually due to the impact of total body irradiation (TBI) and/or conditioning chemotherapy. It has been reported that the prevalence rate of POI exceeds 90% of female patients who have received myeloablative conditioning (MAC) [3]. The incidence of POI is lower with reduced-intensity conditioning (RIC) but the data on this are less robust [4].

1. Diagnostic Procedures

a. Screening for sex hormone levels is recommended no later than 1 year post-HCT. Often assessment will be done prior to the 1-year time frame due to patient symptoms of estrogen deficiency, including hot flashes, change to menstrual cycle, vaginal dryness, poor sleep, and decreased libido. These symptoms may be present with POI.

b. Initial laboratory evaluation includes measurement of FSH concentration and a serum human chorionic gonadotropin (hCG) to rule out pregnancy. The FSH value will be in the postmenopausal range, as defined by the laboratory used. The FSH value can be misleading in a woman who has intermittent

ovarian function. If the FSH value is within a normal range, but POI is suspected, then a gynecologic consult is warranted.

c. It is reasonable to add serum estradiol (E2) as one of the initial tests. Low or normal E2 with an elevated FSH is consistent with POI. Low or normal E2 with a normal or low FSH points to the possibility of an alternate explanation for hypogonadism. An E2 measurement can also help with guiding hormonal therapy.

d. Other potential causes for POI, not related to HCT conditioning include hyperprolactinemia and thyroid disease. In select patients, it is reasonable to test for these alternate explanations by measuring a PRL and TSH.

2. Associated comorbidities

a. POI posttransplant increases the risk of bone loss, cardiovascular disease, stroke, dementia, Parkinson disease, and overall mortality. Health care providers should also address the potential psychological impact of POI [5].

3. Treatment

a. See section "Hormone Therapy", Hormone Therapy

Contraception

Pregnancy is a rare event posttransplant but may occur more frequently as RIC allogeneic HCTs become more widely used in premenopausal women.

1. Contraception is typically recommended for the first 2 years posttransplant, since this is the time period for the highest risk of relapse.
2. Barrier protection is recommended for the first year posttransplant to reduce the risk of sexually transmitted infection (STI). However, barrier protection is not recommended as the only form of contraception due to its relative high failure rate compared to hormonal contraception options.
3. When considering options for contraception, efficacy, risk factors, patient preferences, and noncontraceptive benefits of hormone therapy should be considered so that options can be tailored to the individual patient.

a. The U.S. Medical Eligibility Criteria for Contraceptive Use (U.S. MEC) covers recommendations for contraceptive methods for patients with various medical conditions and other characteristics [6].

4. In a patient of reproductive age, who has been diagnosed with POI, use of a combined estrogen/progestogen oral contraceptive pill will offer both contraception as well as hormone therapy in a hypogonadal patient.
5. There are limited safety data on Intrauterine Device (IUD) use in women with immunosuppression due to cancer treatment. The concern is for any increased complications or increased risk of infection. The World Health Organization (WHO) and the Center for Disease Control (CDC) state that IUDs can be safely used by cancer patients (level B). This recommendation is based on studies of IUD use in HIV-positive women.

6. Women who are posttransplant and have findings of osteopenia or osteoporosis should avoid injectable progestin-only contraception, due to an adverse effect on bone mineral density (Level B). The levonorgestrel IUDs do not adversely affect bone mineral density. Estrogen-containing contraceptives may be beneficial to women with osteoporosis without cancer, but this same impact may not hold true in the posttransplant population; more research is needed.
7. There are no studies published on the use of the emergency contraceptive pill in women who have undergone HCT.

Gynecology Preventive Practice Guidelines

This section includes a list of preventive practice, screening procedures, and counseling opportunities in posttransplant gynecology care [1].

1. Pelvic exam

   a. Annual gynecologic exam starting at 12 months posttransplant

      i. Consider earlier evaluation and more frequent evaluation based on clinical symptoms of concern.

   b. Continue annual gynecologic exams, including screening for cGvHD of the genital tract and secondary cancers

2. Sex hormone evaluation

   a. FSH and E2 at 12 months posttransplant.
   b. Reassessment annually, based on previous results, patient presentation, and goals of care.

3. Cervical cancer screening

   a. Long-term allogeneic-HCT survivors have a 13-fold increased risk of squamous cell carcinoma of the cervix, compared to the general population.
   b. Abnormal Pap smear cytology was detected a median of 51 months post-HCT. Prolonged systemic immunosuppressive therapy for cGvHD was associated with the highest risk [7].
   c. Current guidelines for frequency of Pap smear screening varies by professional organization. *ASBMT*: pap smears every 1–3 years. *Children's Oncology Group*: follow age-based guidelines for general population. *ASCO*: recommends more frequent Pap smear screening in immunosuppressed patients, but does not specify a specific interval.

      i. Given the increased risk of SCC of the cervix compared to the general population, consideration should be given to annual Pap smear cytology. Annual gynecologic exams are recommended for cGvHD screening; therefore, annual Pap smear cytology could be obtained at that time as well.

    ii. Special consideration for increased screening should be given to those patients on intravaginal immunosuppression for GvHD [8] as well as those on prolonged systemic immunosuppressive therapy, as these present a higher risk for abnormal cervical cytology.

4. Sexual function

  a. Include query about sexual function during review of systems starting at 6 months posttransplant and repeat annually

    i. Consider use of a validated screening tool if initial query indicates potential concern, such as the Brief Sexual Symptom Checklist for Women (SSF-A) or the Female Sexual Function Index (FSFI).
    ii. Identify patients who desire a referral for further evaluation and management: psychotherapy, couples counseling, sex therapy, and/or cancer survivorship clinic with sexual health care, if available.

5. Fertility

  a. Counsel patients of reproductive age group about contraception posttransplant starting at 6 and 12 months posttransplant. Revisit this counseling annually.

    i. Recommend condom use for 1st year and then preferred contraception. Method for minimum of 2 years posttransplant (see section "Contraception").

  b. Recommend delaying pregnancy for at least 2 years posttransplant as this is the time frame for the highest risk of relapse
  c. Refer patient to fertility specialist when they desire a consult on family building options

Hormone Therapy

For patients who were in menopause prior to HCT, decisions on menopausal hormone therapy (MHT) posttransplant can follow the same evidence-based guidelines that are laid out by The North American Menopause Society, Endocrine Society Clinical Practice Guidelines, or ACOG Practice Bulletin. Hormone therapy in the HCT recipient with POI focuses on replacing hormones that would have been produced prior to the age of menopause. This approach is different from MHT that focuses on the treatment of menopause symptoms. The remainder of this section will focus on the hormone therapy for the posttransplant patient with POI.

1. Estrogen/progestogen therapy

  a. Estrogen dose strategy is to mimic a physiologic dose range while achieving symptomatic relief of a hypoestrogen state
  b. Estradiol (17-beta-estradiol) has the same molecular structure as the estrogen produced by the ovary.

c. Initiate full replacement dose of transdermal estradiol (100 mcg daily), estradiol vaginal ring (100 mcg daily), or oral micronized estradiol 2 mg daily. Dose can be titrated as necessary for symptom management. These doses are not high enough to provide contraceptive benefit.

d. Transdermal or transvaginal estradiol has the advantage of lower risk of venous thromboembolism.

e. A progestogen is required in a patient with an intact uterus to prevent estrogen-induced endometrial hyperplasia and carcinoma.

   i. Micronized progesterone 200 mg po per day is administered for first 12 days of the month which will cause a monthly withdrawal bleed. An alternative is 100 mg po per day continuously. This progestin has the same molecular structure as the progesterone produced by the ovary.

   ii. Medroxyprogesterone acetate 5–10 mg po daily is administered for first 12 days of the month which will cause a monthly withdrawal bleed. An alternative is 2.5 mg po daily continuous dose. This progestin has been most widely studied including in the Women's Health Initiative (WHI). It has an increased risk of breast cancer and an adverse impact on serum lipids.

f. The contraceptive levonorgestrel-releasing IUD (Kyleena®, Mirena®) is approved in some countries for endometrial protection in menopausal women taking estrogen. It is not approved for this indication in the United States, but clinicians are using them off-label for this purpose.

g. Oral contraceptive pills (OCPs) are an alternative for hormone therapy. They have the benefit of being a single pill to take daily while providing contraception. The dose of estrogen in OCPs is higher than necessary for hormone therapy but is still a reasonable alternative in patients without contraindications. When a patient no longer needs/desires contraceptive benefit, they could be transitioned to the replacement doses listed above in section "Hormone Therapy"(3 and 5).

h. Duration of hormone therapy is recommended until the age of natural menopause, age 50–52 to women with POI.

i. Systemic estrogen therapy may not be adequate to manage the urogenital atrophy and/or dyspareunia associated with local mucosal changes associated with POI. Women with these findings may need local vulvovaginal estrogen therapy in addition to their systemic estrogen treatment.

Sexual Well-Being

Sexual well-being is a broad concept that extends into a patient's self-identity, relationship dynamics, physical functioning, and emotional health. HCT can profoundly impact the sexual well-being of patients. Sexual health concerns are often under-addressed by clinicians and under-reported by patients. In one of the largest studies to date on the subject, 191 female allogeneic HCT recipients reported the following: loss of libido (83%), painful intercourse (73%), less enjoyment of sex (68%),

vaginal dryness (73%), and genital GvHD (22%). This section will provide an overview of the potential sexual health concerns of a female HCT recipient.

1. Body image: Alopecia, weight gain/loss, and GvHD skin changes are examples of the physical changes brought on by treatment that impact a patient's sense of sexuality, a change in self-identity, and self-perceived attractiveness [9].
2. Genital tract GvHD: Directly and often severely disrupts sexual function due to mucosal changes, dyspareunia, and/or alteration of anatomy.
3. Dyspareunia: GvHD changes as above, urogenital mucosal atrophy from POI, and/or pelvic floor muscle dysfunction.
4. Cancer and fear: Fears related to recurrence, mortality, loss of function, or loss of role fulfillment can lead to personal distress and decrease a patient's connection to their sexual self and interpersonal relationships.
5. Infertility: It is important to acknowledge the grief associated with this loss and direct patients to resources for grief support/counseling if needed.

GvHD of the Female Genital Tract

GvHD of the female genital tract can have significant adverse impact on a woman's quality of life and sexual function. Regular screening and appropriate intervention may help prevent more severe anatomic and physiologic changes from occurring.

1. Incidence

   a. Unclear but likely underestimated

      i. 2002 study: 3% bone marrow, 15% peripheral blood recipients
      ii. 2006 study: 35–49% of allogeneic HCT survivors [10]

2. Risk factors

   a. Unclear if GvHD of other organ sites represents a risk for genital tract GvHD development.
   b. The severity of genital tract symptoms does not appear to correlate with the severity of GvHD found in other organ systems.
   c. There has been no association found between genital tract GvHD and age, vaginal infection at time of transplant, or pregnancy history.
   d. There is evidence that genital GvHD-associated changes can develop soon after or during the tapering of systemic immunosuppression. This timeframe is an important patient education opportunity.

3. Onset

   a. In a case series of 32 women [8] followed after allogeneic HCT, the median time-to-onset of genital tract GvHD was 13 months with a range of 5–47 months.
   b. The risk of late onset disease identifies the need for long-term gynecologic care of these patients.
   c. Vulvar involvement will often precede vaginal involvement.

4. Symptoms

    a. Genital tract GvHD can overlap and mimic symptoms of the hypoestrogen state from primary ovarian failure, which is commonly observed in this patient population.

    b. Vulvar or vaginal pain with touch, itching, dysuria, dyspareunia, sensation of vaginal narrowing and/or shortening, and postcoital bleeding.

5. Clinical findings and grading

    a. Physical findings include mucosal abnormalities and sclerotic changes of the vulva and vagina.

    b. More severe changes include labia fusion, vaginal synechiae, and complete vaginal closure.

    c. A grading system for vulvovaginal GvHD was first developed by Spinelli et al. 2003 [11], and then revised by Stratton et al. 2007 [12] as follows:

        i. Grade I (minimal):

- Generalized erythema and edema of vulvar structures
- Patchy erythema of mucosa and glandular structures of vulvar vestibule
- Erythema around openings of vestibular glands

        ii. Grade II (moderate) includes Grade I findings plus:

- Erosions of mucosal surfaces of the labia
- Fissures in vulvar folds, i.e., interlabial sulci; fourchette

        iii. Grade III (severe) includes Grade II findings plus:

- Agglutination of clitoral hood
- Introital stenosis
- Vaginal synechiae
- Hematocolpos or complete vaginal closure
- Fasciitis or spasticity of levator sling

    d. Biopsy findings of affected mucosa show histologic findings consistent with mucocutaneous GvHD

        i. The diagnosis can often be made clinically based on symptoms, physical findings, and rapid response to superpotent topical steroid therapy. Biopsy can be reserved for atypical presentation, or when there is poor response to therapy.

6. Management

    a. Evidence for the optimum treatment plan is insufficient.

    b. Dual therapy with estrogen and a topical superpotent steroid is the most widely accepted plan of care.

    c. Estrogen delivery can be systemic, local, or both, tailored to the specific patient need with the goal of eliminating any concomitant estrogen deficiency component.

    d. Superpotent topical glucocorticoid ointment is the mainstay of therapy. The ointment base tends to be less irritating to the skin compared to a cream base. This ointment is applied once daily at bedtime to affected areas until adequate response is achieved, often 4–6 weeks. A taper in dose frequency can be designed according to response. Maintenance dosing of 2–3 times a week can be continued if discontinuing completely allows for return of symptoms.

    e. If response to topical corticosteroid is suboptimal, a topical tacrolimus ointment 0.1% or cyclosporine ointment can be added.

    f. For vaginal findings of stenosis or adhesions, vaginal dilator therapy should be used 3–5 times weekly. Topical estrogen and topical steroid ointment can be applied to the dilator for internal application. It is reasonable to recommend that patients without findings of vaginal GvHD should develop self-awareness of vaginal anatomy with home dilator use weekly so that early changes could be detected and addressed.

    g. Surgical lysis may be needed for patients with complete agglutination of the vaginal canal or extensive vulvovaginal adhesions. After surgical treatment, diligent use of local estrogen therapy, topical corticosteroids, and vaginal dilator therapy is needed to maintain vaginal capacity and prevent new adhesions.

Emergent Therapy for Suppression of Heavy Menstrual Bleeding with Thrombocytopenia

Heavy menstrual bleeding in the setting of thrombocytopenia is a gynecologic complication in female patients during the peritransplant period. Medical management options include the use of estrogen with or without a progestin and progestin-only methods. Surgical management options are available but reserved for only when medical management options have failed.

1. Medical management

    Choice of medical management can depend on whether a hormonal agent is already in use for therapeutic menses suppression. In HCT patients not receiving suppression, the rate of moderate-to-severe bleeding can be as high as 40% [13].

    a. Combined oral contraceptives (COCs)

        i. Contain both ethinyl estradiol (E2) and a progestin

           • Dose of E2 is characterized as high dose (>0.05 mg daily) or standard dose (<0.05 mg daily).

    ii. In a hemodynamically stable patient, standard dose therapy can be initiated and titrated up to high dose therapy if bleeding does not resolve.

    iii. High-dose COCs should be reduced to standard dose as soon as hematologic indices and bleeding pattern allow to prevent endometrial hyperplasia from long-standing high-dose use.

    iv. COCs must be given continuously.

    v. Increased risk of thromboembolic events, sinusoidal obstruction syndrome as well as liver dysfunction due to E2 component. Consideration for these risks needs to be tailored to the individual patient.

    vi. Alternative delivery methods of combined hormone therapy, i.e., vaginal ring or transdermal patches are not usually recommended due to risk of cutaneous reactions, vaginal mucositis during treatment, and specific risk of infection with insertion of a vaginal ring [14].

    vii. Progestin-only methods may be preferable if there are contraindications or concerns about estrogen use.

b. Oral medroxyprogesterone acetate (MPA) [Provera®]

    i. There is no standardized dose of MPA for emergent control of acute menstrual bleeding in this patient population. Two dosing strategies are as follows:

- MPA 60–120 mg (5 mg every 1–2 h) po for the first day followed by 20 mg daily for 10 days [15].
- MPA 20 mg po TID for 7 days followed by 20 mg daily for 3 weeks [16]

    ii. Less risk for thromboembolic events, compared to estrogen-containing options [14].

c. Intravenous conjugated equine estrogen (Premarin®)

    i. For emergent bleeding intervention or when oral therapy is contraindicated

    ii. Only treatment with US Food and Drug Administration approval for the treatment of acute abnormal uterine bleeding

    iii. Data on its use in this patient population are limited.

    iv. Conjugated equine estrogen given at a dose of 25 mg IV every 6 h for 24 h.

    v. Transition to high dose or standard dose COCs after 24 h to maintain control of bleeding

    vi. Increased risk of thromboembolic disease with conjugated equine estrogen; risk/benefit ratio must be weighed

d. Other hormonal therapies

    i. Leuprolide (Lupron®), levonorgestrel-releasing IUDs (Kyleena®, Mirena®), DMPA (Depo-Provera®), implantable etonogestrel rod (Nexplanon®) are not appropriate for management of acute bleeding because of delayed onset of action and potential irregular bleeding pattern associated with these methods.

2. Surgical management

   a. When medical management has failed to control bleeding or if the hemodynamic status of the patient requires more immediate intervention.

   b. Surgical options could include intrauterine balloon tamponade, uterine dilation and curettage, uterine artery embolization, endometrial ablation, or hysterectomy.

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Chapter 40
Men's Health for Hematopoietic Cell Transplant Patients

Check for updates

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Introduction

Men who have undergone hematopoietic cell transplantation (HCT) will typically follow up with their oncologist/hematologist for many years, often times without evaluation by other medical providers for their nontransplant-related health care needs. As such, it is important to have a basic understanding of health issues that affect men post-HCT and in particular, the impact of chemotherapy and transplantation on erectile dysfunction, infertility, hypogonadism, benign prostatic hyperplasia, and male-organ-specific neoplasms of prostate and testicular cancer. This chapter addresses appropriate evaluation and management of these issues at the level of primary care and the potential diagnoses and treatments that may require referral to a urologist.

Erectile Dysfunction (ED) [1–3]

1. Etiology [1, 2]

   a. Vasculogenic (40%)

      i. Arteriogenic
      ii. Veno-occlusive

   b. Neurogenic (5%)

      i. Peripheral neuropathy
      ii. Prior surgery or trauma

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   c. Psychogenic (1%)
   d. Endocrine (3%)

     i.   Thyroid dysregulation
     ii. Pituitary

   e. Diabetes mellitus (30%)

     i.   Chronic liver failure
     ii. Chronic kidney disease

   f. Pelvic surgery/radiation (6%)
   g. Medication induced (15%)

     i. Antihypertensives

- Beta blockers
- Thiazide diuretics
- Angiotensin converting enzyme inhibitors
- Spironolactone

     ii. H2 blockers
     iii. Psychiatric medications

- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants
- Benzodiazepines
- Antipsychotics
- Phenytoin

     iv. 5-Alpha reductase inhibitors
     v. Antiandrogens
     vi. LH–RH agonists/antagonists
     vii. Opioids
     viii. Others including anticholinergics, alcohol, tobacco, digoxin

   h. Most often, ED is a combination of multiple factors. It is important to investigate thoroughly prior to treatment as ED may be the first indication of a more serious condition.

2. Evaluation [1]

   a. Complete history and physical exam including cardiovascular, neurologic, endocrine, psychosocial, and genitourinary
   b. Consider questionnaires that quantify degree of erectile dysfunction

     i.   International Index of Erectile Function (IIEF-5)
     ii. Sexual Health Inventory for Men (SHIM)

   c. Investigate any potential comorbidities that could contribute to ED
   d. Laboratory assessments to consider:

     i.   Lipid panel: hyperlipidemia could indicate coronary artery disease (CAD).
     ii. Basic metabolic panel (BMP): underlying renal disease.

      iii. Thyroid panel.

      iv. Testosterone, luteinizing hormone (LH): hypogonadism.

- Low testosterone is a part of, but usually not the driving factor in ED.

      v. Fasting glucose or A1C: diabetes.

3. Treatment [1, 3]

  a. Appropriate treatment for any identified underlying disease with lifestyle modifications as needed

      i. Patients at increased risk for cardiac disease should avoid sexual activity and be evaluated and treated appropriately prior to engaging in sexual activity or being treated for ED.

  b. Consider psychological therapy or couple's therapy if a psychogenic component is identified.

  c. Medical treatment

      i. Phosphodiesterase (PDE$_5$) inhibitors are the first line in medical management [3] (see Table 40.1):

Table 40.1 Phosphodiesterase (PDE$_5$) inhibitors

	Sildenafil	Vardenafil	Vardenafil ODT	Tadalafil	Avanafil
Brand name	Viagra®	Levitra®	Staxyn®	Cialis®	Stendra®
Recommended Dosage	25–100 mg/day	5–20 mg/day	10 mg/day	5–20 mg PRN or 2.5–5 mg daily	50–200 mg/day
When to administer	1 h prior to sexual activity	1 h prior to sexual activity	1 h prior to sexual activity	At least 30 min prior to sexual activity	At least 30 min prior to sexual activity
Time of efficacy	30 min to 4 h	–	–	Up to 36 h	As early as 15 min
Common adverse reactions	Headache, flushing, dyspepsia, nasal congestion, nasal pharyngitis, visual disturbances	Headache, flushing, dyspepsia, nasal congestion, nasal pharyngitis, visual disturbances	Headache, flushing, dyspepsia, nasal congestion, nasal pharyngitis, visual disturbances	Headache, flushing, dyspepsia, nasal congestion, nasal pharyngitis, back pain, myalgia	Headache, flushing, dyspepsia, nasal congestion, nasal pharyngitis,
Time required to wait from last dose of nitrate medications	24 h	24 h	24 h	48 h	12 h

- Start at lowest recommended dose and increase as needed to achieve effect and prevent adverse side effects.

    ii. Intracavernosal injections

    - Injection into the lateral side of the penis of a vasoactive agent (or combination of agents) directly into the corpora cavernosa.

    - Trimix

        – Combination of alprostadil (PGE1), papaverine, and phentolamine.

    - Bimix

        – Combination of papaverine and phentolamine.

   iii. Vacuum erection device

    - Mechanical device that creates a vacuum around the flaccid penis drawing venous blood into the penis.
    - Usually used with a constriction device at the base of the penis that prevents venous outflow and helps maintain the erection.

   iv. Muse™

    - Intraurethral suppository of alprostadil (PGE1) that is administered via the urethral meatus.
    - Burning is a common side effect.
    - May be cost-prohibitive.

    v. Penile prosthesis

    - Device surgically implanted within the penis and scrotum that allows a man to achieve a mechanical erection independent of arousal. Very high satisfaction rate.
    - Complications include infection, erosion, and mechanical failure.

Infertility

1. Infertility is defined as the inability to achieve pregnancy after 1 year of regular, unprotected intercourse. Until patients fit this definition, it is recommended that they forgo treatment for infertility; however, earlier treatment for older couples desiring children may be considered as fertility decreases with advanced age [5].

    a. Infertility is an expected adverse event of chemotherapy and immunosuppressant used prior to and during HCT.

b. Infertility counseling should be initiated prior to starting chemotherapeutic agents that inhibit sperm production. It is especially important to discuss this topic in young adult and pediatric patients prior to the initiation of chemotherapy or HCT, as the effects on fertility are usually permanent.

c. Sperm banking is an option, even for pediatric patients if they have completed puberty [4] (see also Chap. 9):

    i. It can be difficult to bring up the topic of fertility or suggest getting a sperm sample from a teenager who already must cope with the stress of a diagnosis of malignancy.

    ii. A survey demonstrated that only half of oncologists discuss fertility with adolescents and young adult males prior to chemotherapy. Reported concerns included cost of sperm preservation, delay in cancer treatment, or that the conversation would be uncomfortable and cause undue stress to the patient and family [4].

        • Patients who discussed fertility options prior to chemotherapy expressed gratitude that sperm preservation potentially allowed for future fertility and provided something to look forward to after the diagnosis of cancer [4].

        • As of now, there is no way to preserve germ cells (future sperm cells) from prepubescent patients for future fertility use.

d. Etiology [5]: Male infertility is usually multifactorial. It involves production of viable sperm in the testis and transportation of that sperm to a viable egg. Many events can interrupt this pathway.

    i. Common causes of infertility

        • Varicocele: A dilation of the pampiniform plexus that drains blood from the testicles.

            – Varicocele may affect the production of viable sperm and recent literature has shown it can also have a detrimental effect on testosterone production contributing to hypogonadism.

            – Only varicoceles that can be palpated are considered clinically significant. Therefore, it is recommended that providers *do not* order scrotal ultrasounds to identify low grade, nonpalpable varicoceles.

    ii. Medications: Many medications can impact sperm production, testosterone production, libido, and erectile function, all of which can contribute to infertility. Common drugs that may be utilized by HCT patients include but are not limited to:

        • Antidepressants: paroxetine (Paxil®), venlafaxine (Effexor®).

        • Steroids: prednisone, methylprednisolone.

        • Antihypertensives: nifedipine (Adalat CC®, Afeditab CR®).

        • Antineoplastic: bleomycin, etoposide, vinblastine.

        • Hormonal agents: testosterone, finasteride (Propecia®, Proscar®) (see Table 40.2).

- Immunosuppressants: methotrexate, mycophenolate (CellCept®).
- Anticonvulsants: lamotrigine (Lamictal®).
- Opioids.
- This list is certainly not complete. Thorough evaluation of a patient's medications, both prescription and nonprescription (supplements, illicit drugs, over-the-counter meds), should be done in the assessment of infertility.

   iii. Hypogonadism: Adequate levels of testosterone within the testicle are required for the regulation of sperm production. Low testosterone levels within the testicle may result from a failure anywhere along the pituitary axis or from exogenous testosterone that causes inhibitory feedback on the pituitary axis and downregulates production of intratesticular testosterone, leading to decreased sperm production.

- See also section "Contraception".
- It is important to note that exogenous testosterone acts as a negative feedback on the hypothalamus–pituitary–testicular axis and causes the testicles to atrophy. Therefore, although circulating levels of testosterone may be high, the negative feedback mechanism of exogenous testosterone may also impact fertility by decreasing testicular testosterone levels.
- Once a patient has attempted unprotected intercourse for a sufficient period of time without pregnancy, the patient and partner should be referred to infertility specialist for semen analysis and further work up and treatment.

Hypogonadism [6]

1. Hypogonadism is defined as a 2 a.m. serum testosterone, levels below 300 ng/dL, in the setting of appropriate symptoms (fatigue, reduced hair, reduced muscle mass, obesity, depressive symptoms, reduced cognitive function and concentration, irritability, low libido, erectile dysfunction).
2. Etiology

   a. Primary: Testicular failure
   b. Secondary: Pituitary dysfunction
   c. Tertiary: Hypothalamus dysfunction (e.g., Kallman's syndrome)
   d. Medication induced: Medications can impact testosterone levels anywhere along the hypothalamus–pituitary–testicular axis

      i. Opioids
     ii. Spironolactone
    iii. Antineoplastic
    iv. Corticosteroids

   e. Obesity: Aromatase in the fatty tissue converts testosterone to estrogen.

3. Work up

  a. Thorough history and physical exam to identify any contributing factors or underlying disease process

    i. Labs

      - CBC: testosterone replacement can cause polycythemia.
      - Early morning testosterone x 2 as mentioned above.
      - Prostate-specific antigen (PSA): screen for prostate cancer in appropriate age men.
      - LH.
      - Prolactin level if LH is low.

4. Treatment [6, 7]
   See Table 40.2.

Table 40.2 Medications for treatment of hypogonadism

Formulation	Trade name	Dosing	Advantages	Disadvantages and risks
Intramuscular	Depo-Testosterone (Testosterone Cypionate), Delatestryl (Testosterone enthanate)	50–200 mg every 1–2 weeks	Can self administer	Pain and infection at injection site
	Aveed (Testosterone undecanoatre)	750 mg once, then in 4 weeks, then every 10 weeks	Long acting	Must be done in office by REMS- certified provider due to risk of pulomnary oil microembolism and anaphylaxis
Transdermal Gel	Androgel, Fortesta, Axiron, Testim	Varies 10–12 mg daily based on preparation	Ease of application, steady testosterone concencration	Risk of transfer to other that come in contact with application site or clothing. Skin irritation. May not reach sufficent doses
Patch	Androderm	2–6 mg daily	Limited risk of transfer, no injection	Skin irritation
Implanted pellet	Testopel	150–450 mg every 3–6 months	No risk of transfer, infequent dosing	Infection, scarring of insertion site, spontaneous dislodgment. Must be placed in clinic by trained provider using sterile technique
Nasal	Natesto	1 nasal spray in each nare 3 time daily	Minimal risk of transfer	Frequent dosing, sinusitis, nose bleed, rhinorrhea
Buccal	Striant SR	30 mg twice daily	Ease of application	Gingival irritation, frequent dosing

Enlarged Prostate/Benign Prostatic Hyperplasia (BPH)

Hyperplasia of the prostate leading to bladder outlet obstruction through increased mass of prostatic tissue and greater smooth muscle tone [8]

1. Evaluation [9–11]

    a. History, including onset and severity of lower urinary tract symptoms.
    b. Physical exam, including digital rectal exam (DRE), assessment for bladder distention and neurologic evaluation.
    c. Symptom scale evaluation: American Urologic Association-Symptom Index (AUA-SI) or International Prostate Symptoms Score (I-PSS) questionnaire (available online).
    d. Frequency voiding journal for nocturia-predominant symptoms.
    e. Urine analysis and culture to rule out infection and other causes.
    f. PSA level for men with a life expectancy greater than 10 years.
    g. Additional testing may be warranted for specific situations, such as obtaining a post-void residual (PVR) if urinary retention is suspected or urodynamics if concern for bladder involvement (predominantly urgency and frequency symptoms).

2. Treatment [9, 11–16]

    a. Lifestyle modifications, such as modulating fluid intake, reducing alcohol/caffeine intake, and diet/weight loss.
    b. Alpha blockers (tamsulosin [Flomax®], doxazosin [Cardura®], alfuzosin [Uroxatral®], terazosin [Hytrin®]) to relieve prostatic smooth muscle tone

        i. "First dose" effect can cause orthostatic hypotension with first use but generally improves thereafter.
        ii. Should not be used in patients in need of cataract surgery due to "floppy iris syndrome."
        iii. Decreased ejaculate volume is very common.

    c. Alpha-reductase inhibitors (finasteride [Propecia®, Proscar®]/dutasteride [Avodart®]) prevent the conversion of testosterone to dihydrotestosterone (DHT). Absence of DHT shrinks prostatic tissue over time

        i. Sexual dysfunction is a common side-effect, including ED, loss of libido, and decreased ejaculate. Symptoms often improve after 1 year of therapy.
        ii. These medications will reduce serum PSA by 50%, which can mask prostate cancer.

    d. Antimuscarinic (anticholinergic) therapy for overactive bladder symptoms

        i. May be more effective in combination with alpha-blocker therapy.
        ii. Most common reported side-effects are dry mouth and constipation but can trigger other anticholinergic symptoms.
        iii. Mirabegron (Myrbetriq®) is a beta-3 agonist that has similar bladder effects as the anticholinergics but does not have the associated side effects.

    e. Referral to urology for refractory symptoms or concerning cases for consideration of surgical management

        i. Minimally invasive options

- Rezum™: Endoscopic ablation of prostatic tissue through injection of heated water vapor into prostatic tissue.
- Prostatic urethral lift (UroLift™): Endoscopic procedure that mechanically opens the prostatic urethra through placement of retracting implants.

        ii. Laser vaporization: Endoscopic vaporization or enucleation of the prostate using noncontact laser energy with no skin incisions.

        iii. Transurethral resection of the prostate (TURP): Surgical removal of the prostate endoscopically through the urethra with no skin incisions.

    f. Multiple randomized controlled trials have indicated that over-the-counter herbal remedies fail to provide any improvement in symptoms/quality of life compared to placebo or observation [17].

Prostate Cancer Screening

1. There is a moderate level of evidence that overdiagnosis of prostate cancer due to extended screening is estimated to be between 23% and 66% with a lead time to diagnosis of 5–15 years [18].
2. Screening includes a serum PSA level and a DRE.
3. American Urologic Association recommends screening as follows [19]:

    a. Screening *advised against* for men under age 40.
    b. Screening *not* recommended for men age 40–54.
    c. Screening should be discussed for men between ages 55–69 through shared decision-making.
    d. Screening is *not* recommended for men over age 70 or with <10 year life expectancy

4. Important information to discuss during shared decision-making:

    a. Lifetime risk of dying from prostate cancer is 3%, while the chance of being diagnosed is 17% [20].
    b. No screening test is perfect. DRE has low-sensitivity and will miss many cancers, while PSA has a low-specificity and has a high chance of generating false positives [21].
    c. Further diagnostic measures, such as prostate biopsies, carry risks. An estimated one-third of men who undergo a prostate biopsy will experience an adverse event such as pain, fever, bleeding, infection, or problems urinating [22].
    d. If prostate cancer is diagnosed, there is an option for active surveillance rather than definitive treatment for low-risk disease.

e. In the general population, for men who pursue cancer treatment, there are further risks. Of every 1000 men who undergo treatment for prostate cancer, 2 will have serious cardiovascular events, 1 will develop a deep venous thrombus or pulmonary embolus, 29 will develop erectile dysfunction, 18 will develop incontinence, and less than 1% will die from treatment [23].

f. Ultimately, for every 1000 men who agree to undergo screening, 4 will die of their disease within 10–14 years. For every 1000 men who defer screening, 5 will die of their disease within 10–14 years, amounting to one life saved per 1000 [23].

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Chapter 41
Psychiatric Complications

Kristina Chechotka, Emina Bajrovic, and Anne Gross

Introduction

Patients are generally counseled extensively regarding the medical impact of hematopoietic cell transplantation (HCT). They attend educational visits with providers and transplant staff, supplemented by information available on the Internet, from special interest groups such as the American Cancer Society, the Leukemia & Lymphoma Society, the BMT InfoNet, and BetheMatch™, and from their referring providers. A great deal of attention is focused on determining performance status and the potential risk of the procedure based upon the patient's preexisting comorbid medical conditions. However, less attention is paid to the potential psychological and psychiatric complications of the HCT procedure.

A wide variety of psychiatric concerns can develop in the HCT patient, ranging from delirium and psychosis to depression, insomnia, and anxiety. This chapter will discuss the diagnosis of and intervention for the most commonly encountered psychiatric complications in this patient population.

Delirium and Altered Mental Status

While HCT patients undergo daily laboratory and physical evaluations, close attention must also be paid to mental status changes. Delirium, one manifestation of altered mental status or encephalopathy, is common in the hospital setting. It is estimated that up to 50% of patients undergoing HCT will develop delirium in the month following transplantation, with the first 2 weeks being the time of highest

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risk [1]. Delirium confers risk of prolonged hospital stay, functional and cognitive decline, and mortality [2–4]. While delirium is increasingly recognized as a serious complication of hospitalization in the medically ill, *the great majority of patients with delirium are underrecognized*. Presentation may be subtle, necessitating careful and thorough examination of the patient. Changes in level of arousal, slowed cognition, abrupt mood, or behavioral changes, as well as agitation or new-onset hallucinations, should trigger an immediate mental status evaluation. If delirium is identified, workup for the underlying medical etiologies should promptly ensue.

1. Evaluation and diagnosis

    a. Delirium is defined by the new onset of fluctuating disorientation, disturbance of memory, language, perception, visuospatial abilities, attention, and level of awareness over the course of hours to days.
    b. There are three subtypes: hypoactive, hyperactive, and mixed.

        i. Patients with hypoactive delirium are commonly undiagnosed because they present as primarily withdrawn and they are assumed to be depressed.
        ii. Hyperactive and mixed delirium cases present with agitation or obvious fluctuations in mental status and are easier to detect because of the disruptive nature of symptoms.

    c. At a minimum, mental status evaluation should include explicit testing of orientation and attention as well as short-term and long-term memory.
    d. Collateral information from nursing staff and family is recommended to discern the patient's baseline and to detect fluctuations.
    e. Consider the use of structured delirium assessment tools such as the Confusion Assessment Method (CAM) or Delirium Rating Scale-98.

2. Risk factors and underlying etiologies

    a. Pretransplant executive dysfunction, which could arise from a history of neurologic injury or neurocognitive disorder, is predictive of development of posttransplant delirium [1].
    b. Alcohol or benzodiazepine withdrawal can cause delirium in patients with physiologic dependence and is suggested by autonomic instability, tremulousness, and diaphoresis.
    c. Sleep-wake cycle disruptions, electrolyte and metabolic disturbances, hypoxia, dehydration, nutritional deficiencies, and infection are common causes.
    d. The medication list should be an area of focus. Deliriogenic medications often precipitate or contribute to delirium, especially when there is polypharmacy.

        i. Opioids for pain control, including patient controlled analgesia (PCA) in patients with mucositis
        ii. Anticholinergic or antihistamine agents used for vertigo and chemotherapy-induced nausea and vomiting (CINV).

      iii. High-dose steroids for nausea or as part of a chemotherapy regimen.

      iv. Use of benzodiazepines for nausea, anxiety, or sleep.

      v. Impairment of hepatic or renal clearance results in accumulation of medications and can precipitate delirium.

  e. It is important to rapidly exclude life-threatening etiologies.

      i. Imaging for neurologic insults, such as infarct, hemorrhage, or posterior reversible encephalopathy syndrome (PRES).

      ii. Lumbar puncture and cerebrospinal fluid testing to evaluate for central nervous system (CNS) infection.

      iii. Complete blood cell count (CBC) and blood culture to evaluate for sepsis.

      iv. Electroencephalogram (EEG) to evaluate for seizures.

      v. Vital signs and Clinical Instrument for Withdrawal Assessment (CIWA) to evaluate for alcohol or benzodiazepine withdrawal.

  f. Once immediately life-threatening etiologies of delirium are ruled out, other serious conditions, such as graft-versus-host disease, should be systematically investigated.

  g. Transplant pharmacy specialists can provide critical insights in identifying pharmacologic causes of delirium.

3. Management

  a. Identify and address the underlying causes.

  b. Nonpharmacologic management:

      i. Eliminate any noncritical deliriogenic medications and dose adjust necessary medications for renal and hepatic function.

      ii. Frequent reorientation with clock, calendar, and familiar objects at the bedside.

      iii. Mobilize and ambulate as soon and as much as safely possible.

      iv. Address any sensory limitations by providing patient with glasses or hearing aids.

      v. Behavioral interventions to promote normal sleep-wake cycle.

  c. Pharmacologic management of delirium with antipsychotics are standard of care but not Food and Drug Administration (FDA) approved

      i. Haloperidol (Haldol®)

- The gold standard of treatment, not highly sedating. Available PO (oral), IV (intravenous), and IM (intramuscular).
- Recommended dosing: 0.25–1 mg IV every 4 hours PRN (as needed).

     – Can give as often as every 30 minutes IV in cases of severe agitation.

     – Convert to PO as soon as possible.

     – Maximum daily dose 20 mg, but consider lower maximums in the frail or elderly.

- Cardiac monitoring is required while haloperidol is administered IV due to association with prolonged QTc and torsades de pointes; do not administer if QTc is >500 ms.

ii. Olanzapine (Zyprexa®)

- Antiemetic, anxiolytic, and sedating properties. Available PO and IM.
- Recommended dosing: 2.5–5 mg PO every 4 hours PRN.

    – Maximum daily dose 10 mg.
    – Do not combine with parenteral benzodiazepines due to risk of respiratory compromise.

iii. Quetiapine (Seroquel®)

- Sedating and anxiolytic. Only available PO.
- Recommended dosing: 12.5–25 mg PO every 4 hours PRN.

    – Maximum daily dose of 150 mg.

iv. Risperidone (Risperdal®)

- Modest sedation. Only available PO.
- Recommended dosing: 0.25–0.5 mg PO every 4 hours PRN.

    – Maximum daily dose of 2 mg.

v. Benzodiazepines are not recommended as monotherapy for delirium unless etiology is due to seizures, alcohol withdrawal, or benzodiazepine withdrawal.

- Lorazepam (Ativan®)

    – Renally excreted, available PO, IM, or IV.
    – Recommended dosing: 0.25–1 mg every 1–2 hours.
    – Maximum daily dose of 10 mg.

Depression

Major depression is a psychiatric disorder characterized by a sustained period of low mood or anhedonia, feelings of guilt or hopelessness, anorexia, lack of energy, difficulty concentrating, slowed thought or movement, and, sometimes, recurrent thoughts of death or suicide. Prevalence of depression is estimated to be as high as 30% in the 5 years following HCT in certain populations [5]. Depression is a complex disorder caused by biological, psychological, and social factors. It impacts quality of life (QOL) and worsens treatment outcomes. There is some evidence that pretransplant depression is associated with slower recovery of posttransplant white blood cell count [6, 7]. It is important to distinguish major depression from

adjustment disorder, grief, and hypoactive delirium since the treatment of each of these entities is distinct.

1. Diagnosis

    a. Depression does not impact orientation or attention; hypoactive delirium should be considered for any abrupt mood changes with fluctuating sensorium.

    b. To meet criteria for major depression, a patient must experience at least five depressive symptoms for a period of at least 2 weeks [8].

    c. At least one of the symptoms must be depressed mood or loss of interest for the majority of the day most days of the week.

    d. Other symptoms include poor appetite, insomnia or hypersomnia, changes or slowing in psychomotor activity, fatigue, feelings of worthlessness or inappropriate guilt, indecisiveness or impaired concentration, and thoughts of death or suicide.

    e. Other signs of depression may include low volume speech, social withdrawal, poor eye contact, and increased touching of the face but are not included in the formal diagnostic criteria.

    f. Severe depression may include mood-congruent auditory hallucinations or delusions of guilt, ruin, or poverty. Visual hallucinations are atypical and should prompt a medical workup, especially if disorientation is also present.

    g. Grief reactions may resemble major depression, but sadness tends to come and go, centers around the loss, and patients have intact self-esteem, presence of positive emotions, or capacity for joy.

    h. An adjustment disorder may have some symptoms of depression but has a trigger and does not meet full criteria for major depression.

    i. Screening for a history of mania or hypomania is important to exclude a diagnosis of bipolar disorder. Treatment of bipolar depression is different from unipolar depression.

2. Treatment

    a. For mild depression, counseling is often sufficient [9]. For patients with moderate to severe depression, antidepressant medication should be prescribed in addition to therapy.

    b. Selective serotonin reuptake inhibitors (SSRIs) are first-line due to the tolerability and relatively benign side effect profile.

    c. Medications may take up to 4 or more weeks for effect. Milder cases may respond as early as 2 weeks [10].

        i. Side effects of antidepressant medications commonly include nausea, diarrhea, headaches, weight gain, and sexual dysfunction.

        ii. Syndrome of inappropriate antidiuretic hormone (SIADH), platelet dysfunction, and gastrointestinal (GI) bleeds, though less common, are also potential risks.

Table 41.1 Selection of antidepressants for medical comorbidities [18–23]

Patient condition	Suggested antidepressant drug of choice
Depression with anxious distress	SSRI
Depression with lethargy and amotivation	Fluoxetine (Prozac®), bupropion (Wellbutrin®), or venlafaxine (Effexor®)
Preexisting cardiac disease	
Congestive heart failure/coronary artery disease	SSRI, bupropion (Wellbutrin®)
Heart block	SSRI, bupropion (Wellbutrin®)
Hypertension	SSRI
Hypotension	Venlafaxine (Effexor®), SSRI, bupropion (Wellbutrin®)
Neurologic disease	
Parkinson's disease	SSRI
Cerebrovascular accident (stroke)	SSRI
Migraine headaches	Amitriptyline (Elavil®), venlafaxine (Effexor®)
Miscellaneous	
Prostatic hyperplasia	Bupropion (Wellbutrin®), SSRI [excluding paroxetine (Paxil®)]
Irritable bowel syndrome	Amitriptyline (Elavil®), desipramine (Norpramin®)
Diabetes	SSRI
HIV	Mirtazapine (Remeron®)
Thrombocytopenia and leukopenia	Bupropion (Wellbutrin®)
Sexual dysfunction	Bupropion (Wellbutrin®)

SSRI selective serotonin reuptake inhibitors, *HIV* human immunodeficiency virus

iii. Selection of the agent is based upon side effect profile, drug-drug inter-actions, history of positive response, cost, and concurrent medical conditions (see Tables 41.1 and 41.2).

iv. Geriatric and HCT patients with complicated medical histories should begin at 50% dose with slower increases, no more often than every 3–7 days.

v. Patients with psychomotor retardation and neurovegetative symptoms such as anorexia, profound fatigue, and excess sleep may respond earlier.

vi. Partial response may indicate a need for dose escalation, while no response suggests the need to augment or change medications.

vii. If switching antidepressants, a 1- to 2-week washout is recommended for most agents, and up to 5 weeks for fluoxetine. Consider a cross-taper if the patient requires more aggressive treatment.

viii. When treatment response is achieved, medication should be continued for a minimum of 6 months. If the patient has experienced a depressive episode before, discontinuing medications may result in recurrence of depression in the future.

Table 41.2 Select antidepressants and dosing (consider starting at 50% dose if elderly or debilitated) [24]

Drug	Starting dose (daily)	Dosing range (daily)	Comments
Selective serotonin reuptake inhibitors (SSRI)			
Citalopram (Celexa®)	10–20 mg	20–40 mg	QTc prolongation increased with doses > 40 mg/day with a minimal increase in benefit
Escitalopram (Lexapro®)	10 mg	10–20 mg	Doses above 20 mg may confer little additional benefit
Fluoxetine (Prozac®)	10–20 mg	10–80 mg	More activating than other SSRIs
Paroxetine (Paxil®)	10–20 mg	20–50 mg	Possibly more anxiolytic than other SSRIs but more anticholinergic
Sertraline (Zoloft®)	25–50 mg	50–200 mg	High incidence of GI side effects
Serotonin norepinephrine reuptake inhibitors (SNRI)			
Duloxetine (Cymbalta®)	40–60 mg	60–120 mg	Dosed twice daily, best evidence for diminishing neuropathic pain as collateral benefit
Venlafaxine (Effexor®)	37.5–75 mg	150–225 mg	High risk of discontinuation syndrome, associated with hypertension at higher doses
Desvenlafaxine (Pristiq®)	25–50 mg	50–100 mg	Associated with hypertension
Levomilnacipran (Fetzima®)	20–40 mg	40–120 mg	May cause tachycardia
Other antidepressant agents			
Amitriptyline (Elavil®)	25–50 mg		Anticholinergic, sedating TCA
Bupropion (Wellbutrin®)	150 mg	300 mg	Many formulations, no sexual side effects, activating, helps with tobacco cessation
Methylphenidate (Ritalin®)	5 mg	15–30 mg	Divided TID dosing. Stimulant, off-label use
Mirtazapine (Remeron®)	15 mg	15–45 mg	May diminish nausea and increase appetite
Nortriptyline (Pamelor®)	50–75 mg	75–150 mg	Least anticholinergic TCA
Vilazodone (Viibryd®)	10 mg	20–40 mg	Take with food
Vortioxetine (Trintellix®)	5–10 mg	10–20 mg	Serotonin modulator

TCA tricyclic antidepressant

- If discontinuing an antidepressant, gradual taper should occur to avoid antidepressant discontinuation syndrome.
- Abrupt cessation results in flu-like symptoms, gastrointestinal distress, emotional lability, anxiety, agitation, as well as sensory and sleep disturbances, which can last 1–2 weeks [11].

- If discontinuation symptoms are significant, the agent can be reinstituted with a more gradual taper or changed to an agent with a longer half-life, such as fluoxetine, prior to tapering [12].

d. Grief and adjustment disorders are not typically treated with medication. Referral to grief counseling or psychotherapy is recommended.

Anxiety

Stress, in small amounts, may serve an adaptive purpose in motivating patients to adhere to treatment and follow-up. However, distress or excessive anxiety can be functionally impairing and may drastically impact QOL.

1. Anxiety disorders are among the most common mental health diagnoses in the general population.
2. Patients may present with generalized anxiety or panic attacks, episodes of intense physical and/or cognitive discomfort that typically subside within 30 minutes.
3. Anxiety may manifest as a stand-alone diagnosis or as part of a depressive illness. It may also be seen as hyperarousal in posttraumatic stress disorder.
4. Fortunately, psychotherapy, SSRIs, and serotonin norepinephrine reuptake inhibitors (SNRIs) provide relief of anxiety due to a broad spectrum of causes.

    a. Pharmacologic treatment is initiated in a similar manner as for a depressive illness.
    b. If anxiety is only intermittent, as can be the case with panic attacks, judicious use of a benzodiazepine with rapid onset can be considered for as-needed use only.
    c. Refer to Tables 41.2 and 41.3 for additional information on SSRIs, SNRIs, and select anxiolytic medications.

Sleep Disorders

Sleep disturbances are common in the HCT population. About 26% of patients meet clinical diagnostic criteria for insomnia in the first 100 days and many patients still report sleep difficulties at 1 year posttransplant [13–15]. In the oncologic setting, sleep difficulties may be secondary to the routines of the hospital setting or medication effects, such as urinary frequency due to diuretics or activation from steroids. These disorders can also result from untreated psychiatric conditions, such as depression or anxiety. The majority of oncology patients with insomnia are not asked about and do not discuss the problem with their healthcare providers. The consequences of insomnia can include impaired cognitive functioning, decreased

Table 41.3 Characteristics of selected anxiolytics and hypnotics [24]

Drug	Mechanism of action	Common dose	Half-life (hours)	Notes
Diphenhydramine (Benadryl®)	Antihistamine	25–50 mg HS	2–8 Elderly: 13.5	Potentially deliriogenic
Hydroxyzine (Atarax®)	Antihistamine	10–50 mg TID PRN	14–20	Anxiolytic; potentially deliriogenic
Eszopiclone (Lunesta®)	Non-BZD; interacts with GABA$_A$ receptor	Adult: 1–3 mg HS Elderly: 1–2 mg HS	6	High-fat meal delays absorption
Ramelteon (Rozerem®)	Melatonin receptor (MT1 and MT2) agonist	8 mg HS	1–5	High-fat meal delays absorption
Temazepam (Restoril®)	BZD, acting on benzodiazepine receptor	7.5–30 mg HS	8.8	Serum level may be increased by grapefruit juice
Zolpidem (Ambien®)	Non-BZD; interacting with GABA$_A$ receptor	10 mg HS, 12.5 mg ER Elderly and Women: 5–10 mg HS, 6.25 mg ER	2–3	Food may delay absorption
Alprazolam (Xanax®)	BZD	0.25–1 mg TID PRN	6–12	Fast onset, deliriogenic
Lorazepam (Ativan®)	BZD	0.5–2 mg TID PRN	12–18	Deliriogenic
Clonazepam (Klonopin®)	BZD	0.25–1 mg BID PRN	30–40	Deliriogenic
Buspirone (Buspar®)	Non-BDZ; 5-HT$_{1A}$ agonist	10–60 mg divided BID to TID	2–3	Takes 1–2 weeks to have effects

HS at bedtime, *TID* three times daily, *PRN* as needed, *BZD* benzodiazepine, *GABA* γ-aminobutyric acid, *ER* extended release, *BID* two times daily

adherence to treatment, increased accidents and falls, fatigue, increased perception of physical pain, increased risk of developing depression, and overall decline in QOL [16]. For these reasons, patients should be screened for insomnia and offered appropriate treatment.

1. Diagnosis

    a. The International Classification of Sleep Disorders-3 (ICSD-3) characterizes insomnia as follows:

        i. A disruption of sleep lasting 30 minutes or more when falling asleep, awakening during the night, or awakening earlier in the morning than intended.

    ii. The disturbance must occur at least three times per week and result in compromise of daytime functioning such as fatigue, anergia, excessive daytime sleepiness, social or vocational impairment, accidents, poor concentration, or behavioral changes.

    iii. Short-term insomnia lasts less than 3 months. Chronic insomnia lasts for 3 or more months.

2. Treatment

    a. Nonpharmacologic management includes stimulus control, relaxation training, sleep restriction, biofeedback, and/or referral to cognitive-behavioral therapy for insomnia (CBTI)

    b. Pharmacologic interventions should be undertaken if insomnia persists despite nonpharmacologic interventions.

    c. Untreated insomnia may contribute to delirium, but aggressive treatment with sedative/hypnotics can also result in delirium.

    d. Medication often does not restore normal sleep architecture and most result in diminished levels of deep sleep and increased periods of REM sleep.

    e. Of the available agents, ramelteon (Rozerem®) has the greatest likelihood of providing a sleep cycle more near to that which occurs without medication assistance.

    f. See Table 41.3 for treatment options and dosing recommendations.

Mania, Psychosis, and Substance Abuse

1. While less common, HCT patients may develop mania and/or psychosis.
2. Symptoms of mania include euphoria or irritability, sleeplessness, rapid speech, distractibility, grandiosity, increased goal-directed activity, impulsivity, and, sometimes, hypersexuality.
3. Psychosis often includes paranoia, hallucinations, and disorganization of thought.
4. Delirium, which can overlap, would have a fluctuating course and should first be excluded.
5. If delirium is not felt to account for symptoms, medications should be examined next.

    a. Steroids, stimulants, and antidepressant medications can precipitate mania or psychosis, especially in patients with an underlying bipolar spectrum disorder or primary psychotic illness.

    b. Consider psychiatric consultation for additional assistance in management.

6. In patients with a history of steroid-induced mania or psychosis requiring a course of high-dose steroids, consider initiation of a prophylactic agent, such as olanzapine (Zyprexa®) 5–10 mg PO nightly.

7. If treatment-emergent mania occurs, decrease or discontinue the offending agent if possible.
8. Even if there is a history of depression, when a patient demonstrates manic symptoms, antidepressants should be discontinued and a mood-stabilizing medication started in exchange.

   a. Antipsychotic medications are fairly well-tolerated, effective mood stabilizing agents.
   b. Valproic acid (Depakote®) and lithium are also standard mood-stabilizing medications but can become toxic if not closely monitored.

      i. With close monitoring, these medications can also be safe if a patient has a history of robust response and/or intolerability of other agents.

9. If a patient exhibits unexpected behavioral changes not attributable to delirium, an underlying psychiatric diagnosis or medication effect, substance abuse should be considered on the differential and a urine drug screen should be obtained.

   a. Patients may use illicit substances to cope with disease symptoms, medication side effects, or emotional distress.
   b. Identifying and treating anxiety or depression, if present, may aid in achieving sobriety.
   c. Abrupt discontinuation of prescribed benzodiazepines or opioids is not recommended as an initial step due to risks of withdrawal.
   d. Referral to community sobriety support resources and collaboration with an addiction specialist is recommended in more complicated cases.

Drug Interactions and Dose Adjustments

1. Many psychotropic medications have drug interactions, the most relevant of which involve the CYP450 family of hepatic enzymes.

   a. The inhibition or induction of these enzymes can result in adverse drug reactions, toxicities, or reduced medication efficacy.
   b. Select agents' potential for interacting with specific enzymes is listed in Table 41.4. Weak (W) interactions are not clinically relevant, while moderate (M) and strong (S) interactions should be discussed with a pharmacist for potential dose adjustments.

2. The intent in medication dosing in patients with potential drug interactions or organ dysfunction is to adjust the dose to one that achieves a comparable whole body or receptor targeted dose as that seen in individuals with normal organ function.

   a. Once the agent is initiated, dose titration should occur at slower intervals (approximately 1.5–2 times longer) to allow the patient to reach a steady state blood concentration and allow both clinical effects and side effects to be assessed prior to further dose titration (see Table 41.5).

Table 41.4 Drug interactions involving the CYP450 families of enzymes [25–28]

Drug	1A2	2A6	2B6	2C8	2C9	2C19	2D6	2E1	3A4
Bupropion (Wellbutrin®)	–	–	–	–	–	–	W	–	–
Citalopram (Celexa®)	W	–	W	–	–	W	W	–	–
Desipramine (Norpramin®)	–	M	M	–	–	–	M	W	M
Diphenhydramine (Benadryl®)	–	–	–	–	–	–	M	–	–
Duloxetine (Cymbalta®)	–	–	–	–	–	–	M	–	–
Escitalopram (Lexapro®)	–	–	–	–	–	–	W	–	–
Eszopiclone (Lunesta®)	–	–	–	–	–	–	–	–	–
Fluoxetine (Prozac®)	M	–	W	–	W	M	S	–	W
Haloperidol (Haldol®)	–	–	–	–	–	–	M	–	M
Mirtazapine (Remeron®)	W	–	–	–	–	–	–	–	W
Olanzapine (Zyprexa®)	W	–	–	–	W	W	W	–	W
Paroxetine (Paxil®)	W	–	M	–	W	W	S	–	W
Quetiapine (Seroquel®)	–	–	–	–	–	–	–	–	–
Ramelteon (Rozerem®)	–	–	–	–	–	–	–	–	–
Risperidone (Risperdal®)	–	–	–	–	–	–	W	–	W
Sertraline (Zoloft®)	W	–	M	W	W	M	M	–	M
Temazepam (Restoril®)	–	–	–	–	–	–	–	–	–
Venlafaxine (Effexor®)	–	–	W	–	–	–	W	–	W
Zolpidem (Ambien®)	–	–	–	–	–	–	–	–	–

W = weak, M = moderate, S = strong

Table 41.5 Suggested dose adjustments for estimated renal function (mL/min) and degree of hepatic dysfunction [24]

	Renal dysfunction (estimated creatinine clearance in mL/min)			Hepatic dysfunction		
Drug	*30–50*	*10–30*	*< 10 and dialysis*	*Mild*	*Moderate*	*Severe*
Bupropion (Wellbutrin®)	None	None	50%	None	Consider ↓ 25%	75 mg maximum
Citalopram (Celexa®)	None	None	None	None	↓ 25%	↓ 50%
Diphenhydramine (Benadryl®)	None	↓ 25%	↓ 50%	None	↓ 25 %	↓ 50%
Duloxetine (Cymbalta®)	60 mg maximum	Do not use	Do not use	None	Do not use	Do not use
Escitalopram (Lexapro®)	None	None	None	None	↓ 25%	50%
Eszopiclone (Lunesta®)	None	None	None	None	None	1 mg, max dose 2 mg
Fluoxetine (Prozac®)	None	None	None	None	↓ 25%	↓ 50%
Haloperidol (Haldol®)	None	None	None	None	None	↓ 50%
Mirtazapine (Remeron®)	None	↓ 30%	↓ 50%	None	None	↓ 30%

Table 41.5 (continued)

	Renal dysfunction (estimated creatinine clearance in mL/min)			Hepatic dysfunction		
Olanzapine (Zyprexa®)	None	None	None	None	None	None
Paroxetine (Paxil®)	None	None	None	None	↓ 25%	↓ 50%
Quetiapine (Seroquel®)	None	None	None	None	↓ 30%	↓ 50%
Ramelteon (Rozerem®)	None	None	None	None	None	Do not use
Risperidone (Risperdal®)	None	↓ 25%	↓ 50%	None	None	↓ 40%
Sertraline (Zoloft®)	None	None	None	None	↓ 25%	↓ 50%
Temazepam (Restoril®)	↓ 25%	↓ 50%	↓ 90%	None	None	None
Venlafaxine (Effexor®)	↓ 25%	↓ 50%	↓ 75%	None	↓ 30%	↓ 90%
Zolpidem (Ambien®)	None	None	↓ 50%	None	None	↓ 50%

↓ = decrease dose by

Capacity

1. Legal capacity is not a gray area – a patient is either lawfully entitled or not entitled to make a given decision about his or her health care.
2. In order to demonstrate capacity, a patient must meet specific criteria. The criteria set forth by Appelbaum and Grisso [17] are commonly utilized. A patient must:

    a. Express a clear, consistent choice.
    b. Understand the relevant information provided.
    c. Reason and weigh the risks/benefits.
    d. Recognize the consequences of the current circumstances.

3. Any physician is empowered to complete a decision-making capacity evaluation.

    a. Multiple formalized tools are available.

4. The level of reasoning and understanding demonstrated by a patient should be commensurate to the risk entailed in the decision.
5. It should be noted that an inability to demonstrate capacity for one decision does not necessarily imply global incapacity; a patient may be able to designate a surrogate decision maker to assist.
6. Ideally, if a patient is determined to be incapacitated, the underlying etiology should be identified and, if possible, rectified in order to restore patient autonomy.
7. Sometimes, circumstances demand that capacity assessments are completed by a psychiatrist or obtained in conjunction with institutional ethics committees.

Psychiatric Consultation

Psychiatric consultation should be considered throughout the continuum of care of the HCT patient. Pre- and posttransplant consultation offers the possibility of optimizing a patient's medication to allow maximal stability throughout the transplant process and should be considered in any patient with a complicated psychotropic regimen, risk of serious medication interactions, or history of serious psychiatric illness. Consultation in the hospital should be considered at any time there is a psychiatric diagnostic or management question.

Collaborating with specialists, inpatient or outpatient, can both improve outcomes and help provide crucial psychosocial care for the HCT patient.

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Chapter 42
Graft Failure

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Introduction

Graft failure and/or poor graft function after hematopoietic cell transplantation (HCT) is a complication that necessitates workup to rule out reversible causes. Mortality rates are high in patients with complete graft failure, often necessitating second transplantation procedures for salvage.

Graft Failure and Poor Graft Function

Graft failure (GF) is the term used when donor cells do not engraft. This complication can occur initially after hematopoietic stem cell transplantation (HCT) with no establishment of donor hematopoiesis (primary or early graft failure) or can occur late, after donor hematopoiesis had initially been achieved (secondary or late graft failure). Many of the same factors that can impact the kinetics of engraftment are also risk factors that are predictive for graft failure. The incidence of graft failure is difficult to accurately assess but is likely 1–3% (or lower) for autologous transplants and up to 2–20% of allogeneic transplants.

Poor graft function, on the other hand, is a term that describes clinically significant cytopenias that occur after initial engraftment, with evidence of a hypoplastic marrow with some degree of ongoing donor hematopoiesis.

1. Primary graft failure is defined as, in the absence of relapse:

   a. Absence of initial donor cell engraftment with peripheral blood (PB) Absolute Neutrophil Count (ANC) < 0.5×10^9/L by day +28 after alloHCT [1] and by

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day +42 after umbilical cord blood transplant [1, 2]. In reduced intensity conditioning (RIC) allogeneic transplant, <5% donor hematopoietic chimerism threshold is required [3] to meet the definition

b. After autologous transplant procedures, failure to achieve an ANC ≥ 0.2×10^9/L by day +21 or >0.5×10^9/L by day 28.

c. Primary graft failure is often considered synonymous with primary graft rejection, although some investigators attempt to distinguish nonengraftment from immunologic rejection, thus guiding subsequent interventions.

2. Secondary (a.k.a. late or delayed) graft failure is defined, in the absence of relapse as:

a. Loss of donor cells after initial engraftment and recurrent ANC < 0.5×10^9/L with continued transfusion support [1]

3. Poor graft function is defined as severe cytopenia involving at least two cell lines and/or transfusion requirement for >2 consecutive weeks beyond day +28, after an initial engraftment AND:

a. Hypoplastic bone marrow
b. Established donor chimerism with >5% donor hematopoiesis [3, 4]
c. No evidence of relapse

4. Causes of graft failure

a. Following an *autologous* transplant:

   i. Infusion of inadequate cell dose (poor viability, poor collection)
   ii. Damaged marrow microenvironment secondary to prior therapies
   iii. Concomitant infections, e.g., cytomegalovirus (CMV)/human herpes virus 6 (HHV6)
   iv. Medications: ganciclovir (Cytovene®), folate antagonists
   v. Deficiency states: folic acid, Vitamin B$_{12}$

b. Following an *allogeneic* transplant:

   i. Potential causes and how these causes impact engraftment and mitigating approaches are outlined in detail in Table 42.1.

5. Diagnostic approach to graft failure or poor graft function

a. Rule out relapse

   i. Bone marrow aspirate and biopsy

   • In both autologous and allogeneic recipients, if relapse is not readily determined by examination, bone marrow studies demonstrate a hypocellular marrow with absent/reduced identifiable myeloid, erythroid, or megakaryocytic precursors.
   • Disease-specific studies other than marrow:
   • BCR/ABL PCR in Philadelphia chromosome-positive disease

Table 42.1 Risks and mitigating approaches for graft failure

Risk factor	Impact	Mitigating factors
Graft dependent		
Low CD34+ cell dose	A minimum threshold dose of progenitor cells is needed to ensure engraftment; varies with the type of transplant and graft source [3]. TNC dose of $<3 \times 10^8$/kg recipient weight is associated with increased GF risk with MAC alloHCT [3]	Ensure meeting minimal cell dose for product type: *BM*: 3×10^8 TNC/kg recipient weight *PBSC*: Minimal: $>2 \times 10^6$ CD34+/kg recipient weight; Optimal: $>4 \times 10^6$ CD34+/kg recipient weight *UCB*: $>2.5–3 \times 10^7$ TNC/kg is recommended [5] *Auto*: Minimal $>1 \times 10^6$ CD34+ cells/kg; optimal $>2 \times 10^6$ CD34+ cells/kg
Low CD3 dose T-cell depletion	*Ex vivo* T-cell depletion (a.k.a. CD34+ cell selection) is associated with increased risk of graft rejection [6]	Use of a CD34+ megadose ($>10^7$/kg) has been shown to overcome the risk of rejection in the setting of HLA-mismatch [7]
Graft source	BM is associated with delayed neutrophil and platelet engraftment for all transplants [5]. GF incidence is not different for HLA-identical MRD [8], but it is higher with URD (9% vs. 3%, for BM and PB respectively) [9]. UCB transplant is associated with high GF rate and delayed neutrophil and platelet recovery in children and adults [10, 11]	Choose PB graft over BM or UCB if high risk for GF
Donor age/sex	Older donors and female donor to male recipient are associated with higher risk of graft rejection	Choose younger donor [12] and male donor (over female)
Patient factors		
Splenomegaly	Splenomegaly increases the risk of graft failure	Consider splenic irradiation or splenectomy prior to transplant
HLA-disparity	Higher risk of GF in mismatched (vs. well-matched and partially matched) unrelated grafts [13]	Choose the best available HLA-matched donor
ABO mismatch	Major ABO incompatibility may be a risk factor for primary GF [13] and has been associated with post-HCT pure red cell aplasia [3]	1. If BM graft is to be used for HCT, avoid major ABO mismatch 2. Aim for a higher TNC/CD34+ target during BM harvest to allow for hematopoietic progenitor cell loss during red cell depletion
Primary disease	Hemoglobinopathies (thalassemia [14, 15], sickle cell disease [16]) and SAA have higher incidence of GF due to sensitization to red cell antigens [17] Increased risk of primary GF is reported with MDS, CML, and MPN [3] related to lack of pre-HCT intensive chemotherapy and presence of residual host effector cells, defective marrow environment [18, 19], and/or enlarged spleen [20]	Myelofibrosis: splenectomy or splenic radiation, early hematopoietic growth factor support [3, 21] SAA and hemoglobinopathies: ATG and TBI as part of conditioning regimen CML: use MAC if possible; add ATG if URD Lymphoma/myeloma: consider collecting and saving autologous back up [3, 22] for rescue of graft failure after allogeneic or autologous transplant

(continued)

Table 42.1 (continued)

Risk factor	Impact	Mitigating factors

Anti-HLA antibodies	Anti-HLA (or DSA) is associated with higher risk of GF after haploidentical transplant and UCB transplant [23–25]	1. Screen alloHCT candidates (if mismatched or unrelated donor) for DSAs
		2. Choose alternative donor if DSAs positive, if available
		3. Desensitization treatment: [5, 26]
		  a. DSA removal: Plasmapheresis before HCT
		  b. Inhibition of DSA production: Rituximab® or Bortezomib®
		  c. Ab neutralization: Infusion of platelet units sharing donor antigens or buffy coat pre-HCT

Transplant factors		
Conditioning intensity	RIC is associated with a higher incidence of graft rejection due to residual host CTL and NK cells [27]. Increasing the intensity of MAC conditioning protocols does not reduce GF incidence [5]	1. Consider MAC over RIC when possible 2. Early chimerism testing after RIC; DLI to convert persistent mixed or falling chimerism; requires multiple, usually escalating doses
Preparative regimen	Cy and ATG for SAA: the use of ATG in combination with Cy seems to reduce the incidence of GF [5, 28], though a prospective trial comparing Cy with Cy+ATG reported similar GF rates [29]. The addition of 2 Gy TBI to Flu/Cy did not reduce the incidence of GF in SAA [5]	1. TBI in conditioning improves engraftment after CBT [30] 2. For SAA and hemoglobinopathies, using ATG and TBI as part of conditioning results in lower GF rates
Posttransplant immunosuppression	Post-HCT immunosuppression for GvHD prevention is critical to maintain donor/recipient chimerism. PTCy after haploidentical transplant appears to abrogate the effect of HLA-mismatch on engraftment	1. If persistent mixed or falling donor chimerism, consider pre-emptive rapid withdrawal of immune suppression [30] and confirm improved donor chimerism 2. PTCy is the prophylactic regimen of choice for haploidentical transplant [31] and is most widely used

TNC total nucleated cells, *GF* graft failure, *MAC* myeloablative conditioning, *HCT* hematopoietic cell transplantation, *BM* bone marrow, *PSBC* peripheral blood stem cell, *UCB* umbilical cord blood, *HLA* human leukocyte antigen, *MRD* matched related donor, *URD* unrelated donor, *SAA* severe aplastic anemia, *MDS* myelodysplastic syndrome, *CML* chronic myeloid leukemia, *MPN* myeloproliferative neoplasms, *ATG* antithymocyte globulin, *TBI* total body irradiation, *DSA* donor-specific antibodies, *Ab* antibody, *RIC* reduced intensity conditioning, *CTL* cytotoxic T lymphocytes, *NK* natural killer, *DLI* donor lymphocyte infusion, *Cy* cyclophosphamide, *PTCy* post-transplant cyclophosphamide

- Myeloma biochemical studies
- Lymphoma imaging

ii. Chimerism studies (allogeneic transplants)

- FISH/cytogenetics for sex-mismatched recipient/donor
- Lineage specific chimerism using variable number of tandem repeats (VNTR) for sex-matched recipient/donor. These studies generally require pre-HCT storage of DNA material (generally collected from peripheral blood) from both donor and recipient.

iii. Rule out graft-versus-host disease (GvHD)
iv. History/physical exam/chemistries
v. Endoscopic examination/imaging with biopsy as appropriate
vi. Rule out infection as appropriate:

- CMV PCR, HHV6 PCR, parvovirus PCR, adenovirus PCR
- Blood cultures
- Urinalysis/culture
- Chest X-ray
- Fungal serologies

vii. Metabolic studies

- Methylmalonic acid, homocysteine, and copper levels
- Thyroid function studies

viii. Consider the following etiologies/differential:

- GvHD (acute and/or chronic): [3] see above
- Infections: see above [17]
- Sinusoidal obstruction syndrome: [32] check liver function tests, ultrasound with Doppler examination of the hepatic and portal veins
- Hemophagocytic lymphohistiocytosis: check ferritin, triglycerides, and fibrinogen
- Drugs such as ganciclovir (Cytovene®) [33], trimethoprim/sulfamethox-azole (TMP-SMZ, Bactrim®), mycophenolate (Cellcept®), sirolimus (Rapamune®), tyrosine kinase inhibitors, lenalidomide (Revlimid®)
- Pretransplant iron overload [34]
- Underlying disease: marrow fibrosis [3, 32]
- Inadequate number of hematopoietic progenitor cells [32]
- Extensive pretransplant chemotherapy and/or radiation [3]

6. Management of graft failure/poor graft function

a. Growth factors

i. G-CSF (e.g., Neupogen®): A trial of posttransplant G-CSF support is appropriate after *autologous* transplant patients with delayed neutrophil recovery. The role of growth factors is unclear in patients with poor graft function after *allogeneic* transplant.

ii. Eltrombopag (Promacta®): This oral thrombopoietin-receptor agonist is considered safe and effective as treatment of poor graft function manifesting as thrombocytopenia and possibly as pure red cell aplasia after allogeneic HCT, in several small studies [35–37]. An 8-week trial of eltrombopag may alleviate the need for more expensive and logistically difficult therapy such as a CD34+ selected donor graft boost in an allogeneic HCT patient with poor graft function.

iii. Augmenting donor T-cell function:

- Donor lymphocyte infusion (DLI) or withdrawal of immune suppression

  - DLI can be recommended for decreasing levels of donor T-cell chimerism after allogeneic HCT [5].
  - The majority of patients require multiple doses of DLI to convert to full donor chimerism [38].
  - The timing and dose schedules (see also Chap. 53) of pre-emptive DLI is unclear and requires careful consideration of the pros and cons [3].
  - The benefit of conversion to full donor chimerism needs to be weighed against the risk of inducing GvHD [38–40]. However, if the graft has been rejected and that is the cause of graft failure, DLI can cause marrow aplasia [41].
  - The role of DLI is, therefore, mostly limited to patients with persistent mixed chimerism [3].
  - Similar considerations apply to withdrawal of immune suppression as an option to boost donor T-cell function among those with mixed donor T-cell chimerism and poor graft function. This maneuver also entails the risk of acute GvHD and/or aplasia and requires careful consideration.

iv. CD34+ cell boost

- In patients with poor graft function after allogeneic HCT, defined as at least two lines of cytopenias after day +28 with mixed or full donor chimerism, a CD34+ selected cell boost administered to the patient without conditioning regimen can repopulate the marrow and result in count recovery without significant risk of GvHD.
- The cell boost procedure should be performed only after other potential etiologies that result in cytopenias such as infections, GvHD, drugs, and disease relapse have been excluded.

v. Retransplant

- A second allogeneic transplant is the only potential long-term curative option for patients with graft rejection (without any evidence of disease relapse) [42–45].
- There is no conclusive evidence to support the choice of using the same donor used for the first alloHCT or an alternative donor for the second

Table 42.2 DLI vs CD34+ boost vs. second transplant for graft failure

Modality	Indication
DLI	*Persistent mixed or dropping donor chimerism*, generally after a trial of rapid immune suppression taper
Donor CD34+ cell boost	*Poor graft* function, i.e., at least two lines of cytopenias and mixed or full donor chimerism [47], >28 days after transplant If mixed donor chimerism, consider unmanipulated allograft If full donor chimerism, consider CD34+-selected boost to avoid GvHD
Second allogeneic transplant or re-grafting	*Primary/secondary graft* rejection, i.e., cytopenias and <5% donor hematopoiesis. Recommend using RIC [3] (e.g., Flu/Cy or Flu/TBI) [42] before infusion of preferably PB unmanipulated graft. Consider using ATG, if unrelated donor [5]

*Relapse must be excluded before decision is made to use any of the interventions
DLI donor lymphocyte infusion, *GvHD* graft-versus-host disease, *RIC* reduced intensity conditioning, *Flu* fludarabine, *Cy* cyclophosphamide, *TBI* total body irradiation, *PB* peripheral blood, *ATG* antithymocyte globulin

allograft [33, 41]. However, in patients who experience an immunologic graft rejection, the use of an alternative donor is recommended [33].
- Peripheral blood stem cells (PB) rather than bone marrow (BM) is commonly preferred as the graft source for salvage alloHCT to improve engraftment rate [46], even though there is no evidence for favorable survival with PB or G-CSF-mobilized PB graft if the donor is HLA-matched [3].
- There is also a need for conditioning regimen before the infusion of allograft. RIC regimens are usually recommended to avoid cumulative toxicity of the two consecutive conditioning regimens given in close proximity [42].
- There is a higher risk of GvHD with the second allografting, with an expected long-term survival of approximately 30% [42].

vi. Choosing between DLI, CD34+ boost, and second allograft? See Table 42.2.

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Chapter 43
Second Primary Malignancies

Ashley Manning and Bronwen E. Shaw

Introduction

Approximately 50,000 patients undergo hematopoietic cell transplantation (HCT) worldwide each year. Advancements in the field have led to increased survival rates for these patients. Long-term HCT survivors are at risk for developing secondary malignancies, representing the fourth leading cause of non-relapse-related death in patients who survive more than 2 years after HCT [1]. Although relatively rare, second primary malignancies are often associated with significant morbidity and mortality. The incidence of second primary malignancies continues to increase across the survivor's lifespan requiring heightened awareness and ongoing surveillance for the duration of the transplant recipient's life [2].

General Risk Factors

1. Underlying disease

    a. Certain diseases that can be cured by HCT are at a higher risk of developing a subsequent malignancy, e.g., Fanconi anemia

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2. Total body irradiation (TBI)

   a. Increased risk with higher total cumulative doses
   b. Decreased risk with fractionated dosing
   c. Patients transplanted at a younger age who are exposed to TBI are at greater risk of secondary malignant neoplasm (SMN) than older patients [2]

3. Chemotherapy agents (prior treatment exposures)

   a. Alkylating agents (see Table 43.1)

      i. Latency period of 3–8 years.
      ii. Commonly associated cytogenetic abnormalities include 5-, 7-, 5q-, and 7q-.
      iii. May present with myelodysplasia [3]

   b. Topoisomerase inhibitors (see Table 43.1)

      i. Latency period of 2–3 years.
      ii. Commonly associated cytogenetic abnormalities include 11q23 deletion and translocation.
      iii. Does not typically present with myelodysplasia.

   c. Lenalidomide (Revlimid®)

      i. There is increasing utilization of lenalidomide maintenance postautologous HCT for multiple myeloma (MM), given studies that have shown a benefit in both progression-free and overall survival.
      ii. Randomized trials have shown an increased numerical incidence of secondary primary malignancies of 8% in patients receiving lenalidomide maintenance compared to 3–4% of those patients not receiving maintenance therapy. This observation was not statistically significant.
      iii. Cause is likely multifactorial.
      iv. A meta-analysis published in 2014, which included approximately 2500 multiple myeloma patients who received lenalidomide as primary ther-

Table 43.1 Characteristics of tMDS/AML

	Alkylating agents	Topoisomerase II inhibitors
Latency	3–8 years	2–3 years
Incidence	2–20%	2–12%
Myelodysplastic phase	Present	Absent
FAB type	M1, M2	M4, M5
Cytogenetics	5-, 7-, 5q-, 7q-	11q23 deletion and translocation
Pathogenesis	Tumor suppressor genes, RAS mutations	Translocations

apy, the cumulative incidence of second malignancies at 5 years was 6.9%, compared with 4.8% in patients who did not receive lenalidomide:

- 3.8% incidence of solid malignancy
- 3.1% incidence of hematologic malignancy [4]

v. A panel of International Myeloma Working Group members reviewed relevant published data and has made recommendations based on this literature review:

- Overall the risk for second primary malignancy (SPM) in MM is low, multifactorial, and partially related to the length of patients' survival and MM intrinsic susceptibility.
- There is higher incidence of SPMs when lenalidomide is administered either following, or concurrently with oral melphalan.
- Risk of death from MM was significantly higher than the risk from SPM, with lenalidomide possibly providing a survival benefit.
- Risk of SPMs should not alter the current therapeutic decision-making process in MM.
- Regimens such as lenalidomide plus dexamethasone are preferred over lenalidomide plus melphalan [5].

4. Chronic graft-versus-host disease (cGvHD) following allogeneic HCT

a. SPM occur at 2–3× the general population rates of de novo malignancy.
b. The most frequent organs involved include the skin, oropharynx, and esophagus.
c. Immunosuppressive agents (and the length of treatment with these) have been associated with increased risks.
d. cGvHD may be associated with a lower incidence of central nervous system (CNS) malignancies [6].

5. Oncogenic viruses, including human papilloma virus (HPV) and Epstein–Barr virus (EBV)
6. Predisposition to carcinogenesis

a. Age
b. Gender
c. Lifestyle choices, e.g., tobacco use, sun exposure, obesity

7. Clonal hematopoiesis of indeterminate potential (CHIP)

a. Somatic mutations that can develop in the general population as they age.
b. CHIP is more common in patients who have undergone autologous HCT and is associated with an increased risk of therapy-related myeloid malignancies.
c. CHIP can also be transferred from healthy stem cell donors and found in the patient's blood after HCT [7, 8].

Incidence

1. Reported cumulative incidence of SPMs, although low early posttransplant, the risk continues to increase with time:

   a. Postallogeneic HCT [9]

      i. 1.2–1.6% at 5 years
      ii. 2.2–6.1% at 10 years
      iii. 3.8–14.9% at 15 years

   b. Postautologous HCT for lymphoma [10]

      i. 2.54% at 5 years
      ii. 6.79% at 10 years
      iii. 9.14% at 15 years

   c. Postautologous HCT for MM [11]

      i. 5.3% at 5 years
      ii. 11.2% at 10 years

Onset

1. Typically, there is a latency period of 3–5 years preceding development of SPMs following HCT but cases occurring earlier have been reported.
2. Therapy-related myeloid malignancies often occur earlier posttransplant than solid tumor malignancies [3].

Types of Second Primary Malignancies

1. Therapy-related myelodysplastic syndrome (tMDS) and acute myeloid leukemia (AML) following autologous HCT [12].

   a. Estimates of incidence of tMDS/AML vary widely between 1% and 14% at 3–15 years after autologous HCT for lymphoma and MM

      i. 0–1% at 1 year
      ii. 1–2% at 3 years
      iii. 1–4% at 5 years
      iv. 3–6% at 10 years

   b. tMDS/AML is thought to be a consequence of the initial cytotoxic therapy for the primary malignancy rather than of the HCT procedure and may represent a mutated stem cell pool that is transferred within the thawed cryopreserved product. Incidence may be even higher because of the substantial cumulative

chemotherapy and radiotherapy received pretransplant, as well as chemotherapy-based stem cell mobilization.

   c. Risk factors

     i. Age
     ii. Extent of pre-HCT therapy
     iii. Exposure to alkylating agents and TBI
     iv. Stresses imposed on stem cells during mobilization therapy and engraftment

       • Priming chemotherapy induces genotoxic damage in hematopoietic stem cells, which are later infused during autologous HCT.
       • Proliferative stress during engraftment with many replication cycles has been proposed to contribute to genomic instability through telomere shortening.

   d. Prognosis

     i. Median overall survival of tMDS/AML after autologous HCT is 6–12 months although data regarding survival after salvage treatment with allogeneic HCT are limited.

2. MDS and AML following allogeneic HCT [2]

   a. Limited data are available regarding tMDS/AML following allogeneic HCT.
   b. Risk often exceeds 10-fold when compared to that of other cancer survivors who have received similar cytotoxic chemo and radiotherapy.
   c. May be underreported if believed to be a relapse of the original disease

3. *Donor-derived* MDS/AML following allogeneic HCT [2]

   a. Incidence has been reported at <1%.
   b. A European Society for Blood and Marrow Transplant (EBMT) study demonstrated median time to onset of 17 months with no specific risk factors identified.

4. Posttransplant lymphoproliferative disorder (PTLD) [2, 13, 14]

   a. A heterogeneous group of abnormal B-lymphoid proliferations that typically occurs in the setting of profound immunosuppression after allogeneic HCT and presents as clinically aggressive and frequently fatal lymphomas.
   b. Vast majority are associated with EBV.

     i. After allogeneic HCT, PTLD is identified in the marrow derived, or adoptively transferred donor cells, differing from PTLD occurring in solid organ transplantation where it is of recipient origin.

   c. Incidence

     i. Cumulative incidence is 1–2% but may be as high as 8–10% among patients with multiple risk factors.
     ii. PTLD is rare following autologous HCT and most commonly occurs in those patients requiring immunosuppressive therapy (i.e., steroids).

However, there has been an increase in reported cases with the use of CD34+ selected autologous HCT in both adult and pediatric patients.

- 80% of PTLDs occur within 6 months to 1 year post-HCT and incidence declines among survivors > 1 year post-HCT.

d. The two strongest risk factors are exposure to EBV and degree of immunosuppression, particularly T-cell-depleted allografts. Active surveillance, often weekly, for EBV reactivation using quantitative PCR is being increasingly advocated in high-risk patients. High-risk patients include those who received:

 i. In vivo T-cell depletion with antithymocyte globulin (ATG; ATGAM®; Thymoglobulin®) or alemtuzumab (Campath®)
 ii. Ex vivo T-cell depletion
 iii. Alternative donor transplants such as haploidentical donors or cord blood

e. Pre-emptive therapy with CD20-active agents such as rituximab (Rituxan®) is being studied on the basis of polymerase chain reaction (PCR) determination of rising EBV transcript levels.

f. Treatment requires restoration of immune response against EBV and elimination of EBV and neoplastic B-cells.

 i. Withdrawal of immunosuppression if possible.
 ii. Infusion of non-specific donor T cells although the risk of GvHD is high.
 iii. Infusion of EBV-specific T cells is under investigation.
 iv. Anti-B cell therapy such as rituximab (Rituxan®).

5. Second primary solid malignancies

a. Skin/oral [15]

 i. Occur in both autologous and allogeneic HCT recipients
 ii. A large cohort of patients studied at the Fred Hutchinson Cancer Research Center (FHCRC) found the incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) to be 6.5% and 3.4% at 20 years, respectively, after allogeneic HCT.
 iii. TBI was a significant risk factor for BCC with higher incidence in younger and light-skinned patients as well as those who received myeloablative conditioning.
 iv. Acute GvHD increased risk of SCC whereas chronic GvHD increased the risk of both BCC and SCC.
 v. Male patients have higher incidence rates of SCC.
 vi. SCC of the head and neck can arise from the buccal mucosa, salivary glands, gingiva, lip, or tongue.
 vii. Risk factors for melanoma include myeloablative TBI conditioning, T cell depletion, and female gender.
 viii. Risk factors for oral cancer include oral cGvHD, underlying Fanconi anemia, cumulative duration of immunosuppressive therapy, male gender, and younger age (<10 years).

b. Lung [16]

  i. Recent study of patients receiving busulfan-cyclophosphamide conditioning reported an increase risk of lung cancer, especially among those with a prior history of smoking.

c. Hepatic [17]

  i. Long-term survivors with chronic hepatitis C virus (HCV) represent a particularly high-risk cohort for cirrhosis and subsequent hepatocellular carcinoma. Other risk factors include TBI and younger age (< 34 years).

  ii. Incidence

    • One historical retrospective analysis of patients infected with HCV during the HCT period showed the incidence of cirrhosis to be 11% and 24% at 15 and 20 years, respectively.
    • Incidence of secondary cancer has been shown to reach 16% in HCV-positive patients at 20 years.

d. Thyroid [18]

  i. Large cohort studied by the EBMT showed an increased incidence of thyroid cancer in patients who had undergone HCT.

    • The standardized incidence ratio of thyroid cancers in the population who underwent HCT was 3.26 in comparison with the general population.

  ii. Risk factors

    • Younger age (<20) at HCT was the strongest risk factor.
    • Irradiation.
    • Female sex.
    • Chronic GvHD.

e. Breast cancer [19]

  i. A retrospective analysis of 3,337 female allogeneic HCT survivors > 5 years post-HCT (FHCRC and European bone marrow transplant (EMBT) registries) showed the cumulative incidence of breast cancer to be 11% at 25 years. This incidence is compared to the overall incidence of 12% over a woman's lifespan.

  ii. Risk factors

    • Exposure of the breast tissue to radiation and/or myeloablative TBI
    • Disruption of ovarian function by alkylating agents
    • Younger age (<18) at transplant
    • Longer time since HCT
    • Use of growth factors and/or ATG

f. Central nervous system (CNS) SPM [20]

   i. Risk factors include CNS disease and radiation therapy prior to conditioning
   ii. Chronic GvHD has been associated with lower risk for development of CNS SPM.

Survival Following Secondary Malignancies

Two recent publications have specifically addressed outcomes of patients diagnosed with subsequent solid malignancies in recipients of HCT [1, 20].

1. Age at onset is less than that at onset of similar primary malignancies in the general population.
2. Survival after development of the SMN is dependent on the type of malignancy and is similar to or worse than in the general population.

   a. For example, cancers of the thyroid, breast, and skin are associated with a good outcome (similar to general population).
   b. Cancers of the liver, lung, and CNS are associated with a poor outcome.

3. In general, for those who do develop an SMN, this malignancy is the most common cause of death.
4. One study showed that the longer after the HCT the SMN developed, the lower the mortality.

Screening and Preventive Practices

A large group of experts from the Center for International Blood and Marrow Transplant Research (CIBMTR) and EBMT recently published consensus guidelines for secondary solid cancer screening following HCT. These guidelines are evidence based where possible or rely on expert opinion where not. They reviewed the general population screening guidelines established by the American Cancer Society (ACS) and the National Comprehensive Cancer Network (NCCN) [21].

1. For certain SMNs, there was no evidence to suggest that guidelines should differ from guidelines that have been clearly established in the general population, including prostate, testis, endometrium, ovary, liver, and colorectal cancers.
2. For certain SMNs there was insufficient evidence to suggest recommended guidelines other than clinical vigilance. These malignancies include cancer of the stomach, CNS, and sarcomas.
3. For several other SMNs, specific guidelines are given:

a. Skin: Annual physical examination is recommended. Photoprotection counselling is critical. Patients who may require additional vigilance are those with GvHD and/or who have had TBI. Suspicious lesions should be promptly addressed.

b. Thyroid: Annual physical examination is recommended. There is no evidence for routine ultrasounds. Heightened awareness is warranted for pediatric long-term survivors, female patients, TBI recipients, and patients with cGvHD.

c. Oropharyngeal: Annual physical examination by a dentist or an oral surgeon is recommended. For high-risk patients (GvHD or transplanted for Fanconi Anemia), six monthly examinations are warranted. Counseling to stop smoking is important.

d. Esophageal: Patients with persistent upper GI symptoms should have prompt endoscopy performed. Vigilance should be increased for patients with ongoing GvHD.

e. Lung: The most important aspect is the avoidance of smoking in all patients.

f. Breast: Self-examination and breast awareness should be promoted. For patients who received chest radiation or TBI, special consideration should be given for annual clinical breast examination, mammography, and breast magnetic resonance imaging beginning at age 25 years or 8 years after radiation or TBI, whichever occurs later, but no later than 40 years of age.

g. Cervix: Annual pelvic examinations should be performed for females. Vaccination against HPV is recommended in an age-specific manner and following CDC guidelines.

  i. HPV vaccination is routinely recommended for all 11- and 12-year-old girls and boys.

  ii. The vaccine series can be started beginning at age 9 years.

  iii. Vaccination is also recommended for 13- through 26-year-old females and 13- through 21-year-old males who have not completed the vaccination series.

  iv. In 2018, the US Food and Drug Administration approved the use of Gardasil 9® in women aged 27 through 45 years.

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Chapter 44
Relapse After Hematopoietic Cell Transplantation

Michael R. Bishop

Introduction

Relapse of disease is the major cause of death and treatment failure following both allogeneic and autologous hematopoietic cell transplantation (HCT) [1]. Over, the past 40 years, there has been very little improvement in outcomes of patients who relapse following HCT. In the case of allogeneic HCT, this lack of improvement has occurred despite a greater understanding of the biology underlying the graft-versus-tumor/leukemia (GVT) effects and the introduction of donor leukocyte/lymphocyte infusion (DLI) as a treatment option [2]. These results are even more disappointing when placed in the context that the relapse risk is significantly higher in individuals who undergo allogeneic HCT following nonmyeloablative and reduced-intensity conditioning.

As options are extremely limited once disease has recurred following autologous HCT, research efforts have focused on prevention by enhancing conditioning regimens and through maintenance therapies. In contrast, research on relapse following allogeneic HCT has primarily focused on treatment, particularly on immunotherapeutic approaches such as withdrawal of immune suppression and DLI. There is a paucity of data on the epidemiology, prevention, and monitoring for relapse of various diseases following either autologous allogeneic HCT [3]. This chapter provides an overview on the understanding of disease biology, disease monitoring, preventive measures, and treatments approaches for post-HCT relapse with a particular emphasis on allogeneic transplantation.

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Biology of Relapse After HCT

1. The malignant cells that ultimately lead to clinical relapse must initially survive the cytotoxic effects of the conditioning regimen. Agents within the regimen may have no effect on the malignancy or the therapeutic index may be too low to enable destruction of the neoplasm while preserving normal cells.

2. Clinical experience has shown that when a patient is rechallenged with a therapy, efficacy is reduced due in part to the biologic selection of resistant clones, including clones that generate protective microenvironments for themselves. Neoplastic cells acquire epigenetic and genetic alterations including point mutations, small insertions and deletions, translocations, large-scale copy number changes, and loss of heterozygosity, as well as hyper- and hypomethylation of promoter regions [4].

3. A therapeutic intervention changes the microenvironment of a neoplasm and alters the selective pressures on those cells. Cells that can survive and proliferate better than their competitors under the therapeutic exposure will tend to dominate the remaining neoplasm. Some neoplastic cells may reside in sites where a drug cannot penetrate. Survival signals and other components of the microenvironment may prevent apoptosis of some neoplastic cells. An agent may select for an epigenetic variant clone that is relatively resistant to the drug.

4. In the allogeneic HCT setting, cells that survive the conditioning regimen are susceptible to the GVT effects of donor cells. Soon after the first allogeneic transplants were performed, it became evident that donor T cells were not only responsible for graft-versus-host disease (GvHD) but were also associated with a reduced risk of relapse [5]. Further proof of donor T cells mediating a GVT effect came from successful treatment of relapse following allogeneic HCT with DLI [6]. However, other effectors, such as NK cells and B cells, may be involved in the GVT effect [2].

5. For a clinical GVT effect to occur, several immunological phenomena have to take place [4]. First, cells have to be activated leading to the appropriate production and expansion of T cells, NK cells, or antibodies. Cells may be activated by recognition of minor histocompatibility antigens (mHAs), which are presented on the cell surface by MHC class I and II molecules, where they can be recognized by donor CD8^{+} and CD4^{+} T cells, respectively. Many mHAs are expressed on both hematopoietic and nonhematopoietic cells, suggesting that T-cell responses to these antigens could contribute to both GVT and GvHD. Cells and antibodies must home to the tumor sites and mediate effector mechanisms leading to destruction of the malignancy. Preferentially, following a contraction phase of the immune response, a memory response should develop capable of sustained control of the disorder. Defects in any of one of these steps, the development of resistance, expression of inhibitory factors, and recruitment of T-regulatory cells by malignant cells permit evasion of the allogeneic immune reaction.

Risk of Relapse After HCT

1. The identification of the patient at risk for relapse is a key factor in the decision of proceeding to transplant and subsequently monitoring and potentially intervening before relapse occurs.
2. Disease status, relative to chemotherapy sensitivity and extent of systemic disease, is the major determinant of relapse risk. The presence or absence of minimal residual disease (MRD) has increasingly become an important determinant.
3. There is some controversy relative to the stem cell product utilized and the risk of relapse. In a meta-analysis of randomized studies of mobilized peripheral blood versus bone marrow grafts, peripheral blood was associated with more grade 3–4 acute and extensive chronic GvHD, but lower relapse rates [7]. This benefit in relapse reduction was apparent in patients with late-stage disease.
4. Comparison studies relative to conditioning regimens suggest there are higher relapse rates after reduced-intensity as compared to myeloablative regimens [8].
5. The clinical syndrome of GvHD is strongly linked to the GVT effect. Numerous reports have suggested reduced risk of relapse in patients with mild to moderate GvHD, but mortality from severe GvHD precludes a survival benefit from its accompanying GVT. Several observational studies demonstrate that chronic GvHD is associated with lower relapse rates.

Monitoring for Relapse After HCT (See also Chap. 59)

1. Although outcomes of relapse after transplantation are generally poor, intervention prior to florid relapse improves outcome for certain hematologic malignancies.
2. To detect early relapse or MRD after HCT, methods such as molecular genetics, tumor specific molecular primers, fluorescence in situ hybridization (FISH), and multiparameter flow cytometry are commonly used to monitor patients, particularly in the allogeneic setting (see Chap. 59). While monitoring after HCT has been clearly shown to be predictive of outcome in specific diseases (e.g., chronic myeloid leukemia), disease monitoring has not been standardized or accepted for the majority of hematologic malignancies.
3. Detection of pretransplant MRD in pediatric and some adult studies is highly predictive of relapse following allogeneic HCT and, coupled with posttransplant MRD evaluation, may guide early posttransplant intervention, such as early withdrawal of immunosuppression, administration of DLI, or addition of posttransplant maintenance therapy (e.g., targeted tyrosine kinase inhibition for BCR/ABL+ leukemias).
4. Imaging studies (computed tomography, magnetic resonance imaging, and positron emission tomography) can play a role in disease monitoring, particularly in

lymphomas, but there is a lack of evidence that earlier detection by these methods results in improved outcomes.

5. Most transplant centers repeat the previously positive tests at 3, 6, and 12 months posttransplant. Many centers continue to repeat these tests on at least on a yearly basis typically for 5 years post-HCT. The clinical benefit of frequent repeated tests is unknown.

Prevention of Relapse After HCT

1. Efforts to decrease relapse rates after HCT initially focused on intensification of cytoreductive therapy, either by increasing chemotherapy and/or total body irradiation (TBI) doses or adding additional chemotherapeutic agents. These attempts were met with only limited success, as the various regimens were composed of relatively nonspecific agents, such as TBI or high-dose alkylating agents [9, 10].

2. There is evidence to suggest that the incorporation of specific agents (e.g., busulfan in myeloid malignancies) or treatments (e.g., TBI in acute lymphocytic leukemia) are associated with decreased risks of relapse in specific diseases.

3. The use of maintenance therapy after HCT has increasingly been demonstrated to decrease the risk of relapse.

    a. The use of lenalidomide (Revlimid®) following autologous HCT in multiple myeloma has demonstrated improved progression-free and overall survival [11].

    b. The use of monoclonal antibodies, specifically rituximab (Rituxan®), following autologous HCT has resulted in improved progression-free survival in follicular lymphoma and mantle cell lymphoma [10, 12].

    c. There is evidence that maintenance therapy with hypomethylating agents (azacitidine [Vidaza®] or decitabine [Dacogen®]) may be effective following allogeneic HCT for myeloid malignancies [13].

    d. There is evidence that the use of agents that target specific mutations in myeloid malignancies (e.g., midostaurin [Rydapt®] against FLT3) may decrease relapse after allogeneic HCT [14–16].

4. A small number of studies have investigated the role of prophylactic DLI in the allogeneic HCT setting. Dosing and timing for prophylactic DLI has not been established. Transplantation using T-cell depleting agents such as anti-thymocyte globulin (ATG) and alemtuzumab (Campath®) has been most successful in creating a platform for prophylactic DLI [17].

5. Other preventive strategies, including the use of vaccines, interleukins, immunomodulatory agents, DNA methyltransferase inhibitors, and histone deacetylase inhibitors, are currently under investigation.

Treatment of Relapse After Autologous HCT

1. When considering treatment options for patients who relapse after autologous HCT, several issues must be taken into careful consideration (Fig. 44.1). Patients who relapse after transplant are an extremely heterogeneous group. Some may be quite ill and may still be suffering from morbidities of transplant. Furthermore, the biology, responsiveness, and prognosis of diseases that relapse rapidly and early after transplant are likely very different than diseases that relapse later after transplant. Treatment options are also affected by response to prior therapies.

2. Specific recommendations have not been established for patients who relapse following autologous HCT, as treatment options that provide meaningful clinical benefit are very limited in this setting and primarily include either a second autologous HCT or allogeneic HCT (Table 44.1). Notable exceptions include novel agents (e.g., brentuximab vedotin [Adcetris®]) and checkpoint inhibitors (e.g., nivolumab [Opdivo®]) in relapsed Hodgkin lymphoma and lenalidomide [Revlimid®]) in myeloma, respectively, when these agents were not used as maintenance therapy [14, 18].
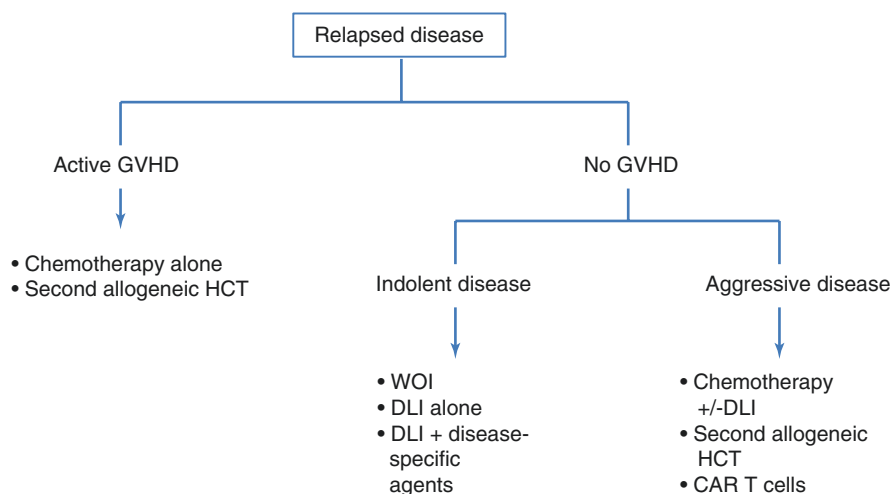
Fig. 44.1 Treatment algorithm for disease relapsing after allogeneic hematopoietic cell transplantation. *GVHD* graft-versus-host disease; *WOI* withdrawal of immune suppression; *DLI* donor lymphocyte infusion; Disease-specific agents: lenalidomide for multiple myeloma, rituximab for CD20+ lymphomas, tyrosine kinase inhibitors in BCR/abl+ leukemias; *CAR* chimeric antigen receptor

Table 44.1 Treatment options for relapsed disease following hematopoietic cell transplantation

Relapse after autologous HCT
• Second autologous HCT
• Allogeneic HCT
• Conventional chemotherapy
• CAR-T cells
• Special indications
Immunomodulatory drugs (e.g., lenalidomide) in multiple myeloma
Brentuximab vedotin in Hodgkin lymphoma
Monoclonal antibodies (e.g., rituximab) in CD20$^+$ non-Hodgkin lymphomas
Checkpoint inhibitors (e.g., nivolumab) in Hodgkin lymphoma
Relapse after allogeneic HCT
• Withdrawal of immune suppression
• Donor lymphocyte infusion alone or with
Chemotherapy
Disease specific monoclonal antibodies (e.g., rituximab in CD20$^+$ lymphomas)
Immunomodulatory drugs (e.g., lenalidomide) in multiple myeloma
Tyrosine kinase inhibitors (e.g., imatinib, nilotinib) in BCR/ABL+ leukemias
• Second allogeneic HCT (same donor vs. alternative donor)
• CAR-T cells
• Checkpoint inhibitors (e.g., ipilimumab)

HCT Hematopoietic Cell Transplantation, *CAR-T* chimeric antigen receptor T cells

3. A second autologous HCT can result in improved progression-free and possibly overall survival as compared to conventional therapy, but it is highly dependent on the time to relapse after the first transplant and subsequent disease chemosensitivity [19].

4. Allogeneic transplant has been considered to be a preferred treatment option for patients who relapse after autologous HCT. The success is highly dependent on disease chemotherapy sensitivity, donor availability, and patient performance status and comorbidities.

   a. The introduction of nonmyeloablative and reduced-intensity conditioning regimens broadened the applicability of allogeneic HCT to patients with recurrent disease after autologous HCT.

5. Chimeric antigen receptor (CAR) engineered T cells have demonstrated a high rate of sustained complete remissions in patients with B-cell lymphomas and multiple myeloma who have relapsed after autologous HCT [20].

Treatment of Relapse After Allogeneic HCT

1. Similar to the setting of autologous HCT, there is no standard approach to treating relapse after allogeneic HCT. However, treatment options include withdrawal of immune suppression, DLI, and the use of a second allogeneic HCT (Table 44.1) [10, 21].

2. Withdrawal of immune suppression should be considered as the first treatment option in patients who are actively receiving immunosuppressive agents and do not have clinical evidence of GvHD. The optimal taper schedule of immune suppression has not been established, but it is generally recommended to be performed as a taper over 2–4 weeks with close attention for the development of GvHD.

3. DLI is often considered the treatment of choice for relapse after allogeneic HCT [6, 22] (see Chap. 55).

   a. The use of DLI may be limited by procurement, especially in the setting of transplant from unrelated donors, and is not an option after cord blood transplantation.
   b. DLI is contraindicated in the setting of active GvHD.
   c. Specific recommendations cannot be made relative to starting dose, dose escalation, or frequency of DLI administration.
   d. Dosing is highly dependent on the stem cell source.

      i. Starting dose of 1×10^6 CD3$^+$ cells/kg is one recommended approach with HLA-matched sibling donors.
      ii. Starting dose of 1×10^5 CD3$^+$ cells/kg is one recommended approach with unrelated and related haploidentical donors.

   e. Cytoreductive chemotherapy (e.g., cytarabine) may be of benefit in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).
   f. Cytokine "mobilized" DLI may augment hematopoietic recovery when chemotherapy is employed.

4. Conventional and novel chemotherapy, cytokines (interferon-α, interleukin-2, GM-CSF, G-CSF), monoclonal antibodies (e.g., rituximab), and targeted therapies, alone or in combination with other modalities, have been utilized to treat relapse after allogeneic HCT.

5. Augmentation of GVT effect has been attempted by using checkpoint inhibitors such as anti-CTLA-4 monoclonal antibody ipilimumab (Yervoy®) and the anti-PDL1 antibody nivolumab (Opdivo®) [23, 24].

6. Disease-specific approaches:

   a. Chronic myeloid leukemia (CML)

      i. If relapse occurs while a patient is receiving immunosuppressive therapy, the drugs can be discontinued either as a primary therapy for relapse or in preparation for administration of DLI.
      ii. The use of tyrosine kinase inhibitors (TKI) as treatment of relapse after HCT is highly dependent on the disease state at relapse with patients relapsing in chronic phase (CP) having significantly better outcomes than those in accelerated (AP) or blast phase (BP).
      iii. Relapse in CP can be further subdivided into molecular, cytogenetic relapse, or hematological relapse.
      iv. CML is highly susceptible to the GVT effect, and therefore, highly responsive to DLI. The majority of patients with CP CML who have

molecular, cytogenetic, or hematological relapses enter sustained remissions after treatment with DLI with prognosis correlating with the sensitivity of relapse detection [25].

   v. DLI combined with chemotherapy with or without TKI may be necessary in more advanced states (AP, BC) of CML.

  vi. The use of TKI is limited to patients who were not previously resistant to these agents. Presence of GvHD at relapse complicates this approach; there is little evidence that response will be seen in this setting.

 vii. Administration of alpha interferon has also been used to control disease and to further augment GVT effects.

b. Acute myeloid leukemia (AML)

   i. Withdrawal of immunosuppression is unlikely to be of benefit except possibly in setting of a molecular or cytogenetic relapse.

  ii. DLI is considered the treatment of choice for relapsed AML after allogeneic HCT. However, responses rates to DLI vary from 0% to 60%, which inversely correlate with disease burden. Monitoring and detection of MRD may play an increasingly important role.

 iii. Data suggest that use of chemotherapy prior to DLI appears to improve results as compared to DLI alone, although, it appears to have minimal benefit in patients who relapse within 6 months after transplant [26].

  iv. Targeted agents have been successfully used to treat AML with specific mutations (e.g., sorafenib [Nexavar®] for mutated FLT3) [27].

   v. Patients with AML and MDS relapsing after allogeneic HCT have been treated with low-dose azacitidine (Vidaza®), resulting in a 20% long-term disease control rate for patients with "indolent" relapses without the need for immunosuppression withdrawal. This drug has also been investigated in combination with DLI [9].

  vi. Second allogeneic HCT can be considered in selected patients. The likelihood of benefit from a second transplant for relapsed AML is increased by achievement of CR (or a lower disease bulk) prior to the second transplant and a longer time from the first to relapse (often somewhat arbitrarily set at >6 months). Younger age is beneficial, as is the general health status of the recipient, although this is less documented in large registry-based retrospective analyses [28]. As with DLI, donor availability is a major issue for second transplants. It is unclear if a second using a donor different than the original donor leads to improved outcomes [28].

c. Acute lymphocytic leukemia (ALL)

   i. The outcomes of patients with ALL experiencing recurrent disease after allogeneic are extremely poor [29].

ii. Complete remissions are occasionally observed after withdrawal of immunosuppression and/or DLI alone, but the reported response rates are low (0–20%) and responses are generally not durable.

iii. Chemotherapy is generally administered prior to DLI. The response rates of ALL to DLI are higher in the setting of molecular or cytogenetic relapse than in patients with hematologic relapse.

iv. Second allogeneic transplants should involve careful consideration of the appropriate donor.

v. BCR/ABL-positive ALL should be considered for treatment with a TKI, which have produced long-term molecular remissions with or without DLI.

vi. The anti-CD19/anti-CD3 bispecific antibody, blinatumomab (Blincyto®), which has high clinical activity in relapsed ALL, requires functional T cells for activity and thus may have increased activity following allogeneic HCT.

vii. Clinical trials with CAR-T cells engineered against CD19 have demonstrated sustained complete remissions in patients with post-HCT relapsed ALL [30].

viii. Studies of recombinant anti-CD22 Pseudomonas-based immunotoxins have demonstrated clinical activity against ALL after allogeneic HCT.

d. Hodgkin and non-Hodgkin lymphomas

i. The clinical benefit of tapering or abrupt withdrawal of immunosuppression has been demonstrated in practically every subtype of lymphoma, but this has been most effective in indolent and mantle cell NHL.

ii. Reported responses with DLI have been broadly consistent in multiple series with an overall response rate of 43% and complete response rates of 29%. Responses have been durable in a small but significant number of patients (approximately 25%) [31].

iii. Patients with CD20⁺ B-cell NHL who relapse following allogeneic HCT may be considered for treatment with rituximab. This treatment has minimal hematologic toxicity and is usually well tolerated.

iv. Patients may be considered for treatment with checkpoint inhibitors, particularly Hodgkin lymphoma, which is inherently associated with high PD-L1 expression [32, 33]. Patients need to be closely monitored for the development of GvHD.

e. Multiple myeloma

i. Report response rates of DLI range from 40% to 67%.

ii. Immunomodulatory drugs (IMIDs) induce enhanced T-cell activation and NK-cell activation. IMIDs can be considered as single agent therapy or combination with DLI to enhance the GVT effects [9].

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Chapter 45
Safe Pain Management with Opioids in Posttransplant Patients

Melissa Weimer

Introduction

The prevalence of pain in patients who survive cancer is estimated to be as high as 40% [1]. As cancer treatments improve, it is estimated that there will be more than 500,000 HCT survivors by 2030 [2]. Many guidelines have been developed to address acute pain management in patients with cancer or advanced disease [3], but only recently was a specific guideline developed to address chronic pain in cancer survivors [4]. These new recommendations discuss the provision of long-term pain treatments using multimodal pharmacologic and nonpharmacologic therapies, reducing harms from pain treatments with use of universal precautions, improving functional gains, and limiting long-term adverse effects from treatment [4].

These guidelines and changes in pain practice and opioid management are necessary considering the current opioid overdose epidemic in the United States that has taken many people's lives since 1999. Although the total number of opioids dispensed has reduced by up to 7% since 2010 due to national efforts to reduce opioid prescribing, the United States continues to see a rise in opioid overdose deaths [5]. The current precipitous rise in opioid-related deaths appears to be driven mostly by illicit opioids such as heroin and synthetic opioids (i.e., fentanyl), but deaths related to prescribed opioids remains at unprecedented levels, particularly in the Eastern United States [6, 7].

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Pain Assessment

The chronic pain experience is multifaceted and shaped by biological, social, emotional, cognitive, environmental, and behavioral factors [8]. A thorough pain assessment can uncover these various factors, greatly inform patients' overall treatment plan, and likely lead to more effective pain outcomes. Pain assessment should occur prior to initiation of any pain treatments and should involve the following, particularly if opioids are being considered for treatment:

- Pain-focused history
- Subjective pain evaluation using evidence-based tools
- Comprehensive medical exam
- Screening for psychiatric and substance use histories
- Establishment of patient centered treatment goals
- Opioid risk evaluation

A thorough assessment will inform the biopsychosocial complexity underlying chronic pain and identify specific treatment risks early on. This assessment also provides an opportunity to show empathy, encouragement, and hope, which is many times lost amidst quantitative evaluation tools [9]. At the end of a thorough pain assessment and evaluation, a specific pain diagnosis(es) should be rendered.

1. Pain-focused history includes the following: [10]

   a. Pain intensity
   b. Pain location and radiation
   c. Onset and duration of pain
   d. Pain exacerbators and alleviators
   e. Past and current pain treatments
   f. Pain effect on patient's life functioning and quality of life
   g. Pain description

      i. Nociceptive pain is from a somatic source such as muscles or bones or a visceral source and is typically described as dull, aching, throbbing, or cramping.
      ii. Neuropathic pain is from peripheral nerves or the central nervous system and is typically described as burning, sharp, radiating, or stinging.

2. Subjective pain evaluation tools

   a. Unidimensional pain scales such as the Visual Analog Scale or the Numeric Rating Scale (0 = no pain; 10 = worst pain) [11] can easily be integrated into busy practices, but they fail to capture the complexity of the chronic pain experience and its effects on function, quality of life, emotion, and other psychosocial factors [9, 12].
   b. Multidimensional scales, such as the McGill Pain Questionnaire or the Brief Pain Inventory, are widely recognized to provide a better-rounded

understanding of complex, chronic pain; however, they are impractical for most busy medical practices.

c. The Pain, Enjoyment, and General Activity Scale (PEG) is practical for busy medical practices, has been validated in primary care, and captures clinically meaningful outcomes that can be tracked over time [13]. The PEG scale asks the following three questions:

  i. What number best describes your pain on average in the past week (0, no pain, to 10, worst pain)
  ii. What number best describes how, during the past week, pain has interfered with your enjoyment of life (0, no interference, to 10, complete interference)
  iii. What number best describes how, during the past week, pain has interfered with your general activity (0, no interference, to 10, complete interference)

3. Comprehensive medical exam: Many patients may have chronic noncancer pain in addition to cancer-related pain. It is important to differentiate the two as treatment recommendations may differ. An exhaustive review of exam guidelines is beyond the scope of this handbook, but the following should become routine in the evaluation for most patients.

a. General conditioning and body habitus observation: Patients with poor physical conditioning may have more severe pain. Overweight patients with elevated glucose levels should be further evaluated for diabetes as this can mediate pain.

b. Skin: Rashes or other characteristic signs may indicate an underlying autoimmune disorder or complications of HCT such as GvHD. Track marks or numerous scars may indicate active or past illicit substance use. Jaundice may be a complication of their cancer or indicate severe liver disease from possible alcohol use disorder.

c. Musculoskeletal: This exam should be tailored to the area of the body where the patient is experiencing pain. For instance, if a patient is having shoulder pain, a shoulder exam should be completed to differentiate from common causes of pain such as bursitis, rotator cuff tendonitis, or rotator cuff tear.

d. Neurologic

  i. Gait evaluation.
  ii. Evaluate for allodynia or hyperalgesia. A patient exhibiting allodynia (pain from a normally nonpainful stimulus) should be considered for a central pain syndrome. This sign can be determined by gently repeatedly touching a painful area to determine if pain increases. A patient with hyperalgesia may have significant neuropathy or opioid induced hyperalgesia. This sign can be determined by palpating a painful area. If the patient exhibits pain out of proportion to the palpitation, this could be a sign of hyperalgesia.

      iii. Muscle strength.
      iv. Peripheral neurologic evaluation: Vibration sensation, proprioception, and hot/cold sensation. Abnormalities of these could be signs of a neuropathy.

  e. Psychiatric: General evaluation of affect and mood, though use of evidence-based screening tools is recommended for more formal evaluation.

4. Psychiatric and substance use history screening: Several validated questionnaires are practical for use in outpatient medical practice and serve as important screening tools to evaluate common comorbidities of patients who are experiencing chronic pain.

  a. Screening for depression: Utilize the Patient Health Questionnaire-2 (PHQ-2). If this is positive, administer the PHQ-9 [14].
  b. Screening for anxiety: Utilize the Generalized Anxiety Disorder-2 (GAD-2). If positive, administer the longer GAD-7 [15].
  c. Screening for post-traumatic stress disorder (PTSD): Utilize the Primary Care PTSD Screen [16].
  d. Screening for suicidality: Utilize the Ask Suicide-Screening Questions (ASQ), four-item screen [17].
  e. Screening for substance use disorder

      i. Tobacco use: Ask about tobacco use history.
      ii. Alcohol use: The single question screener to assess for unhealthy alcohol use is "How many times in the last year have you had 5 or more drinks (for men) or 4 or more drinks (for women)?" Any response other than "never" is a positive test [18].
      iii. Drug use: The single question screener for drug use is "How many times in the past year have you used an illegal drug or used a prescription medication for non-medical reasons?" Any response other than "never" is a positive test [19].

5. Evaluation of patient centered treatment goals:

  a. It is important for the patient to identify a personal goal for pain treatment. Many patients may state that they want their pain to "go away," but this outcome may not be possible. Therefore, it is important to help the patient establish functional goals that he/she hopes to achieve.
  b. These goals can utilize the SMART framework, meaning the goal is specific, measurable, action oriented, realistic, and time sensitive [20].
      i. An example of a SMART goal for a patient who is highly debilitated and largely sedentary would be to trial chair exercises — one to two times a day or walk to the mailbox once a day.
      ii. A SMART goal for a more active patient may be to walk 0.5 miles or 1 mile — two to three times a week.
      iii. These goals can be monitored and assessed for patient progress over time.

   c. Another way to measure function over time would be to ask the patient how his/her life differs now compared to before starting a specific pain treatment. The patient will likely mention several functional changes. If the patient is not able to identify any specific functional improvements, the treatment effectiveness should be in question.

6. Assessment of prescription opioid risks

   a. Review prior medical provider records if patient is already prescribed opioids. Better yet, speak with the provider.
   b. Check the state prescription drug monitoring program.
   c. Check a baseline urine drug test with confirmation.
   d. Obtain information from collateral sources such as spouse, significant other or family if there is high concern.
   e. Utilize an evidence-based screening tool such as the opioid risk tool (ORT) that considers many of the known risk factors that appear to make patients more vulnerable to substance use disorder [21]. One should recognize that there is no gold standard for screening, and all screening tools lack rigorous testing, though the ORT has been successfully implemented in one oncologic practice in Virginia [22].

Opioid Overview

Prescription opioids are medications that work as agonists at the opioid receptors that are distributed throughout the brain, spinal cord, peripheral nerves, and digestive track. They include natural opiates (codeine and morphine), semisynthetic opiates (hydrocodone, hydromorphone, oxycodone, and oxymorphone), and synthetic opioids (methadone, meperidine, and fentanyl). Opioids work by directly effecting ascending and descending pain signals in the central nervous system and preventing activation of peripheral nociceptors. All opioids also activate the reward system in the brain. Additionally, opioids cause physiologic adaptations from chronic exposure called tolerance and physical dependence. Tolerance pertains to the need to increase the dose of the medication to produce a specific effect. Physical dependence means that when the medication is abruptly stopped or tapered rapidly, the patient will show signs and symptoms of opioid withdrawal.

Opioid efficacy for chronic noncancer pain shows mixed and modest results. When compared to placebo, opioids show statistically significant but small improvement in pain and physical functioning [23, 24]. Compared to nonopioids like NSAIDs or acetaminophen, opioids were not superior in recent literature [25]. Throughout HCT, opioids may be indicated for cancer-related pain that develops; however, after successful HCT, the efficacy of opioids for persistent noncancer-related pain is in question. As many medical providers and patients have experienced, the process to taper or stop opioids can be a very difficult one. Once physical dependence develops—which can develop as quickly as 2 weeks on a modest dose

of opioid medication—opioid taper or opioid cessation can be quite challenging because the symptoms of withdrawal are unpleasant and can persist for several months. Armed with this knowledge, medical providers may consider a more conservative approach to the use of opioids for cancer-related pain and be better equipped to help their patients in the setting of physical dependence.

1. Indications for opioid treatment [26]

   a. Pain is severe.
   b. Pain type is potentially opioid responsive.
   c. Pain impairs function.
   d. Pain negatively impacts quality of life.
   e. Inadequate benefit from nonopioid modalities.

2. Opioid pharmacology: There are two formulations of opioids—short acting/ immediate release (IR) and long acting/extended release (ER). IR formulations are typically used for patients who are opioid naïve and have episodic pain. ER formulations should be reserved for patients who have established opioid tolerance and have continuous pain.

   a. Short acting/immediate release opioids: morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, tramadol, tapentadol, fentanyl (transmucosal), and codeine (www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass).
   b. Long acting/extended release opioids: morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, tramadol, tapentadol, buprenorphine (transdermal, sublingual), fentanyl (transdermal), and methadone (www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass).
   c. Side effects

      i. Allergies are rare.
      ii. Immunosuppression: Higher rates of invasive pneumococcal disease [27]
      iii. Possible dysimmune or tumor proliferative effects: These effects have been described in the literature, but further evidence is needed to determine the clinical relevance [4].
      iv. Organ toxicity: Suppression of the hypothalamic–pituitary–gonadal axis, increased fracture risk [28].
      v. Adverse effects: Nausea, sedation, constipation, urinary retention, sweating, and pruritis.
      vi. Opioid overdose: Annual risk of overdose for patients prescribed opioids is 1.8% [29], though certain factors can increase patient's risk including [30]:

         • Use of high dose opioids (>100 morphine mg equivalents (MME)) confers a ninefold increase in fatal overdose risk.
         • Long-term opioid use (>3 months).

- Use of ER opioid formulations.
- Use of ER opioids in the initial 2 weeks of treatment.
- Combination use of opioids with benzodiazepines.
- History of opioid overdose.
- Mental Illness.
- Substance use disorder.
- Age > 65.
- Sleep disordered breathing.

  vii. Opioid misuse: Rates of misuse among patients prescribed opioids are estimated to be 21–29%, though rates may be higher in certain populations [31].
  viii. Opioid use disorder (OUD): Rates of OUD are estimated to be 8–12% and can be as high as 25% in certain populations [31]. Risk factors include the following [30]:

  - Use of high dose opioids (>100 MME).
  - Long-term opioid use (>3 months).
  - Mental Illness.
  - Substance use disorder.
  - Family history of substance use disorder.
  - Age <45.
  - Legal history.
  - History of sexual abuse.

  d. Drug Interactions

    i. CNS depressants like benzodiazepines, sedative hypnotics, tricyclic antidepressants, and monoamine oxidase (MAO) inhibitors can increase respiratory depressant effects of opioids.
    ii. Alcohol can cause certain opioids to be rapidly released by a phenomenon called "dose dumping" that can increase risk of unintentional overdose.
    iii. Diuretics can reduce efficacy of opioids.
    iv. Certain opioids like methadone have many drug interactions.
    v. For more information about drug interactions, refer to http://dailymed.nlm.nih.gov/dailymed.

3. Safe opioid doses

  a. High-dose opioids are considered >100 MME.
  b. High-dose opioids are associated with analgesic tolerance [32], hyperalgesia [33], reduced function [34], unintentional opioid overdose [29], and immunosuppression [27].
  c. Consider changes in liver and renal function when dosing opioid medications.

Universal Precautions for Prescribed Opioids

The principle of universal precautions can be used to guide monitoring processes for patients who are prescribed opioids. This principle applies because predicting opioid misuse is imprecise, care should be standardized for all patients because all are potentially at risk, and utilization is resonant with all expert guidelines on the topic [35].

Universal precautions include the following pain assessment (discussed above), opioid misuse assessment (discussed above), patient–provider agreement, regular face-to-face visits, coprescription of naloxone, routine monitoring of objective markers of opioid use including urine drug testing and prescription drug monitoring. The monitoring interval should be based on the patient's risk of opioid misuse. Lower risk patients can be monitored less frequently, and higher risk patients should be monitored more frequently. See Table 45.1 for an example of how you might structure care for patients based on their level of opioid misuse risk as determined by the Opioid Risk Tool [21] (Webster, 2006). Your approach should be consistent, but your monitoring strategy can be tailored to each patient. Implementation of these monitoring practices can be a challenge for many busy medical practices, so office staff and procedures will likely need to be developed to facilitate the process.

Refer to *SCOPE of Pain* (www.scopeofpain.org) and *My Top Care* (www.MyTOPCARE.org) for additional resources.

1. Patient–provider agreements (PPA): These documents can serve as a counseling tool to inform the patient of the risks and benefits of opioid therapy, establish clear expectations of care, establish monitoring practices, and provide a mutually agreed upon plan of care. The PPA should be reviewed face-to-face with the patient and signed by both the patient and the provider prior to the initiation (or continuation) of chronic opioids. Establishing clear expectations of care will likely reduce issues in the future [36]. PPAs function best if they are revisited from time to time per level of risk.

Table 45.1 Example monitoring approach based on opioid risk tool evaluation

Universal precaution	Low risk	Medium risk	High risk[a]
Patient-provider agreement	Once every other year	Once every other year	Yearly
Face-to-face visit for pain review	Every 3–6 months	Every 3 months	Every 1–2 months
Urine drug monitoring	1–2 times a year	2–3 times per year	3–4 times per year
Prescription drug monitoring check frequency	Every 3–6 months	Every 3 months	Every 1–2 months
Pill count	1–2 times a year	2–3 times a year	1–2 times a year
Prescription duration allowance	Every 28 days, no refill	Every 28 days, no refill	Every 7–14 days, no refill

[a]Monitoring strategy may need to be more frequent for certain patients with the highest risks

2. Face-to-face visits

    a. Low-risk patients will likely benefit from a minimum of four visits per year to address and monitor pain and opioid use [37].

    b. High-risk patients will likely benefit from 6 to 12 visits per year to address and monitor pain and opioid use [37].

    c. Document the "6 A's" at your visits [38]

        i. Analgesia.

        ii. Activities.

        iii. Adverse effects.

        iv. Aberrant behaviors.

        v. Affect.

        vi. Adherence.

        vii. Document your rationale for continuing treatment or changing treatment and directly discuss the risk versus benefit of the treatment.

3. Coprescription of intranasal naloxone: Consider the coprescription of intranasal naloxone for the following patients who are at higher risk of unintentional opioid overdose [29]:

    a. Prescription of opioids >50 mg MME

    b. Concomitant use of opioids with sedative hypnotics or benzodiazepines

    c. Sleep disordered breathing

    d. History of opioid overdose

    e. History of substance use disorder or mental illness

    f. Age >65

    Naloxone training and overdose recognition training should also be given for their significant others and/or caregivers [39].

4. Objective measure to confirm adherence and potential harms

    a. Urine drug monitoring: Provides evidence of therapeutic adherence and screens for use of illicit drugs; however, quantitative levels of substances in urine is not a validated way to confirm opioid adherence. See Table 45.1 for recommended frequency of screening. Consider performing point of care urine drug testing to avoid large costs to patients [40].

        i. Step 1: Ask the patient when he/she last took their prescribed opioid. Ask if any unexpected findings will result from the test. Anticipate the results of the test (see Table 45.2).

        ii. Step 2: If urine is collected in your office, assess the validity of the sample. Check color, temperature (90–100F), pH range 4.5–8.5, creatinine concentration >20 mg/dL.

        iii. Step 3: Evaluate the urine drug screening result and compare it to expected results. If results are appropriate, no further testing is needed.

        iv. Step 4: For unexpected results (positive or negative), perform gas chromatography/mass spectrometry urine drug confirmatory testing.

Table 45.2 Expected results of urine drug screening test[a]

Prescribed opioid	Result from screening opiate immunoassay	Result from confirmatory test
Codeine	Positive	Codeine, morphine
Fentanyl	Negative	Fentanyl
Heroin	Positive	6-Monoacetylmorphine (MAM), morphine
Hydrocodone	Positive	Hydrocodone, hydromorphone
Hydromorphone	Positive	Hydromorphone
Methadone	Negative	Methadone, methadone metabolite
Morphine	Positive	Morphine
Oxycodone	Negative	Oxycodone, oxymorphone
Oxymorphone	Negative	Oxymorphone

[a]Methadone, oxycodone, and fentanyl require their own specific urine screening tests for methadone, oxycodone, and fentanyl, respectively

    v. Step 5: Review and discuss unexpected results with the patient. Identify a toxicologist who can help you interpret these results.

  b. Prescription drug monitoring (PDMP): Most states have prescription drug monitoring programs that track controlled substances dispensed to patients in that state. Some states have mandates that the PDMP must be checked prior to the prescription of a controlled substance. Data are currently limited on the effect of PDMPs on opioid overdose deaths [41].

  c. Pill counts: Pill counts can be a very informative monitoring measure. Counts will confirm that the patient is taking their prescription as prescribed (or not as prescribed), can be a deterrent to diversion, and are most informative when done in a random, unpredictable manner (i.e., call patient mid-refill and ask him/her to present within 48 h for a pill count).

5. Collateral opioid risks: Discuss safe opioid storage practice with patients so that children or adolescents do not have access to prescribed opioids. Opioids should remain in a lock box. Educate family members about the risks of opioids as a form of prevention.

Addressing Aberrant Behaviors

Implementing monitoring processes within your practice necessitates an ability to address abnormalities when they are identified. A practice that has previously not screened all patients who are prescribed opioids will need to be prepared to discover potentially unsafe opioid use and develop action plans and referral networks as needed. This section will review commonly encountered aberrant behaviors and recommended responses. Partnership with an addiction medicine provider or behavioral health specialist will be helpful, if not essential, to manage the most challenging cases.

The most important component of addressing these concerning behaviors is the provider's frame of judgement. When prescribing opioids for chronic pain in HCT survivors, it is important to maintain a risk versus benefit point of view. In this way the judgement is of the opioid treatment rather than the patient. Ask "Does this opioid therapy benefit more than harm the patient?" Avoid judgmental questions such as "Is the patient good or bad?", "Does the patient deserve opioids?", or "Should the patient be punished or rewarded?" [20]. See www.MyTOPCARE.org for more information on this topic.

Additionally, not all worrisome opioid-taking practices signify problematic use [26]. It is necessary to speak with the patient and/or see the patient in a visit along with monitoring tests to work through the differential diagnosis of pain relief seeking, drug seeking, or pain relief and drug seeking. Pain relief seeking may be secondary to inadequate analgesia due to disease progression, opioid tolerance, opioid induced hyperalgesia, or poorly opioid-responsive pain. Drug seeking may be secondary to opioid use disorder, use of medication for symptoms other than pain (i.e., psychiatric cause), or diversion. Pain relief and drug seeking can cooccur. An example would be a patient who takes some of his/her medication for the purpose it was intended but also diverts a portion of it or occasionally takes more than prescribed when he/she feels more stressed and anxious.

Management of aberrant behaviors:

1. Early refill requests: These requests may occur frequently in your practice, particularly if you do not have a systematic way of addressing refill requests. When addressing this issue with a patient, it is important to reeducate him/her on the goals and expectations of treatment as well as reassessing risks and benefits of treatment. Attempt to determine if the patient has taken more medication than prescribed or used the opioid for a purpose other than what is intended, recognizing this may be difficult to ascertain.

   a. See patient for an office visit; RN visit also acceptable.
   b. Reeducate patient about the existing PPA.
   c. Perform a urine drug test and pill count.
   d. Check PDMP.
   e. Obtain collateral information from trusted source, if possible.
   f. Document that benefit outweighs risk based on the above evaluation, if that is the case. If risks outweigh benefit, consider taper of the opioid.

      i. If inadequate analgesia or opioid tolerance is suspected, consider an increase in the opioid dose or opioid rotation as a trial.
      ii. If opioid induced hyperalgesia or opioid nonresponsive pain is suspected, consider opioid taper.

   g. Transition patient to a 28-day refill pattern so that prescriptions are always due on the same day and never fall on the weekend.
   h. Prescribe naloxone, if not already done, as overuse of patient's opioid places him/her at increased risk of unintended opioid overdose.

2. Lost or stolen prescription

   a. See patient for an office visit; RN visit also acceptable.
   b. Provide reeducation on safe storage of opioids. Ensure patient is using a lock box for unused medication and only carrying a small supply with him/her day-to-day.
   c. Perform a urine drug test.
   d. Check PDMP.
   e. Obtain collateral information from trusted source, if possible.
   f. Prescribe naloxone, if not already done.
   g. Consider asking the patient to file a police report, but this is not mandatory.
   h. Document that benefit outweighs risk based on the above evaluation, if that is the case. If risks outweigh benefit, consider taper of the opioid.
   i. Consider seeing the patient more often, particularly if there is a pattern of lost or stolen medications more than once.

3. Missing provider appointments

   a. Reeducate on the PPA and reestablish expectations.
   b. Check PDMP and consider urine drug test.
   c. For first occurrence, reschedule the appointment.
   d. For second occurrence, prescribe only a short prescription until another appointment.
   e. If this behavior continues, hold prescription until patient is seen by provider.
   f. Consider opioid taper as safe monitoring of the prescription is not possible.
   g. If there are signs of dangerous use of substances, consider stopping opioids immediately and refer or initiate treatment immediately.

4. Failure to attend other recommended treatments like physical therapy, specialist appointments.

   a. Inquire into barriers to attendance and attempt to reduce barriers.
   b. Reeducate on PPA and reestablish expectations.
   c. Check prescription drug monitoring program and consider urine drug test.

5. Abnormal urine drug test results

   a. Medication prescribed is not present: concern for lack of opioid adherence

      i. Ensure result is abnormal with confirmatory testing; obtain expert advice if needed.
      ii. Ask patient to come for a face-to-face visit to discuss.
      iii. Review when patient last took his or her medication prior to the test.
      iv. Assess for harms including opioid use disorder and diversion. If it is not clear, consider increasing monitoring strategies including more frequent urine drug testing and random pill counts.

   b. Opioid medication (or other prescription medication) that is not prescribed
      is present

      i. Ensure the result is abnormal with confirmatory testing; obtain expert
         advice if needed.
      ii. Check PDMP.
      iii. Ask patient to come for a face-to-face visit to discuss and inquire about
         the result.
      iv. Assess for harms by reviewing differential diagnoses.

         • If diagnosis is not clear, consider increasing monitoring strategies
           including more frequent urine drug testing and random pill counts.
         • If opioid use disorder is suspected, stop or taper opioids and refer for
           opioid use disorder treatment.
         • If other substance use is suspected, weigh risks versus benefits for
           ongoing opioid treatment and refer for treatment of the substance use
           disorder.

      v. Provide education around risks of unintentional overdose.

   c. Presence of an unexpected substance

      i. Marijuana

         • Re-educate or discuss programmatic stance on the use of marijuana
           with prescribed opioids.
         • Consider the safety of the patient's ongoing marijuana use with pre-
           scribed opioids.
         • If risks of ongoing opioid prescription outweigh benefits, consider
           opioid taper.

      ii. Cocaine, heroin, methamphetamine, or other illicit substance

         • Ensure the result is accurate with confirmatory testing; obtain expert
           advice if needed.
         • Check PDMP.
         • Ask patient to come for a face-to-face visit to discuss and inquire
           about the result, assess for a substance use disorder using Diagnostic
           and Statistical Manual of Mental Disorders (DSM)-5 criteria [42].
         • Increase monitoring strategies including more frequent urine drug
           testing and random pill counts.
         • If opioid use disorder is suspected, stop or taper opioids and refer for
           opioid use disorder treatment.
         • If other substance use is suspected, weigh the risks versus benefits for
           ongoing opioid treatment, increase monitoring strategies, and refer
           for treatment of the substance use disorder.
         • Provide education around risks of unintentional overdose and provide
           naloxone prescription.

     iii. Alcohol use

- Ask the patient to come for a face-to-face visit to discuss and inquire about the result.
- Assess for risky alcohol use and alcohol use disorder using the Alcohol Use Disorders Identification Test-C (AUDIT-C) [43] or DSM -5 criteria [42].
- If there is no pattern of unhealthy alcohol use, provide education and recommend alcohol abstinence.
- If there is concern for at-risk drinking (but not alcohol use disorder), provide education, recommend abstinence, and increase monitoring measures

  - If alcohol use continues, consider taper of opioids.

- If alcohol use disorder is suspected but not confirmed, provide education, recommend abstinence, increase monitoring strategies including urine drug testing and pill counts.
- If alcohol use disorder is confirmed, stop or taper opioids and refer for alcohol use disorder treatment with alcohol withdrawal treatment first, if necessary.
- For all the above, provide education around risks of unintentional overdose with alcohol use and prescribe naloxone.

6. Abnormal pill count

   a. Check PDMP.
   b. Inquire about result with patient.
   c. Obtain urine drug test.
   d. If diversion is confirmed, stop opioids. Recognize it is difficult to completely confirm diversion.
   e. If diversion is suspected, increase monitoring strategies including more frequent urine drug testing and random pill counts.

Opioid Tapering

Opioid tapering can be one of the most challenging practices in medicine, particularly for survivors of cancer who have already gone through much suffering. However, the development of severe physical dependence or opioid use disorder can arguably cause similar, if not worse, suffering [44]. Helping patients taper off of opioids in a humane manner when indicated is therefore an essential component of good medical and cancer care. In this section, three cases are reviewed using the opioid tapering framework called "BRAVO" developed by Anna Lembke, MD at Stanford and provided on the Oregon Pain Group website [45] (www.oregonpain-guidance.org) and the Stanford continuing medical education (CME) course (see section "Patient Education" for website) (Figs. 45.1 and 45.2).

B	Broaching the Subject	- Schedule enough time with your patient to dicsuss this difficult topic
		- Anticipate the patients strong emotional reaction
		- Identify the feelings, normalize those feelings and express empathy with the concerns they may have
R	Risk-Benefit Calculator	- When assessing benefits, weigh a patient's pain relief against their functionality
		- Involve family members for more objective views on a patient's opioid use
		- Track common risks such as tolerance and opioid induced hyeralgesia
		- Include all of these factors with discussing reasons for tapering off of opioids
A	Addiction Happens	- Addiction is defined by the Three C's: Compulsive Use, Continued use despite consequences, and use that is out of control
		- Dependence happens when the body relies on a drug to functional normally
		- Dependence and Addiction are not equivalent
V	Velocity Matters – and So Does Validation	- Go slowly, take the necessary time to ease your patients down on their doses
		- Let the patient be involved when deciding how much to decrease and at what time
		- It is okay to take breaks in lowering the dosage
		- Never go backwards; your patient's tolerance will increase and progress will be lost
O	Other Strategies for Coping with Pain	Teach patients these 3 Dialectical Behavior Therapy (DBT) practices:
		- STOP: Stop, Take a breath, Observe internal and external experiences, and Proceed mindfully
		- Opposite Action Skills: acting opposite to a negative emotional urge in the service of pursuing values or goals
		- Radical Accceptance: accepting reality as it is and not as we wish it would be

Fig. 45.1 BRAVO framework for opioid tapering. (Used with permission from Anna Lembke, MD and Oregon Pain Group)

Throughout the cases, general principles of tapering are highlighted including the following:

1. Calculation of MME to determine total daily dose of opioid. Refer to the Center for Disease Control (CDC) Opioid Mobile App or website for more information (https://www.cdc.gov/drugoverdose/prescribing/app.html).
2. Evaluation of risk versus benefit and patient time on the opioid to determine how quickly the taper proceeds. There are no validated protocols for opioid taper.

   a. In general terms, a reduction of 5–10% of the total MME is recommended for each increment, but each taper plan should be individualized to the patient and his/her situation
   b. For some patients, each 5–10% dose reduction should occur every 1–2 weeks
   c. For some patients, particularly those on opioids for longer and higher dose, each 5–10% dose reduction may need to occur every 1–3 months as long as this remains a safe interval.
   d. Patient functional status, mental health, and tolerance of the taper should be closely monitored as opioid taper can be extremely challenging and destabilizing for some patients

3. Involve the patient in the design of the taper, but ultimately the decision to taper is based on a risk versus benefit determination made by the prescriber.
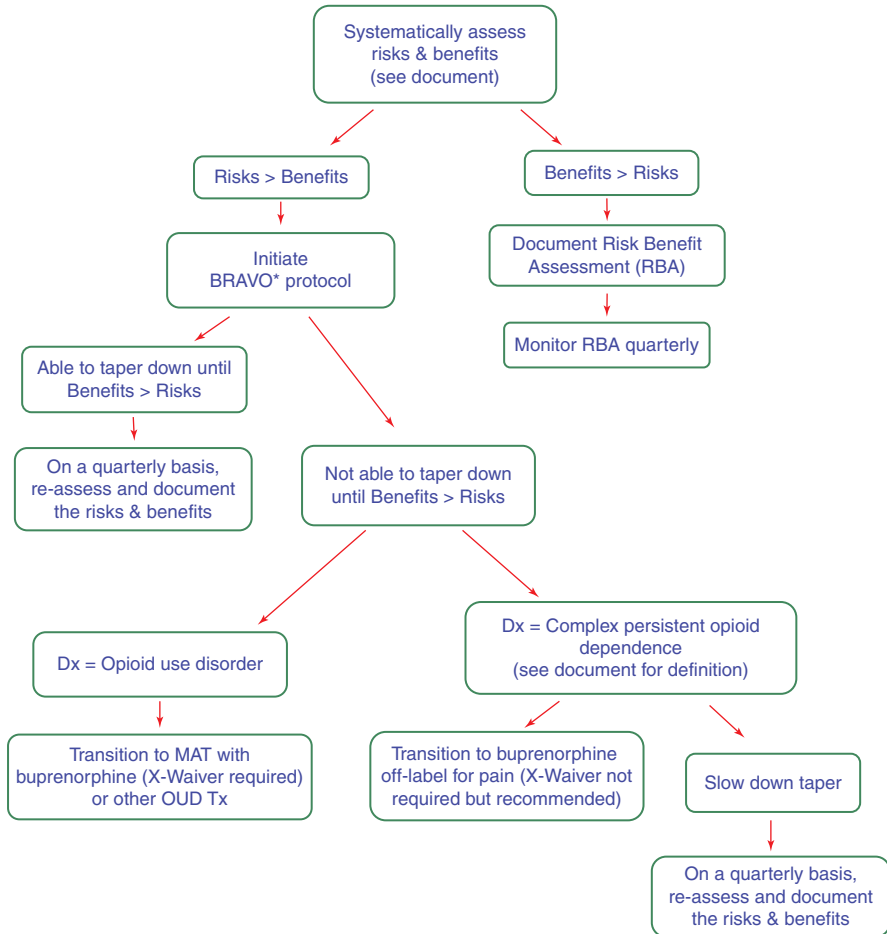
Fig. 45.2 Opioid tapering framework. (Used with permission from Anna Lembke, MD and Oregon Pain Group)

4. Patients may feel worse from the symptoms of opioid withdrawal before they feel better. Recognizing and validating this potential consequence is important.

   a. Symptoms of opioid withdrawal can include restlessness and restless leg, increased pain, anxiety, muscle aches, insomnia, sweating, yawning, rhinitis, abdominal cramping, diarrhea, nausea, and vomiting.

5. Adjuvant medications such as the following may help ease opioid withdrawal symptoms if they occur.

   a. Anxiety: Hydroxyzine 25 mg oral every 4–6 h as needed.
   b. Anxiety and increased sympathetic activity: Clonidine 0.1 mg po three times a day as needed.
   c. Pain: NSAIDs and/or acetaminophen 500 mg oral every 4–6 h as needed.

    d. Fluid loss: Liberal fluid intake.

    e. Diarrhea: Loperamide 4 mg po x 1, then 2 mg po for each loose stool (max 16 mg/d).

    f. Insomnia: Melatonin 3 mg oral at bedtime as needed or trazodone 50 mg oral at bedtime as needed.

    g. Nausea: Ondansetron 4 mg po twice daily as needed.

    h. Muscle cramps: Hot bath, acupuncture.

6. If opioid use disorder is suspected, refer for treatment with an evidence-based treatment such as buprenorphine or methadone.

7. There are times when risks outweigh benefit and opioid taper is not indicated. Those include:

    a. Evidence of diversion.

    b. Patient with an active opioid use disorder who is not willing to seek treatment referral.

Case 1 A 28-year-old cancer survivor with a history of irritable bowel syndrome (IBS) who has been prescribed oxycodone 20 mg every 3 h as needed for the last 5 years while undergoing cancer treatments is presented. She has not shown concerning opioid use and has followed her opioid regimen as prescribed. She has, however, developed severe constipation from the treatment despite using multiple different agents to treat her constipation. She was recently admitted to the hospital for abdominal pain and vomiting possibly related to opioid withdrawal when she was not able to keep down her oxycodone for 48 h from her illness. Assessment indicates risks of treatment outweigh the benefits as she is no longer having the severe pain for which the medication was initially prescribed, and she has developed severe side effects.

1. Discuss your concern with the patient and she agrees to an opioid taper.

2. Continue efforts to improve her constipation and consider trial of a selective serotonin reuptake inhibitor (SSRI) for her history of IBS.

3. Together with the patient, discuss a taper as follows with the option to pause the taper if she struggles with increased pain or opioid withdrawal.

    a. 2–4 weeks: Oxycodone 20 mg every 4 h as needed (total dose 120 mg, total MED 240 mg).

    b. 2–4 weeks: Oxycodone 15 mg every 4 h as needed (total dose 90 mg, total MED 180 mg).

    c. Continue to decrease dosing by oxycodone 7.5 mg (half tablet) every 1–2 weeks until tapered completely off; consider slowing the taper if she develops uncomfortable opioid withdrawal symptoms.

Case 2 A 45-year-old cancer survivor with a history of depression, anxiety, fibromyalgia, and diabetes is presented. Her cancer has remained in remission for the last 2 years, but she remains on an opioid dose of 250 MME for widespread pain. She was recently hospitalized for unintentional opioid overdose in the setting of severe

hyperglycemia and acute kidney injury. She was placed on an opioid taper by the inpatient hospital team during her stay that quickly reduced her total dose to 100 MME. She is having severe pain and opioid withdrawal symptoms from this dose reduction and would like to resume her previous opioid regimen.

1. After assessment, it is felt resuming her previous opioid dose is not safe given her history of overdose and her high prescribed dose.
2. Discuss concerns with the patient, and she agrees to remain on the opioid taper but would like to slow down the taper. Adjuvant medications can be added to reduce her symptoms.
3. Ensure that she has naloxone at home.
4. Reassure her that if she does not do well with this regimen, alternate treatment with buprenorphine for treatment of complex pain will be considered.

Case 3 A 45-year-old cancer survivor with a history of depression and anxiety is presented. Her cancer has been in remission for the last 5 years, but she remains on an opioid dose of 300 MME. She has been intolerant of any attempt at opioid taper or opioid rotation. Two recent urine drug tests contained methadone even though she is prescribed morphine; this has caused increased concern. A recent pill count was also abnormal, and she has missed many recent clinic appointments. She was invited to come for a clinic appointment, and she admits that she has lost control of her use of the prescribed opioids, takes her morphine even when she is not having pain, and takes a friend's methadone most months because she runs out of her prescription too early.

1. After assessment, she is diagnosed with an opioid use disorder and referred immediately for induction on buprenorphine. She is given information about a methadone treatment program if she does not keep that appointment.
2. Naloxone is prescribed and health concerns are discussed.
3. She asks for a short refill of her opioid prescription, but is declined due to determination that the risks outweigh the benefits.
4. Adjuvant medications to treat an opioid withdrawal that may occur during the transition to buprenorphine are offered.

Opioid Use Disorder

Opioid use disorder (OUD) is a complex disorder of the brain reward centers that is one of the most severe complications of long-term prescription opioid use. It is diagnosed with the formal DSM-5 criteria [43], but in clinical practice is recognized by a pattern of behaviors known as the "4 C's": loss of control, compulsive use, continued use despite harm, and craving [46]. Opioid withdrawal from physical dependence and opioid tolerance are part of the DSM-5 criteria, but they do not define OUD as they are expected side effects of prescribed opioids. When making a

diagnosis of OUD, one would not include those criteria unless the patient was prescribed opioids and not taking the opioids as prescribed. In other words, having physical dependence from long-term opioids is not equivalent with having an OUD; a patient can have physical opioid dependence and not have OUD.

In practice, signs of OUD could include any of the following: taking more medication than prescribed, running out of medication early on a regular basis, frequently using other opioids or other substances due to running out of prescribed opioids early, taking the medication for a purpose other than why it was prescribed, spending a great deal of time trying to procure the medication, going to various medical providers including emergency departments and dentists to maintain their prescription, personal chaos or problems at work, school or with their family due to substance use, difficult to treat pain and poor adherence to recommended treatments other than opioids.

When discussing OUD, it is important to show concern, give timely feedback, remember patients can experience both pain and OUD, recognize the benefits of prescribed opioids no longer outweigh the risks, and refer for treatment [47]. It is not safe to continue prescribed opioids for a patient with active, untreated OUD. Medications for the treatment of opioid use disorder are highly effective and are the standard of care for patients with OUD. All patients who are diagnosed should be referred and offered treatment. For more information on OUD and its treatments, please refer to the Substance Abuse and Mental Health Services Administration Treatment Improvement Protocol 63 (SAMHSA TIP 63) or the Providers Clinical Support System (PCSS).

1. Medication treatment: There are three Food and Drug Administration (FDA) approved medications for the treatment of OUD:

   a. Methadone

      i. Can only be prescribed through an opioid treatment program

   b. Buprenorphine

      i. Can be prescribed outside of an opioid treatment program with valid Drug Enforcement Administration-X (DEA-X) waiver training
      ii. Can be prescribed in an opioid treatment program

   c. Naltrexone

      i. Not a controlled substance and can be prescribed in typical ambulatory care

2. Purpose of medication

   a. Treat opioid withdrawal
   b. Block reinforcing effects of opioids
   c. Alleviate drug cravings
   d. Normalize changes that have occurred in the brain

3. Outcomes of treatment: all three medications have shown

    a. Reduced mortality
    b. Reduced morbidity
    c. Reduce HIV and HCV risk
    d. Increased treatment retention
    e. Reduced criminality

Patient Education

1. Stay Safe Oregon, https://staysafeoregon.com/: A free, online resource for patients that discusses risks of opioids, pain education, real patient stories and videos, and safe disposal practices.
2. FibroGuide, https://fibroguide.med.umich.edu/fibroguide.html: A free University of Michigan resource for the management of fibromyalgia or centralized pain syndrome.
3. Self-management handbooks

    a. *Manage Pain Before it Manages You* by Margaret Caudill
    b. *The Pain Survival Guide: How to Reclaim Your Life* by Dennis Turk

4. Centers of Disease Control and Prevention Opioid overdose: Information for patients.
5. Substance Abuse and Mental Health Services Administration: SAMHSA is a governmental agency that leads public health efforts to advance behavioral health. Treatment providers can be searched from their website.

Additional Provider Resources

1. My Top Care (www.mytopcare.com): A free, online resources for providers and patients from Boston Medical Center to reduce risk from long-term prescription opioids for chronic pain
2. Boston University School of Medicine, SCOPE of Pain (www.scopeofpain.org): A free, online resource for medical providers that reviews best practice around safe and competent opioid prescribing for chronic pain. This training site has additional resources for starting monitoring practices in medical offices.
3. Providers Clinical Support System (www.pcssnow.org): A free, online resource for providers that offers evidence-based training and resources on chronic pain treatment and treatment of opioid use disorder.
4. Oregon Pain Guidance (www.oregonpainguidance.org): A free, online resource for providers and patients on various topics related to opioids and chronic pain. Additionally, has resources on implementing safe prescribing into medical practice.

5. Stanford CME system: How to Taper Patients Off of Chronic Opioid Therapy (https://cme.class.stanford.edu/courses/course-v1:CME+045+2017/info)
6. Prescribe to prevent (www.prescribetoprevent.org): Online resource with information about how to add naloxone to your practice

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Chapter 46
Complementary Medicine: Acupuncture

Angela Rademacher

Introduction

Acupuncture is a form of traditional Chinese medicine that has been practiced for over 2500 years. Its therapeutic use has been well utilized in the United States since the 1970s with increased acceptance after the National Institutes of Health 1997 Consensus Development Conference Statement on Acupuncture which concluded, "promising results have emerged showing efficacy of acupuncture in adult postoperative and chemotherapy nausea and vomiting and in postoperative dental pain" [1]. Since this time, advances in scientific research have shown acupuncture to have considerable benefits for symptom support and have accelerated its use in a variety of settings including oncology.

Integrative Oncology

The use of acupuncture in oncology has grown to be widely used with estimates between 1.7% and 31% of all patients [2–4]. As medicine continues to strive for comprehensive care, many institutions have begun to incorporate integrative medicine into interdisciplinary care models. Integrative oncology utilizes evidence-based mind–body and whole systems medicine alongside traditional medical care to support the well-being and overall health status of the patient. Oncology acupuncture, incorporated into many cancer center programs as adjunct care, is considered safe and effective. The collaborative effort in providing patients with diverse services supports patients with complex issues, and yields empowerment and a sense of proactivity by the patient while easing symptom burden throughout oncology care.

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Use of Acupuncture: Symptom Support in Cancer Care and Hematopoietic Cell Transplantation (HCT)

1. Chemotherapy-induced peripheral neuropathy (CIPN).

   a. Multiple chemotherapeutic agents contribute to CIPN in the HCT population including plant alkaloids (vincristine), immunomodulating drugs (lenalidomide), and proteasome inhibitors (bortezomib). Additionally, taxanes and platins utilized in solid tumor therapy may also contribute to CIPN [5].

   b. Symptoms [6, 7]:

      i. Motor weakness
      ii. Sensory and proprioception loss often with a stocking and glove distribution
      iii. Balance issues
      iv. Difficulties with walking and driving

   c. Few treatments are available for management of motor and sensory neuropathy and neuralgia with varying degrees of success in improving symptoms, often with undesirable side effects.

   d. Pharmacologic agents utilized to mitigate CIPN include [8–12]:

      i. Gabapentin (Neurontin®) or pregabalin (Lyrica®)
      ii. Tricyclic antidepressants
      iii. Serotonin and norepinephrine reuptake inhibitors
      iv. Carbamazepine
      v. Opioid-type analgesics

   e. Acupuncture has emerged as a potentially effective treatment for improving CIPN though studies are limited to validate its efficacy [13–18].

      i. Published evidence include mainly case studies, random controlled trials (RCTs), and retrospective analysis.
      ii. Size of studies ranging from approximately 5–80 individuals.
      iii. Screening tools utilized commonly include:

         • European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30)
         • Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy (QLQ-CIPN20)
         • Health Related Quality of Life (HRQOL)
         • Visual Analog Scale (VAS)
         • Functional Assessment of Cancer Treatment Gynecologic Oncology Group—Neurotoxicity (FACT/GOG-Ntx)
         • Patient Neurotoxicity Questionnaire (PNQ)
         • Nerve conduction studies

      iv. Commonly used acupuncture points: Ba Feng, Ba Xie, LV3, PC6, ST36, LI11, LV3, CV6, GB34, SP6 and LI4 [13, 15, 18–20].

    v. Improvements have been observed in sensation, gait, balance, pain control, and nerve conduction [17, 20].

    vi. Studies exploring CIPN caused by common chemotherapeutic agents administered to HCT recipients show improvements in numbness and tingling in hands and feet, cold sensitivity, unpleasant feeling and function [18, 21, 22].

    vii. One RCT by Rostock et al. found no significant difference using electroacupuncture (EA) compared with hydroelectric bath, daily vitamin B, or daily placebo capsules [23]. Additionally a pilot by Bao et al. found no improvement in nerve conduction with use of acupuncture in bortezomib (Velcade®)-induced peripheral neuropathy [22].

    viii. Further RCTs with larger sample sizes are needed to confirm the role of acupuncture in the management of CIPN.

2. Chemotherapy-induced nausea and vomiting (CINV):

  a. Despite numerous available antiemetics, CINV may be refractory in some patients and undesirable side effects such as extrapyramidal symptoms, [24] constipation, diarrhea and anorexia [25] may result from use of these medications.

  b. Acupuncture has become an additional non-pharmacologic method to manage CINV [26, 27].

    i. Significant number of RCTs have been completed although notable most with high risk of bias [28].

    ii. Study sizes ranging approximately 10–747 individuals.

    iii. Screening tools utilized commonly include:

- Nausea intensity rating numeric score
- Total emesis episodes
- VAS score
- Rhodes Index for Nausea, Vomiting, and Retching (RINVR)

    iv. Commonly used acupuncture points: PC6, ST36, CV12.

    v. Both manual acupuncture (MA) and EA have shown to be beneficial for acute CINV though not for delayed nausea and vomiting [29].

- One early RCT with low bias by Shen et al. concluded adjuvant EA was more effective at decreasing the number of emesis episodes compared to minimal needling and antiemetic pharmacotherapy alone in high-dose, multiple-day, multiple-drug myeloablative chemotherapy in high-risk breast cancer patients [26].
- A review by Wu et al. found therapeutic evidence for acupuncture support in CINV [30].

    vi. Pharmacologic antiemetics and corticosteroids were provided per standard protocol for chemotherapeutic regimen in conjunction with MA or EA in most studies [29, 31].

3. Cancer-Related Pain.

   a. Pain is one of the most commonly experienced and distressing symptoms in cancer patients. A review by van den Beuken-van Everdingen et al., pooled data from 52 articles showed that pain was very common in patients with cancer: 33% in cured patients, 59% in patients receiving anti-cancer treatment, and 64% in patients with metastatic or advanced-stage disease [32].

   b. Mechanisms vary considerably but may include tumor expansion in organs or bone and treatment-related from chemotherapy, hormonal therapy, radiation therapy, HCT, or surgical intervention [33, 34].

   c. Musculoskeletal symptoms including arthralgias and myalgias may be long-term effects of cancer therapies, often seen with aromatase inhibitor use in breast cancer patients [35] and from various chemotherapeutic agents [36–39]. Alkylating agents and total body irradiation (TBI), used regularly in the HCT setting, have been associated with increased prevalence of musculoskeletal complications [40, 41] and are often reported in long-term survivors [42, 43].

   d. Acupuncture has been used in treating cancer-related pain and is recommended by the American Society of Clinical Oncology (ASCO) for chronic pain in adult cancer survivors.

      i. Hormone therapy-related: Treatment with acupuncture for aromatase inhibitor-related arthralgias has shown modest improvement in pain levels in early stage postmenopausal breast cancer patients [44]. A meta-analysis by Chen et al. that included five RCTs with 181 patients concluded that acupuncture significantly reduced pain and worst pain at 6–8 weeks [45].

      ii. Chemotherapy-related: Zhou et al. observed that patients with gastric cancer-related abdominal pain ($n = 56$) who received acupuncture had a decrease in the number of diarrhea and vomiting episodes and had shorter bouts of nausea and abdominal pain [34, 46].

      iii. Radiation therapy (RT)-related: A study including women with cervical cancer and endometrial cancer experiencing RT-related cystitis ($n = 42$) experienced shorter symptomatic duration of symptoms with use of acupuncture compared to standard supportive care [47]. These patients also showed significant relief and shorter symptomatic duration of proctitis ($n = 50$) than patients receiving standard supportive care [46, 47]. However, another study found no evidence that chemotherapy- and radiation therapy-induced pain had any significant treatment effect from acupuncture [48].

      iv. Surgical-related pain: In a review of RCTs studying the effects of acupuncture-point stimulation (APS) for post-op pain control, Liu et al. concluded there was insufficient evidence to conclude that APS is an effective method for controlling postoperative pain in surgery patients, although this intervention may reduce patients' analgesic requirement with no significant adverse effects [49]. A review by Wu et al. similarly concluded acupuncture reduced opioid use and post op pain on day 1 after surgery [46, 50].

v. Malignancy-related pain: Chen et al. observed improvement in pancreatic cancer pain with use of EA compared to sham acupuncture [51]. Additional studies have found EA to be as effective as fentanyl transdermal patch in hepatocellular carcinoma pain [52]. A systematic review and meta-analysis by Chui et al. concluded acupuncture is effective in treating malignancy-related pain [48].

vi. Compared with the drug therapy alone, acupuncture plus drug therapy resulted in increased pain remission rate, shorter onset time to pain relief, longer pain-free duration, and better quality of life (QOL) without serious adverse effects [53].

vii. Screening tools utilized commonly include:

- VAS
- Numeric Rating Scale (NRS)
- Brief Pain Inventory—Worst Pain (BPI-WP)

viii. Point selection varied according to pain location and cause.

4. Cancer-related fatigue (CRF).

a. Fatigue is one of the most common and debilitating symptoms experienced by HCT patients [54]. Weakness, lack of concentration, and mental and physical fatigue despite adequate rest are distinctive elements of CRF (see also Chap. 47) [55, 56].

b. There are numerous causes of CRF including treatment- and disease-related factors, neurobehavioral factors, chronic pain, and decreased physical activity. Graft versus host disease (GvHD) in the HCT population may also give rise to fatigue [57].

c. Studies show positive benefits of acupuncture for improvement of CRF.

i. Numerous RCTs have been completed although several studies are of poor quality related to lack of control subjects, inadequate patient numbers leading to conclusions that were underpowered, high risk of bias, and flaws in methodology.

ii. Study sizes range approximately 12–302.

iii. Screening tools utilized commonly include:

- Brief Fatigue Inventory (BFI)
- Multidimensional Fatigue Inventory (MFI)
- Edmonton Symptom Analysis Scale (ESAS)
- Functional Analysis of Chronic Illness Therapy—Fatigue (FACIT-F)

iv. Commonly used acupuncture points: SP6, LI4, ST36, KI3, RN4, RN6 [58].

v. A meta-analysis including 689 subjects from seven RCTs conducted by Zeng et al. showed improvement of fatigue with use of acupuncture though duration of follow-up was only up to 10 weeks [59]. A 2018 review by Zhang et al. (n = 1327, 10 RCT) concluded acupuncture is effective for CRF management [58].

5. Depression (see also Chap. 41).

   a. Depression amongst HCT patients is common with estimates of moderate to severe depression in the first-year post-transplant ranging from 26% to 36% [60]. The presence of chronic pain and severity of chronic GvHD are risk factors for depression [61]. Depression may become chronic [62, 63] and is present in 30% of patients 5 years post-transplant [64].

   b. Patient-reported outcomes and QOL are now considered significant secondary endpoints in HCT studies. Psychological support and QOL (including fatigue/insomnia/anxiety) have been shown to be improved with acupuncture [65].

      i. Multiple RCTs have been performed with varying risk of bias. Issues include lack of blinding of participants and personnel. Some issues lie in reporting methods with recommendations to improve by using Consolidated Standard of Reporting Trials (CONSORT) and Standards for Reporting Interventions and Clinical Trials of Acupuncture (STRICTA) guidelines.

      ii. Study sizes ranging approximately 44–187 participants.

      iii. Screening tools utilized commonly include:

         • Hospital Anxiety and Depression Scale (HADS)
         • Hamilton Rating Scale for Depression (HAMD-17)
         • Personal Health Questionnaire Depression Scale (PHQ-8)
         • Toronto Extremity Salvage Score (TESS)
         • Severity of Dependence Scale (SDS)

      iv. Commonly used acupuncture points: GV20, EXHN3, PC6, LR3, LI4, HT7, EXHN1, GV14, SP6, GB20, ST40, and shenmen. Electrotherapy was often employed.

      v. A review by Chan et al. found acupuncture combined with antidepressant medication is effective, has an early onset of action, and has greater therapeutic efficacy than selective serotonin reuptake inhibitor (SSRI) therapy alone in adults with a diagnosed depressive disorder [66].

      vi. Dong B et al. concluded that acupuncture was more effective in treating depression-related insomnia compared with Western medicine and in combination had a better effect on sleep quality and degree of depression than Western medicine alone [67].

      vii. Several studies have found acupuncture improves cancer-related depression and QOL [65, 68–70]. In contrast, Tao et al. [71] found acupuncture did not improve symptoms of depression. This may be due to heterogeneity of outcomes reported and variance in depression symptoms depending on cancer type.

      viii. More high-quality RCTs are needed to evaluate the clinical benefit and long-term effectiveness of acupuncture in the treatment of depression [66], specifically in the oncology setting.

Side Effects and Contraindications

1. Adverse events are rare, reported at 0.05 per 10,000 treatments [72]. Of the events reported, infection is the most common followed by internal organ or tissue injury [73].
2. Side effects may include but are not limited to:

   a. Bruising (3.2%)
   b. Minor bleeding (1.4%)
   c. Localized skin irritation
   d. Orthostatic problems (0.5%)
   e. Feeling of discomfort at insertion site (3.3%) [74]

3. Contraindications to acupuncture use include:

   a. Altered mental status
   b. Thrombocytopenia (recommendations range from <25,000/μL to 50,000/μL)
   c. Neutropenia (absolute neutrophil count <500/μL)
   d. Needling at or into a wound, surgical site, or infection

Conclusion

Acupuncture as an adjunct to conventional oncology treatment has been shown to be of benefit for multiple symptoms experienced by patients throughout the continuum of care. As one looks to ease the side effects of cancer therapies, additional attention should be given to the entirety of the patient experience. Acupuncture, in conjunction with standard supportive care measures, provides an additional modality of care to be utilized for personalized and effective support.

The body of research in oncology acupuncture is significant; yet, additional evidence is needed. Larger and adequately powered trials will help to substantiate current knowledge. There are few studies using acupuncture in HCT patients; therefore much of the information must be extrapolated from studies performed in a variety of cancer types. Specific acupuncture research in HCT recipients is warranted to address the unique experiences of this population.

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Chapter 47
Complementary Medicine: Medications and Supplements

Aaron Pham

Introduction

Complementary medications such as herbal (botanicals, including cannabis), dietary or nutritional supplements, vitamins, and minerals are popular with patients due to the perception that these agents are *natural* and therefore "safe" and promote healthy living [1, 2]. With limited or a complete lack of evidence for efficacy of many complementary medicines, consumption of these exogenous substances may not only be non-beneficial but also a risk to patient safety if not evaluated by a medical professional [1, 2]. Best practice requires healthcare providers to explicitly ask patients during medication reviews about any over-the-counter (OTC) medications, herbals, dietary, or vitamin supplements. This chapter provides an overview of complementary medicine issues in hematopoietic cell transplantation (HCT) patients.

Generally, patients undergoing HCT, particularly those undergoing allogeneic procedures, are advised to avoid complementary medications at crucial time periods:

- A minimum of one week before conditioning therapy
- During engraftment
- While receiving post-HCT chemotherapy
- During the first 100 days post-HCT

Supplements should only be restarted post-HCT barring any contraindications (e.g., presence of active graft-versus-host disease [GvHD]). Compelling evidence of complementary medicine's efficacy is lacking and potential harm from therapy far outweighs "benefit" during those *crucial HCT time periods* stated above [1, 3]. While most harm is theoretical or extrapolated, these agents are not required

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to undergo the rigorous Food and Drug Administration (FDA) processes for safety and efficacy evaluation like other "conventional" prescription or OTC drug products that are assessed for purity and potency [1]. In fact, the burden of proof for safety of these agents falls on the FDA (i.e., the FDA must provide evidence to remove a product from market that it deems unsafe) [1]. While regulations are in place for good manufacturing practices (GMPs), it is not uncommon for complementary medicine products to be tainted (including with microbial contaminations) and have incorrect dosages in the dosing unit [1, 3, 4]. Agents found in food are usually acceptable at dietary amounts but can be problematic when consumed in larger quantities ("megadoses") seen in supplements [1]. In general, when reviewing for appropriateness, determine if the complementary agent can cause direct or indirect drug interactions with critical therapies or alterations in laboratory values, can potentiate disease states or side effects (e.g., bleeding, GvHD), or has known toxicities [1–4].

This chapter describes common drugs and drug classes (in alphabetical order) that should be avoided or used with caution in immunosuppressed/HCT patients. Patients should be advised to review all supplements with a pharmacist specializing in oncology and HCT prior to beginning or continuing any of these agents or any other agents not described in this chapter.

1. Antioxidants:

   a. Common agents: beta-carotene, blueberry extract, coenzyme Q10, cranberry extract, green tea, lycopene, lutein, melatonin, selenium, vitamin A, vitamin C, and vitamin E

   b. Perceived benefits: prevent or slow cellular damage (wear and tear) by combating free radicals and oxidative stresses created during exercise and normal metabolic processes

   c. Concerns:

      i. Antioxidants may promote cancer progression by neutralizing radical oxygen species (ROSs) critical to tumor DNA damage, as speculated with vitamin E and beta-carotene and their possible role in accelerating lung cancer development [5–7].

      ii. Radiation and select chemotherapies, specifically the classes of anthracyclines, alkylators, and platins, exert anti-tumor effects via ROS production and oxidative stress [5].

   d. Recommendations:

      i. Avoid megadoses and supplemental doses during crucial HCT time periods (moderate dietary amount are appropriate).

      ii. Once-daily general multivitamin products can be consumed outside of the crucial HCT time periods; however, supplemental iron should be avoided in the absence of laboratory testing as many post-HCT patients have transfusion-related iron overload.

2. Black cohosh:

   a. Perceived benefits: relieve symptoms relating to menopause (e.g., hot flashes)
   b. Concerns: may decrease effects of cisplatin (in tissue model), inhibit cytochrome P450 (CYP) 2D6 enzymes (common metabolic pathway for antidepressants), and increase risk of hepatotoxicities [5]
   c. Recommendations:

      i. Avoid due to risk of sinusoidal obstruction syndrome and worsening liver GvHD.
      ii. If management of menopausal symptoms is desired, recommend FDA-approved agents.

3. Citrus fruits (pertinent fruits listed below):

   a. Bitter oranges (Seville orange, sour orange, marmalade orange, and bigarade orange), grapefruit, and pomelo
   b. Perceived benefits: see *Antioxidants;* prevent or shorten cold or flu episodes
   c. Concerns:

      i. Inhibits CYP 3A4 enzymes, a common metabolic pathway for many drugs including immunosuppressants (i.e.*,* tacrolimus, cyclosporine, and sirolimus) [5]
      ii. Bitter orange contains synephrine that is structurally similar to ephedra, a substance banned by the FDA for its cardiotoxicities [1, 5]

   d. Recommendations:

      i. Avoid dietary and supplements during crucial HCT time periods and while on CYP 3A4 metabolized critical medications such as the immunosuppressants.
      ii. Bitter oranges should be avoided altogether due to risks for cardiotoxicities.

4. Coenzyme Q10, see *Antioxidants*:

   a. Perceived benefits: prevention of heart disease

5. Echinacea, see *Immune Boosters*
6. Essential oil/aromatherapy:

   a. Perceived benefits: *various;* reduction of stress, anxiety, pain, indigestion, nausea, and vomiting
   b. Concerns:

      i. Intentional or accidental ingestion can lead to systemic side effects (e.g., methyl salicylate and bleeding) [1, 4].

    ii. Some aromatherapy agents such as lavender, camphor, and eucalyptus can lead to central nervous system side effects such as sedation and seizures [4, 5].

    iii. When applied to skin, concerns exist for photosensitizing effects, especially when patients are also receiving photosensitizing chemotherapy [5].

  c. Recommendations: avoid ingestion and application to large areas of the skin (especially if the area is not intact); relatively low toxicity profile via inhalation route

7. Fish oil (omega 3-fatty acids):

  a. Perceived benefits: reduce the risk of heart disease and lower triglycerides

  b. Concerns:

    i. Contains a fatty acid (16:4 [$n - 3$]) that promotes resistance to cisplatin and possibly to other platinum chemotherapies [8].

    ii. High doses of fish oil may have anti-platelet effects and can increase risk of bleeding [5].

  c. Recommendations:

    i. Avoid supplementation and promote omega 3-fatty acid intake via fish in diet.

8. Flaxseed oil:

  a. Perceived benefits: treat and prevent constipation, diabetes, and high cholesterol

  b. Concern: decreases platelet aggregation resulting in increased risk of bleeding in patients who are thrombocytopenic [5]

  c. Recommendation: avoid use while thrombocytopenic, and/or receiving anticoagulation or antiplatelet therapies

9. Garlic (allicin):

  a. Perceived benefits: prevent heart disease (high blood pressure and cholesterol), common cold

  b. Concerns

    i. Platelet dysfunction due to inhibition of thromboxane A2 and binding to fibrinogen resulting in increased bleeding risk and decreased clot formation.

    ii. In a human study, the allicin constituent of garlic reduced serum levels of saquinavir (Invirase®), an antiviral medication metabolized by CYP 3A4 enzymes [9].

  c. Recommendations:

    i. Avoid supplements during crucial HCT time periods, while thrombocytopenic, or while receiving anticoagulation, antiplatelet therapies, or critical medications metabolized by CYP 3A4 enzymes.

    ii. Appropriate to use in dietary amounts and as a spice.

10. Ginger:

    a. Perceived benefits: treat and prevent nausea, vomiting, and arthritis
    b. Concerns:

        i. Inhibits thromboxane synthase, which can inhibit platelet aggregation and increase risk of bleeding [5].
        ii. In an animal model, ginger juice decreases the bioavailability of cyclosporine [10].

    c. Recommendation: avoid supplements during crucial HCT time periods, while thrombocytopenic, or while receiving anticoagulation, antiplatelet therapies, or cyclosporine.

11. Ginkgo biloba:

    a. Perceived benefits: prevention of dementia/Alzheimer's disease
    b. Concerns:

        i. Interferes with multiple metabolic enzymes (CYP 1A2, 2C19, 2C9, 2D6, and 3A4) and therefore can increase or decrease the bioavailability of other medications [5]
        ii. Similar to ginger and garlic, inhibits platelet aggregation and increases risk of bleeding [1, 4, 5]

    c. Recommendation: avoid in all situations

12. Ginseng, see *Immune boosters*
13. Glucosamine:

    a. Perceived benefits: improves joint (cartilage) health
    b. Concern: reduces the effect of chemotherapy agents that inhibit topoisomerase II (e.g.*,* etoposide and anthracyclines) [5]
    c. Recommendation: avoid around the time of chemotherapy

14. Green tea, see *Antioxidants*
15. Immune boosters:

    a. Perceived benefits: stimulate immune system to fight infections (e.g., cold and flu)
    b. Echinacea, panax/Siberian/American ginseng, vitamin C (see *Antioxidants*), and zinc (see separate *Zinc* section below)
    c. Concerns:

        i. As proposed immune-stimulating agents, immune boosters can interfere with any immunosuppressant therapy required for suppression of GvHD and may negatively impact control of hematologic malignancies [5]
        ii. Echinacea and ginseng can also inhibit and/or induce multiple CYP enzymes responsible for drug metabolisms [1, 5]

            • In particular, these two agents affect the CYP 3A4 enzymes that are responsible for metabolism of many critical drug therapies including anti-GvHD immunosuppressants and chemotherapies [5].

iii. Ginseng can interfere with platelet activities and increase risk of bleeding [4, 5]

c. Recommendations:

   i. Avoid echinacea and ginseng supplements
   ii. See separate recommendations for vitamin C and zinc.

16. Melatonin, see *Antioxidants*

   a. Perceived benefits: treats insomnia

17. Milk thistle:

   a. Perceived benefits: treats and prevents liver disorders (e.g., hepatitis and cirrhosis)
   b. Concern: milk thistle (and its constituents silibinin and silymarin) interacts with several metabolic CYP enzymes (1A2, 2C9, 2D6, 3A4, and 3A5) and P-glycoprotein, which can alter the serum levels of critical drugs, notably certain antidepressants, tamoxifen, cyclosporine, and sirolimus [5]
   c. Recommendations:

      i. Avoid consumption.
      ii. If liver protectant therapy is required, consider ursodiol.

18. Minerals (*divalent cations* aluminum, calcium, manganese, magnesium, iron, and zinc):

   a. Perceived benefits: *various*; supplement diet by providing recommended amount not received from food alone
   b. Concerns:

      i. Divalent cation minerals chelate to some oral medications in the GI tract (when taken concomitantly) and can decrease absorption and serum levels of these medications [5].
      ii. Therapies pertinent to HCT patients include certain classes of antivirals and antibiotics (e.g., fluoroquinolones, tetracyclines, and cephalosporins), eltrombopag (Promacta®), and thyroid medications.

   c. Recommendation:

      i. If given concomitantly with oral antibiotics or antivirals (or other affected medications), consult with a pharmacist for appropriate spacing time between medications.

19. Multivitamins (see *Antioxidants* and *Minerals*)
20. Probiotics; *Lactobacillus* spp., kombucha

   a. Perceived benefits: promote digestive and immune health by maintaining a healthy community of microorganisms
   b. Concerns:

      i. Probiotics and kombucha should be used with caution in immunosuppressed patients due to risks for developing bacteremia and fungemia [5].

      ii. *Lactobacillus* spp. are common in most probiotic supplements and while nonpathogenic can become opportunistic in immunosuppressed patients [5, 11, 12].

      iii. Probiotics and kombucha may also contribute to GI symptoms (e.g., diarrhea) that mimic or potentiate GI GvHD [5]

  c. Recommendations: avoid probiotic supplements and limit consumption of kombucha and dietary products with probiotics in the crucial HCT time periods and while receiving immunosuppressants.

21. St. John's wort:

  a. Perceived benefits: antidepressant

  b. Concern:

      i. Well documented inducers of multiple CYP enzymes (including 3A4) and P-glycoprotein which can decrease serum levels of critical drugs and chemotherapies [5]

  c. Recommendations:

      i. Avoid consumption.

      ii. If antidepressant therapy is desired, recommend FDA-approved agents.

22. Saw palmetto:

  a. Perceived benefits: treats urinary symptoms related to benign prostatic hyperplasia

  b. Concerns:

      i. Prolongs bleeding time

      ii. Anti-estrogenic effects that can increase risk of bleeding for patients on hormonal therapy for menorrhea [5]

  c. Recommendations:

      i. Recommend FDA-approved drugs for benign prostatic hyperplasia (for males).

      ii. Avoid use while thrombocytopenic or while receiving anticoagulation or antiplatelet therapies.

23. Slippery elm and other "throat coat" agents:

  a. Perceived benefits: relieve symptoms of sore throat

  b. Concern: coating of the GI tract with mucilage content can slow and decrease the absorption of other oral medications [5]

  c. Recommendations:

      i. Avoid consumption *OR*

      ii. Use with caution if able to space these agents two hours before or two hours after administration of other oral medications

24. Turmeric (curcumin):

    a. Perceived benefits: anti-inflammatory agent for various diseases
    b. Concerns:

        i. Inhibits CYP 3A4 enzymes; there is one case report of nephrotoxicity from increased serum levels of tacrolimus in the setting of turmeric therapy [5, 13]
        ii. Contradicting studies have shown turmeric may decrease or even augment activities of several chemotherapy agents in breast cancer via inhibition of ROS and apoptotic pathways [14]
        iii. Turmeric also has antiplatelet activities [5]

    c. Recommendations: avoid supplements and limit food containing turmeric (especially during crucial HCT time periods).

25. Vitamins A, C, and E; see *Antioxidants*
26. Zinc

    a. Perceived benefits: treat common cold and flu, prevent ocular and hepatitis diseases
    b. Concerns:

        i. In animal models, zinc stimulates production of metallothionein, a metal-binding protein that can inactivate platinum chemotherapies [5, 15, 16].
        ii. As a divalent cation, zinc can bind to certain oral medications and decrease bioavailability, see also *Minerals*.

    c. Recommendations:

        i. Avoid during administration of platinum chemotherapies.
        ii. If given concomitantly with oral antibiotics or antivirals (or other affected medications), consult with a pharmacist for appropriate spacing time between medications.

27. Other agents to avoid (toxicities) [1, 4, 5]

    a. Aristolochia (nephrotoxicity)
    b. Camphor (hepatotoxicity)
    c. Comfrey (sedation and hepatotoxicity)
    d. Dong quai (lead toxicity and bleeding)
    e. Ephedra (stimulant; cardiotoxicity)
    f. Kava (sedation and hepatotoxicity)
    g. Valerian (hepatotoxicity)
    h. Willow bark (bleeding)

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Chapter 48
Complementary Medicine: Cannabinoids and the Hematopoietic Cell Transplant (HCT) Recipient

Joseph Bubalo

Introduction

Naturally derived cannabinoids and cannabis products are proliferating in use within the United States and in many countries across the world. Individuals entering into the hematopoietic cell transplant (HCT) process may be new or experienced users of cannabinoids, and the safe use and integration of naturally derived cannabis products with this process is not well defined. Patients and their families may have strongly held personal beliefs, and highly euphemistic messages are common in the lay press, making it challenging to have a medical discussion of cannabis product use with someone about to undergo a HCT. This chapter provides a brief overview of current knowledge of cannabinoids to support medical practitioners as they approach these discussions. This chapter should enable the practitioner to discuss drug interactions, assist with potential product selection, and identify at-risk populations for harm from cannabis products when reviewing patient medication preferences for their comorbid conditions.

1. Pharmacology:

   a. Marijuana is the dried flower, bud, and/or leaves of *Cannabis sativa* and *indica* plants and contains >100 phytocannabinoids [1, 2].
   b. The most common cannabinoids of interest are delta-9-tetrahydrocannibinol (THC) and cannabidiol (CBD).
   c. Each cannabinoid has a different affinity and activity at the human G-protein-coupled cannabinoid receptors, CB1 and CB2.

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  d. In use for thousands of years in different forms, intense activity in plant breeding has created many unique cannabis cultivars with varying concentrations of specific cannabinoids in attempts to increase the desired effects in individuals [2, 3]. Cultivars high in THC are generally used recreationally as THC mediates most of the effects sought by those users.
  e. While research into cannabinoids and the endocannabinoid system has led to an increased understanding of the physiology of cannabis effects, there remains a large gap between the laboratory and the ability of discern how it should be used clinically.

2. Current understanding of cannabis pharmacology:

  a. Cannabinoid Receptors:

       i. The CB1 receptor was discovered in 1988, and the endogenous ligand, anandamide, was identified in 1992. It is now known that the endocannabinoid system is composed of CB1 and CB2 receptors and their endogenous ligands, anandamide and 2-arachidonyl glycerol, and this system is involved in many aspects of mammalian physiology.
      ii. The effects of the CB1 receptors appear to be mainly neuromodulatory while those of the CB2 receptors likely result in changes in immune function, anti-inflammatory effects, and anti-nociceptive effects [1].

  b. CBD:

       i. Lacks binding to CB1 receptors and binds weakly to CB2 receptors.
      ii. Appears to promote the activity of and increase levels of endogenous endocannabinoids while antagonizing the effects of some phytocannabinoids including THC [2].
     iii. Impacts a variety of other endogenous receptors which are felt to be at least partly responsible for its physiologic actions.

  c. THC:

       i. A high-affinity partial agonist at the CB1 and CB2 receptors with the majority of its effects mediated by the CB1 receptor [2]. As a partial agonist, it blocks the effects of natural endocannabinoids at the receptors.
      ii. Due to its interactions with the CB receptors and the subsequent psychotropic effects, risk for cardiac side effects, tolerance, and dependence on THC has limited the applications for therapeutic benefit [2].
     iii. Cannabidiol antagonizes the psychotropic effects of THC resulting in many individuals using combined products that allow the delivery of overall higher cannabinoid doses with fewer perceived side effects [4].

  d. Other compounds in cannabis plants include flavonoids and terpenoids which have been shown to potentially modulate psychogenic and possibly therapeutic effects of cannabinoids to varying degrees [5].

3. Delivery methods of cannabis:

a. Smoking marijuana, while very common, is an undesirable delivery system due to the delivery of harmful substances along with any potentially beneficial cannabinoids [6]. Smoking cannabis releases benzene, toluene, and naphthalene, carbon monoxide, and tars which are inhaled along with the cannabinoids.

b. Heating of cannabis without combustion, as with a vaporizer, can deliver THC with reduced levels of combustion products.

   i. One small study showed similar self-report of THC effects with measurably decreased carbon monoxide when comparing smoked cannabis with a vaporized product of equal potency [6]. THC levels were similar over a 6 hour window with higher THC levels at 30 and 60 minutes from initiation suggesting that absorption may be more rapid with a vaporizer. Thus a vaporizer may effectively deliver THC with lower exposure to combustion gases than seen when smoking marijuana cigarettes.

c. A recent crossover study of smoked vs. vaporized cannabis in healthy adults showed a 40% higher blood concentration when individuals used a vaporizer over inhalation with a pipe [7].

d. Increasingly cannabinoids are also available as oral and topical formulations.

4. Bioavailability:

a. Marijuana can be smoked, vaporized, or consumed orally in capsules or food.

   i. Inhalation provides an onset of action within minutes, peak effects are seen in 15–30 minutes, and the half-life is 1–2 hours resulting in a return to baseline by 3–4 hours after intake in healthy individuals [3, 7].

   ii. When taken orally onset is delayed to 1–2 hours, peak effects occur at 2–3 hours, and the half-life is 3–6 hours.

   - About one-third as much cannabinoid is absorbed orally compared with inhalation due to the degrading effects of stomach acid and first pass extraction of cannabinoid by the liver after absorption from the GI tract.
   - Excretion is primarily fecal with up to 20% of metabolites renally excreted.
   - THC is hepatically metabolized to the psychoactive 11-hydroxy metabolite. Lower production of the 11-hydroxy metabolite occurs when inhaled vs. when consumed orally.

   iii. The bioavailability of topical or transdermal products remains to be elucidated in humans. Cannabinoids are lipophilic and are absorbed topically with a likelihood of little first pass effect when given via this route.

5. Drug Interactions (see Table 48.1):

Table 48.1 Cannabis interactions [1, 3, 8–11]

	1A2	1B1	2B6	2D6	2C8	2C9	2C19	3A4	3A5
Cannabidiol (CBD)	+/−		+/−		−	S/−	S/−−	S	
Dronabinol (Marinol®)						S		S	
Marijuana (THC)	++		+/−			S		S/−	
Nabilone (Cesamet®)					−	−			

CBD inhibits UGT 1A9 and 2B7, in addition to the CYP effects noted in this table

All inductive and inhibitory activity is dose related, increasing with dose, with 1 A2 induction seen only is smoked marijuana

Inducer (+ mild, ++ moderate, +++ strong), S = substrate, inhibitor (− mild, −− moderate, −−− strong)

    a. CBD has been shown to inhibit cyclosporine metabolism in vitro and in mice; this study has not been replicated in humans [3].

    b. Based upon Food and Drug Administration (FDA)-approved cannabinoids (dronabinol [Marinol®], nabilone [Cesamet®]) marijuana usage is likely to potentiate the CNS depressant effects of opioids, alcohol, and benzodiazepines [1].

    c. It can also increase the clearance of theophylline and some protease inhibitors diminishing their efficacy via induction of CYP 1A2 [8].

    d. Use with fluoxetine (Prozac®) may lead to manic episodes in bipolar individuals while use with lithium may increase lithium levels.

    e. Use with sildenafil (Viagra®) can increase the risk for myocardial infarction.

    f. There have been multiple reports of tachycardia and delirium when taken with tricyclic antidepressants.

    g. Use with anticholinergic agents or alpha agonists can lead to tachycardia and hypertension.

    h. Naltrexone (ReVia® or Vivitrol®) may increase the euphoric effects of marijuana and use with disulfiram (Antabuse®) has led to hypomanic episodes.

    i. Marijuana has also been shown to decrease the efficacy of neuroleptic antipsychotics while increasing the risk for extrapyramidal effects.

6. Adverse effects (see Table 48.2):

    a. THC-containing products and synthetics of THC have a similar adverse effect profile.

      i. Dizziness and drowsiness are most common followed by euphoria, confusion, feeling intoxicated, sedation, dysphoria, hallucinations, and paranoia [16].

      ii. Less common but significant side effects include arterial and postural hypotension.

    b. Oral cannabis products have a poorly characterized adverse effect profile at this time despite broadening social use. The degradation of cannabinoids by stomach acid and hepatic first pass effect make absorption slow and somewhat erratic and the onset of effect and side effects unpredictable.

Table 48.2 Select cannabis side effects [5, 10–15]

	Cannabidiol (CBD) (seizure syndrome dosing)	Dronabinol (Marinol®)	Nabilone (Cesamet®)	Nabiximols (Sativex®)	Marijuana
Abnormal thinking	NR	3–10%	2%	4%	Common
Appetite increase	13–28% decrease	FDA approved use	2%	1.4% (2.4% decrease)	Common
Diarrhea	19–31%	<1%	<1%	5.5%	NR (constipating)
Dizziness	NR	3–10%	59%	25%	Common
Dry mouth					7.3%
Emesis	10–15%	3–10%	<1%	3.5%	NR)
Euphoria	NR	8–24%	11–38%	2.2%	Common
Fatigue	20%	<1%	<1%	12.5%	NR
Hypotension	NR	<1%	8%	5%	Dose related, including orthostatic
Infections	11% (URI)	NR	<1%	Rare thrush	Reported
Nausea	NR	3–10%	4%	9.6%	0.3%
Somnolence	15–36%	3–10%	3–66%	8.2%	Drowsiness common
Visual changes	NR	<1%	13%	1.9%	Common

NR, not reported; *URI*, upper respiratory tract infection

   c. Cannabis use is associated with a lifetime risk of 9% for cannabis use disorder, also known as cannabis addiction or abusive dependence, with daily use increasing the incidence to up to around 19% [4]. This risk is increased in individuals with a concomitant psychiatric disorder, males, daily use, and those who begin use at a younger age [17].

   d. Product contamination is a significant concern when acquiring cannabis products. Most states in the United States (US) have some level of testing for pesticides and herbicides; however, it is unclear how successful these systems are at ensuring all lots are tested prior to delivery to the end consumer or prior to being processed into one of the many cannabis derived consumable products.

   e. Bacteria and molds are ubiquitous on the surface of cannabis plants.

      i. The most prominent bacterial contaminant is Enterobacteraciae and the most common mold is Aspergillus.

     ii. Cannabinoid administration by smoking or vaporizing cannabis buds thus delivers pathogens directly to the lungs of the individual.

    iii. Both bacteria and fungus/molds are documented in the literature as causing infections in the immunocompromised patient.

    iv. While sterilization of cannabis buds is possible, it is not currently done routinely and not at all in the United States. Without sterilization, the baked or processed oral cannabis products appear to have the lowest risk of pathogen contamination in products tested but this did not eliminate the risk for delivering pathogens [18].

7. Therapeutic uses:

    a. Potential uses of cannabinoids are many with scant evidence for any non-FDA-approved product indications. There is also limited evidence for FDA-approved products outside of their approved indications.

    b. The proliferation of anecdotal reports in the public literature and social media continues to make it challenging to provide realistic expectations of benefit in specific disease or symptom states.

    c. Currently three conditions, pain, nausea and vomiting, and spasticity, have adequate evidence to support potential benefit. Thus this review will focus on those three uses with additional comments on psychiatric uses of cannabis given the prevalence of use for psychiatric-related conditions [16]. It is also notable that a Canadian survey of medical marijuana users found their functional status was much worse than that of the general population. Some populations showed small improvements in health-related quality of life (HRQoL) while others demonstrated diminished HRQoL [17, 19].

      i. The most common indication for medicinal cannabis use worldwide is pain management [4].

        • Widespread claims of cannabis benefits for analgesia have raised interest in cannabinoids as an alternate to opioids as overdoses associated with opioids continue to increase.

        • Current studies in cannabis for analgesia are limited by differing study designs and endpoints, short study durations, and inconsistent product selection for study.

        • The consensus result is that there appears to be benefit in the control of neuropathic pain of limited durations (weeks). Long-term studies with a universally available product are needed.

        • There is little potential benefit for headache, rheumatologic conditions, or back pain [17].

      ii. Cannabis for the management of nausea and vomiting should only be considered after all prescription options have been attempted as there is considerable evidence for use of these products with little to none for cannabis [17].

        • Additionally, cannabis should never be used for pregnancy-related emesis given the potential for fetal harm.

        • There is little evidence in the setting of patients actively receiving chemotherapy as opposed to nausea or vomiting in the palliative setting which has also not been studied adequately [5].

iii. Cannabis for the use of spasticity has been validated with the use of nabiximols (Sativex®) in the setting of multiple sclerosis and spinal cord injury.

- Given their side effect profile, it is suggested that cannabis only be used in the setting of spasticity refractory to all current established therapies [17].
- Currently, nabiximols is under investigation for use in the United States but is available for medical use in other countries.

d. There have been studies of CBD for the prevention of graft-versus-host disease (GvHD).

   i. A phase II study of CBD 300 mg given orally daily from 7 days prior to stem cell infusion until 30 days after cell infusion found this dose to be safe and potentially beneficial [20].

   - This open label, non-controlled study was performed in 48 consecutive, unselected allogeneic patients (35 ablative). The incidence of acute GvHD was decreased with a delayed onset when compared to a historical, matched 101 patient cohort.
   - Engraftment occurred in 47 out of 48 individuals with primary graft failure in a patient with aplastic anemia who subsequently engrafted with a second transplant from the same donor; neither CBD nor methotrexate was utilized as part of the GvHD prevention regimen.
   - No grade III/IV toxicities related to CBD were noted.

   ii. A placebo-controlled trial is recommended to further investigate this potential therapeutic use of CBD.

e. Consumer use of cannabis is frequent with claims of benefit for insomnia, depression, post-traumatic stress disorder (PTSD), and anxiety [4, 21–23].

f. Regular use of cannabis has been shown to increase the risk for a variety of psychiatric disorders including bipolar disease and schizophrenia; thus, it should be avoided in individuals with a history of psychiatric disorder [24].

   i. With regard to CBD as opposed to mixed cannabinoid products, a recent report of cannabidiol in those with chronic schizophrenia showed no benefit in either cognition or symptoms though no worsening of symptoms in a 6-week placebo-controlled trial of a 600 mg daily dose [25].

8. Cannabis products:

a. Regardless of the type of cannabis product selected for patient use, the expectation is that it would be free of contamination with pesticides, herbicides, heavy metals, other legal or illegal pharmaceuticals, bacteria, fungus, or unwanted residues from the processing method.

b. All current cultivars have been genetically modified or cultivated to produce different levels of specific cannabinoids.

c. While there may be a preference for organically grown cannabis, the process for certification does not currently exist in the United States and thus expectations for organic cultivation cannot currently be met.

d. Commercially approved cannabinoids products:

   i. Dronabinol (Marinol®) and nabilone (Cesamet®) are FDA-approved synthetic THC analogs largely acting upon the CB1 receptor and approved for the management of nausea and vomiting with chemotherapy [10, 11]. Dronabinol has an additional indication for management of anorexia in individuals with acquired immunodeficiency syndrome (AIDS) [11].

   ii. Naabiximols (Sativex®) is composed of two cannabis extracts enriched in THC and CBD in an approximately 1:1 ratio:

   • It has been licensed in Canada since 2005 for the relief of pain in adults with cancer and spasticity from multiple sclerosis (MS) [2].
   • This drug has also shown benefit against neuropathic pain in MS with no evidence of tolerance at 2 years of use.
   • A purified cannabidiol solution has also been approved for treatment of specific pediatric seizure disorders [9].

e. Naturally derived products (see Table 48.3):

   i. Based upon the limited evidence currently available, purified cannabinoid products such as nabiximols or synthetic THC mimics, dronabinol

Table 48.3 Product listing [9–11, 24]

Brand name	Generic name	Contents	Dosage form	Comments
Sativex®	Nabiximols	2.7 mg THC and 2.5 mg CBD + terpenoids per spray	Sublingual spray	
Marinol®, Syndros®	Dronabinol	2.5, 5 mg capsules, 5 mg/mL solution	Oral capsule and solution	
Cesamet®	Nabilone	1 mg capsule	Oral capsule	
Epidiolex®	Cannabidiol	100 mg/mL solution	Oral solution	Strawberry flavored, in sesame oil
Many	Marijuana	Dried plant parts, contents vary by cultivar and plant part	Requires further preparation for inhalation	Wide variety of potencies and contents
Many	Oral and topical cannabis preparations	Vary by product but are often standardized by state to standard divisible portions based upon THC content	Oral candies, liquids, oils, baked goods, and others	Potency may be higher per divisible portion in medical as opposed to those intended for recreational sale
Many	Topical cannabis preparations	Vary by product with no standard concentration	Topicals as creams, ointments or transdermal patches	

and nabilone, may not provide similar therapeutic benefit and have different side effect profiles (generally higher) than mixed cannabis products extracted from cannabis cultivars [4].

ii. It is currently unclear if this finding is due to inherent bias in trial design, anecdotal pressure upon results reporting, an incorrect mixture of cannabinoids for experimentation, or the need for isolation of specific or more active cannabinoids for different therapeutic indications.

iii. Thus some individuals may desire a natural alternative to the pharmaceutical company products. The ability to grow and process their own cannabis is allowed in many countries and multiple states within the United States making an exploration of home cannabis use a necessity in many geographic locations of patient care.

iv. The availability of medical and recreational cannabis products varies by state in the United States with a complex web of distribution, oversight, and registration systems for medical and recreational cannabis users.

- It is impossible to predict or ensure that a medical or recreational cannabis user will be able to receive a specific dose of any cannabinoid.
- Multiple studies of available products show unreliable product labeling which may result in above or below target cannabinoid doses from that intended.
- Currently, the most reliable distribution appears to be state-organized dispensary systems.
- Product should never be obtained via the Internet due to the unclear integrity and lack of oversight of the web-based ordering and delivery systems [26, 27].
- In most cases the products desired for recreational use have different cannabinoid content from that used by most medicinal users [4].

9. Dosing:

a. Inhaled marijuana is the least preferred route given the inherent risks of smoking or vaping.

i. If the patient is insistent upon using this method, a low THC product (<10%) should be used starting with a single inhalation from a cannabis cigarette (joint) followed by a 15 minute waiting period.

ii. If the patient's therapeutic need has not been met, they may increase by one inhalation every 30 minutes until desired symptom control has been achieved or the product is deemed to be ineffective [4, 24].

iii. Generally, it is suggested to start low, go slow, and stay low.

b. When using an oral product, a 2.5–5 mg portion should be tried with no additional product ingested for a minimum of 6 hours.

i. Based upon the response of the target symptoms, additional portions can be consumed up to four times daily.

    ii. Currently there is not adequate guidance on the optimal cannabinoid ratio (e.g., 1:1 THC to CBD or other cannabinoid combination) to suggest a product based upon that level of guidance.

    iii. The use of a chosen product is guided by achievement of symptom control simultaneous with avoidance of adverse side effects.

    iv. Dosing above 25 mg of THC per dose is thought to be of little benefit for pain control. Note counseling guidance below.

10. Patient counseling:

    a. Patients should not drive, work a safety-sensitive job, or perform potentially dangerous activities for 3–4 hours after inhaling marijuana, 6 hours after oral consumptions, or 8 hours after feelings of intoxication ("high") were noted with use.

    b. If feeling impaired, regardless of the time since dosing, patients should not drive or work safety-sensitive jobs [24].

    c. Cannabis should not be used if there is potential for a female to be pregnant or is attempting to get pregnant, and for at least 60 days from when a male might cause a pregnancy.

11. Summary

Cannabis is not a preferred agent for treating any side effect of or as a supportive modality to the HCT process. Currently the evidence behind safe use is slim and there are many unknowns with the use of cannabis-derived products. Endocannabinoid effects are widely spread through the human system and most of cannabis-related immunologic, developmental, and psychiatric actions or effects are poorly understood. Its use by popular request or due to the beliefs of patients or providers should be pursued only after a complete discussion of the risks and benefits associated with usage of the different forms. This section is meant to increase the understanding of cannabis products by health professionals to support a productive discussion with the interested patient. Currently, topical and oral products appear to have the least risk for harm when used appropriately though current dosage for any condition, and the optimal mix of cannabinoids is unknown.

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Chapter 49
Management of Neurocognitive Effects and Fatigue During and After Hematopoietic Cell Transplant

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Introduction

Fatigue and cognitive dysfunction ("chemo brain") occur in a significant percentage of those undergoing hematopoietic cell transplantation (HCT). Typically, symptoms occur acutely and may be explained by physiological changes (i.e., anemia) and/or medications (i.e., phenothiazines for nausea, benzodiazepines for anxiety) that are part of the transplant pathway. In some patients, fatigue and neurocognitive changes become chronic symptoms that persist for years. In both instances, their acute and chronic manifestations, fatigue, and neurocognitive changes may cause significant patient distress and negatively impact quality of life (QOL) for patients undergoing, and for long-term survivors of, HCT. By reviewing proposed causes of these symptoms and highlighting how to most effectively assess and treat them, patients can improve their overall function and QOL.

Neurocognitive Dysfunction or "Chemo Brain"

The negative neurocognitive effects of chemotherapy and other cancer treatments are widely acknowledged, if poorly understood. These effects are variously referred to as "chemotherapy-induced cognitive impairment," "chemo brain," and "chemo fog." "Chemo brain/fog" typically refers to relatively acute cognitive dysfunction related directly to the administration of cancer treatments, most typically chemotherapy. Neurocognitive dysfunction often refers to ongoing neurocognitive deficits in survivors of cancer who have received treatments including HCT.

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In HCT patients, problems with attention and concentration, processing speed, and executive function (which includes both self-regulation and goal-directed action) commonly occur. HCT conditioning can worsen both acute and chronic neurocognitive deficits related to chemotherapy compared even to other cancer patients, as those undergoing HCT typically receive higher doses of chemotherapy and radiation than do other cancer patients.

Neurocognitive impairment is not solely associated with the acute posttransplant period. Studies suggest an incidence of neurocognitive impairment for survivors of HCT of up to 60% at 22–82 months posttransplant that translates into significant morbidity for patients, potentially resulting in persistent interpersonal and professional impacts. For example, patients who report a higher level of neurocognitive dysfunction are more likely to remain on disability for longer periods of time following transplant and may be unable to return to work at all. Therefore, recognizing and treating neurocognitive dysfunction can greatly improve overall QOL of HCT survivors.

The exact etiology of "chemo brain" and chemo-related cognitive dysfunction remains unclear. Most current research into the pathophysiologic mechanisms that cause neurocognitive dysfunction suggests that chemotherapeutic agents are toxic to healthy brain cells in addition to the cancer cells that they are meant to target. These toxicities include inducing oxidative stress and inhibiting neuronal regeneration. Studies have shown increased inflammatory markers in patients who complain of long-term neurocognitive dysfunction related to chemotherapy compared to those who do not, indicating that there is likely a long-term underlying pathophysiologic mechanism at work. Risk factors for both acute and chronic neurocognitive dysfunction related to HCT include chemotherapy regimens that include neurotoxic agents, total body irradiation, graft versus host disease (GvHD), and prolonged hospitalization. Patients who require the use of centrally acting medications for symptom management (including opiates, benzodiazepines, and phenothiazines) may experience cognitive dysfunction as a side effect of medication. In addition, the primary cancer itself may have a cognitive impact, especially in cases of central nervous system involvement.

In addition to treatment-related causes of neurocognitive dysfunction, personal characteristics such as anxiety, depression, sleep disturbance, and uncontrolled pain also affect manifestation of patients' neurocognitive symptoms. Pretreatment cognitive dysfunction is also under-recognized, but likely plays a role in chronic neurocognitive dysfunction, as any underlying deficits may be exacerbated by HCT conditioning regimens.

Given the multifactorial nature of cognitive changes associated with HCT, patients who experience these symptoms can benefit from multimodal therapy. An overview of treatment for neurocognitive dysfunction is reviewed following discussion of fatigue, as the treatments for neurocognitive dysfunction and fatigue overlap significantly.

1. Assessment

   a. Many assessment tools are available to identify specific neurocognitive deficits and dimensions of fatigue.
   b. As with other subjective symptoms, it is not necessary for patients to undergo specific assessments prior to being treated for these symptoms.
   c. Assessments can be effective in identifying specific areas of deficit and, when conducted over time, may help monitor the clinical course of treatment and evaluate their efficacy.
   d. Neuropsychiatric testing is most typically administered by a trained neuropsychologist and is employed to identify specific areas of neurocognitive dysfunction, using validated tools to identify deficits in psychological ability that are associated with specific brain structures.

      i. Tests can be arduous, typically taking between 2 and 5 hours. In patients already debilitated by cognitive deficits and fatigue, testing can take up to 8 hours or may simply be impossible to complete.
      ii. Depending on patients' insurance and location, the cost of testing may be prohibitive, and there may be an extended wait from time of referral until testing can be completed. Nevertheless, for patients who report ongoing neurocognitive dysfunction after HCT, neurocognitive testing should be pursued.
      iii. While neuropsychiatric testing provides the most detailed information about various neurocognitive domains, it is imperfect.
      iv. Testing identifies deficits but does not determine causality.
      v. Areas of deficit will be identified in an estimated 4–24% of the general population, making it difficult to determine whether any deficits are the result of HCT without performing both pre- and post-HCT testing.
      vi. The effects of HCT may magnify subtle pre-existing deficits.
      vii. In addition, the results of neuropsychological testing do not clearly correlate with patient self-report of symptoms. Instead, report of distressing symptoms is most closely associated with psychological distress, such as anxiety or depression.
      viii. Well-validated and user-friendly measurement tools such as the Patient Health Questionnaire-9 (PHQ-9) for depression and the Generalized Anxiety Disorder-7 (GAD-7) for anxiety can be easily administered in an office visit and may be useful in evaluating complaints of neurocognitive dysfunction, as well as in tracking response to treatments.

   e. The Mini Mental Status Exam (MMSE) is a useful tool for assessing dementia, a condition atypically seen after HCT conditioning. However, neurocognitive deficits related to HCT do not typically resemble dementia, and studies

   have *not* shown that MMSE results correlate with specific neurocognitive deficits or with patients' self-reported neurocognitive symptoms.

2. Treatment

   a. Non-pharmacologic treatments

      i. The treatment of patients who self-report symptoms is often performed as there is not consistent congruity between patients' report of neurocognitive dysfunction as the result of cancer treatment and results of standardized testing (i.e., neuropsychiatric evaluation). Therefore, it is reasonable to treat patients based on their report of symptoms; testing for deficits prior to treating is not necessary.

      ii. Referral to Speech Language Pathology

   b. Cognitive rehabilitation to improve memory, executive function, attention, and other domains of neurocognitive function

      i. Medication review

   c. Review medications and minimize centrally acting medications when able (i.e., benzodiazepines, opiates, phenothiazines)

      i. Evaluate for underlying emotional distress

         • There appears to be causal relationship between emotional distress and neurocognitive dysfunction.
         • Medications to treat anxiety and depression may improve neurocognitive function if mood symptoms are contributing.

Fatigue

As with cognitive dysfunction, fatigue related to HCT may be acute or chronic. Regardless of time frame, fatigue negatively impacts overall QOL in significant ways. Cancer-related fatigue is understood as physical, emotional, or cognitive tiredness that is distressing and persistent, is out of proportion to activity, and interferes with the patient's overall function.

   In the immediate posttransplant period, direct treatment-related effects such as anemia and myelosuppression may contribute to fatigue. In addition, the hospital environment itself, with necessary frequent patient assessments, can interrupt sleep and exacerbate fatigue. The anxiety and uncertainty that affect many HCT patients may also contribute to feelings of fatigue. However, there is also a subset of patients who may experience prolonged fatigue even after physical recovery from HCT, reported in up to 35% of patients for years following transplant. Although in the acute posttransplant period there is a direct relationship between

more aggressive treatments and fatigue, chronic fatigue does not seem to be related to specific higher-dose conditioning regimens or to severity of initial disease. Instead, risk factors for persistent fatigue include psychosocial factors, such as fear of cancer recurrence, ineffective coping with initial cancer, and poor social support, and lifestyle factors, such as dysregulation of sleep and physical activity. As with any patients who experience neurocognitive dysfunction, fatigue in the HCT population should be assessed and treated, as this may significantly improve a patient's QOL.

1. Assessment

    a. As with neurocognitive dysfunction, a patient's self-report of fatigue should be considered an adequate cause to initiate treatments focused at alleviating this symptom.

        i. The best validated instrument to measure fatigue is the Brief Fatigue Inventory (BFI), available through M.D. Anderson Cancer Center, which explores the presence of "tiredness" and "weariness" and specifically how these symptoms impact day-to-day function.

        ii. As in patients experiencing neurocognitive dysfunction, assessment of psychiatric symptoms can be helpful in evaluating fatigue. For example, depression may cause fatigue independently or cause sleep disturbances that lead to fatigue.

        iii. Similarly, anxiety can impact sleep or create symptoms such as mind racing, which can be exhausting.

        iv. If psychiatric symptoms are identified, treating them with standard therapies such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) and/or counseling may alleviate the underlying psychiatric causes of fatigue and reduce the symptoms.

    b. Consider anemia, electrolyte disorders, and liver dysfunction as possible causes.

    c. In patients reporting acute or chronic fatigue, questions related to sleep pattern, use of centrally acting medications, nutrition, and daily physical activity may also help identify causes and, correspondingly, treatments that may improve their symptoms.

    d. It is important to keep in mind that a patient's self-report is the most important measure of both of these symptoms.

    e. Regardless of whether or not specific deficits or causes are identified through measurement tools, it is reasonable to offer treatment for patients who report distress around neurocognitive change or fatigue associated with their HCT, as doing so may improve their overall QOL.

2. Non-pharmacologic treatment

   Focuses on the treatment of potentially reversible etiologies.

   a. Physical activity

      i. Encourage patients to maintain optimal activity level
      ii. Consider referral to physical therapy and medical exercise program if safe.

         • Patients should be evaluated for fall risk and comorbid conditions such as cardiac disease that may make exercise hazardous
         • Physical therapy referral for instruction in energy conservation, improvement of deconditioning
         • Yoga has been shown in some studies to combat fatigue

   b. Psychosocial interventions

      i. Cognitive Behavioral Therapy (CBT)
      ii. Mindfulness-based stress reduction
      iii. Supportive therapies (group counseling, journal writing)

   c. Optimal nutrition

      i. Referral to dietician

   d. Sleep management

      i. Good sleep hygiene (many tip sheets available online).
      ii. CBT.
      iii. Sleep medications should be used judiciously as these can also contribute to fatigue.

   e. Sleep study if concerned for sleep apnea (body habitus, high-dose opioids)

      i. Evaluate for underlying emotional distress.
      ii. There appears to be a causal relationship between emotional distress and fatigue.

   f. Medication review

      i. Review medications and minimize centrally acting medications when able (i.e., benzodiazepines, opiates, phenothiazines)

   g. Laboratory evaluation

      i. Evaluate and treat for underlying lab abnormalities
      ii. Anemia
      iii. Electrolyte disorders, liver dysfunction
      iv. Hypothyroidism
      v. Hypogonadism

Pharmacologic Treatments

Pharmacologic intervention may be used when symptoms of fatigue or neurocognitive dysfunction persist despite optimal non-pharmacologic management (see Table 49.1).

Table 49.1 Pharmacologic options for treatment of neurocognitive dysfunction and fatigue

Medication	Indication	Dosing	Side effects	Cautions
Methylphenidate (Ritalin®, Concerta®)	Fatigue/ neurocognitive dysfunction	Start with 2.5 mg in the morning and midday. Can increase by 2.5–5 mg q3–4 days to a maximum dose of 30 mg/day	Anxiety, insomnia (can be ameliorated by moving dose earlier in day), decreased appetite (common in children; not common when used for fatigue/ cognitive dysfunction), abuse potential	Avoid in patients with history of substance abuse, especially amphetamines Use caution in those with comorbid anxiety disorders, psychosis Avoid in patients with history of mania
Modafinil (Nuvigil®)	Fatigue/ neurocognitive dysfunction	Start 100 mg/day. Increase by 100 mg/week. Maximum daily dose 400 mg	Nausea, headache, warning regarding Stevens-Johnson syndrome, abuse potential	CYP3A4 inducer: decreases efficacy of many medications, *including cyclosporine* Very expensive. May not be covered by insurance
Amodafinil (Provigil®)	Fatigue/ neurocognitive dysfunction	Start at 50 mg/day. Increase by 50 mg/week to a maximum of 250 mg/day	Same as modafinil	Same as modafinil
Donepezil (Aricept®)	Neurocognitive dysfunction	Not recommended for management of general neurocognitive dysfunction related to HCT		No evidence for efficacy outside the setting of whole brain radiation therapy or brain tumor/ brain metastasis
American Ginseng	Fatigue	2000 mg/day	Generally well tolerated. <1% report agitation, anxiety, insomnia, nausea	CYP3A4 inducer: decreases efficacy of many medications, *including cyclosporine*

Conclusion

Neurocognitive dysfunction and fatigue related to high-dose chemotherapy affect a large percentage of patients who undergo HCT, and symptoms can negatively impact quality of life for years. Asking about the presence of these symptoms, evaluating their severity, testing for alternative or contributing causes, and offering treatment to improve them can greatly enhance the lives of those who have undergone a HCT.

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Chapter 50
Palliative Care

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Introduction

Patients and their families undergoing hematopoietic cell transplantation (HCT) experience profound changes from diagnosis, during HCT, and through recovery, relapse, or death. Factors affecting their quality of life include pain and physical symptoms, emotional and psychological stresses, alterations in traditional roles and self-concept, and the social and economic impact of serious illness. Given the impact of HCT on patients and their families, the prolonged period of decreased functional capacity, high symptom burden, and uncertainty of outcome, the integration of palliative care into the model of care for this patient population is indicated.

The benefits of early referral to palliative medicine have been demonstrated for patients with newly diagnosed advanced non-small cell lung cancer. Patients were randomly divided into two groups with one group receiving traditional oncologic care. The second group received traditional oncologic care and underwent evaluation by a palliative care specialist within 3 weeks of enrollment and then at least monthly thereafter. Patients who were seen by a palliative care specialist had improved pain and symptoms, improved mood, a more accurate perception of their prognosis, and improved median survival by 2.6 months. It is impossible to make a direct comparison to the patients undergoing HCT. However, this randomized study confirms there can be benefits to early referral to a palliative care specialist.

Three main concerns raised by hematologist-oncologists regarding referrals to palliative care specialists have been identified in the literature [1, 2]. These include:

1. Prognostication is difficult given the often rapid and unpredictability of change in a patient's status.
2. Palliative care clinicians lack experience providing care to patients with hematologic malignancies.
3. There may be a perception of different goals between the two specialists.

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The care of patients undergoing HCT includes many issues approachable by palliative care. However, care experts may not agree regarding the appropriate timing of a palliative care consult. Many oncologists view a palliative care consult as appropriate when all treatment options have been exhausted, while palliative care specialists may view supportive interventions provided by oncology as non-beneficial and burdensome. Patients with hematologic malignancies have an unpredictable trajectory associated with episodes of critical illness and recovery or rapid change in status and life-ending complications. The challenge is for the two specialties to reach a mutual understanding of what each can bring to enhance the quality of life of patients and their families [3].

The World Health Organization (WHO) defines palliative care as an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems—physical, psychological, and spiritual. It is applicable early in the course of an illness in conjunction with other therapies that are intended to prolong life such as chemotherapy or radiation [4].

A common misconception is that palliative care and hospice are identical, while in reality there are significant differences [3].

1. Palliative care can be provided while all other disease-modifying therapies are continued.
2. WHO recommends referral to palliative medicine be based on patient needs and be offered at any stage of treatments with a focus on supporting both the patient and their family members.
3. Referral to palliative medicine can be patient and purpose specific. The reason for a referral is based on the patient's needs and may consist of a single visit which is symptom specific, several visits to manage ongoing symptoms until a durable plan is created, or ongoing visits with both clinicians focusing on different patient needs.

Core Functions of Palliative Care Related to Direct Patient Care

The skill and knowledge required to provide expert palliative care are determined by the following core functions:

1. Prevention, assessment, and treatment of pain and other physical symptoms, including dyspnea, nausea, insomnia, delirium, agitation, confusion, anorexia, vomiting, constipation, and fatigue.
2. Emotional, spiritual, and psychological support for patient and family.

3. Communication of the expected illness trajectory, including prognosis, while assisting the patient, or family, to clarify values and goals of care that support emotional well-being throughout the course of the disease.
4. Development of a safe plan for discharge connecting the patient and family with community resources that can provide adequate support.
5. Transition to hospice services when the patient is eligible and desires that level of support.

A referral to palliative care is appropriate when the patient's needs exceed the available skills or resources that the HCT team can provide to address core functions of palliative care. Palliative care specialists work together with the HCT team to develop a treatment plan with the focus of lessening patient and family suffering throughout the treatment course. The involvement of palliative care early in the treatment process establishes relationships which will ease the transition to hospice care and intensive symptom management if cure is not attainable [5, 6].

The American Society of Clinical Oncology (ASCO) promotes and provides an evidenced-based quality of care framework that leads to outstanding treatment for oncology patients. Along with the National Quality Forum (NQF), ASCO has developed the Quality Oncology Practice Initiative (QOPI). This initiative has established quality standards in the domains of core practice, end-of-life care, symptom management, and disease-specific measures to guide optimal oncology treatment. Using QOPI measures as a guide, this chapter will discuss advance care planning, care of the caregiver, and the physical side effects that most commonly produce suffering in the HCT recipient [6, 7].

Even though HCT may be the only option for survival, it is potentially life altering or fatal; recipients may feel overwhelmed with these truths. The patient's perspective guides treatment choices throughout all phases of the HCT process. For that reason, it is important to provide a balanced supportive treatment approach focusing on both physical and psychological well-being. If the multidimensional causes of suffering are addressed adequately, the treatment experience can be positive for everyone: patient, family, and care providers. Outcomes are enhanced when the patient receives holistic care, addressing the combination of physical, social, psychological, emotional, and spiritual stressors the patient and family may endure [3].

Advance Care Planning

An important task for patients and their families when diagnosed with a life-threatening illness is to plan for the potential of the patient not surviving their illness or for times when they may not be able to make important decisions. It is challenging for many patients, as well as clinicians, to discuss these issues due to the fear of

not being optimistic, of taking away hope, or of causing the event by discussing its possibility. In studies with patients and families, most report that even when the discussion is difficult, they are grateful for accurate information related to the risks associated with their illness [3].

1. Every patient should be given the opportunity to complete an advance directive for health care.

   a. Identifies a surrogate decision maker and the scope of their authority, and insight into the patient's values and decisions they would make for themselves.
   b. Completion of this task frequently eases the burden on surviving family and friends, increases the chance that decisions are being made which are consistent with the patient's values, and are being made by the person of their choice.
   c. Frequently when patients become acutely ill in the hospital setting, there are regrets that this task was left undone.

2. Additional tasks to be addressed

   a. Financial power of attorney
   b. Completion of wills
   c. Sharing of information necessary to the smooth running of the household, employment process, and personal legacy work [3]

3. By providing guidance, encouragement, information, and support to our families to complete these tasks, future regrets and hardships may be avoided.

Support for Caregivers

HCT recipients are dependent on caregivers during the treatment and recovery phases of their illness.

1. Fatigue is a major symptom leading to reliance on caregivers for completion of daily tasks, coordination of medical appointments, management of medications and ongoing medical tasks, monitoring for side effects, provision of emotional and psychological support, recognition of complications, and physical care.
2. Caregivers report a significant amount of stress associated with this role, disruption of their own life, stress on multiple family members, and financial burdens.

   a. The relationship between the patient and their caregivers influences the coping of both parties [8].

3. Palliative care interventions are focused on both the patient and the caregiver.

   a. The focus for the caregiver is on assessment of their strengths, resources, role enactment, degree of caregiver burden, and early interventions to reduce caregiver burdens, provision of support for the caregiver, and addressing ongoing concerns.

Common HCT-Associated Side Effects [9–12]

1. Suffering

    a. Invasive medical procedures, distressing physical symptoms, social isolation, uncertainty regarding outcomes, changes in body image, and a lost sense of control all increase a patient's vulnerability and suffering.
    b. If these multidimensional features of suffering are improved, the experience of everyone concerned—patient, family, and the HCT team—will improve.
    c. Relieving the suffering associated with HCT begins with an understanding of the patient's unique perspective of the experience.

        i. Although it is important to know the diagnosis, pre-HCT comorbidities, source of stem cells and degree of histocompatibility, conditioning regimens, and complications, it is equally important to remain aware of the patient's understanding throughout the process.
        ii. This awareness will require obtaining feedback from the patient and the people that support them in their life.

2. Pain

    a. The first goals of pain management are to gain and sustain the patient's trust. To achieve those goals, one must work quickly and effectively to achieve relief.

        i. There are multiple reasons for the undertreatment of pain, including malabsorption, underdosing of analgesics, and nausea/vomiting.
        ii. Understanding pharmacokinetics of the medications used and the different routes of administration will improve dosing efficacy.
        iii. The best approach is to involve an interdisciplinary team, including a clinical social worker, psychologist, or psychiatrist.

            • Consider antidepressants and anxiolytics
            • Provide routine follow-up by a palliative care team provider

    b. The hospitalized HCT patient's pain treatment differs from the standard approach to cancer pain management.

        i. These patients are frequently unable to take oral, subcutaneous, rectal, or transdermal opioids due to effects of therapy on the skin graft-versus-host disease (GVHD) and lining of the GI tract (mucositis, infection, graft-versus-host disease (GVHD)).
        ii. Thrombocytopenia may also lead to excessive bruising or bleeding if using the subcutaneous route.
        iii. Effective adjuvant therapy using acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are often contraindicated and typically can only be dosed orally.
        iv. Opioid administration is often necessary and most effective in this patient population.

  c. A common mistake is to choose a "standard" dose rather than a dose that is ideal for the patient.

     i. It is best to give an initial "standard" dose and observe the effect.
     ii. After a clear assessment of the change in pain level (e.g., using a 0–10 pain scale), consider doubling the dose if the pain remains severe (8–10 on the pain scale). Continue to double the dose until the patient experiences an improvement in the pain reported or experience dose-limiting side effects.
    iii. Continue to assess for intolerance of medications, such as sedation and hallucinations.
     iv. Consider continuous infusion narcotic dosing as indicated as this may provide more sustained pain relief than bolus or intermittent dosing.

  d. To calculate appropriate continuous infusion narcotic dosing, total the amount of opioid required to achieve relief from the bolus doses administered during the dose-finding period. Divide the total by the amount of time to achieve relief; the product is the new basal rate.

     i. The most common mistake seen is the practice of incremental changes in the basal rate without dose calculations of the appropriate bolus dose.

  e. Frequently, patients may have physical symptoms enhanced by their emotional status and psychological coping strategies.

     i. Addressing fear, anxiety, depression, prior trauma, and drug abuse is necessary to adequately assess their pain.
     ii. Patients who chemically cope with stressful situations can be expected to continue this coping mechanism while hospitalized.

       • These patients may exhibit behaviors such as requesting specific opiates and dosing techniques and dosing more frequently than prescribed.
       • These patients may present a challenge to the treatment team due to clinician's fear of contributing to an addiction and resentment of being controlled by the patient's requests.

    iii. For optimal treatment, it is important to remember that this behavior may reflect undertreated pain rather than addiction. This is known as pseudoaddiction.

       • Pseudoaddiction is an iatrogenic collection of behaviors mimicking addiction that occurs as a result of undertreated pain.
       • The prevention of pseudoaddiction is accurate management of pain.

3. Nausea and vomiting (N/V) (see also Chaps. 6, 32 and Table 50.1)

  a. Because nausea is highly subjective, a thorough assessment must be undertaken to identify all potential causes.
  b. Effective treatment geared to the specific emetic pathways can be accomplished with a thorough and accurate history and physical examination.

Table 50.1 Antiemetic agents [13–16]

Antiemetic agent	Action	Dosage	Side effects
Anticholinergics/ antimuscarinics	A direct depressant action on the VC An antispasmodic action on the gut *Useful for motion sickness and post-operative N/V (PONV)*	*Hyoscine* (scopolamine) SC, IV, IM 0.3–0.6 mg q4–8 hours prn *Glycopyrrolate* 1–2 mg q8–12 hours. *Useful with colicky N/V associated with mechanical bowel obstruction*	"Central cholinergic syndrome" (confusion, disorientation, visual hallucinations) may occur in the elderly Pupil dilation, blurred vision, drowsiness, urinary retention, and dry mouth
Antihistamines	Antagonize the action of histamine at the H_1 receptor *Useful for treating nausea associated with motion sickness, mechanical bowel obstruction, or ↑ ICP*	*Meclizine* 25–50 mg 3–4 times/day *Diphenhydramine* 25–50 mg po 3–4 times/day *Hydroxyzine* 25 mg po, IV 3–4 times/day	Drowsiness, blurred vision, confusion
Butrophenones/ phenothiazines	Dopamine (D_2) antagonists act primarily in the CTZ *First-line agents for most types of end-of-life N/V*	*Droperidol* IV, IM: 2.5–5 mg q3–4 hours *Haloperidol* 0.5 mg–5 mg q4–6 hours prn or routinely. Ceiling dose at 30 mg/day *Prochlorperazine* IV, IM, PR, or po: 5–20 mg q4–6 hours prn or routinely. Slow onset of action at 2–4 hours after peak plasma concentrations May increase to 1-2mg/kg as 1–2 mg/kg with increased risk of restlessness, sedation, and dry mouth. *Effective in PONV Chlorpromazine* IV, PR 25–50 mg q6–12 hours. Also effective for hiccups *Promethazine* (H_1-receptor antagonist) – avoid use due to excessive sedation and minimal efficacy	Sedation, hypotension, anticholinergic effects, and EPS (dystonia and akathisia) May prolong QT interval, provoking ventricular arrhythmias (more so with Droperidol) *Dexamethasone adds to efficacy of Haloperidol and Metoclopramide Dronabinol adds to Procholoperzine's efficacy for chemo-induced N/V Give Metoclopramide with Haloperidol only if Haloperidol is a low dose and EPS s/e are not present*

Table 50.1 (continued)

Antiemetic agent	Action	Dosage	Side effects
Steroids	Action not clear; may involve serotonin turnover in the CNS and mediate the cerebral cortex pathway to the VC *Considered second line and can be adjuvant as mentioned above* *Will stimulate appetite and reduce somatic and visceral pain*	*Dexamethasone* IV & po: 0.5–8 mg q6–12 hours	Euphoria, insomnia, hyperglycemia, HTN, and immunosuppression in long-term use *Used as a prophylactic agent for acute and delayed nausea d/t chemotherapy* *Synergistic with serotonin antagonists, metoclopramide, and phenothiazines*
Hormone, antidiarrheal	Globally decreases GI secretions. *Effective in refractory nausea, first line for bowel obstruction*	*Octreotide (Sandostatin) – must be given as a SQ injection 3 times/day. 50–100 mcg q8 × 48 hours. Or 10 mcg/h continuous infusion SC or IV*	Minimal
Neuroleptic Atypical Neuroleptic		*Quetiapine* 25 mg po BID and titrate *Olanzapine*: 2.5 mg po QD. May advance to 5–10 mg QD. *Perphenazine*: 8–16 mg po 2–4 times/day (ceiling dose: 64 mg/day; 24 mg in ambulatory patients)	Dizziness, hypotension, hyperkinesia, somnolence, nausea
Benzodiazepines	Amnesic and anxiolytic activity at the GABA receptors found in the cerebral cortex. *Not to be used as a single agent for N/V Most effective for anticipatory N/V associated with chemotherapy, abdominal radiotherapy, and other noxious treatments*	*Midazolam* Inj: 1,5 mg/ml q3 hours prn or 0.5–5.0 mg/h sc continuous infusion *Lorazepam* SC, IV & po: 1–4 mg q6–8 hours	Drowsiness, confusion, somnolence

Table 50.1 (continued)

Antiemetic agent	Action	Dosage	Side effects
Cannabinoids	Depresses the higher cortical pathways that stimulate the VC *Considered third-line therapy.* *Used instead of steroids in diabetic patients, or any other contraindication to steroids*	*Dronabinol (Marinol)* po: 2.5 q6–12 hours and titrate *Nabilone* po: 1–2 mg BID started 1–3 hours before chemotherapy (ceiling dose: 6 mg/day in 3 divided doses)	Sedation, euphoria, dysphoria, hallucinations, memory loss, and motor incoordination
Promotility agent/ substituted benzamide	Metoclopramide: At low doses – D_2 antagonist and $5HT_4$ agonist. At higher doses – $5HT_3$ antagonist. Also acts in the gastrointestinal tract by increasing motility. *First-line agent for most types of end-of-life N/V*	*Metoclopramide* IV & po: 10–20 mg. Q6 hours (reduce to compensate for renal failure) 2 mg/kg (over 15 minutes q2–3 hours × 3–6 doses for greater efficacy in cisplatin chemotherapy *Dexamethasone adds to efficacy* *Give Metoclopramide with Haloperidol only if Haloperidol is a low dose and EPS s/e are not present* *Trimethobenzamide* po: 300 mg q8 hours	Sedation, diarrhea, EPS *EPS can be relieved by lorazepam or diphenhydramine*
Serotonin antagonists	Block serotonin type 3 receptor on vagal afferent neurons in the GI tract Considered second and third line due to cost. Highly effective for chemo- and radiotherapy. Considered first line in patients with altered mental status d/t least amount of CNS effects	*Dolasetron (Anzemet)* IV & po: 100 mg q24 hours. Give 1 hour before chemotherapy or 2 hours before surgery *Granisetron* (Kytril) IV: 1 mg q24 hours. po: 1–2 mg q24 hours. Give 1 hour before chemotherapy and 12 hours later *Ondansetron* (Zofran) IV, po: 4–16 mg q8–12 hours *Palonosetron* po: 5 mg 1 hour before chemotherapy	H/A, constipation, occasional increases in liver transaminases

Table 50.1 (continued)

Antiemetic agent	Action	Dosage	Side effects
Substance P/ neurokinin 1 receptor antagonist		*Aprepitant* po: with a corticosteroid. 125 mg 1 hour before chemotherapy on day 1: 80 mg po in am of days 2 and 3 *Fosaprepitant* IV: with a corticosteroid. 115 mg 30 minutes before chemotherapy on day 1. 115 mg infused IV over 15 minutes on days 2 and 3, followed by 80 mg of aprepitant po in the am	

   c. An initial gastrointestinal (GI) assessment should include questions similar to:

      i. Does N/V occur prior to or after meals?
      ii. Does vomiting occur after nausea, or coughing, or without warning?
      iii. Is the N/V associated with colicky pain, diarrhea, fever, or chills?
      iv. Is there a pattern or specific times of the day that N/V occurs?
      v. Is it intermittent or continuous?
      vi. Any recent changes in bowel habits or medication regimen?
      vii. Any pain or burning sensations related to N/V?
      viii. Are there any other causes that you suspect are triggering the N/V?
      ix. Include information regarding appetite, dysphagia, food intolerance, allergies, pain, bowel habits, characteristics of N/V, and past abdominal history (surgeries, liver disease, chemo- or radiotherapy, etc.).
      x. Additional information includes a current medication list, along with a history of headache, vertigo, and anxiety.

   d. A physical examination should involve

      i. Inspection of the mouth for oral candidiasis or other oral lesions.
      ii. While auscultating the abdomen, high pitched or hyperactive bowel sounds may signify a partial or total obstruction.
      iii. Hypoactive or absent bowel sounds suggest an ileus.

   e. Laboratory tests should rule out fluid and electrolyte imbalances along with assessment of renal and liver function.
   f. Treatment

      i. The first-line treatment is to reverse any underlying causes.

        • The Education for Physicians on End-of-Life Care (EPEC) Project simplifies the major causes of nausea and vomiting to "11 M's of emesis." These causes include the following: metastases, meningeal irrita-

tion, movement, mentation, medications, mucosal irritation, mechanical obstruction, motility, metabolic, microbes, and myocardial.

  ii. Selection of the most effective antiemetic treatment involves identifying the suspected causes of N/V and identifying the pathway(s) causing N/V triggers.

- Choosing the antagonist most responsive to the identified receptor and the route of administration that will ensure the drug reaches the site of action are initial concerns.

  iii. Routine administration of the antiemetic, symptom reassessment, and medication titration are important in optimal treatment.

g. Intractable N/V

  i. Even with the identification of triggers and the implementation of receptor-specific antiemetics, a minority of patients develop intractable N/V.

  ii. Younger patients with pelvic malignancies, patients experiencing anxiety due to treatment or disease unknowns, and those identified with autonomic failure are high incidence populations of intractable N/V.

  iii. If symptoms persist and a single agent has been titrated to the maximum recommended dose, adding treatments that are specific to other receptors is frequently effective as more than one emetic pathway is often involved.

h. There are five classes of antiemetics drugs and a group of adjunctive drugs used to treat N/V (see Table 50.1).

  i. Empiric treatment begins with a single medication targeting the presumed mechanism of N/V.

  ii. Optimize the dose before adding a second medication with a different mechanism of action. Combination therapy may be required in some patients.

i. Chemotherapy-associated N/V

  i. Acute nausea/vomiting occurs within the first 24 hours after chemotherapy, typically within 1–2 hours with peak occurring at 4–6 hours.

  ii. Delayed nausea/vomiting occurs >24 hours after chemotherapy.

- Cisplatin: N/V peaks 48–72 hours after therapy and then gradually subsides for 2–3 days.
- This delay is also seen with carboplatin, cyclophosphamide, and the anthracyclines.
- The antineurokinin class is the first to show a definitive, yet small, effect.

  iii. *Anticipatory nausea/vomiting* is a conditioned response to previous negative experiences. It is a learned response—it is not mediated by the usual emetic neurotransmitters, although benzodiazepines have been used with some efficacy.

    j. Opioid-induced N/V

        i. Acute nausea is a side effect of initial opiate therapy and is thought to be due to the direct effects in the chemoreceptor trigger zone and the vestibular apparatus.

       ii. Antiemetic treatment should begin with opiate initiation anticipating this side effect.

     iii. Patients normally develop a pharmacologic tolerance to this side effect within 5–7 days of initiating therapy, and antiemetics can then be discontinued.

     iv. For some patients, changing to a different opioid is also effective.

      v. Nausea that emerges after chronic use is most likely due to diminished gut motility and constipation, causing pseudo-obstruction. Management is then directed at increasing gut motility and relieving constipation.

     vi. Combinations are required for patients with a variety of causes of nausea.

    vii. Anti-nausea therapy should maximize the dose of a drug of a single class before combining it with maximized doses of other classes. Combining low doses of drugs of the same classes should be avoided.

4. Mucositis (see also Chap. 31)

    a. The most predictable symptom in patients undergoing HCT.

    b. Usually observed within 5 days of beginning chemotherapy, with a peak in severity within 7–10 days post-therapy.

    c. Commonly occurs in patients receiving melphalan, cyclophosphamide, or total body irradiation.

    d. Prevention is considered the standard of care with adherence to oral evaluation and oral hygiene.

        i. Human keratinocyte growth factors such as palifermin (Kepivance®) were developed for mucositis prevention.

       ii. Currently, mucositis is managed with the use of topical oral formulations, such as equal parts of lidocaine and diphenhydramine (Benadryl®); plus aluminum sulfate, magnesium sulfate, or simethicone. Dexamethasone, ibuprofen, morphine, and other opioids can be added to the mixture.

     iii. Ketamine can improve pain from mucositis.

         • Based on current literature, dilute 20 mg of IV ketamine in 5 mL of artificial saliva substitute or normal saline, swish for 1 minute, and then spit every 3 hours.

     iv. Gelclair® is a concentrated bioadherent oral gel indicated for the relief and management of pain. Initial results were promising with this agent, but benefit did not outweight the cost of the medication.

      v. Rincinol®, an over-the-counter agent, has the same active ingredient as Gelclair® and is much less expensive.

vi. It may be necessary to couple topical therapy with an opiate treatment administered by a patient-controlled analgesia (PCA) device.

vii. Prevention of emesis also contributes to prevention/reduction of mucositis by avoiding local trauma.

e. Mucositis typically resolves with recovery of neutrophils. Until then, rigorous oral hygiene is necessary as the patient remains at high risk for infectious complications.

5. Diarrhea (see also Chap. 32)

a. HCT recipients may experience multiple episodes of diarrhea post HCT.

b. Management begins with an assessment of volume status and evaluation to identify the underlying cause.

i. Diarrhea-associated infections may involve *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Clostridium difficile*, *Candida*, *Cryptosporidium*, enteroviruses, adenovirus, rotavirus, or cytomegalovirus.

c. Most HCT recipients receive at least one course of antibiotics and are at a high risk of developing *C. difficile* infection.

i. *C. difficile* continues to develop antibiotic resistance, substantially increasing the prevalence and virulence of this opportunistic pathogen.

d. Acute graft-versus-host disease (GVHD) of the lower GI tract may also cause diarrhea resulting in depletion of protein stores.

i. Management of intestinal acute graft-versus-host disease (GVHD) consists of nutritional counseling, maintenance of fluid and electrolytes, corticosteroids and other immunosuppressive agents, and monitoring for secondary infectious complications.

ii. Once infectious causes have been ruled out, patients may find relief from careful titration of loperamide (Imodium®) 2–4 mg po after each loose stool, maximum dose 16 mg po daily, or Octreotide (Sandostatin®) by subcutaneous or IV bolus or continuous infusion.

6. Anorexia

a. A decrease in appetite is common due to high dose chemotherapy, pain, mucositis, N/V, constipation, diarrhea, and psychosocial issues.

b. Management must effectively improve the nutritional health of HCT patients.

c. Treatment-related dietary restrictions render food preparation more difficult and less palatable.

d. Consider total enteral or parenteral nutrition to supply nutrients.

e. Corticosteroids are known to be effective appetite stimulants. However, this option is not ideal for HCT patients as their effect is time limited and they result in muscle weakness/loss.

f. Megastrol (Megace®) can be used at doses ranging from 100 mg to 1600 mg/day titrated as necessary. This drug should be used cautiously with patients with a known history of thromboembolic disease.

g. Dronabinol (Marinol®) 2.5–5 mg po daily or BID once or twice a day has been shown to increase appetite and stabilize body weight. However, this therapy is less effective than megestrol for improving appetite and weight gain.

h. There is some evidence that eicosapentaenoic acid (EPA) improves appetite and weight gain; however, this remains under scrutiny.

i. Exercise has been shown to improve an overall sense of well-being, strength, endurance, and appetite. Aerobic exercise including weight training can prevent deconditioning and aid in recovery.

7. Delirium

a. Delirium is considered a cognitive disorder with changing consciousness manifesting in inattention, disorganized thinking, disorientation, memory impairment, or hallucinations.

b. Presentation can be acute in onset with fluctuation related to an underlying medical cause.

c. Associated with longer hospital stays, decrease in activities of daily living, increase in medical complications, loss of physical strength or function, and even death.

d. Haloperidol (Haldol®), risperidone (Risperdal®), olanzapine (Zyprexa®), and quetiapine (Seroquel®) are commonly used with scheduled dosing and additional doses as needed for agitation.

e. If delirium persists despite treatment, titration of the dose of antipsychotic is preferred rather than switching to another agent.

Summary

Palliative medicine specialists are an important member of the HCT treatment team, enhancing efforts to provide quality physical and emotional symptom management to recipients and their family members. Many health care settings have palliative medicine consultation teams available for all complex medical treatment plans. Consultation should be considered upon the diagnosis of all life-threatening illnesses, regardless of the treatment intention. Aggressive curative treatment deserves aggressive symptom management guided by specialists in the field of palliative medicine.

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Chapter 51
Long-Term Follow-Up and Survivorship

Susan Schubach Slater and Lisa K. Hansen

Introduction

There are multiple definitions of a cancer survivor. Some define survivorship as beginning with initiation of therapy, while others suggest it begins at completion of therapy, at 5 years after diagnosis, or at other points between initiation and completion of therapy.

The number of hematopoietic cell transplants (HCT) performed worldwide continues to increase with a parallel rise in survival rates. These increases are multifactorial in origin including extended age limits including individuals in their ninth decade of life, reduced intensity and non-myeloablative conditioning regimens, expanded indications, increasingly available alternative donor options, marked improvements in supportive care, and involvement of new specialties such as palliative care. In 2009, it was estimated there were approximately 109,000 transplant survivors in the United States (US). Using simulation models, it is estimated that by the year 2030, the number of HCT survivors in the US will increase to 500,000 with 25% of those survivors undergoing their transplant procedure at an age ≥60 years [1].

In 2005, the Institute of Medicine released a report entitled *From Cancer Patient to Cancer Survivor: Lost in Translation* recommending cancer patients be provided with a summary of their care and a clear follow-up plan on completion of therapy [2]. The American College of Surgeon's (ACS) Commission on Cancer endorsed this recommendation. This care plan should include:

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1. Diagnostic tests performed and results
2. Important disease characteristics including site, stage and grade, and cytogenetic or molecular markers
3. Type and dates of therapies delivered including surgery [site], chemotherapy [agents used, total doses], radiation therapy [site, total dosage], hormonal or gene therapy, and transplant details [conditioning regimen, graft-versus-host disease (GvHD) prophylaxis, donor match/source], as well as identifying data of clinical trials
4. Psychosocial, nutritional, and other supportive services delivered
5. Contact information for main providers and institutional details
6. A clear follow-up plan with evidence-based standards when possible along with identification of the coordinator for continuing care

The field of cancer survivorship has matured over the past 30 years with the support of the National Cancer Institute's Office of Cancer Survivorship and the LiveStrong™ Foundation (http://www.livestrong.org). Efforts within the HCT field have been coordinated by the National Marrow Donor Program (NMDP), the American Society for Transplantation and Cellular Therapy (ASTCT), the European Group for Blood and Marrow Transplantation (EBMT), and the Center for International Blood and Marrow Transplant Research (CIBMTR), along with patient advocacy groups such as the National Bone Marrow Transplant Link (see Table 51.1).

Studies have shown the mortality rate of HCT survivors typically plateaus around 6 years post-transplant [3]; however, additional data demonstrate HCT recipients face a significantly increased risk for chronic health conditions and premature death, even 10–15 years from their transplant procedure. The Bone Marrow Transplant Survivor Study (BMTSS) followed patients who survived at least 2 years post-HCT; data showed the conditional survival probability at 5 years after allogeneic HCT was 90%, and 80% at 15 years post-HCT [4]. Additionally, HCT survivors have a 6- to 14-fold risk of late mortality compared with the general population [5]. For autologous HCT recipients, mortality rate is also higher for the first 10 years of survivorship before approaching that of the general population [6].

Risks associated with increased late mortality post-HCT include older age at the time of transplant, unrelated donor transplantation, total body irradiation (TBI)-based conditioning regimens, and chronic graft-versus-host disease (GvHD) [5].

Many survivor's medical home remains with their HCT providers, while some patients successfully transition back to their primary care providers. Careful health surveillance, promotion of healthy lifestyle choices, and prompt management of medical conditions are essential to reduce non-relapse mortality and improve quality of life of HCT survivors.

Table 51.1 Resources for survivors and their caregivers

NCI Office of Cancer Survivorship	http://cancercontrol.cancer.gov/ocs/
LiveStrong™ Foundation	http://www.livestrong.org
National Marrow Donor Program	http://www.bethematch.org
National Bone Marrow Transplant Link	http://www.nbmtlink.org

An international working group led by the NMDP with contributors from the CIBMTR, ASTCT, EBMT, Asia-Pacific Blood and Marrow Transplant Group (APBMT), the Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ), the East Mediterranean Blood and Marrow Transplantation Group (EMBMT), and the Sociedade Brasileira de Transplante de Medula Ossea (SBTMO) has developed screening and preventive practice guidelines for HCT recipients (summarized in Table 51.2) [7]. The recommendations that follow will be focused on survivors who are alive more than 1 year post-HCT and are meant to be a general overview of complications and screening recommendations. For a more in-depth review, please refer to additional chapters within this text as referenced.

Table 51.2 Recommended screening and preventive practices for post-HCT patients

Recommended screening and prevention	Six months	One year	Annually
Liver			
Liver function testing	All	All	As indicated
Serum ferritin if patient received RBC transfusions		As indicated	As indicated
Respiratory			
Clinical pulmonary assessment	All	All	All
Smoking tobacco avoidance	All	All	All
Pulmonary function testing	cGvHD as indicated	Allo only	As indicated
Chest radiography	As indicated	As indicated	As indicated
Musculoskeletal			
Bone density testing (women, allo transplant, and patients with prolonged corticosteroid or calcineurin inhibitor use)		All	As indicated
Screen for corticosteroid-induced muscle weakness	cGvHD*	cGvHD*	cGvHD*
Physical therapy consultation as indicated	cGvHD*	cGvHD*	cGvHD*
Treatment of osteopenia with bisphosphonates		Those at risk	Those at risk
Kidney			
Blood pressure screening	All	All	All
Urine protein screening	All	All	As indicated
BUN/creatinine testing	All	All	All
Nervous system			
Neurological clinical evaluation		All	As indicated
Endocrine			
Thyroid function testing		All	All

(continued)

Table 51.2 (continued)

Recommended screening and prevention	Six months	One year	Annually
Growth velocity in children		All	All
Gonadal function assessment (prepubertal boys and girls)	All	All	All
Gonadal function assessment (post-pubertal women)		All	All
Vascular			
Cardiovascular risk factor assessment		All	All
Fasting lipid profile and blood glucose		All	All
Immune system			
Encapsulated organism prophylaxis	cGvHD*	cGvHD*	cGvHD*
PJP prophylaxis	All	cGvHD*	cGvHD*
CMV testing	cGvHD*	cGvHD*	As indicated
Consider antifungal prophylaxis	cGvHD*	cGvHD*	cGvHD*
Prophylaxis for VZV for those at risk	All	All	cGvHD*
Endocarditis prophylaxis with dental procedures-AHA guidelines	All	All	All
Immunizations—See Chap. 13, See Appendix 9	All	All	All
Second cancers			
Second cancer vigilance counseling		All	All
Breast/skin/testes self-exam		All	All
Clinical screening for second cancers		All	All
Pap smear, mammogram for women over age 40 (see text)		All	All
Psychosocial			
Psychosocial/QOL clinical assessment	All	All	All
Mental health counseling for recognized psychosocial problems	As indicated	As indicated	As indicated
Sexual function assessment	All	All	All
Oral complications			
Dental assessment, intraoral malignancy assessment	All	All	All
Ocular			
Ocular clinical symptom evaluation	All	All	All
Ophthalmologic exam of visual acuity and fundus		All	As indicated

All = Allogeneic and autologous patients; RBC = red blood cell; cGvHD* = chronic graft-vs-host disease. Recommended for any patient with ongoing chronic GvHD or immunosuppression; BUN = blood urea nitrogen; PCP = pneumocystis jiroveci pneumonia; CMV = cytomegalovirus; VZV = varicella zoster virus; AHA = American Heart Association; QOL = quality of life

As Indic. = Reassessment recommended for abnormal testing in a previous time period or for new signs/symptoms

Adapted from Majhail et al. [7]

Infection [7–11] (See Also Chap. 30)

The risk of serious infection persists in HCT recipients months to years after their procedure. Laboratory evidence of immune recovery generally occurs at 12 months for autologous patients but may be delayed in allogeneic recipients.

1. Risk factors for late infection

    a. Presence of chronic graft-versus-host disease (cGvHD)
    b. Ongoing immunosuppressive therapy (IST)
    c. Cord blood, HLA mismatched, or T-cell-depleted graft
    d. Presence of relapsed disease

2. Surveillance

    a. Complete blood count (CBC) at least annually
    b. Assessment of immune reconstitution (see also Chap. 29 for in-depth discussion)

        i. Immune reconstitution occurs more rapidly in recipients of peripheral blood stem cell products versus bone marrow products.
        ii. Higher numbers of donor-derived $CD4^+$ T cells early post-HCT may be predictive of improved long-term survival.
        iii. Post-allogeneic HCT monitoring of T, NK, and B-cell subsets (CD3, CD4, CD8, CD45RA/R0, CD56, CD16, CD19, CD20) and quantitative immune globulins at various milestones post-transplant will provide insight into immune function and therefore help inform ongoing risk of infectious complications.

    c. Cytomegalovirus (CMV) PCR based on risk factors including intensity of IST regimen, presence of cGvHD, post-HCT maintenance therapy, etc.

3. Interventions

    a. Antimicrobial prophylaxis (see also Chap. 10)

        i. Encapsulated bacteria prophylaxis due to impaired opsonization in HCT recipients who require extended IST; consideration should be given for those patients who are surgically/functionally asplenic.
        ii. Pneumocystis jirovecii pneumonia (PJP) prophylaxis for the first 6 months post-autologous HCT; continue for the duration of IST in allogeneic HCT recipients.
        iii. Varicella zoster virus (VZV) prophylaxis should continue for at least 1 year post HCT, longer in those patients who require prolonged IST.
        iv. Fungal prophylaxis is indicated for high-risk patients, specifically those with cGvHD requiring prolonged IST.
        v. Post-HCT vaccinations based on published guidelines (see Appendix 9 for a sample re-vaccination guideline).

Cardiovascular [7, 12–17] (See Chap. 34)

HCT survivors are four times as likely as the general population to develop cardiovascular (CV) disease than the general population. CV complications post-transplant include diseases of cardiac function such as heart failure, valvular disease and arrhythmias, and arterial disease such as coronary artery, peripheral vascular, and cerebrovascular disease. Many factors contribute to the pathogenesis of CV disease post-HCT (see Fig. 51.1).

1. Risk factors

   a. Cumulative anthracycline dose >550/m^2 daunorubicin equivalent
   b. Thoracic radiotherapy with heart in the radiation field, either before or after HCT
   c. TBI-based conditioning regimens resulting in increased risk of diabetes, endocrine dysfunction (growth hormone insufficiency, hypothyroidism, and gonadal dysfunction), sarcopenic obesity (obesity in the setting of low muscle mass in the major skeletal muscles), and endothelial damage
   d. Iron overload associated with multiple transfusions, especially those patients with iron stores documented by cardiac magnetic resonance imaging (MRI)
   e. Metabolic syndrome (see also Chap. 37)

      i. A constellation of hypertension, insulin resistance, abdominal obesity, elevated triglycerides, reduced HDL ➜ three of these five signs constitute metabolic syndrome
      ii. Patients with metabolic syndrome have a 2–3 times higher risk of developing cardiovascular disease.
      iii. Prevalence in HCT survivors is 2–3 times that of the general population.
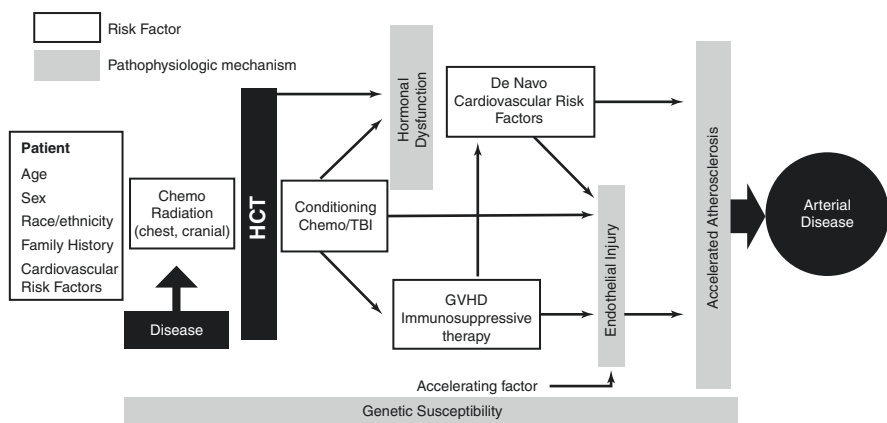
Fig. 51.1 Proposed multifactorial mechanism for accelerated atherogenesis and arterial disease in HCT survivors. (Reprinted with permission from Armenian et al. [13])

  f. Hypertension, both pre- and post-HCT, has been identified as one of the most important risk factors associated with CV disease.

  g. Traditional factors associated with CV disease including age, race, family history, tobacco use, sedentary lifestyle, and nutrition habits.

2. Surveillance

  a. Blood pressure screening at every visit with additional workup and management as per the American Heart Association (AHA) guidelines if hypertension identified

  b. Screening for cardiovascular risk annually

  c. Fasting lipid panel

    i. Standard-risk patients including autologous HCT recipients and patients without personal risk factors should be screened every 5 years for men age $\geq$35 and women age $\geq$45 years in accordance with the United States Preventative Services Task Force (USPSTF) recommendations.

    ii. Allogeneic HCT recipients should undergo initial post-HCT screening around day +100.

    • If normal indices and no additional risk factors, continue screening per USPSTF recommendations.

    • If ongoing transplant-related risk factors exist such as corticosteroid, calcineurin inhibitor (CNI), or sirolimus therapy, continue monitoring every 3–6 months.

  d. ECG or Holter monitoring as clinically indicated; routine screening is not recommended for asymptomatic patients or those without a concerning family history

  e. Echocardiography for patients identified as higher risk based on age at the time of transplant and cumulative radiation and anthracycline exposure

3. Interventions

  a. Early intervention for identified risk factors (i.e., hypertension, dyslipidemia, etc.)

  b. Encourage healthy lifestyle choices including cardiac prudent diet, exercise, and smoking cessation

  c. Endocarditis prophylaxis per AHA guidelines (see Chap. 10)

  d. Cardiology referral and evaluation as indicated

Pulmonary [7, 18, 19] (See Also Chap. 33)

Serious pulmonary complications generally develop during the first weeks or months post-HCT. However, pulmonary function can become compromised in long-term survivors as a consequence of late infection, obstructive, or restrictive disease.

1. Risk factors

   a. cGvHD
   b. Immunosuppressive medications
   c. CMV disease and other infections
   d. Conditioning regimens including busulfan, carmustine, or TBI. Melphalan is associated with pulmonary toxicity, but to a lesser degree.
   e. Pre-HCT pulmonary dysfunction
   f. Older age

2. Surveillance

   a. History and physical exam, including pulse oximetry
   b. Pulmonary function testing (PFT) for allogeneic recipients at 1 year. However, as early presentation of bronchiolitis obliterans is asymptomatic and prognosis is poor for symptomatic disease, consider PFT monitoring as early as 3 months post HCT.

      i. More frequent PFT monitoring (every 3–6 months) may be indicated in patients with cGvHD, identified dysfunction, or new clinical symptoms of pulmonary dysfunction

   c. Appropriate imaging for symptomatic patients (CXR, high-resolution CT chest without contrast with expiratory views)

3. Prevention and intervention

   a. Annual inactivated influenza vaccination for patients and close contacts
   b. Smoking cessation
   c. Education of patient and family on infection control measures to reduce exposure to community respiratory viral infections
   d. Prompt treatment of respiratory infections

Neurologic [7, 20–24] (See Also Chaps. 36 and 49)

Neurologic complications vary widely in incidence and severity. As the upper age limit for HCTs increases, so do the number of neurologic complications as older patients undergo this procedure. Decreased quality of life (QOL) and overall survival have been reported in HCT survivors with neurologic complications. The most common late effects are described below.

1. Cognitive dysfunction
   Pediatric HCT survivors suffer the greatest burden of neurologic effects post-HCT. Adult HCT patients can be plagued by cognitive dysfunction. However, the majority recover normal function by 1 year.

   a. Risk factors

      i. Patient age
     ii. Unrelated donor > matched sibling > autologous
   iii. Medications including calcineurin inhibitors (CNIs), methotrexate, busulfan, fludarabine, tyrosine-kinase inhibitors, and monoclonal. antibodies. Long-term CNI has been shown to be significant offender in the > age 70 subgroup.
    iv. Prior cranial radiation or intrathecal therapy
     v. Possible genetic predisposition (E4 allele of apolipoprotein)
    vi. Pre-existing cognitive deficits

   b. Surveillance and diagnosis

      i. Annual neurologic exam

        • Careful history from patient and family of intellectual, social, and physical functioning

     ii. Serum electrolytes, renal and liver function tests
   iii. MRI of brain if indicated
    iv. Referral for neurologic consultation and neuropsychological testing as indicated

   c. Interventions

      i. Treatment is individualized based on age, degree of cognitive disruption, and presumed etiology
     ii. Research suggests physical exercise improves cognitive function

2. Peripheral neuropathy
   Ten to 20% of patients treated for a malignant disease develop peripheral neuropathy which may impair mobility, increase fall risk, and may require chronic narcotic analgesia. Neuropathy symptoms may gradually improve.

   a. Risk factors

      i. History of treatment with neurotoxic chemotherapeutic agents (vinca alkaloids, platinum compounds, bortezomib, thalidomide, taxanes)
     ii. CNIs
   iii. Older age
    iv. Diabetes mellitus and liver disease can exacerbate pre-existing symptoms

   b. Interventions

      i. Gamma aminobutyric acid for painful neuropathy

        • Gabapentin (Neurontin®) beginning at 100–300 mg po qhs, increasing dose to 900–3600 mg daily in dose increments of 50–100% every 3 days. Slower titration recommended for elderly or medically frail patients. Dose adjust for renal insufficiency.

- Pregabalin (Lyrica®) 50 mg po TID; may be increased to 100 mg po TID. Slower titration recommended for elderly or medically frail patients. Dose adjust for renal insufficiency.

    ii. Antidepressants (e.g., duloxetine [Cymbalta®] 30–60 mg po daily) for burning pain
   iii. Narcotic analgesics
    iv. Topical application of compounded 2% amitriptyline and 1% ketamine
     v. Lidocaine topical patches (Lidoderm®)
    vi. Cannabidiol (CBD) preparation (where permitted) has anecdotal support
   vii. Acupuncture
  viii. Consider available clinical trials

3. Central nervous system (CNS) complications

   a. Includes vascular complications such as cerebrovascular accidents and CNI-induced neurotoxicity, infectious complications, leukoencephalopathy secondary to intrathecal chemotherapy, and secondary brain tumors
   b. Risk factors

       i. Infections
      ii. Metabolic encephalopathy
     iii. Intrathecal chemotherapy and/or cranial radiation
      iv. History of CNS disease
       v. Prolonged IST, especially with CNIs
      vi. cGvHD

   c. Surveillance

       i. Neurologic exam at least annually to screen for neurologic complications
      ii. Consider more specific testing in symptomatic patients

Hepatic [7, 25–27]

1. Hepatitis B virus (HBV) or hepatitis C virus (HCV) reactivation

   a. A large multi-institutional retrospective study showed no significant difference in the incidence of treatment-related mortality, survival, GvHD, and hepatic toxicity in HBV- and HCV-positive HCT recipients compared with controls with median follow-up of 5.9 years.
   b. HBV in post-HCT survivors typically manifests as mild to moderate disease
   c. HCV

       i. Often asymptomatic aside from fluctuating transaminases
      ii. Approximately 35% incidence of cirrhosis and end-stage liver disease related to chronic HCV among 40-year HCT survivors with progression to cirrhosis more rapid than in non-HCT patients.

- 11% at 15 years
- 24% at 20 years

 d. Interventions

  i. Monitor liver function tests at least annually.
  ii. Liver biopsy 8–10 years after HCT to assess for cirrhosis may be considered.

2. Iron overload

 a. Mainly transfusion-related, however ineffective erythropoiesis or hereditary hemochromatosis may contribute to development
 b. May be etiologic basis of elevated liver enzymes which is often overlooked by providers
 c. Associated with increased incidence of infection and non-relapse mortality
 d. Surveillance

  i. Serum ferritin is not a reliable predictor of tissue iron overload as ferritin is an acute phase reactant.
  ii. Consider Ferriscan® or T2 MRI or superconducting quantum interference devise (SQUID) as these are non-invasive and sensitive/specific for quantifying liver iron concentration.
  iii. Liver biopsy may be beneficial to rule out other potential etiologies of liver dysfunction.

 e. Interventions [28]

  i. Consider phlebotomy or chelation for patients with demonstrated liver iron concentration >5–7 mg/g dry weight liver iron and signs of liver dysfunction

   • Deferasirox

    – Exjade® 20 mg/kg po daily, rounded to the nearest whole tablet [125, 250, or 500 mg]; adjust dose every 3–6 months by 5–10 mg/kg based on serum ferritin trends. Max dose 40 mg/kg
    – Jadenu® 14 mg/kg po once daily, rounded to the nearest whole tablet [90, 180, or 360 mg tablets or sprinkle granules]; adjust dose every 3–6 months by 3.5–7 mg/kg based on serum ferritin trends. Max dose 28 mg/kg

   • Deferoxamine (Desferal®)

    – 20–40 mg/kg/day SQ over 8–24 hours daily
    – 40–50 mg/kg/day IV over 8–12 hours, 5–7 days/week

3. Chronic GvHD

 a. Main clinical finding is elevated liver enzymes, specifically serum alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transpeptidase; rarely is hyperbilirubinemia observed except in late-stage disease.

   b. Consider liver biopsy to rule out alternative etiologies prior to initiation of immune suppression.

Ocular [7, 29–31]

1. Keratoconjunctivitis sicca syndrome

   a. Typically a manifestation of cGvHD with signs/symptoms including

      i. Inflammatory destruction and fibrosis of the conjunctiva and lacrimal glands.
      ii. Decreased goblet cell density.
      iii. Decreased tear production with low tear turnover rate, high evaporation and osmolarity, and an unstable lipid layer.
      iv. Patient symptoms include complaints of dry eye, photophobia, wind-intolerance, and/or foreign body sensation.
      v. May progress to corneal ulceration or perforation.

   b. Develops in 40–60% of allogeneic HCT recipients and 60–90% of patients with GvHD

   c. Treatment Options

      i. Preservative-free saline drops, ointments, or gels prn
      ii. Steroid eye drops (ensure patient has no signs of viral or bacterial keratitis before initiation)
      iii. Cyclosporine eye drops (Restasis®) although this medication is generally poorly tolerated due to burning with instillation
      iv. Lifitegrast (Xiidra®) ophthalmic solution 5%; decreases inflammation by inhibiting the release of pro-inflammatory cytokines
      v. Punctual plugs
      vi. Hyprolose (Lacrisert®)
      vii. Antibiotic drops
      viii. Scleral lenses
      ix. Autologous serum eye drops
      x. Platelet-rich plasma preparation ocular drops are currently under study

2. Cataracts

   a. Risk factors

      i. TBI; single dose > fractionated dosing
      ii. Prolonged steroid therapy
      iii. Allogeneic > autologous transplant recipients

   b. Incidence varies widely due to differences in conditioning regimens, supportive care, and length of follow-up

3. Ischemic microvascular retinopathy

    a. Patients present with decreased visual acuity or abnormalities in color vision

    b. Clinic examination may reveal cotton wool spots, telangiectasias, microaneurysms, retinal hemorrhage, and/or optic disc edema

    c. Conditioning regimens including busulfan, carmustine or TBI, steroid and/or cyclosporine use, and hypertension may contribute to development

    d. Prevention/treatment

        i. Avoid causative agents when possible.

        ii. Maintain therapeutic levels of cyclosporine with withdrawal of drug if symptom develops.

        iii. Treat hypertension.

    e. Typically resolves within 2–4 months of presentation and permanent loss of vision is rare therefore aggressive intervention is not indicated

4. Surveillance

    a. Annual evaluation by an ophthalmologist experienced with post-HCT complications beginning 1 year after HCT or sooner as needed for symptoms

Oral [7, 32–34] (See Also Chap. 31)

1. Risk factors for oral complications include

    a. Oral cGvHD

    b. History of radiation to the head/neck

    c. Underlying diagnosis of Fanconi anemia

    d. Age of the patient at time of HCT

2. cGvHD of the oral mucosa and/or salivary gland

    a. Signs/symptoms include oral ulcerations and erythema with formation of lichen planus, mucoceles, and pseudomembranes, oral pain or dry mouth, intolerance of spicy/acidic foods or toothpaste, and difficulty swallowing.

    b. Sclerotic changes of the oral mucosa and lips as well as Cushingoid changes related to prolonged steroid therapy may result in decreased oral opening (purse string changes on examination)

3. Xerostomia due to medications or cGvHD

    a. May result in increased incidence of dental caries, periodontal disease, and/or cancer of the oropharynx

4. Squamous cell carcinoma

    a. May arise from the buccal mucosa, salivary glands, gingiva, lip, or tongue

    b. Higher risk in patients with Fanconi anemia and those with history of cGvHD of the oral mucosa

5. Surveillance

    a. Close attention to oral mucosa at every visit with oral examination by a dental professional every 6 months for patients at high risk and every 12 months for lower-risk patients.

    b. Encourage healthy behaviors including preventative oral health, avoidance of smoking and smokeless tobacco, avoidance of sugar-containing beverages and intraoral piercings.

6. Interventions

    a. Fluoride-containing toothpaste and/or oral rinse for patients with decreased saliva production to decrease the incidence of dental caries.

    b. Consider topical steroid preparations (dexamethasone mouth wash, beclomethasone ointment), topical CNI preparations, systemic or intrabuccal steroid injections for treatment of oral GvHD. Additionally PUVA or photobiomodulation therapy may be beneficial along with oral physical therapy exercises.

    c. Additionally, patients should follow the AHA recommendations for endocarditis prophylaxis with dental procedures.

Endocrine [7] (See Also Chap. 37)

1. Hypothyroidism [35–37]

    a. Hypothyroidism is a common late complication of both autologous and allogeneic HCT recipients

       i. Estimated to occur in 7–50% of HCT recipients depending on their pre-HCT treatment and the HCT conditioning regimen

      ii. Typically occurs within the first 2–3 years post HCT; however, this diagnosis has occurred as late at 14 years post-treatment

    b. Less commonly, autoimmune thyroiditis and thyroid neoplasms may occur post-HCT

    c. Risk factors

       i. TBI; single dose > fractionated dose

      ii. Age at the time of transplant

     iii. Involved field radiotherapy to the neck region

     iv. High-dose alkylating agents in conditioning regimen (busulfan, cyclophosphamide)

      v. Prolonged corticosteroid therapy

     vi. Family history

   d. Surveillance

       i. Annual thyroid function testing including thyroid-stimulating hormone (TSH), T3 and free T4

   e. Interventions

       i. Thyroid hormone replacement as indicated

2. Hypogonadism [7] (see also Chaps. 39 and 40)

   a. Ovarian failure [38, 39]

       i. Incidence varies among female HCT recipients based on pre-transplant exposures, HCT conditioning regimen, and age at the time of transplant

           • Highest risk in patients who receive TBI or busulfan
           • Lower risk in patients who are treated with cyclophosphamide alone

       ii. Typically irreversible in adults
       iii. Surveillance

           • Annual gynecologic exams to evaluate for symptoms associated with early menopause and/or cGvHD such as vaginal atrophy

       iv. Interventions

           • Consider early hormone replacement therapy to increase libido, decrease vaginal atrophy, and prevent cardiovascular and osteoporotic complications of early menopause.
           • Vaginal lubrication, dilators
           • Individual and couples counseling

   b. Germ cell damage [40–42]

       i. Effects ~92% of male HCT recipients

           • Highest risk in patients who receive high-dose radiation or chemotherapy

       ii. Surveillance

           • Testosterone levels recommended based on symptoms

       iii. Interventions

           • Consider testosterone replacement therapy with frequent monitoring for complications

               – Injectable esters (Depotestosterone®, Delatestryl®)
               – Implantable pellets (Testopel®)
               – Patches (Testoderm®, Androderm®)
               – Transdermal gel (AndroGel®, Testim®, Fortesta®, Axiron®)
               – Buccal (Striant®)

3. Diabetes [4, 17, 43]

    a. Steroid-induced diabetes is common in allogeneic transplant patients requiring corticosteroids for control of GvHD.

    b. Metabolic syndrome (see section "Cardiovascular" above) predisposes patients to type II diabetes and cardiovascular disease.

    c. Findings from the BMTSS revealed that allogeneic HCT recipients were 3.7 times more likely to report a diagnosis of diabetes than their matched sibling cohort. Obesity and at least two components of metabolic syndrome were increased nearly threefold in childhood cancer survivors.

    d. Risk factors

        i. Corticosteroid therapy
        ii. Obesity
        iii. Family history of diabetes
        iv. Physical inactivity
        v. Pre-transplant insulin resistance

    e. Surveillance

        i. For standard-risk patients (autologous transplant recipients, patients who are not overweight without CV risk factors) $\geq$ age 45, check blood glucose or HgbA$_1$c every 3 years.
        ii. For high-risk patients (including patients receiving high-dose steroids), check fasting glucose around day +100, then every 3–6 months.

    f. Interventions

        i. Hypoglycemic agents
        ii. Lifestyle modification for weight loss, increased physical activity
        iii. Close monitoring for cardiovascular risk factors

Musculoskeletal Complications [7, 44–47] (See Also Chaps. 37 and 39)

1. Osteopenia/osteoporosis

    a. Compression fractures occur in 30–50% of patients within the first 5 years of chronic steroid therapy

        i. The incidence is related to the dose and duration of steroid therapy
        ii. Compounded by additional non-HCT-related risk factors such as age, menopause, physical inactivity, family history, smoking history, and underlying malignancy
        iii. May result in increased morbidity due to significant pain and decreased mobility, diminished quality of life

    b. Post-transplant risk factors

        i. Chronic corticosteroid therapy
       ii. Therapy-induced menopause or hypogonadism
     iii. Renal dysfunction resulting in wasting of calcium and/or magnesium and decreased vitamin D production
     iv. Use of calcineurin inhibitors

    c. Surveillance

        i. Patients should be counseled regarding their risk for osteoporosis.
       ii. Dual energy x-ray absorptiometry (DEXA) at 1 year post-transplant, then as needed based on findings.

    d. Interventions

        i. Calcium and vitamin D supplementation
       ii. Regular weight-bearing exercise as tolerated
     iii. Vitamin D supplementations if deficiency identified
     iv. Pharmacologic interventions if indicated; dental evaluation prior to initiation of bisphosphonates with frequent follow-up exams to evaluate for osteonecrosis of the jaw
      v. Consider estrogen replacement for women after evaluation of risk–benefit ratio
     vi. Consider a preventative approach in patients requiring chronic steroid therapy including calcium and vitamin D supplementation, correction of vitamin D deficiency, and physical therapy for implementation of a strategy of weight-bearing exercise and fall prevention.

2. Avascular necrosis (AVN)

    a. AVN is a late complication with a reported incidence of 4–19%.
    b. Commonly affects weight-bearing joints in a bilateral distribution.

        i. Hips are most commonly affected; however, knees, ankles, and wrists may also be affected.

    c. Risk factors

        i. Corticosteroid therapy, typically with prolonged exposure, however may occur with a short course or low-dose therapy.
       ii. TBI, particularly high total doses.

    d. Surveillance and diagnosis

        i. Careful patient history, focusing on quality, intensity, and duration of joint pain
       ii. MRI of symptomatic joints

          • Plain films do not show early changes of AVN

   e. Interventions

      i. Analgesia
      ii. Orthopedic devices
      iii. Core decompression to relieve pressure and create channels for new blood vessels to improve blood flow to the joint
      iv. Definitive treatment requires total joint replacement

3. Myopathy

   a. Proximal muscle weakness, typically affecting the quadriceps, is a frequent complication of protracted corticosteroid use.
   b. Risk factors

      i. Protracted corticosteroid therapy
      ii. Inactivity

   c. Surveillance and diagnosis

      i. Patient history
      ii. *Timed Up and Go Test* which measures the time it takes a person to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down

   d. Interventions

      i. Physical therapy consult with home safety evaluation as indicated
      ii. Durable medical equipment as indicated (e.g., cane, walker, bedside commode, shower chair)

Second Malignancies [7, 48–50] (See Also Chap. 43)

1. Individuals diagnosed with a malignancy are twice as likely to develop a second cancer as age and gender-matched individuals who lack a cancer history. For HCT survivors, the risk is magnified 2–3 times.
2. The incidence of secondary malignancies in HCT survivors is estimated to be 3–4% at 10 years and 10–12% at 15 years post-HCT.
3. Risk factors

   a. Diagnosis of Hodgkin lymphoma
   b. Radiation therapy including TBI
   c. Antithymocyte globulin-containing preparative regimens
   d. Long-term immunosuppressive therapy
   e. Chronic GvHD

4. Secondary malignancies in HCT survivors

   a. Basal and squamous cell carcinomas
   b. Squamous cell carcinoma of the oral cavity with a higher incidence in patients with a history of oral cGvHD
   c. Solid tumors of the liver, cervix, thyroid, bone/connective tissue, breast
   d. Central nervous system tumors
   e. Non-Hodgkin lymphomas
   f. Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)
   g. Post-transplant lymphoproliferative disorder (PTLD)

5. Surveillance

   a. Physical exam with specific attention to signs and symptoms of secondary malignancies
   b. Annual dermatology evaluation
   c. CBC, comprehensive chemistry
   d. Routine cancer screenings per the American Cancer Society recommendations including mammography, cervical cancer screening, colonoscopy, etc. (http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer)

      i. For females who received TBI or chest radiation, screening mammography should begin at age 25, or no later than 8 years from radiation therapy, whichever comes first.

6. Counseling and Interventions

   a. Survivor counseling regarding increased risk with instruction on self-monitoring for signs and symptoms.
   b. Lifestyle modifications to reduce risk: smoking avoidance, heart healthy diet, exercise to maintain normal weight.
   c. High sun-protective factor sunscreen and sun-protective clothing.
   d. PTLD may be effectively managed, as first line, with a reduction in immuno-suppressive medications and administration of anti-B-cell monoclonal antibody therapy (e.g., rituximab).

7. Outcome of secondary MDS/AML is generally poor despite aggressive therapy.

Sexuality and Reproductive Issues (See Chaps. 39 and 40 for In-Depth Discussion and Review) Psychosocial Concerns [51–53]

1. Depression, anxiety, and post-traumatic stress disorder (PTSD) compound the physical challenges associated with long-term recovery from HCT.
2. Astute clinicians will include a careful history to screen for depression and psychosocial adjustment disorders during follow-up visits.

3. Formal quality of life (QOL) studies indicate that autologous HCT recipients enjoy excellent QOL at 1 year post HCT; however, 31% of allogeneic recipients report a poor QOL post-transplant with significant improvements at >5 years post-HCT.

   a. QOL is generally higher in younger HCT recipients
   b. Negative contributors to QOL

      i. Chronic extensive GvHD
      ii. Older age at time of transplant
      iii. Short term follow-up

4. Multiple factors may influence patient's ability or desire to adhere to recommendations for screening and preventive measures including financial/insurance concerns, physical functioning or restrictions, or lack of knowledge or education.

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Chapter 52
CAR T Cells for Hematologic Malignancies

Craig W. Freyer and David L. Porter

Introduction

The ability of T cells to fight cancer has been recognized for many years. Early examples include the observation of a T-cell-mediated graft vs. leukemia effect in patients undergoing allogeneic hematopoietic cell transplant (alloHCT), the ability of donor lymphocyte infusions (DLI) to rescue post alloHCT relapse in chronic myeloid leukemia (Chaps. 44, 55), and adoptive transfer of tumor infiltrating lymphocytes for melanoma. Checkpoint inhibitors antagonize programmed cell death protein-1 (PD-1), PD ligand-1 (PDL-1), or cytotoxic T lymphocyte associated antigen-4 (CTLA-4), resulting in T cell activation and antitumor effect in solid and hematologic malignancies. Bispecific T cell engager (BiTE) molecules such as blinatumomab bring T cells and tumor cells together, resulting in T-cell-mediated tumor cell lysis (see Chap. 57). The culmination of these efforts to elicit an antitumor T cell response may be the emergence of chimeric antigen receptor (CAR) T cells, which to date have demonstrated unprecedented efficacy in relapsed/refractory (RR) B cell malignancies while associated with unique toxicities.

1. *What is a chimeric antigen receptor (CAR) T cell?* [1, 2]

   a. An autologous or allogeneic T cell genetically modified to express a chimeric antigen receptor (a fusion protein surface receptor against a tumor surface antigen).

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b. Cell modification occurs typically using a lentiviral or retroviral vector, or possibly transposon/transposase systems using DNA plasmids, leading to permanent integration of the CAR gene into the host cell genome. Non-viral genetic transfer techniques include RNA electroporation, leading to transient CAR expression which may limit toxicity.

c. The CAR contains:

   i. An extracellular immunoglobulin-derived single-chain variable fragment
   ii. A hinge region
   iii. A transmembrane domain
   iv. An intracellular signaling domain (containing the T cell receptor signal transduction molecule CD3ζ) and for "second generation" CARs, a costimulatory molecule (typically either 4-1BB or CD28)

d. The CAR enables HLA-independent T cell activation; antigen processing and presentation on major histocompatibility complex (MHC) molecules is unnecessary, which is advantageous as cancer cells may downregulate HLA to avoid antitumor immune surveillance. As a consequence of MHC independence, only extracellular surface antigens can be the molecular targets for CAR T.

e. CAR T cells can undergo physiologic trafficking to sites containing cells that express the target antigen.

f. Upon binding its target, CAR T activation occurs, resulting in pro-inflammatory cytokine release, tumor cell death, and potentially massive CAR T cell expansion. The release of tumor antigens from dead cells can further augment the antitumor immune response by stimulating both CAR T and non-CAR T cells (cross priming).

g. CAR T cells can persist for years in the peripheral blood and bone marrow to maintain antitumor surveillance following remission in patients with B cell malignancies.

2. *Generations of CAR T development* [1, 2]

a. First-generation CAR T contained only the activating signal transduction molecule CD3ζ, resulting in limited cellular activation and expansion. Clinical responses were not sustained.

b. Second-generation CAR T contain CD3ζ and typically either CD28 or 4-1BB (CD137) costimulatory domains, leading to dual activation signaling.

   i. Costimulatory domain selection may influence rate of CAR T expansion, persistence, and risk of T cell exhaustion; all appear greater with CD28 compared to 4-1BB.

c. Third-generation CAR T cells are in development and contain >1 costimulatory molecule (CD28 and 4-1BB or OX40 [CD134]) [3].

d. Fourth-generation CAR T are in development. They have additional modifications to enhance antitumor effect such as secretion of cytokines upon CAR activation or inclusion of signals that prevent CAR T cell inhibition and/or

exhaustion. The term "armored CARs" has been coined to describe some of these constructs [3]. Possibilities for new CAR constructs are discussed below.

3. *Preparation for CAR T cell therapy* Fig. 52.1

    a. Autologous T lymphocytes are collected via leukapheresis [1–5].

       i. It may be difficult to collect and manufacture CAR T cells from patients who are lymphopenic, whether due to their underlying disease or due to prior therapies.

      ii. For commercial products currently available, the leukapheresis product is frozen (tisagenlecleucel/tisa-cel [Kymriah®]) or shipped fresh (axicabtagene ciloleucel/axi-cel [Yescarta®]) to a central manufacturing facility.

    b. T cells are isolated from the leukapheresis product followed by introduction of the genetic sequence containing the CAR gene typically with a viral or plasmid vector containing the CAR sequence.

    c. T cells containing the CAR gene are expanded ex vivo prior to administration, frozen and shipped to treatment facility to be reinfused to the patient. The entire process of leukapheresis, cell manufacturing, and reinfusion can take 2–4 weeks.

    d. Patient preparation and cell reinfusion can be summarized as follows:

       i. "Bridging therapy" may be needed for disease control during manufacturing, depending on the disease burden and rate of growth. The role and
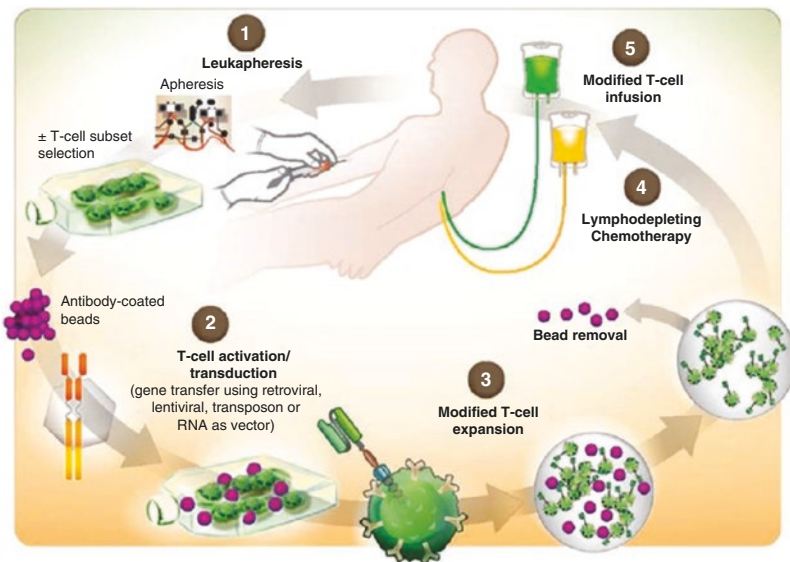
Fig. 52.1 Overview of T cell collection, CAR T manufacturing, and patient preparation for tisagenlecleucel. (Reproduced from Frey NV, Porter DL. CAR T-cells merge into the fast lane of cancer care. Am J Hematol 2016;91:146–50 (ref 45)

necessity for bridging therapy is not well defined, particularly in NHL. For instance, bridging therapy was not allowed in the pivotal ZUMA-1 trial [6] that led to the US Food and Drug Administration (FDA) approval for axi-cel, while it was permitted in the pivotal JULIET trial [7] that led to approval of tisa-cel.

  ii. Within a few days to 2 weeks prior to CAR T infusion, the patient typically receives lymphodepleting chemotherapy (LDC). LDC may promote homeostatic proliferation of the infused CAR T cells, limit host-immune-mediated rejection of the CAR T cells, and provide additional disease control until CAR T expansion.

  iii. The choice of LDC may impact outcomes after CAR T cells.

- Initial LDC regimens consisted of single-agent cyclophosphamide. Addition of fludarabine to cyclophosphamide further promotes CAR T expansion and persistence and improves overall response rates (ORR) [8].
- Bendamustine may also be used, particularly in patients with NHL but has not been compared directly to other LDC regimens [4, 7].

  iv. Patients who are markedly lymphopenic may not require LDC.

e. Patient selection

  i. Performance status and comorbidities may determine if a patient will tolerate potentially life-threatening toxicities such as cytokine release syndrome (CRS) and neurotoxicity (see Chap. 58).

  ii. A sufficient absolute lymphocyte count (ALC) is required. Some guidelines recommend ALC > 500 cells/mcL (or a peripheral blood CD3 count of >150 cells/mcl) to collect adequate T cells for manufacture [9, 10].

  iii. Lymphotoxic therapies must be discontinued in advance of leukapheresis to permit drug washout and avoid impairment of T cell collection.

  iv. CAR T cells manufactured from patients with relapsed disease after allo-HCT are typically donor-derived. After infusion of the CAR T product, therapeutic results can be achieved in the absence of significant GvHD [11].

- For the NHL trials of axi-cel and tisa-cel, patients with prior alloHCT were excluded [6, 7].
- For acute lymphoblastic leukemia (ALL) trials, patients with a prior alloHCT could not be on systemic immunosuppressants. Patients with grade 2–4 GvHD and extensive chronic GvHD were excluded [12].
- Original clinical trials excluded patients with active malignant central nervous system (CNS) involvement or primary CNS lymphoma [6, 7, 12].

4. *Currently FDA-approved CAR T Cells*

a. B cell ALL: Tisagenlecleucel (tisa-cel) [Kymriah®], FDA approved 8/30/17 [4].

  i. Created using a lentiviral vector and a 4-1BB costimulatory domain.

ii. Current approval: RR B cell ALL in second or later relapse in patients ≤25 years old.

iii. FDA approval is based on the phase 2 ELIANA trial ($N = 75$) [12].

iv. Patient characteristics: median age 11 years (range 3–23 years), median 3 prior therapies, 61% with prior alloHCT, and high disease burden (median 74% marrow blasts).

v. LDC (fludarabine + cyclophosphamide) was received by 96% of patients, followed by tisa-cel $0.2–5.4 \times 10^6$ cells/kg.

vi. Complete remission (CR) or complete remission with incomplete count recovery (CRi) obtained in 81% of patients, all of whom were minimal residual disease (MRD) negative.

vii. 12-month relapse free survival (RFS): 59%, 12-month overall survival (OS): 76%. Only 11% of patients received a subsequent alloHCT.

viii. Most relapses were due to loss of CD19 expression ("antigen-escape").

ix. B cell aplasia is a surrogate for CAR T persistence in ALL and appears necessary to maintain remission. Median duration of CAR T persistence in the peripheral blood was 168 days in responding patients.

x. Adverse events (AE).

- CRS: 77% all grade, 46% grade 3–4 (graded using PENN scale).

  – Median onset 3 days, 37% received tocilizumab (Actemra®, RoActemra®).

- Neurologic events: 40% all grade, 13% grade ≥3 (graded using NCI CTCAE v4.03).
- Grade 3–4 infections: 24%.
- All responding patients had B cell aplasia and most received immunoglobulin supplementation (IVIG).

b. NHL:

i. Axicabtagene ciloleucel (axi-cel) [Yescarta®], approved 10/18/17 for adults with RR large B cell lymphoma after 2 or more lines of therapy, including diffuse large B cell lymphoma (DLBCL), DLBCL arising from follicular lymphoma (FL), high-grade B cell lymphoma, and primary mediastinal B cell lymphoma [5].

- Created using a retroviral vector and a CD28 costimulatory domain.
- FDA approval is based on the phase 2 ZUMA-1 trial ($N = 101$) [6, 13].
- Patient characteristics: median age, 58 years (23–76 years); 69% had at least 3 prior lines of therapy and 21% had prior autologous HCT (autoHCT).
- All patients received LDC (fludarabine + cyclophosphamide) followed by axi-cel 2×10^6/kg.
- Bridging chemotherapy not permitted.
- The ORR was 83% with CR observed in 58% of patients.
- The median progression-free survival (PFS) was 5.9 months. OS at 18 months was 52%.
- 27% of patients that relapsed were found to have lost CD19 expression.

- Median duration of CAR T persistence in the peripheral blood was 32 days.
- AE
  – CRS: 94% all grade, 11% grade 3–4 (graded using the Lee scale).

    Median onset 2 days; 43% received tocilizumab.

  – Neurologic events: 87% all grade, 32% grade ≥3 (graded using NCI CTCAE v4.03).
  – Grade ≥3 infections occurred in 28% of patients.
  – Hypogammaglobulinemia (all grades) was observed in 15% of patients.

ii. Tisagenlecleucel (tisa-cel) [Kymriah®], FDA approved 5/1/18 for adults with RR large B cell lymphoma after 2 or more lines of therapy, including DLBCL, DLBCL arising from FL, and high-grade B cell lymphoma [4]

- Approval based on the phase 2 JULIET trial ($N = 93$) [7]
- Patient characteristics: median age, 56 years (22–76 years); 52% had at least 3 prior lines of therapy; 58% had prior autoHCT.
- Most patients (93%) received LDC (73% received fludarabine + cyclophosphamide; 20% received bendamustine). Patients received a median tisa-cel dose of 3×10^8 cells ($0.1–6 \times 10^8$ cells).
- Bridging chemotherapy was received by 92% of patients.
- The ORR was 52% with CR observed in 40% of patients.
- The 12-month RFS was 65% and median OS was 12 months.
- Median duration of CAR T persistence was 289 days in responding patients.
- AE
  – CRS: 58% all grade, 22% grade 3–4 (graded using the PENN scale).

    Median onset 3 days; 14% received tocilizumab.

  – Neurologic events: 21% all grade, 12% grade ≥3 (graded using NCI CTCAE v4.03).
  – Grade ≥3 infections occurred in 20% of patients.
  – 30% of patients received IVIG supplementation to manage hypogammaglobulinemia.

Note added in proof: Brexucabtagene autolecuel (Tecartus®) was approved July 24, 2020 by the FDA for the treatment of adult patients with relapsed/refractory mantle cell lymphoma, representing the third FDA approved CAR-T product.

c. General principles of CAR T in NHL

  i. Clinical responses are dynamic and may improve with continued CAR T persistence. Patients with stable disease and partial responses may ultimately obtain CR with long-term follow-up [6, 7, 13].

- Up to one-half of patients with a PR at 1 month post-infusion will achieve CR at 3 months.
- Many patients with a PR or CR at 1 month post-infusion may progress by 3 months.
- The majority of relapses occur within 6–12 months after CAR T cell infusion.

ii. Unlike ALL, B cell aplasia and CAR T persistence do not appear necessary for long-term remissions in NHL. Some patients had B cell recovery with ongoing CR at 3 or 6 months following tisa-cel [7].

iii. It is currently not possible to directly compare axi-cel and tisa-cel for NHL. The approval trials had different inclusion criteria and treatment parameters. For instance, ZUMA-1 did not permit bridging chemotherapy while JULIET did. This variance may have selected for different patient populations (i.e., patients requiring bridging therapy may have more aggressive disease) [6, 7, 13].

5. *Practical considerations for the clinical use of currently approved CAR T products* [4, 5]

   a. Premedicate with acetaminophen and H1 antihistamine to prevent infusion reactions. Steroid pre-medications are avoided due to concerns for impairing CAR T viability.

   b. Two doses of tocilizumab (8 mg/kg/dose) must be available on site for administration within 2 hours of ordering for management of CRS per FDA mandate.

   c. Commercial CAR T cell products require a Risk Evaluation and Mitigation Strategy (REMS) program, requiring all healthcare personnel who prescribe, dispense, or administer CAR T to be trained in toxicity management to ensure safe utilization. This is a mandatory FDA requirement for each CAR T commercial product.

   d. While most cases of neurotoxicity occur within 4 weeks of CAR T infusion, manufacturers currently advise avoidance of driving and operating heavy machinery for at least 8 weeks following CAR T infusion.

   e. Hypogammaglobulinemia may occur following CD19 targeted CAR T, is likely dependent upon the expansion and persistence of CAR T, and appears to be longer lasting in patients with ALL compared to NHL [6, 7, 12, 13].

      i. The use of IVIG supplementation may be personalized without definite recommendations [9, 10].

         - IVIG is advised for high-risk patients with IgG levels <400 mg/dL.
         - IVIG is advised for patients with hypogammaglobulinemia in the setting of recurrent infections.
         - IVIG is advised for any patient with IgG levels <200.
         - The routine use of IVIG in patients with hypogammaglobulinemia without high-risk features or recurrent infections is unclear.

f. There are no formal recommendations available regarding revaccination in patients following CAR T therapy. Limited data suggest humoral immunity to various vaccines may be maintained by CD19(−) long-lived plasma cells [14].

g. Secondary malignancies from insertional mutagenesis could theoretically occur but have not yet been described. Long-term follow-up of at least 15 years post-CAR T infusion is mandated to screen for long-term toxicities.

h. The lentiviral vector used to manufacture tisa-cel may cause a false-positive HIV test.

6. *Future directions in CAR T research*: There are many approaches that could enhance CAR T cell therapy and address some of the current limitations; these are in preclinical or early clinical development. (It is notable that naming of these approaches fairly consistently sticks with the automotive theme of this type of cell therapy!) See Fig. 52.2.

a. Targeting multiple antigens

i. In ALL, relapse with CD19 negative disease is the major limitation to successful therapy. Engineering CARs against ≥1 antigen within a single T cell or sequentially infusing more than 1 CAR T cell product against different antigens may limit the risk of antigen escape.
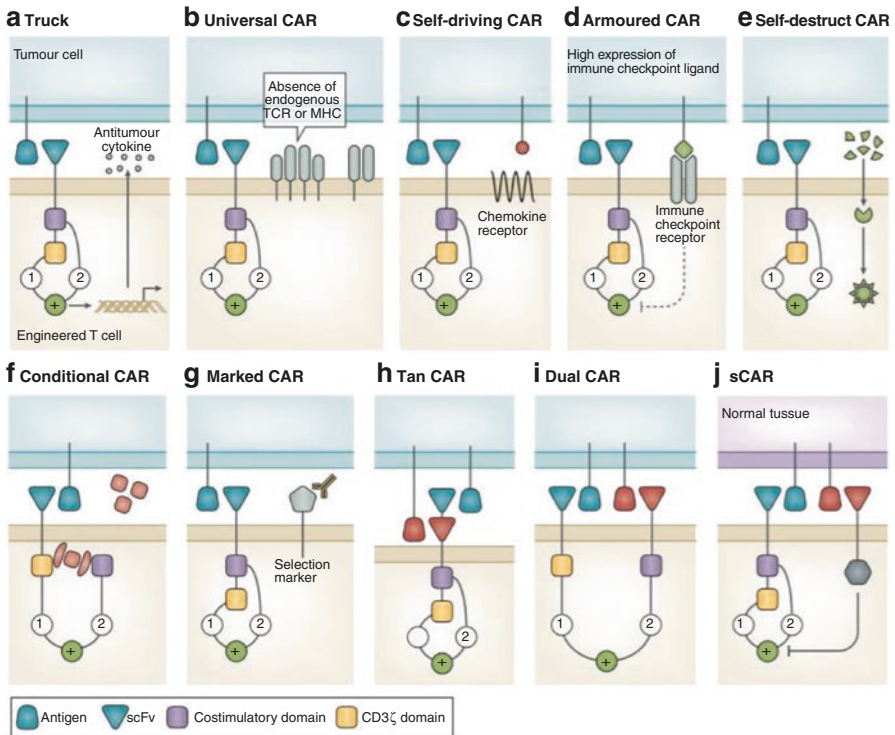
- Sequential administration of CD19 and CD22 CAR T has been studied in patients with RR ALL and RR NHL. MRD (−) CR was observed in 96% with ALL with a median PFS of 13.6 months. CR was observed in 50% of patients with NHL, with a median PFS of 10 months. Dual antigen targeting reduced the number of relapses from antigen escape [15].
- Another bispecific CD19/22 tandem CAR T called AUTO3 is being studied in pediatric ALL and adult NHL. Early results suggest 75% CR in ALL [16] and 80% ORR in NHL [17] when combined with pembrolizumab (Keytruda®) consolidation.

b. CAR T cells combined with immune modulation

   i. Addition of PD-1 or PDL-1 antagonists

- CAR T "exhaustion" is associated with increased PD-1 expression. PD-1 and PDL-1 antagonists may reactivate exhausted CAR T.

Fig. 52.2 New chimeric antigen receptor models and concepts. (Reproduced from Fesnak AD, June CH, Levine BL. Engineered T cells: the promise and challenges of cancer immunotherapy. Nat Rev Cancer. 2016;16:566–81. (Ref 3). (**a**) T cells redirected for universal cytokine killing (TRUCKs) co-express a chimeric antigen receptor (CAR) and an antitumor cytokine. Cytokine expression may be constitutive or induced by T cell activation (for example, interleukin-12 (IL-12)). Targeted by CAR specificity, localized production of pro-inflammatory cytokines recruits endogenous immune cells to tumor sites and may potentiate an antitumor response. (**b**) Universal, allogeneic CAR T cells are engineered to no longer express endogenous T cell receptor (TCR) and/or major histocompatibility complex (MHC) molecules, thereby preventing graftversus-host disease (GVHD) or rejection, respectively. (**c**) Self-driving CARs co-express a CAR and a chemokine receptor, which binds to a tumor ligand (for example, C-C motif chemokine receptor 2 (CCR2)–C-C motif chemokine ligand 2 (CCL2)), thereby enhancing tumor homing. (**d**) CAR T cells engineered to be resistant to immunosuppression (armored CARs) may be genetically modified to no longer express various immune checkpoint molecules (for example, cytotoxic T lymphocyteassociated antigen 4 (CTLA4) or programmed cell death protein 1 (PD1)), with an immune checkpoint switch receptor, or may be administered with a monoclonal antibody that blocks immune checkpoint signaling. (**e**) A self-destruct CAR may be designed using RNA delivered by electroporation to encode the CAR. Alternatively, inducible apoptosis of the T cell (right part of panel g) may be achieved based on ganciclovir binding to thymidine kinase in gene-modified lymphocytes or the more recently described system of activation of human caspase 9 by a small-molecule dimerizer. (**f**) A conditional CAR T cell is by default unresponsive, or switched 'off', until the addition of a small molecule to complete the circuit, enabling full transduction of both signal 1 and signal 2, thereby activating the CAR T cell. Alternatively, T cells may be engineered to express an adaptor-specific receptor with affinity for subsequently administered secondary antibodies directed at target antigen. (**g**) Marked CAR T cells express a CAR plus a tumor epitope to which an existing monoclonal antibody agent binds. In the setting of intolerable adverse effects, administration of the monoclonal antibody clears the CAR T cells and alleviates symptoms with no additional off-tumor effects. (**h**) A tandem CAR (TanCAR) T cell expresses a single CAR consisting of two linked single-chain variable fragments (scFvs) that have different affinities fused to intracellular co-stimulatory domain(s) and a CD3ζ domain. TanCAR T cell activation is achieved only when target cells co-express both targets. (**i**) A dual CAR T cell expresses two separate CARs with different ligand binding targets; one CAR includes only the CD3ζ domain and the other CAR includes only the co-stimulatory domain(s). Dual CAR T cell activation requires co-expression of both targets on the tumor. (**j**) A safety CAR (sCAR) consists of an extracellular scFv fused to an intracellular inhibitory domain (for example, CTLA4 or PD1). sCAR T cells co-expressing a standard CAR become activated only when encountering target cells that possess the standard CAR target but lack the sCAR target.

- In patients with RR NHL post tisa-cel, the PD-1 antagonist pembrolizumab (Keytruda®) 200 mg IV every 3 weeks led to CAR T re-expansion in 75%, an ORR of 27%, and a CR rate of 17% [18].
- The PDL-1 antagonist atezolizumab (Tecentriq®) was given every 21 days post axi-cel in patients with NHL without exacerbating CAR T AE. CAR T expansion and persistence were greater with atezolizumab and axi-cel vs. axi-cel alone [19].
- Clinical trials combining check point inhibition and CAR T cells are ongoing.

ii. Addition of ibrutinib (Imbruvica®)

- The Bruton tyrosine kinase inhibitor (BTK) ibrutinib is efficacious against numerous lymphoid malignancies. It also inhibits IL-2 inducible T-cell kinase, which enhances CAR T expansion in patients with chronic lymphocytic leukemia (CLL) who received extended ibrutinib treatment prior to CAR T. Ibrutinib reduces levels of proinflammatory cytokines when combined with CAR T in animal models [20, 21].
- The addition of ibrutinib prior to and following JCAR014 (a CD19 targeted CAR T with 4-1BB costimulatory domain) infusion resulted in improved ORR and reduced CRS severity compared to JCAR014 alone in patients with relapsed/refractory CLL [22].
- Ibrutinib has been added to fully human CD19 CAR T in CLL, resulting in high rates of MRD-negative remissions. A 41% CR rate by International Workshop on CLL criteria with 94% having no detectable disease in the bone marrow was reported [23].
- Current trials are underway combining ibrutinib with CAR T in an attempt to enhance efficacy while limiting inflammatory toxicities.

c. Fully humanized CAR T

i. Current CARs contain murine sequences and have the potential for host immune rejection and hypersensitivity reactions which may impair longevity and tolerability of CAR T. Fully human CAR T are in clinical development which may limit these issues.

ii. Fully human CD19 CAR T (CTL119) induced CR in 56% of pediatric and young adult patients with RR ALL with relapse following murine derived CD19 CAR T [24]. This important study demonstrates the feasibility and efficacy of human CAR T following murine CAR T.

d. Allogeneic and universal CAR T [25]

i. Tisa-cel and axi-cel are CAR T products of autologous origin.

- Limitations in the current use of autologous CAR T (autoCAR T) include:

  – Time-intensive manufacturing with the potential risk of interim disease progression

- – Preexisting T cell dysfunction or lymphopenia may limit ability to manufacture adequate CAR T.
- – High cost in part because CAR T is a patient-specific generated product.
- – Product is variable patient-to-patient and manufacturing failures do occur.

- • Use of allogeneic CAR T (alloCAR T) could potentially solve some of these issues. AlloCAR T could:

  - – Be donor in origin but obtained from the patient (i.e., post allo-HCT). These cells would likely be tolerized to the patient and perhaps limit the risk of graft vs. host disease (GvHD).
  - – Be donor in origin and obtained directly from the donor (i.e., post alloHCT).
  - – Limited clinical data exist with alloCAR T. There does not appear to be a significant risk of severe GvHD; however experience is limited and patients with uncontrolled GvHD are typically not candidates.

- • Universal CAR T ("off the shelf," acquired from a group of universal donors) could be another potential solution to the limitations of autoCAR T.

  - – Cells would be readily available without the delay of patient-specific manufacturing.
  - – Limitations to universal CAR T include CAR T rejection and GvHD.
  - – Universal CAR T cells could be engineered to be resistant to graft rejection (by removing HLA molecules) and GvHD (by removing the T cell receptor).
  - – This approach is currently under investigation in multiple industry-sponsored clinical trials.

e. Armored CARs (fourth generation) [3]

   i. CAR T cells engineered to be resistant to immunosuppression and inhibitory signals. For instance, cells can be engineered to remove PD-1 and CTLA-4 or contain dominant negative receptors to prevent inhibition. The benefit of third- and fourth-generation CAR T over second-generation CAR T remains to be determined.

f. TRUCKs (T cells redirected for universal cytokine killing) [3].

   i. CAR T cells engineered to express cytokines to enhance activity such as inducible or constitutive IL-12 to induce innate anti-tumor immune responses and limit microenvironment immunosuppression.

g. "Self-driving CARs" [3]

   i. CAR T cells engineered with chemokine receptors to promote homing to sites of tumor.

h. CAR T cells with suicide switches [3]

   i. CAR T could be deactivated in the setting of severe toxicity through the inclusion of viral thymidine kinase (targeted by ganciclovir [Cytovene®]), CD20 (targeted by rituximab [Rituxan®]), epidermal growth factor receptor (EGFR; targeted by cetuximab [Erbitux®]), or small molecule activation of caspase.

i. Suppressive or "safety" CARs [3]

   i. A CAR T with an inhibitory domain fused to the scFv portion of the fusion protein. CAR T cells would be active in tissues that express the scFv target but not the inhibitory domain target. In tissues expressing both targets, CAR T are suppressed to limit on target/off tumor effects.
   ii. CAR T modification of regulatory T cells (T_{regs}); activation would result in expansion of T_{regs} which could be effective to treat autoimmune disease, GvHD, etc.

j. Conditional CARs: [3]

   i. A CAR T that requires recognition of 2 targets for activation (dual CAR) or are active only in the presence of exogenous small molecules that can be added or removed.

k. Special circumstances:

   i. Use of CAR T in patients with CNS involvement

   • Initial CAR T trials excluded patients with primary or secondary CNS leukemia/lymphoma involvement out of concern for propagating neurotoxicity [6, 7].
   • CAR T are known to penetrate the blood-brain barrier (BBB) to eliminate low level disease in pediatric ALL patients. Limited available data suggest the risk of neurotoxicity does not correlate with the presence of CNS involvement by leukemia/lymphoma [12, 26].
   • To date, three separate reports of patients ($N = 18$ total) treated with tisa-cel or lisocabtagene maraleucel (liso-cel) describe an ORR of 50% for patients with secondary CNS lymphoma without apparent increase in neurotoxicity or CRS [27–29]. These limited data demonstrate CAR T adequately cross the BBB to exert antitumor effect with manageable risk of neurotoxicity.
   • CAR T cells were not approved for primary CNS lymphoma.

   ii. Use of KTE-X19 in ALL

   • KTE-X19 (similar to axi-cel with modified manufacturing process) has been studied for adults with RR ALL in a phase 1 dose escalation study (ZUMA-3). Patients treated with the higher dose had a CR rate of 84% with a median EFS of 15 months. The median age was 46 years (18–77 years) [30].

- This new approach may represent an important expansion in the treatment armamentarium for adults with ALL given that the FDA approval of tisa-cel is currently limited to adults up to age 25 [4].
- KTE-X19 is also being studied in pediatric patients with RR ALL in a phase 1 study (ZUMA-4), with preliminary data suggesting CR/CRi (complete response with incomplete hematologic recovery) rates of 64–100% across various dosing cohorts [31].

iii. New CAR T targets in ALL: CD22

- B cell ALL typically expresses CD22, which persists despite loss of CD19 (after treatment with anti-CD19 CAR T or blinatumomab) [Blincyto®]
- Anti CD22 CAR T manufactured with a lentiviral vector, using a 4-1BB costimulatory molecule, have been studied in heavily pretreated patients with ALL, the majority of which received prior allo-HCT and had relapsed or were refractory to CD19 CAR T therapy. CR rates of 57–80% have been reported, with no cases of grade ≥3 CRS or neurotoxicity observed [32, 33].
- Relapses were associated with decreased CD22 density rather than complete loss of CD22 expression.

iv. Lisocabtagene maraleucel (liso-cel, JCAR017)

- Liso-cel is a CD19 CAR T manufactured using a lentiviral vector, with a 4-1BB costimulatory molecule and a truncated EGFR sequence (to detect CAR T by flow cytometry). Liso-cel consists of a product that is manufactured independently and infused in a 1:1 ratio (rather than variable ratio) of CD4/CD8 cells.
- Liso-cel has been studied in DLBCL, primary mediastinal B cell lymphoma, grade 3B FL, and mantle cell lymphoma in TRANSCEND NHL 001. Data reported in 88 patients treated to date show an ORR of 74% with CR in 52% [34].

v. CAR T beyond ALL and NHL

- CLL
    - Challenges in the use of CAR T in CLL include lymphopenia (a result of prior purine antagonists or alemtuzumab [Campath®]) and inadequate CAR T persistence and expansion (due to disease-related T cell dysfunction).
    - CTL019 (which later became known as tisa-cel) was studied in patients with heavily pretreated RR CLL ($N = 14$) with an ORR of 57% and CR in 29%. A median PFS of 7 months and a median OS of 29 months were observed [35].
    - Liso-cel has been studied in 24 patients with CLL who previously failed ibrutinib (some were also refractory to venetoclax). An ORR of 71% was observed with CR in 21% [36].

- – Humanized CD-19 CAR T (CTL119) combined with ibrutinib (Imbruvica®) was studied in patients with CLL without CR despite 6 months of ibrutinib. A 41% CR rate by CLL working group criteria, with 94% meeting CR on bone marrow biopsy was reported [23].

- Multiple myeloma (MM)

  - – CD19 is generally not expressed on MM cells with the exception of a small subset of MM stem cells.

    - ◦ In a small study of heavily pretreated patients with RR post MM autoHCT, a second autoHCT followed by CTL019 resulted in improved PFS compared to a historical cohort. Of note, 30% of patients had a better PFS following their second autoHCT + tisa-cel vs. their first autoHCT [37].

  - – B cell maturation antigen (BCMA) is expressed on the surface of MM, some B cell lymphomas, plasma cells, and on memory B cells. Given the limited expression of CD19 in MM, CAR T targeting BCMA has been investigated.

    - ◦ Sequential administration of CD19 and BCMA CAR T following autoHCT resulted in a CR or very good partial response in 100% of patients, demonstrating the feasibility of dual targeted CAR T in MM [38].
    - ◦ The largest study of BCMA CAR T published to date ($N = 57$; LEGEND-2), studied LCAR-B38M (a dual epitope BCMA CAR T) in patients with RR MM with a median 3 prior therapies. An ORR of 88% was observed with 68% of patients obtaining CR. Median PFS was 15 months [39].
    - ◦ Other trials of BCMA CAR T enrolled more heavily pretreated patients. A phase 1 study of bb2121, a BCMA CAR T made using a lentiviral vector, and a 4-1BB costimulatory domain reported an ORR of 85%, CR in 45%, and a median PFS of 11.8 months [40]. A separate trial assessing another BCMA CAR T product made with a lentiviral vector and 4-1BB costimulatory domain reported an ORR of 48% with median OS of 16.6 months [41].

- Acute myeloid leukemia (AML)

  - – Success thus far in developing CAR T for AML has been hindered by the ability to find a target antigen that is not present on essential hematopoietic cells.
  - – CD123 (IL-3 receptor α chain) is a potential CAR T target for AML but is also expressed on hematopoietic stem cells, thus carrying the risk of myeloablation. This risk may be limited by the use of a tran-

siently expressed CAR (via RNA electroporation), a CAR T with a suicide gene, or coupling this therapy with rescue alloHCT [42].
  – Other potential targets for CAR T in AML are CD44v6, CD33, and FLT3.
  – Clinical data for CAR T in AML are extremely limited at the current time. Early phase trials are currently ongoing.

- Hodgkin lymphoma (HL)

  – While Reed-Sternberg cells (RSCs) do not express CD19, CD19+ B cells are present within the immunosuppressive microenvironment in HL. A small trial showed short-lived responses in 50% of patients treated with CD19 CAR T made using mRNA electroporation [43].
  – RSCs express CD30 which has been successfully targeted with brentuximab vedotin (BV; Adcetris®) for initial therapy and RR HL.
  – Limited numbers of patients have been treated with CD30 CAR T thus far with CRs observed in 75% of patients in one small trial, despite 2/3 having received prior BV [44]. CD30 is also expressed on activated T cells, B cells, and eosinophils; therefore monitoring for on-target-off-tumor effects may be important.

7. *CAR T in earlier stages of disease*

   a. Currently approved CAR T are reserved for use after ≥2 lines of therapy.
   b. Potential advantages of using CAR T earlier in the course of malignancy could include:

      i. Patient with improved performance status (more tolerable of adverse effects).
      ii. Chemosensitive disease would permit tumor burden reduction to limit toxicity.
      iii. Limit the risk of lymphopenia and T cell dysfunction.

   c. Ongoing trials assessing the role of CD19 CAR T vs. chemotherapy salvage followed by autoHCT in patients with RR NHL include BELINDA (tisa-cel), ZUMA-7 (axi-cel), and TRANSFORM (liso-cel).

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Chapter 53
Natural Killer Cell Therapy in Allogeneic Hematopoietic Cell Transplantation

Check for updates

Jennifer N. Saultz

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is the only curative therapeutic approach to date for patients with intermediate- or high-risk European Leukemia Net (ELN) classified acute leukemia [1]. The effectiveness of this procedure is intimately linked to the activity of immunoreactive cells in the graft, most notably T and natural killer (NK) cells which can produce potent graft-versus-leukemia (GvL) effects [2]. Cellular therapies and graft manipulation aimed to foster GvL and reduce unwanted graft-versus-host disease (GvHD) hold promise for improving posttransplant outcomes. NK cells have potent leukemia-specific cytotoxicity and are not associated with GvHD after allo-HCT. In the haploidentical T-cell-depleted stem cell transplant setting, NK cells have been linked to the ability to cure patients with acute myeloid leukemia (AML) [3]. Adoptive NK cell therapies including cytokine-expanded NK cells, allogeneic haploidentical NK cells, cord blood-expanded NK cells, antibody therapies, bi-specific and tri-specific engagers, and chimeric antigen receptor-engineered (CAR) NK cells all hold exciting possibility for therapeutic benefit.

NK Cell Biology

1. Background
   NK cells are innate lymphoid cells that play a critical role in immune surveillance and are important for both maintaining and achieving remission in hematologic malignancies [3–7].

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    a. Comprise only a small percentage (10%) of mononuclear cells in the peripheral blood of normal individuals.

    b. Unlike T cells, NK cells require no prior activation and can directly lyse tumor targets independent of antigen presentation.

    c. Human NK cell development occurs through five functionally distinct stages starting in the bone marrow, progressing in secondary lymphoid tissues, and culminating in the peripheral blood [8].

    d. The two stages of NK cell development in the peripheral blood are identified by the relative CD56 surface expression as demonstrated by flow cytometry (CD56 bright and CD56 dim) [9]. CD56 bright NK cells are naïve NK cells also recognized by co-expression of CD94+ CD16- [10].

2. Function

    a. CD56 bright NK cells, functionally similar to helper T cells, have high cytokine production, robust proliferative potential, very low to no killer-cell immunoglobulin-like receptor (KIR), and high inhibitory NKG2A surface antigen expression.

    b. Considered functionally inert, CD56 bright NK cells must go through an education process or "licensing" event to become mature.

       i. Licensing is a well-defined process by which NK cells gain inhibitory receptors such as KIR to decipher "self from nonself" through engagement of class I major histocompatibility complex (MHC) antigens [11, 12].

      ii. Classical class I HLA molecules (HLA-A, HLA-B, and HLA-C) bind to KIR, while the CD94/NKG2A heterodimer binds to nonclassical class I molecules, such as HLA-E [13]. The CD56 dim subset marks a more mature subgroup with loss of inhibitory NKG2A and KIR acquisition, both critical for NK cell activation against tumor targets [8]. The dynamic interplay between germ line-encoded activating and inhibitory receptors controls NK cell function.

     iii. In general, NK cell cytolytic killing is activated when a target cell engages with the NK cell and does not express its cognate ligand, termed the "missing self-hypothesis", first proposed by Karre and Ljunggen [14]. In haploidentical allo-HCT, disparate MHC genotypes between the donor and recipient result in alloreactivity, contributing to a GvL effect and decreased relapse rate [15]. When activating receptors are engaged on an NK cell such as CD16, antibody-dependent cell-mediated cytotoxicity (ADCC) results in cell lysis [16].

3. Memory NK cells

    a. Adaptive NK cells have recently been described with properties similar to memory T cells that both persist following viral challenge in latent cytomegalovirus (CMV)-positive individuals and are capable of more robust responses to second antigen challenge [17]. These cells are considered the most mature subset of NK cells, expressing CD57+CD16+ CD94−NKG2C+ [18–20].

b. In the allo-HCT setting, Foley et al. showed "memory" NK cells population of mature phenotypic cells to be potent producers of interferon gamma (IFN-γ) (an important cytokine for modulation of the adaptive immune response) during the first year after transplant [21]. Higher levels of "memory" NK cells have been correlated with improved outcomes in acute myeloid leukemia (AML) patients post allo-HCT with both higher frequencies and greater absolute numbers of CD56^{dim}CD57$^+$NKG2C$^+$ NK cells at 6 months after allo-HCT associated with significant lower 2-year relapse risk [18].

Consideration of Natural Killer Cell Alloreactivity

1. Optimizing KIR
   Killer-cell immunoglobulin-like receptor (KIR) is expressed on T and NK cells and plays a significant role in dictating NK cell activity [22].

   a. The KIR gene family, located on chromosome 19q13.4, is highly polymorphic and second only to that of HLA genes in genetic diversity. The family consists of 13 genes (*KIR2DL1, KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1/S1, KIR3DL2,* and *KIR3DL3*) and 2 pseudogenes (*KIR2DP1* and *KIR3DP1*) [23].

   b. Due to the diversity of both HLA genes and KIR genotypes, only 25% of HLA-matched siblings are KIR identical [24].

   c. In T-cell depleted, haploidentical allo-HCT, NK cell alloreactivity defined as KIR ligand mismatch between donor and recipient (KIR ligand incompatibility model) was associated with enhancement of GvL, reduced risk of relapse, and better survival. Interestingly, the improved outcomes with alloreactivity in this trial were restricted to patients with AML and not seen in patients with acute lymphocytic leukemia (ALL) [3].

   d. Characterizing KIR haplotypes into two groups (A and B) based on gene expression allows all individuals to be assigned to one of two groups including A/A genotype (homozygous for haplotype A) or B/x genotype (have 1 or 2 B haplotypes depending on genes KIR2DS1, 2,3,5 KIR2DL2 and KIR2DL5 or -AB or -BB) [25]. Studies have shown that unrelated donors with the B/x genotypes have improved survival with less relapse [26].

   e. In matched sibling donors, KIR alloreactivity was associated with less chronic GvHD and a decrease in relapse rate [24].

   f. In the haploidentical transplant setting, KIR ligand incompatibility has been validated as beneficial in donor selection with improved survival correlated with HLA-DR mismatch, HLA-DP nonpermissive mismatch, KIR receptor–ligand mismatch, and KIR B/x haplotype with KIR2DS2 [22, 27].

   g. Despite published literature showing benefit, guidelines for unrelated donor selection aimed at enhancing potent activation of NK cells remain not to be

considered as standard of care, in the absence of well-designed, prospective, confirmatory trials.

h. In the posttransplant setting, there are many competing factors that control donor-derived GvL activity not strictly defined by KIR and including but not limited to Class I HLA ligands expressed by the recipient, NK cell licensing in the recipient, graft source, conditioning regimen, and tumor antigens.

i. The National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR), jointly with the NMDP Histocompatibility Advisory Group published guidelines in 2019 for unrelated donor selection stating that adult donor selection based on KIR should only be considered within the context of a clinical trial or center-specific practice [28].

Cytokines to Augment NK Cell Activity

1. Essential role of cytokines

   a. Cytokines play a significant role in mediating NK cell survival, maturation, and function [29–32].

      i. Interleukin (IL)-2 was the first identified cytokine to stimulate NK cell cytolytic effector function, proliferation, and survival by inhibiting apoptosis through induction of Bcl-2 expression [32–34].

         • Although IL-2-activated haploidentical NK cell therapy can induce complete remissions (CRs) in 30–50% of patient with relapsed or refractory AML, the procedures have been poorly tolerated and efficacy is limited by expansion of host regulatory T cells (Tregs) [15, 35, 36].

      ii. More recently, other common gamma chain γ_c chain activating cytokines have been used to enhance and expand NK cells, including IL-7, IL-12, IL-15, IL-18, and IL-21 [31, 37].

      iii. Fehniger and others have found that exposure to the cytokines IL-12, IL-15, and IL-18 in vitro is capable of creating a "memory like" NK cell population with enhanced function with potent antileukemic properties [38, 39].

         • In this trial, haploidentical donor NK cells were CD3 depleted and CD56-positively selected and activated in vitro in a good manufacturing practice (GMP) lab for 12–16 hours with rhIL-12, rhIL-15, and rhIL-18 inducing a cytokine-induced memory like (CIML-NK) phenotype with enhanced activation. The cells were then washed and adoptively transferred into patients with relapsed refractory AML who received prior lymphodepleting fludarabine/cyclophosphamide chemotherapy with five of the nine patients achieving clinical

responses and four having CRs [38]. The majority of responders had detectable NK cells in the blood and marrow.

iv. There is a phase 1 clinical trial investigating the role of CIML-NK cells post haploidentical allo-HCT in AML/MDS patients with relapsed disease currently enrolling patients (NCT04024761).

v. A first-in-human multicenter phase 1 trial using IL-15 superagonist complex (ALT-803) alone in patients who relapsed >60 days after allo-HCT showed the agent to have good tolerance and was associated with a 19% response rate [39].

- Of the responders, there was one complete remission lasting 7 months.
- There were no dose-limiting toxicities or significant GVHD flares seen.
- Interestingly, IV administration of ALT-803 was associated with constitutional symptoms related to increased serum IL-6 and interferon-γ, which was alleviated by subcutaneous (SQ) delivery.
- Biologically both the IV and SQ dosing showed in vivo NK and CD8+ T-cell expansion and activation with enhanced activation seen in the usually "functionally inert" CD56 bright NK cells.
- Unlike IL-2, IL-15 was not associated with expansion of regulatory T cells.
- Following the results of the phase 1 study, the novel biologic agent was used in combination with haploidentical NK cell infusion after lymphodepleting chemotherapy in 26 patients with advanced AML with an improved CR rate of 32% [40].
- Experiments using IL-15 and other cytokines remain under clinical investigation.

Enhancing Antibody-Dependent Cellular Cytotoxicity (ADCC)

1. ADCC

   a. ADCC is one of the best-known mechanisms for activating NK cells. Most circulating NK cells express surface CD16. The CD16 receptor is activated by binding the Fc receptor of an antibody which binds tumor antigens. Once activated, cytolytic granules are released and NK cells shed CD16 as well as the adhesion molecule, CD62L.

   b. CD16 loss can be mediated by a metalloprotease called ADAM17. Romee et al. found that by inhibiting ADAM17, NK cell function could be preserved, limiting the loss of CD16 and enhancing ADCC-mediated killing toward tumor targets [41].

   c. Rituximab (Rituxan®) is a monoclonal antibody that enhances ADCC through engagement in the CD16 receptor. Although well known for its success with

CD20 lymphomas and B-cell malignancies, there are now several antibodies that have been developed to enhance NK cell cytolytic activity [42–44].

2. Engineered targets: bi-specific killer engagers (BiKEs) and tri-specific killer engagers (TriKEs)

   a. Other promising antibody therapies include engineered targets.
   b. The University of Minnesota have focused on a platform using BiKEs constructed with a single-chain Fv against CD16 and a single-chain Fv against a tumor-associated antigen (CD33 or CD19) [45].

      i. Using CD16x19 BiKEs (bi-specific engager CD16 and CD 33) and a CD16x19x22 TriKE, investigators have shown that CD16 signaling is enhanced and delivered a potent cytolytic signal, different than the natural recognition of rituximab to promote killing of lymphoma targets [46].
      ii. When the CD16x33 BiKE was combined with ADAM17 to prevent CD16 shedding, enhanced killing of AML cell lines and primary samples were seen.

   c. Although still under investigation, BiKEs and TriKEs are being perfected to deliver drugs to restricted antigen targets.
   d. Most recent studies have shown that with the addition of IL-15 to the CD16x33 BiKE, thus forming a TriKE, NK cells have been shown to expand and generate superior cytotoxicity, degranulation, and cytokine production against CD33(+) HL-60 targets [46].

NK Cells as a Cell-Based Therapy

1. NK cellular therapy

   a. NK cells are generally recognized as the primary immune cells to recover after allo-HCT with higher numbers associated with improved posttransplant outcomes [47–49].
   b. Despite absolute number recovery, NK cell qualitative function remains impaired for several months posttransplant with diminished IFN-γ production noted by NK cells, which can persist up to 6 months post-transplant depending on donor stem cell source (adult unrelated donor versus umbilical cord blood), graft processing methods (T-cell depletion), and degree and type of immune suppression [50].

      i. This defect contributes to impaired tumor surveillance and higher risk for early relapse with many high-risk malignancies relapsing within 100 days posttransplant [51–53].
      ii. Increasing evidence reveals that relapses occur, in part, through immune escape of tumor cells from allogeneic immune control including loss of HLA genes, upregulation of immune-checkpoint molecules, and the

acquisition of novel mutations that drive clonal hematopoiesis [54]. Consequently, there is great interest in the addition or expansion of functional NK cells in the posttransplant period to augment known GvL in high-risk patients to prevent relapse.

c. Initial studies using donor NK cells from healthy donors have been restricted by low number. In general, unmobilized apheresis from healthy donor peripheral blood yields an average cell dose of $1–3 \times 10^7$/kg NK cells for an adult.

d. Ruggeri et al. and others pioneered the therapeutic use of NK cells in AML with remission and even cures seen in the setting of haploidentical T-cell-depleted stem cell transplants [3]. Miller et al. subsequently showed that haploidentical NK cells could both persist and expand in vivo with persistence leading to complete remissions in a subset of AML patients [15].

   i. In this study, 43 patients were enrolled; 19 patients were classified with poor-prognosis AML defined as primary refractory, relapsed or secondary AML from antecedent myelodysplastic syndrome.

   ii. All AML patients received lymphodepleting chemotherapy with fludarabine and cyclophosphamide followed by haploidentical NK cell infusion 5 days later.

   iii. Haploidentical-related donors underwent lymphopheresis for 3–5 hours on day −1 with up to 2×10^{10} peripheral blood mononuclear cells collected followed by CD56 selection, T-cell depletion, and overnight incubation with IL-2.

   iv. The highest CD3-depleted cell dose that could be consistently obtained was 2×10^7 total nucleated cells/kg, and most patient received maintenance IL-2 post NK cell infusion. The infusions were well tolerated without significant cytokine release syndrome (see Chap. 56).

   v. Eight of the 15 evaluable AML patients showed persistent engraftment of donor cells at day 7 postinfusion or beyond; five patients achieved a morphologic remission.[15]

   vi. This study among others led to enhanced interest in utilizing allogeneic NK cells for cellular therapy with NK cell persistence correlating with clinical response [36].

2. "Off-the-shelf" or universal donor NK cells

   a. Umbilical cord blood (UCB) is enriched for greater numbers of NK cells (roughly 30%) compared with peripheral blood (10% of all lymphocytes) and has been increasingly explored as a source of an "off-the-shelf" product for cellular therapy.

      i. Advantages of UCB include availability of frozen units with less rigorous requirements for HLA matching making it an ideal "off-the-shelf" product.

      ii. Expansion of donor NK cells occurs through two main mechanisms:

- Cytokines or cytokine fusion proteins (IL-2, IL-12, IL-15, IL-18, and IL-21)
- Feeder cells derived from Ebstein Bar Virus (EBV)-lymphoblastoid cell lines [55] or the HLA class I restricted cell line K562 transduced to express membrane-bound IL-15, IL-21, or 4-1BBL (CD137L)

iii. Utilizing the K562 cells transduced with both 4-1BBL and membrane-bound IL-15, Fujisaki et al. showed a median 21.6-fold expansion of highly cytotoxic NK cells after 7 days from peripheral blood. This method was superior to expansion protocol using IL-2, IL-12, IL-15, or IL-21 [56].

iv. Gong and colleagues were able to increase peripheral blood purified donor NK cells by 550-fold expansion on K562 expressing CD137L, MICA, and soluble IL-15 in 24 days [57].

v. Over time, methods improved for UCB cell expansion. In 2015, Shah et al. published results using the K562-based artificial antigen-presenting cell (aAPC) expressing membrane-bound IL-21, 41BB ligand with a mean fold expansion of 1848-fold from fresh and 2389-fold from cryo-preserved cord blood cells after 2 weeks [58].

vi. In 2018, Liu et al. successfully engineered cord blood CAR NK cells to express IL-15, CD19, and inducible caspase-9-based suicide gene (iC9). The cells demonstrated enhanced killing of CD19-expressing cell lines and primary leukemia cells and enhanced survival in a xenograft Raji lymphoma murine model [59].

vii. The CNDO-109-activated NK cells (CNDO-109-NK cells) are manufactured from unrelated donors with the thought of providing a short-term stimuli ex vivo via the CTV-1 leukemia cell lysate and NK cell interaction.

viii. Fehniger and colleagues infused the primed allogenic NK cells into AML patients in CR1. Importantly, these NK cells were detectable after adoptive transfer and lead to complete remissions in 12 high-risk AML patients [60].

ix. Despite promising results, responses remain mixed with one major limitation of using primary NK cells isolated from either peripheral blood or umbilical cord blood being the heterogeneity between various donors limiting a "one size fits all approach."

x. Kaufman et al. recently challenged that idea by developing a novel mechanism to grow a more homogenous "off-the-shelf" NK cell derived from human embryonic stem cells or induced pluripotent stem cells (iPSC). These NK cells can be grown and produce functionally mature NK cells capable of large-scale manufacturing [61].

xi. The iPSC-derived NK cells are currently in clinical trials for both solid tumors and treatment of advanced hematological malignancies after receiving US Food and Drug Administration approval (ClinTrialsGov # NCT04023071, NCT03841110).

Conclusion: Ongoing Challenges and Future Directions

In conclusion, NK cell therapies hold great clinical promise in the postallogeneic HCT setting as a cell-based therapy but have limitations. One major limitation to the execution of innovative NK-cell therapy trials is the financial burden of cellular therapy and the need for their generation within GMP laboratories. Capitalizing on the CD16 engagement, bi-specific and tri-specific engagers enhance specific immune response by targeting specific tumor antigens. Adoptive NK cell therapies including CIML NK cells and allogeneic haploidentical NK cells have also shown exciting efficacy with excellent tolerability and no risk of GVHD. Newest to the field include CAR NK cells, expanded NK cells from cord blood or universal donor NK cells, all of which are moving into clinical trials. Future therapies combining NK cell therapies with checkpoint inhibition or small molecular inhibitors are underway. Despite major advance in NK cell therapies, most NK cell therapies remain investigational at this time holding great promise for an expanded series of potential applications in the not-too-distant future.

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Chapter 54
Mesenchymal Stromal Cells: Impact on Hematopoietic Cell Transplantation

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Introduction

Mesenchymal stromal cells (MSCs) were originally characterized as stromal components of the bone marrow microenvironment that could support hematopoiesis. The original investigations were based on the seminal work of Friedenstein et al. [1] who used the colony-forming unit-fibroblast (CFU-F) assay to detect and quantify the influence of these cells. Subsequently, the critical dependence of normal hematopoiesis upon bone marrow stroma was confirmed in mouse models of bone marrow failure. Coculture crossover assays of marrow cells obtained from the mutated W/Wᵛ and Sl/Slᵈ mice were studied [2]. Both murine strains were fated to have limited survival but in vitro combination of the two cells provided interesting findings. Specifically, adherent marrow microenvironment cells obtained from the Sl/Slᵈ mice, when cultured with bone marrow from W/Wᵛ strains, did not restore defective hematopoiesis. On the other hand, the reverse combination contributed to sustained cell proliferation of multiple lineages of hematopoietic cells and growth in colony assays. Subsequently, the molecular basis of the bone marrow failure was identified involving stem cell factor (SCF; mutated in the Sl/Sld mice locus [3]) which binds to the c-KIT receptor (CD 117; mutated in W/Wv mice [4]). These and other studies illustrated how marrow stromal cells are critical for the support of marrow hematopoietic cells.

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Such seminal studies in murine mouse models led to human investigations. The original observations of Caplan et al. [5] identified MSCs as having stem cell characteristics as they exhibited a multilineage differentiation capacity. Further, MSCs could contribute to downstream lineage differentiation pathways of mesodermal cells that differentiated into striated and cardiac muscle, connective tissue, bone, adipose tissue, and marrow stroma. Finally, these cells could undergo self-renewal as well as be transplanted successfully. Immediately thereafter, interesting studies were reported of patients who experienced damage to the bone marrow microenvironment secondary to cytotoxic agent treatment with either radiation or alkylating agents. The stroma from those individuals could not support the growth of healthy hematopoietic stem cells (HSC) [6]. These observations ultimately led to some of the first clinical human MSC treatment studies with the original goals to improve engraftment and support hematopoiesis by regeneration of the marrow microenvironment, specifically the stromal cell compartment.

Biological Properties of MSCs and Impact on Hematopoiesis

MSCs can be isolated from a wide variety of tissue sources including adipose tissue, dental pulp, mobilized bone marrow cells, placenta, and umbilical cord blood (UCB) cells [5, 7]. Importantly, MSC can be expanded many log-fold in vitro. The biologic behavior of MSCs differs according to the tissue of origin. For example, MSCs derived from bone marrow are twice the size, differentiate into bone, fat, and cartilage, are less immune suppressive in vitro and in vivo, and do not need direct cell–cell contact for immune suppression when compared to MSCs derived from placental decidua. Furthermore, marrow-derived MSCs have lower expression of PD-L1, PD-L2, and CD49d, have less procoagulant activity, and less hemostatic properties as opposed to those obtained from placental decidua.

MSCs exert their immune-modulating effects via paracrine secretion of many cytokines and molecules. MSCs polarize the immune system toward type II inflammatory response and inhibit type I response [8–10]. Mediators include prostaglandin E2, indoleamine-2,3-dioxygenase (IDO), nitric oxide (NO), galectins, HLA-G5, and other factors. MSCs can stimulate Tregs (directly or indirectly) and inhibit Th17 differentiation of naïve CD4+ cells. Additionally, MSCs can increase IL-10 producing CD5+ regulatory B cells. Other MSCs' actions are mediated by cell–cell contact and the induction of effector T-cell apoptosis via the PD-1 and Fas-FasL pathways resulting in the inhibition of effector T-cell proliferation.

Of interest, MSC appear to be immunologically privileged and exhibit an immune sanctuary due to minimal expression of MHC class I and no expression of MHC class II molecules. Further, MSCs have very limited ligand expression for adhesion molecules expressed by T cells, thus making them nearly ideal for use as both selective immune-suppressive agents and a product to enhance or regenerate tissue repair.

Given the various tissue sources and some pleomorphic characteristics, the International Society for Cellular Therapy (ISCT) created a consensus definition of

MSC to allow more uniform characterization of cell products, as well as to facilitate comparative studies [11]. The three minimal proposed criteria to define MSC populations include:

1. Plastic adherence
2. Surface expression of CD105, CD73, and CD90 [in the setting of lack of expression of CD45, CD34] and at least 1 of 2 macrophage markers (CD14, CD11b) and B-cell markers (CD79α, CD19)
3. Capacity for trilineage differentiation into mesodermal tissues (such as osteoblasts, adipocytes, and chondroblasts)

This unique biology of MSCs contributed to the concept that the marrow itself was an organ system comprised of HSC as well as marrow stromal cells. Data supporting this concept include the findings that osteoblast monolayers independently can support granulopoiesis and B-cell lymphopoiesis [12]; osteoprogenitors could contribute to sinusoid assembly which proved to be a critical step in the generation of the molecular environment to support HSC [13]. Stromal cells themselves can construct proangiogenic environments which will recruit and maintain HSC and progenitors near the vascular sinusoids. Notably, marrow damaging therapies ultimately can damage the sinusoids; it has been shown that osteoblasts and stromal cells provide sanctuary for HSC while sinusoids are recreated [14].

Recognizing that MSCs are the progenitor population for osteoblasts, there was interest in determining whether allogeneic hematopoietic cell transplantation (HCT) could provide a source of donor MSCs. Early investigations suggested that after allograft, there was little contribution from a bone marrow graft to the donor MSC compartment. Stromal cells identified in Dexter cultures could become progressively donor in origin over time after transplant [15], but overall, using sex mismatched, human leukocyte antigen (HLA)-matched allografts, it was found that the majority of the stromal cell population was host-derived [16]. Some supporting evidence came from allogeneic HCT in osteogenesis imperfecta, a genetic disease of osteoblasts [17]. In children with this disease who underwent allograft procedures of either bone marrow or MSCs alone, over time, bone mineralization increased, spontaneous fractures decreased, and the subjects experienced enhanced growth. This clinical benefit appeared to be associated with very low MSC chimerism with only 1.5–2% donor osteoblast identified.

Almost 20 years ago, Lazarus and colleagues published the first-in-human-specific MSC clinical trial, a phase I feasibility study trial in 23 hematologic malignancy patients in complete remission [18]. Ten mL bone marrow samples were obtained, and MSCs were ex vivo culture-expanded over 4–7 weeks, then infused IV to ascertain safety. No untoward effects were noted, and subsequently, a successor study was executed to ascertain whether MSC could augment hematopoiesis. Recognizing that allogeneic HCT was much more complicated, the next investigation, completed by this same group, was the first-in-human autologous HCT study to address whether MSC adjunctive grafts could enhance hematopoietic recovery [19]. Twenty-eight advanced breast cancer patients undergoing myeloablative conditioning and autologous mobilized blood cell grafts also received an infusion of

$1–2.2 \times 10^6$ autologous MSC/kg. This pilot study suggested efficacy with median time to neutrophil recovery documented at 8 days and sustained platelet recovery above 20,000/mcL at 8.5 days after infusion.

Subsequent studies to augment hematopoiesis targeted situations where HCT was predicted to be suboptimal. Animal transplant studies using a limiting number of HSCs demonstrated that MSC infusions resulted in enhancement of granulopoiesis and megakaryocytopoiesis [20]. These and other such studies spurred the undertaking of further human studies to attempt to augment hematopoiesis in poor engraftment states. Examples included:

1. A single case report of family-directed MSC used alone, more than 2 years beyond autologous HCT for acute myeloid leukemia was shown to reverse critical thrombocytopenia and neutropenia [21].
2. 7 patients with either graft failure or suboptimal HSC engraftment underwent transplantation with HLA-matched or haploidentical MSCs; platelet and neutrophil recovery occurred by day 12, suggesting that second transplants after graft failure may be optimized by use of MSC grafts [22].
3. 2 of 6 patients with delayed engraftment (>30 days after transplant, but still platelets less than 50,000/mcL and neutrophils less than 1000/mcL) were treated with haploidentical MSCs and experienced an improvement in hematopoiesis [23].
4. 14 children undergoing a haploidentical transplant, a procedure associated with a historic 15% graft failure rate, additionally received MSC co-transplantation; all successfully recovered without loss of the hematopoietic graft [24].
5. A single case report presented a child affected by Wiskott-Aldrich syndrome. The direct implantation of MSCs into one hemipelvis was ineffective in improving hematopoiesis; however, bilateral marrow biopsies obtained on day 60 showed that the hemipelvis which received with direct implantation of MSC had a markedly improved marrow cellularity with trilineage hematopoiesis [25].
6. De Lima and colleagues studied engraftment results in 31 adult hematologic cancer patients who underwent hematopoietic cell transplantation using two umbilical cord-blood units, one of which was expanded ex vivo 14 days in coculture with a commercial allogeneic MSC product. Compared to 80 historic control patients, these patients had significantly faster neutrophil and platelet count recovery [26].

In summary, studies suggest that MSC products can be manipulated to assist hematopoiesis. Overall, however, the benefit was modest but potentially could be targeted to subjects who are predicted or are observed to have suboptimal marrow recovery. The studies above demonstrated that MSC infusion probably provided a transient effect via elaboration of cytokine mediators. MSCs constitutively secrete multiple soluble mediators such as SDF-1, IL-6, IL-7, IL-8, IL-11, IL--12, IL-14, IL-15, M-CSF, FLT3-L, and SCF. Using various stimuli, MSCs have the capacity to produce multiple other cytokines, including IL-1a, LIF, G-CSF, CCL2, CCL4, CCL5, CCL20, among others. Detailed proteomic assessments of the MSC secretome have confirmed these findings as well as documented multiple other soluble

mediators that were capable of inducing angiogenesis and immunosuppression as well as other mechanisms for these effects including cell–cell interaction [27]. Interestingly, trans-well studies were utilized to separate MSC populations from other purified cellular populations (such as T cells) and to assess whether the independent populations could exert influence without direct cell: cell contact. Using these technologies, immunologic cross-talk between MSC and T cells demonstrated both induction and suppression of various tissue-specific gene expression and protein production. The studies also characterized differential expression and variations in the immunologic cross-talk between resting and activated T-cell populations when cocultured in the presence of MSCs [28].

These investigations have generated significant interest in the application of MSC in two major clinical approaches: as an immunosuppressive agent and to assist tissue repair. In the former, Caplan and Correa hypothesized that MSCs work as a drug to deliver multiple soluble factors to suppress an activated immune system [29]. For the latter, that is, regenerative medicine, the goal was to provide trophic factors to enhance tissue repair. Ankrum and Karp [30] and Culme-Seymour et al. [31] have reported the burgeoning use of MSCs in trials all over the world, especially given the significant safety profile as reported by Lalu et al. [32].

MSC for the Treatment of Acute GvHD

Acute GvHD is a dynamic, inflammatory process that occurs with temporal and spatial boundaries after an allogeneic HCT procedure. Multiple cell populations have been implicated as well as multiple cytokine mediators, but the molecular epicenter of the syndrome is the T-cell receptor: MHC interaction expressed by the donor T cells recognizing the host MHC molecules. GvHD takes time to develop as T cells need to proliferate in the host after antigenic challenge and need to traffic to target tissues where presentation will be at the subclinical or clinical levels. In the setting of clinically active GvHD, MSCs have been extensively studied [33].

The application of MSC for management of acute GvHD is often considered to have its origin with the seminal study of Leblanc et al. [34]. A young male hematopoietic cell transplant patient developed severe steroid-refractory grade 4 gastrointestinal and hepatic acute GvHD. After failing multiple anti-GvHD interventions, he was given a family-related, haploidentical, sex-mismatched MSC infusion (2×10^6 cells/kg) from his mother. Over a 3- to 4-week period, his condition improved but with subsequent immune suppressant taper, symptoms of diarrhea and jaundice recurred. He again had a dramatic response to a second infusion of MSCs (1×10^6 cells/kg) achieving a GvHD-free complete remission. Important correlative science studies demonstrated female cells within the gastrointestinal tract suggesting the MSCs were able to traffic to the GvHD target organ.

Subsequent small pilot trials were performed as well as large phase 2 studies with key studies including

1. Ringden et al. [35] described 9 patients (8 steroid-refractory acute GvHD; 1 chronic GvHD) of which 8 patients attained GvHD complete remission after receiving either family donor- directed as well as unrelated mismatched donors; this investigation established unrelated donor MSC as a viable therapeutic product.

2. European Society for Blood and Marrow Transplantation (EBMT) registry: [36]. Of 55 patients who had steroid-refractory acute GvHD, 30 attained complete and 9 attained a partial response when treated with related or unrelated donor MSC.

3. Kebriaei and coworkers [37] reported that of 31 patients affected by GvHD, 24 attained complete and 5 a partial GvHD response after therapy with universal donor, unrelated MSCs. 19 of 24 patients complete responders had sustained responses without the need for the addition of second line therapy for 90 days.

4. In a pediatric study, mismatched, third-party donor MSC were administered to 12 patients (median age 6 years) affected by grade III–IV steroid-refractory acute GvHD. Cells were administered twice weekly for 4 weeks followed by a weekly maintenance schedule for subjects who achieved only partial or mixed responses. All patients responded; 7 attained complete response, 2 partial, and 3 a mixed response. Even severe gastrointestinal GvHD appeared to be amenable to such treatment, and complete response was associated with a with a 2-year survival of 68% [38].

These and other studies led to 2 large, industry-sponsored phase 3 randomized (in a 2:1 ratio), placebo-controlled trials using third-party donor mismatch MSC (remestemcel-L; Prochymal®) both as initial therapy for acute GvHD as well as for salvage of steroid-refractory acute GvHD. The primary endpoint was complete remission with 28 days of sustained response without steroid increase and no second-line therapy; and in the case of the new diagnosis acute GvHD study, 90-day survival was the target. To date, both studies have been published only in abstract form [39–41].

1. Steroid-refractory acute GvHD: using an intent-to-treat analysis, no difference was found in the primary endpoint. Placebo exposure was associated with a 30% complete remission rate versus 35% with MSC ($p = 0.3$). However, examining organ-specific responses, there was a 76% MSC response in patients with hepatic disease versus 47% on the placebo arm. In those subjects with gastrointestinal disease, there was an 82% response in the MSC cohort compared to a 68% response with placebo ($p = 0.03$). For patients with three organs affected by acute GvHD, the overall response rate with MSC was 63% versus 0% with placebo. Notably, in the pediatric patients, not only was there an observed higher overall response rate (64% vs. 36%), but the 100-day survival was improved (79 vs. 50%).

2. New diagnosis acute GvHD: Similar to the steroid-refractory acute GvHD, no difference was identified in the primary endpoint when MSCs were added to the standard of care.

Failure to achieve primary endpoints has dampened enthusiasm for pursuing MSCs as GvHD therapy. Multiple post hoc analyses have been performed regarding these results, including evaluations of the trial design, whether the appropriate MSC product was used, and whether the ex vivo culture conditions were appropriate [33]. Further, the use of a cryopreserved rather than a fresh cultured MSC product may have lessened the biologic effect as François and associates have reported a "freezer burn effect" [42]. The complete response to acute GvHD therapy as seen in the studies were far less than in the smaller phase 2 trials performed previously.

In the absence of further phase 3 trial data, meta-analyses suggest that MSC infusions could remain acceptable therapy for patients affected by steroid-refractory acute GvHD for whom no other prior approved agents were available [43]. As such, an open-label pediatric trial examined the use of unrelated MSCs for grade B to D steroid-refractory GvHD in 75 subjects aged 2 months to 17 years. The data reported an overall response rate of 61%; complete responses were noted in 26% of gastrointestinal GvHD patients, 44% in those with cutaneous GvHD, and 33% in patients with hepatic GvHD. Responders had 28-day persistence of response, and 100-day survival was 78% versus 31% for those who failed treatment [44].

Currently, although not approved for use in adults affected by steroid-refractory acute GvHD, the FDA now has accepted the use of remestemcel-L (Ryoncil™) for priority review in steroid-refractory acute GvHD in children. The Biologics License Application currently is under consideration utilizing data from three clinical trials of a combined 309 children with steroid-refractory acute GvHD. Across trials, after a 4-week course of twice-weekly treatment, 66% of patients responded; day 28 responders also had improved survival versus nonresponders (83% versus 38% at day 180). MSC therapy for steroid-refractory acute GvHD in children currently is approved in Canada and New Zealand.

MSC for Prophylaxis of Acute GvHD

MSC have been used for prophylaxis of acute GvHD based on in vitro and preclinical animal studies demonstrating their potent immunosuppressive capacity [33, 45]. Multiple mechanisms for this immune suppression in HCT models have been discussed above.

Lazarus et al. [46] reported the first application of related donor, ex vivo-expanded MSC infusions in the myeloablative allogeneic HCT setting. They demonstrated the feasibility and safety of procuring MSCs as well as hematopoietic cells from the sibling-matched donor, successful ex vivo expansion and subsequent infusion of allogeneic MSC into patients undergoing myeloablative and allogeneic HCT. Specifically, 46 subjects received varying doses of MSCs administered for the same hematopoietic cell donor with the infusion given 4 hours prior to the hematopoietic graft infusion. GvHD prophylaxis was limited to two-drug therapy with a calcineurin inhibitor and only 3 days of methotrexate. No accelerated neutrophil or

platelet recovery was seen but notably, there was no increase GvHD seen as a consequence of the MSC infusion despite the 3-day methotrexate exposure only.

Subsequently, a case-match control study compared the data set from this trial with the EBMT database. The analysis suggested a lower incidence of both acute and chronic GvHD in patients treated with MSC, and although only small numbers, there was a survival advantage at 6 months (96% vs. 68%) [47].

Other small studies performed include:

1. Bernardo et al., reported MSC prophylaxis therapy administered to 13 patients undergoing UCB transplantation. The data suggested a lower degree of grade III/IV acute GvHD than anticipated ($p = 0.05$) [48]

2. Ning and coworkers reported in a small, randomized phase 2 study of patients undergoing allogeneic HCT using HLA-matched sibling donors. With the co-transplantation of MSCs, the incidence of grade 2–4 acute GvHD was lessened, but at the cost of a higher degree of relapse in myeloablative conditioning patients ($n = 10$) versus controls ($N = 15$) [49].

3. Baron et al., reported feasibility with an acceptable nonrelapse mortality at 1 year of only 10% in 20 patients who received HLA mismatched mobilized blood allografts with co-transplantation of the HLA mismatched HSC with unrelated third-party MSC in a phase I/II trial [50].

4. Maziarz and associates reported a 36 patient, multi-arm phase I co-transplant study assessing the potential efficacy of an MSC subset, the universal donor multipotent adult progenitor cell (MAPC), as prophylaxis for acute GvHD unrelated donor transplantation. Trial design included a single dose escalation on day 2 or repeat dose escalation over the first 28 days of transplant course. Similar to other studies, no infusional or drug-related toxicity was reported over the first 30 days of treatment. Engraftment was not affected. The overall grade II–IV acute GvHD rate was 38% (grade III/IV 15%). The cohort of interest was identified as the 1×10^7 MAPC/kg dose administered on day 2 where an 11% grade II–IV acute GvHD incidence was observed with 0% grade 3 and grade 4 [51].

5. Finally, Kuzmina et al. reported a randomized study comparing 34 patients treated with standard acute GvHD prophylaxis versus 32 subjects receiving MSCs, at the time of blood count recovery. At day 100, a threefold decrease in acute GvHD frequency was seen in the experimental group (9.4% vs. 29.3%; $p = 0.041$). Kaplan–Meier survival curves also suggested clinical benefit ($p < 0.05$) [52].

Conclusions

MSCs continue to be evaluated for their immunosuppressive properties. GvHD is a complex syndrome resulting from immunologic interactions developing after tissue damage from transplant conditioning regimens. Further, balancing the benefit of a graft versus leukemia versus GvHD remains an area of study. After 20 years, MSC

therapy has not been confirmed as a standard treatment. However, MSC therapy is an approved therapy for steroid-refractory acute GvHD in the pediatric population in other countries and is currently under consideration in the United States [53].

In the last several years, greater attention for the clinical application of MSC products has focused on regenerative medicine efforts. Multiple phase 2 trials have been undertaken in various areas such as traumatic brain injury, acute lung injury, organ transplantation, myocardial infarction, stroke, autoimmune disorders, inflammatory bowel disease, and multiple sclerosis. The largest use remains in orthopedic clinics where MSC products are grown ex vivo for application in degenerative arthritis. These unproven indications remain under FDA scrutiny and await confirmation based on the gold standard of phase 3 randomized, blinded treatment trials.

The MSC remains a provocative pharmaceutical agent with its excellent safety profile, the multitude of growth factors and small molecules that are secreted, or as recently demonstrated, that can be transferred to the target cell by endosomes [54]. However, like all drugs, if MSC is to be considered as an effective pharmaceutical agent, detailed studies still remain necessary to determine optimal timing of application, optimal dose, optimal route of delivery, whether MSC should be administered as fresh or cryopreserved product, and whether MSC biology will be facilitated by simultaneous small molecule co-treatment.

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Chapter 55
T-Cell Therapeutics: Donor Lymphocyte Infusion, Cytotoxic T-Lymphocyte Infusion, and Other Non-CAR T-Cell Therapies

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Introduction

Cellular therapy is an integral part of cancer immunotherapy that is now considered as the fourth pillar of cancer treatment after surgery, chemotherapy, and radiotherapy. Allogeneic hematopoietic cell transplantation (HCT) is considered the most classic example of cellular immunotherapy. Post-transplant interplay between host and donor immune reactive cells plays a major role in graft-versus-leukemia (GvL) effect and graft-versus-host disease (GvHD). Immune reconstitution of the T-cell

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repertoire has major implications for relapsed disease, GvHD, and post-transplant viral infections. This chapter will focus on the exciting development in cellular therapy in the context of HCT and cell therapy including discussion of the diverse repertoire of T cell products specifically donor lymphocyte infusion (DLI), regulatory T cells, cytotoxic T lymphocytes for viral infections and T-cell receptors gene-modified T cells. In addition, the underlying pathophysiology and mechanism of action of cell-mediated effects with a focus on evidence from clinical studies elaborating the indications, efficacy, and safety of these T-cell-mediated therapies will be discussed, along with a brief overview of future directions and clinical trials exploring the potential of novel cell-mediated therapies in post-transplant settings.

Donor Lymphocyte Infusion

Donor lymphocyte infusion (DLI) is an effective way to induce a graft-versus-tumor effect, leading to complete and durable remissions in some patients who relapse after allogeneic HCT.

1. Mechanism of action [1]
   DLI primarily mediates the graft-versus-malignancy effect through CD4 + T cells, CD8 + T cells, regulatory T cells, natural killer cells, and antigen-presenting cells. It leads to reversal of T-cell exhaustion [a state of reduced function and proliferation of T cells associated with chronic antigen exposure] as well as normalization of the T-cell-receptor repertoire, expansion of allogeneic T cells, and improved coordination of T- and B-cells to mediate its graft-versus-malignancy effect against both non-disease-specific (minor histocompatibility antigens) and disease-specific antigens (e.g., BCR/ABL1 in chronic myeloid leukemia [CML], other leukemia-specific antigens, idiotypic immunoglobulins in plasma cell disorders).

2. Clinical uses of DLI [2]

   a. Treatment of relapsed disease after allogeneic HCT.
   b. Preemptive therapy for minimal residual disease (MRD) after allogeneic HCT and in patients at high risk for relapse.
   c. Promotion of donor engraftment in recipients with mixed donor chimerism to prevent hematologic relapse in certain circumstances. This is not a widely adopted strategy.
   d. Further treatment of uncontrolled post-transplant viral infections in certain circumstances.
   e. Further treatment of post-transplant lymphoproliferative disorder in certain circumstances.

3. Prophylactic DLI
   Prophylactic DLI is used in patients who are in hematologic and molecular remission after allogeneic HCT and are at very high risk of relapse (i.e., T-cell-

depleted platforms) [3]. Single or multiple infusions of prophylactic DLI are usually administered starting day +90 or +100 after HCT, provided patients have no evidence of GvHD and are off immunosuppression for at least 3–4 weeks. This strategy is more commonly utilized in some protocols that incorporate different methods of ex vivo T-cell depletion to prevent upfront GvHD. However, prophylactic DLI is not part of routine practice and is best done on prospective protocols [3].

4. Preemptive DLI
   Preemptive DLI is used after allogeneic HCT at the sign of early relapse (i.e., MRD positivity) and in patients with decreasing donor chimerism who tend to be at high risk for relapse [3]. This strategy can also be employed in patients with persistent MRD post-HCT. DLI can be administered in a repetitive manner at 4- to 12-week intervals using an escalated dose schedule and increasing cell dosage by 5–10 fold at each infusion provided the absence of clinically significant GvHD. The timing of preemptive DLI depends on the timing of MRD positivity and compromised donor myeloid chimerism. If the patient develops GvHD, further DLI is generally held; however, few institutions continue with DLI while a patient continues/starts immunosuppression provided GvHD is ≤ grade 2.

5. Timing and dosing of prophylactic and preemptive DLI
   Timing and dosing for DLI vary based on factors including donor source, time since transplant, and administration of chemotherapy prior to transplant. There are no prospective trials to answer this question. Typical DLI doses for related and unrelated donors are higher compared to haploidentical transplantation.

6. DLI for overt relapse
   For frank relapsed disease after allogeneic HCT, DLI with or without chemotherapy (for disease debulking, especially in acute leukemias) can be considered. As a rule of thumb, this approach is avoided in patients with active GvHD. The dose of DLI is usually 1 order of magnitude higher than the dose used in prophylactic or preemptive strategy [i.e., 1×10^8/kg of recipient weight in the setting of HLA-matched sibling donors (MSD)]. Based on the outcomes, including both disease response as well as GvHD, DLI can be repeated every 4–6 weeks in an escalating dose manner.

7. Factors influencing success of DLI [4]

   a. Graft-Versus-Tumor Susceptibility: Hematologic malignancies show variable responses to DLI based on inherent graft-versus-malignancy susceptibility: CML > low-grade non-Hodgkin lymphoma > high-grade non-Hodgkin lymphoma > Hodgkin lymphoma > acute myeloid leukemia (AML) > multiple myeloma > acute lymphoblastic leukemia (ALL).

   b. GvHD Status: Patients with acute or chronic GvHD requiring ongoing immunosuppression are usually not considered appropriate candidates for DLI due to the associated risk of its exacerbation.

   c. Disease Status: DLI is more effective in eradicating minimal disease. Hence, for relapsed/progressive disease, DLI may be more effective after cytoreductive therapies especially in fast-growing malignancies or bulky relapsed disease.

8. Donor lymphocyte collection

   Donor lymphocytes can be collected by lymphopheresis or derived from mobilized peripheral blood hematopoietic progenitor and stem cells (cryopreserved product) originally collected for transplant purposes. Lymphopheresis is the preferred method, additionally, allowing for T-cell manipulations if desired for a clinical trial.

9. Optimal dose of DLI

   There are no consensus or historical data supporting a standard fixed dose for DLI. The dose depends upon donor–recipient relationship with progressively lower doses from an HLA-matched related (HLA-MRD), unrelated (HLA-URD), and HLA–haploidentical donor sources, respectively. Initial doses above $1x10^8$/kg of recipient weight are associated with high risk of subsequent severe GvHD and usually are avoided.

   Typical unmanipulated CD3+ cell start dose for DLI:

   a. -1×10^8/kg of recipient weight: HLA-MRD
   b. -1×10^7/kg of recipient weight: HLA-URD
   c. -1×10^6/kg of recipient weight: HLA-haploidentical donor

10. Administration

    DLI can either be fresh (short-period apheresis) or previously cryopreserved (a choice if donor is unavailable). The final volume of DLI is around 25–50 mL and depends on the cell dose being collected for initial and subsequent administration. Premedication, as used for any other blood product, is based on institutional preference. DLI can be administered easily in the outpatient setting and does not require a central line placement for infusion. It is important to note that cryopreserved products have dimethyl sulfoxide (DMSO) and carry a higher risk of bedside reactions compared to fresh CD3+ cell products.

11. Disease-specific therapy prior to DLI

    When DLI is used for relapsed/progressive disease, cytoreductive disease-directed therapy is recommended for patients with aggressive relapse and significant disease burden.

12. Lympho-depleting chemotherapy prior to DLI

    Although no optimal regimen has been defined, T-cell-specific lympho-depleting therapy in the form of combination of pentostatin (Nipent®) and low-dose oral cyclophosphamide is often used to release hemostatic T-cell cytokines (IL-7, IL-12, IL-15) to augment T-cell proliferation and activation.

13. Use of immunosuppression with DLI

    The selection of immunosuppressive agent, dose, and duration of therapy has not been clearly elucidated in the literature. For patients at a lower risk of GvHD (no previous GvHD), there is no need for immunosuppression at the time of DLI. For patients at higher risk of GvHD (previous GvHD, matched URD, preceding cytoreductive therapy), a brief course (7–14 days) of tacrolimus, sirolimus (Rapamune®), etc. can be considered, but is not necessary. The risk and benefits of immunosuppressive therapy with DLI should be carefully assessed.

14. Response assessment

Response assessment depends upon chronicity of the disease and kinetics of relapse. Responses may take anywhere from 21 days to a year to manifest and largely depend on the indication for use, disease status, presence of GvHD, and infections. Although waiting for 1 year for evaluation for clinical efficacy is not practically possible, a minimum of 30 days and absence of immunosuppression should be allowed before any response assessment and decision about repeat DLI.

15. Side effects associated with DLI

    a. GvHD [5]: GvHD is observed in about 40–60% of patients. Incidence is determined by underlying disease, donor type, prior GvHD history, use of prophylactic immunosuppressive therapy, presence and type of product manipulation, and lymphocyte dose. Historically, the incidence of GvHD after DLI is higher than what is seen with initial allogeneic HCT given that the underlying premise is to give escalating doses of T cells to achieve a graft-versus-malignancy response. Ciceri et al. [6] investigated the therapeutic potential of donor lymphocytes engineered with the suicide gene thymidine kinase of Herpes simplex virus (TK) in 23 patients with relapsed disease after allogeneic HCT. Long-term follow-up evaluated the efficacy of GvL effect as well as safety with control of GvHD by ganciclovir. Seven received ganciclovir, resulting in the elimination of TK(+) cells and effective and selective treatment of GvHD. This method remains experimental.

    b. Bone Marrow Aplasia: Post-DLI marrow aplasia with resultant cytopenias has been reported in patients with chronic myeloid leukemia (CML) and is reflective of a vigorous GvL effect. Cytopenias require supportive measures and are rarely long lasting with spontaneous recovery over time. This complication is more common especially if donor myeloid chimerism is <30%. The hypothesis is that there might not be enough hematopoiesis support from the donor myeloid compartment provided DLI is effective.

16. Efficacy of DLI [7]

The efficacy of DLI is dependent upon disease status at the time of infusion, recognizing that all patients are not able to receive cytoreductive therapy prior to DLI. An increased time from transplant to relapse has also been associated with better outcomes, with higher disease-free survival reported in patients who relapse more than 12–24 months after HCT compared to those whose disease relapses sooner. Higher mortality is seen in patients with lack of response or occurrence of GvHD following DLI. A summary of response rates and incidence of GvHD is presented in Table 55.1.

17. Disease- specific consideration for DLI [7–10]

    a. CML: CML appears to be highly responsive to DLI with complete remission (CR) rates of 80%. However, these data reflect outcomes from an era where allogeneic HCT was the preferred therapy in the first chronic phase; outcomes of DLI in patients transplanted in later disease phases in the contem-

Table 55.1 Selected trials of DLI after allogeneic transplantation

Study	ClinicalTrials.gov Identifier
Hypomethylating agent +DLI vs DLI preemptive therapy based on MRD for acute leukemia undergoing allo-HCT	NCT03662087
Haplocompatible transplant using TCRα/β depletion followed by CD45RA-depleted donor lymphocyte infusions for severe combined immunodeficiency	NCT03597594
Donor lymphocyte infusion after allo-HCT in treating patients with hematological cancers	NCT01240525
Interferon-α after DLI for the prevention of relapse	NCT02568241
Prophylactic DLI for the prevention of relapse post HCT in patients with high risk myeloid malignancy	NCT02856464
Chemotherapy and DLI for prevention of second relapse in patients with relapsed acute leukemia after allotransplant	NCT03297528

DLI donor lymphocyte infusion, *MRD* minimal residual disease, *allo-HCT* allogeneic hematopoietic cell transplantation

porary tyrosine kinase inhibitor era have not been well described. GvL effect resulting in complete cytogenetic remission is seen at a median of 80 days after DLI with some responses seen as late as 1 year.

b. Acute Myeloid Leukemia (AML): CR is seen in about 25% of the patients. Better outcomes are expected in patients who have achieved cytoreduction prior to DLI and in patients with a longer time from transplant to relapse.

c. Acute Lymphoblastic Leukemia (ALL): CR is seen in <20% of patients. Patients usually require salvage chemotherapy for cytoreduction prior to DLI.

d. Multiple Myeloma: Responses are seen in about 10–20% of the patients and are rarely complete and durable.

e. Low-grade Non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma: CR is seen about 40–50% of patients.

f. Aggressive Non-Hodgkin Lymphoma: CR is not as frequent as in low-grade non-Hodgkin lymphoma and is seen in about 30–40% of patients. Due to aggressive relapse kinetics and the burden of disease, patients frequently require salvage chemotherapy prior to DLI.

g. Hodgkin Lymphoma: Response to DLI is determined by the underlying indication. Based on some reports, patients with relapsed disease have response rates of about 75% after DLI, whereas patients with mixed chimerism have low response rates of about 5% after DLI.

18. Strategies to augment DLI [11]

DLIs have been combined with targeted therapy and immunomodulatory drugs with varying effects on graft-versus-malignancy effect and GVHD. There are several preclinical as well as clinical phase I/II studies evaluating different interventions to augment the response of DLI while minimizing risk of GvHD.

    a. Combinations with interferon α and GM-CSF (Leukine®) have been reported as an intervention to enhance GvL effect.

    b. Immunomodulatory drugs currently under investigation include azacitidine (Vidaza®), lenalidomide (Revlimid®), and HDAC inhibitors (e.g., panobinostat [Farydak®]). The doses and timing of DLI combined with these agents are an active area of investigation, and this strategy needs to be pursued with caution.

    c. Lymphodepleting chemotherapy prior to DLI to augment graft-versus-malignancy effect has been reported, although it is associated with a high incidence of GvHD.

19. Unanswered questions/controversies in DLI

    DLI is most often used to treat disease relapse. Other situations in which DLI can be utilized depend on the specific situation/indication for a patient. This inherent variability has led to inconsistent and widely different practices that tend to be institutional and investigator-specific. Due to lack of standards of care, good-quality data from randomized controlled trials are currently lacking. Hence, there is a need for the following:

    a. Randomized and prospective data related to DLI dose, composition, timing, frequency, manipulation, as well as host preparation in each disease, donor type, and transplant intensity are required to ultimately improve its safety and efficacy.

    b. More data are needed to optimize the use of DLI in haploidentical transplant recipients.

    c. Indications and optimal regimen for pre-DLI lymphodepletion need to be standardized.

    d. The need for immunosuppressive therapy in the peri-infusion setting for patients with low risk of GvHD needs to be addressed.

20. Ongoing challenges and future directions

    a. Most of the data available are based on retrospective studies and institutional experience.

    b. Several clinical protocols are evaluating T-cell manipulation techniques including chimeric antigen receptor (CAR) transfection, activation, cytokine profile skewing, donor lymphocyte specificity, genotype, phenotype, and enrichment of various T-cell subsets. Such trials and investigations are necessary for making DLI safe and efficacious for all hematological malignancies.

    c. Table 55.2 shows the selected list of clinical trials, exploring the role of DLI after allogeneic HCT.

Table 55.2 Highlights of regulatory T-cell Function

	Comment(s)	Reference
CTLA-4	Treg receptor CTLA-4 binds and removes CD80/86 from the dendritic cell surface by internalization and degradation within the Treg (trans-endocytosis) leading to profound dendritic cell suppression. It also causes tryptophan depletion inhibiting T-cell proliferation CTLA-4 induces indoleamine dioxygenase in dendritic cells	Qureshi et al. 2011 [14]
LAG-3	Treg receptor which binds MHC class II and may mediate suppression of Tcons and APC activation	Huang et al. 2004 [15]
Interleukin-2	Expression of high affinity IL-2 receptor chain CD25 on Tregs depletes access of IL-2 for Tcon cells, resulting in apoptosis by cytokine deprivation	Pandiyan et al. 2007 [16]
Interleukin-10	Secreted by Tregs limits inflammation particularly at epithelial barriers with contact to the environment such as the lungs or the skin representing target organs in GVHD	Rubtsov et al. 2008 [17]
Interleukin-35	Inhibitory cytokine that may be specifically produced by Treg cells and is required for maximal suppressive activity	Collison et al. 2007 [18]
TGF-β	Enhances expansion and suppressive activity of Tregs, suppresses effector T-cell proliferation and function. Conversion of peripheral CD4 + CD25- naive T cells to CD4 + CD25+ Tregs by TGF-β induction of transcription factor, Foxp3.	Chen et al. 2003 [19]
CD4+ and CD25+ Treg dynamics	Treg transplants conferred long-term protection from systemic inflammatory challenge consistent with Treg in vivo survival	Nguyen et al. 2007 [20]
CD39, CD73 and adenosine	Adenosine generation catalyzed by CD39 and CD73 expressed on Treg cells mediates metabolic inhibition of effector T cells	Deaglio et al. 2007 [21]
CD30	Treg receptor: Early CD30 signaling is critical for adoptively transferred CD4 + CD25+ Tregs in prevention of acute graft versus host disease	Zeiser et al. 2007 [22]

CTLA-4 - cytotoxic T-cell lymphocyte antigen 4; LAG-3 - lymphocyte activation gene 3; TGF-β - transforming growth factor β; Tcons - conventional T cells; APC – antigen-presenting cells; Tregs - regulatory T cells; GvHD – graft-versus-host disease; Foxp3 - Forkhead-Box-Protein P3

Regulatory T (Treg) Cells

1. Regulatory T cells (a subset of CD4+ cells) were first discovered in 1995 and have been shown to be an anti-inflammatory cell population which attenuates and modulates immune responses on multiple levels including initiation, progression, and termination of inflammation.
2. The cells are characterized by expression of the transcription factor, Forkhead-Box-Protein P3 (FoxP3), which is important for the development of Tregs and its continued immune-suppressive functionality. Mutations within the FoxP3 locus lead to severe autoimmunity termed IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome [12].

3. Also, Tregs strongly express the high-affinity IL-2R α-chain (CD25-a subunit of IL-2 receptor) receptor and suppress other T-cell functions through a multitude of mechanisms (Table 55.2).

4. Dampening the inflammation (e.g., GvHD) by Tregs

   a. Maturation and Antigen Presentation of APC: Tregs are able to impair the maturation, migration, and effector function of innate immune cells. Tregs reduce the costimulatory activity of dendritic cells by means of CTLA-4 binding and destabilize the contact of effector T cells with dendritic cells. They induce apoptosis in B cells and neutrophils [12].

   b. Inhibition of Effector T cells: Tregs constrain proliferation by means of IL-2 depletion. Moreover, they limit cytokine production and survival by inducing a cytokine-deprived milieu and decrease the expression of homing receptors, leading to impaired migration of the effector cells [12].

   c. Effects on Local Inflamed Tissue: Tregs secrete a variety of anti-inflammatory cytokines including TGF-β, IL-10, and IL-35, which dampen inflammation [12, 13] (Table 55.2).

5. A balance among effector total T-cell and Treg cell populations is essential in achieving control of the quality and extent of adaptive immune responses, for establishing self-tolerance, and intolerance to non-self-antigens. The ability of Treg cells to suppress aberrant immune responses, regulate T-cell homeostasis, and maintain tolerance prompted interest in harnessing their function for the treatment of cGvHD. Several preclinical and clinical studies have evaluated the impact of regulatory T cells on GvHD.

6. Evidence from preclinical studies [23]

   a. In murine models, depletion of Tregs has been associated with increase in GvHD mortality.

   b. Conversely, the adoptive transfer of Tregs along with marrow graft reduced GvHD in mice studies.

7. Evidence from clinical studies [24, 25]

   a. The first clinical study evaluating the role of Treg-cell transfer was performed in 28 patients with high-risk hematological malignancies who underwent HLA-haploidentical HCT and showed that the regulatory T cells prevented aGvHD and promoted immune reconstitution without any evidence for an increased relapse.

   b. Safety and efficacy of umbilical cord-derived Treg cells were studied in 23 patients and revealed reduced incidence of grade II–IV aGvHD at 100 days post-transplant when compared to 108 historical controls (43% vs 61%).

8. Interleukin-2 for Treg development

   a. Interleukin-2 (IL-2) is critical for Treg-cell development, expansion, activity, and survival [26].

b. Koreth et al. [27] demonstrated responses to low-dose IL-2 in patients with cGvHD who failed corticosteroids.

 i. In the phase 2 study, 35 adult patients with steroid-refractory cGvHD received daily IL-2 (1×10^6 IU/m^2/day) for 12 weeks.
 ii. Of the 33 evaluable patients, 20 (61%) had clinical responses at multiple cGvHD sites such as the liver, skin, and gastrointestinal tract.
 iii. An important predictor of response seemed to be initiation of IL-2 therapy early after transplantation, suggesting that later established cGvHD is harder to modify by IL-2 treatment.

c. There are ongoing trials evaluating different treatment schedules of IL-2 and in combination with other strategies such as ECP and Treg-enriched infusions.

9. Ongoing Challenges and Future Directions
Clinical use of Treg cells for prophylaxis and treatment of GvHD is an exciting area in clinical research. Characterization of Treg markers has enabled specific enrichment of this cell subtype.

a. Due to the specific response to IL–2 and rapamycin, protocols have been developed for efficient expansion of Tregs with applications in clinical settings.
b. Based on clinical studies, standard prophylaxis and treatment options for GvHD including rapamycin and glucocorticoids have not been found to interfere with and, in fact, possibly enhance a Treg-cell function. This observation has led to combination therapies being explored for a synergistic effect.
c. Clinical trials are evaluating the role of third-party Tregs after cord blood on unrelated donor transplants. This technique needs to be fine-tuned given the decreased survival observed with third-party Treg cells.
d. Another area of need is identification of common antigens inducing GvHD, as with this knowledge, allo-specific Tregs could be generated causing negligible unwanted suppressive activity against allo-reactive conventional T cells.
e. Research to determine the optimal time point of adoptive transfer is ongoing.
f. Table 55.3 shows several strategies that are being investigated to augment the response of Treg cells to prevent and treat GvHD.

Cytotoxic T Lymphocytes for Viral Infections

1. Infectious complications after allogeneic HCT can be a source of significant morbidity and mortality. Viral infections including Epstein Barr virus (EBV), cytomegalovirus (CMV), adenovirus, BK, and HHV-6 are not always adequately treated with antiviral agents.
2. DLI has been employed as a strategy to treat uncontrolled viral infections. However, it is associated with increased risk of GvHD

Table 55.3 Selected clinical trials exploring regulatory T cells for prevention and treatment of graft-versus-host disease

Study	ClinicalTrials.gov Identifier
A Phase 1/2 Trial of Donor Regulatory T-cells for Steroid-Refractory Chronic Graft-versus-Host-Disease	NCT02385019
Ex-vivo Expanded Donor Regulatory T Cells for Prevention of Acute Graft-Versus-Host Disease	NCT01795573
Trial of Regulatory T-cells Plus Low-Dose Interleukin-2 for Steroid-Refractory Chronic Graft-versus-Host-Disease	NCT01937468
Multiple Donor Treg DLI for Severe Refractory Chronic Graft versus Host Disease	NCT02749084
Donor Regulatory T-cells for Steroid-Refractory Chronic Graft-versus-host-Disease	NCT03683498
Fucosylated T cells for Graft Versus Host Disease Prevention	NCT02423915
Daily IL-2 for Steroid-Refractory Chronic Graft-versus-Host-Disease	NCT01366092

Table 55.4 Selected studies of CMV-specific cytotoxic T cells

Study	Number of patients	Indication	Acute GvHD	CMV outcomes
Blyth et al. [33]	50	Prophylaxis	7 of 50	26 of 50 CMV reactivations
Walter et al. [34]	14	Prophylaxis	3 of 14	0 CMV reactivation
Peggs et al. [35]	16	Previous episode of CMV viremia	3 of 16	8 of 16 CMV clearance 2 of 14 CMV reactivations
Peruccio et al. [36]	25	Prophylaxis	1 of 25	7 of 25 CMV reactivations
Peggs et al. [37]	18	7 prophylactic 11 preemptive	8 of 18	Prophylactic: 0 of 7 CMV reactivation Preemptive: 9 of 11 CMV reactivations
Peggs et al. [38]	30	10 preemptive 10 concurrent with antivirals 10 prophylactic	11 of 30	Prophylactic: 3 of 10 CMV reactivation Preemptive: 10 of 10 CMV reactivations
Micklthewait et al. [39]	9	Prophylactic	3 of 9	2 of 9 CMV reactivations
Einsele et al. [40]	8	After failure of antiviral therapy	0 of 8	5 of 7 evaluable with CMV clearance
Feuchtinger et al. [41]	18	After failure of antiviral therapy	1 of 18	15 of 18 CMV clearance

GvHD Graft-versus-Host disease, *CMV* cytomegalovirus

3. Enrichment of virus-specific T cells followed by adoptive transfer has demonstrated an effective treatment strategy for viral infections with the risk of inducing GvHD. Based on some studies, the overall response rate (clinical response and reduction of viral load) to infusion of cytotoxic T lymphocytes has been as high as 80–90%. (Tables 55.4 and 55.5).

Table 55.5 Selected studies of multivirus-specific cytotoxic T cells

Study	Number of patients	CTL virus specificity	Rate of GvHD	Outcomes
Leen et al. [42]	13	Adenovirus and EBV	0	EBV: 3 reactivations AdV: 2 of 13 with viral clearance
Leen et al. [43]	11	CMV, EBV, AdV	0	CMV: 3 reactivations EBV: 3 reactivations AdV: 3 of 5 had reduction in AdV load
Ma et al. [44]	10	CMV, EBV, AdV, VZV	2	VZV: no reactivation CMV: 6 reactivations EBV: no reactivation AdV: no infection
Papadopoulou et al. [45]	11	EBV, CMV, AdV, BKV, HHV-6 8 = already Established viral infections 3 = prophylaxis	1	Prophylaxis: all virus-free for >3 months CMV: 2 CR, 1 PR EBV: 5 CR BKV: 5 CR, 1 PR, 1 NR AdV: 1 CR HHV-6: 2 CR
Hanley et al. [46]	34 PB-derived CTL 8 CB-derived CTL	CMV, EBV, AdV	0	CMV: 8 of 11 with viral clearance EBV: 10 of 10 with viral clearance AdV: 11 of 12 with viral clearance

CTL cytotoxic T lymphocytes, *GvHD* graft-versus-host disease, *EBV* Epstein Barr virus, *AdV* adenovirus, *CMV* cytomegalovirus, *VZV* varicella zoster virus, *BKV* BK virus, *HHV-6* human herpes virus 6, *CR* complete remission, *PR* partial response, *NR* no response, *PB* peripheral blood, *CB* cord blood

4. Strategies to Minimize Risk of GvHD with Virus Specific T cells

   a. To maximize clinical effects and minimize GvHD, several groups have sought to either selectively expand reactive populations by in vitro stimulations or directly isolate circulating virus-specific T cells for immediate infusion. Two isolation approaches that have been tested clinically include multimers selection and interferon γ capture [28].

   b. In vitro stimulation using antigen-loaded antigen-presenting cells to selectively enrich for specific populations has also been explored as a strategy for amplification of virus-specific T-cell populations [29].

   c. Evidence from clinical studies [30–32]

      i. Ex vivo expanded adoptively transferred virus-specific T-cells have proven to be well tolerated, even when administered as a partially HLA-matched third-party product, and effective in treating patients with several simultaneous/sequential infections and virus-associated disease. (Tables 55.4 and 55.5).

      ii. Based on reported outcomes of 30 allogeneic HCT patients with persistent/recurrent CMV, EBV, and adenovirus, administration of virus-spe-

cific T-cell lines generated from 15 donors that were HLA-matched at a median of two HLA antigens were associated with an overall response rate of 93% at 12 months with aGvHD seen in iitwo patients.

   iii. Based on another study of 45 patients, infusion with third-party virus-specific cytotoxic T lymphocytes led to an overall response rate (complete response plus partial response) of 94%, with an increasing circulating frequency of virus-specific T cells post-infusion in 50% of the patients with three cases of grade 1 GvHD.

   iv. 2018 American Society of Hematology Selected Presentations

   v. Abstract 812[a]: The phase I study evaluated the role of multiviral-specific T cells in the immediate post-allogeneic transplant period as a prophylactic measure to rapidly reconstitute antiviral immunity and ameliorate the side effects of early viral reactivation. This phase I study was a 3 + 3 dose-escalation design that evaluated 12 patients with multiviral-specific T-cells targeting against dominant viral proteins of CMV, EBV, BK, and adenovirus. All the patients received T-cell-depleted grafts. The study revealed the process to be safe and efficacious with no dose-limiting toxicity and with a minimal risk of aGvHD.

- Abstract 727[b]: The study (NCT02985775) selected for patients who developed aGvHD before CMV reactivated and started cytotoxic T lymphocytes generation in advance (preemptive approach). This prospective clinical trial enrolled 35 allogeneic HCT patients diagnosed with aGvHD and high risk for developing persistent CMV infection. The experimental arm had antiviral agents combined with cytotoxic T lymphocytes as first-line therapy and was evaluated for long-term safety and irritability of antiviral responses. As a control, 70 high-risk patients and 70 low-risk patients received only antiviral agents as first-line therapy without cytotoxic T lymphocytes. The study showed significant decline in the rate (20% versus 2.86%) and incidence of persistent CMV infection. It also showed a lower 1-year treatment-related mortality and better 1-year overall survival compared to the high-risk control cohort.

- Abstract 0119[c]: This phase I/II study showed prophylactic infusion of multiantigen-specific CD8+ T-cell products (directed against cytomegalovirus antigen, EBV antigen, adenovirus antigen, tumor-associated antigen, and minor history compatibility antigen) prevented viral infections after T-cell-depleted allogeneic HCT.

- Abstract Citations: [a]Blood 2018 132:812; [b]Blood 2018 132:727; [c]Blood 2018 132:119

5. Limitations Associated with Viral-Specific Cytotoxic T Lymphocytes:

   a. They can only be generated from donors with prior viral exposure (precluding the use of cord transplants and seronegative donors).

   b. They require larger volume leukapheresis for collection of adequate number of cells.

   c. The manufacturing process and delivery require 2–3 weeks for the product to be available for clinical use.

6. 'Off the Shelf' Virus-Specific Cytotoxic T Lymphocytes [47, 48]

   a. The complexities associated with generating individualized products for each patient have raised the need to prepare prospectively an alternative "off the shelf" product from healthy donors with diverse haplotypes to treat partially HLA-matched patients with viral infections.

   b. This approach was first published in 2002 and over the past 5 years has had phase 1 and phase 2 studies reported with at least two commercial companies pursuing the development of "off the shelf" viral-specific T cells.
   Based on a study published by Leen et al. [49], 50 patients were successfully treated with a bank consisting of 18 virus-specific T-cell products.

      i. Similarly, based on a study published by O'Reilly et al. [50], a bank of more than 100 CMV-specific and 300 EBV-specific third-party virus-specific T cells was used to treat patients viral infections in allogeneic HCT patients.

      ii. A study published by Withers et al. [51] compared a historical cohort of 146 allogenic HCT recipients with their third-party virus-specific T-cell bank.

         • Using the technique of HLA-restricted antigen specificity for each virus; they created a bank with 30 donors, 14 of which were used to treat 30 allogeneic HCT recipients with recurrent post-transplant viral infections.

         • The study concluded that a virus-specific T-cell bank comprising as few as six products [or fewer if shared alleles between donors and activity through each shared allele] would provide a product for most of the local allogeneic HCT population.

         • However, they also recommended that having a larger virus-specific T-cell bank will lead to increased matching between a virus-specific T-cell product and recipients, will enable treatment of recurrent viral infections (that occur in 10% of the allogeneic HCT population), and be more useful in treating populations that are more heterogeneous.

   c. At this time, third-party/off-the-shelf virus-specific T cells are available only in limited centers throughout the world. The ability to build a third-party virus-specific T-cell bank is of great value as this alternative antiviral treatment option is rapid as well as more cost-effective when compared to donor-directed virus-specific T cells. The cost of manufacturing and regulating the restrictions appear to be the impeding factors in the advancement of this technology.

7. Ongoing Challenges and Future Directions

   a. Previous studies evaluating the role of cytotoxic T lymphocytes in post-transplant viral infections did not include patients with active GvHD disease on steroids. Steroid-resistant cytotoxic T cells are currently being developed in preclinical models with hope for clinical application in future.

Table 55.6 Selected clinical trials exploring cytotoxic T lymphocytes for viral infections

Study	ClinicalTrials.gov Identifier
Using Multi-virus Cytotoxic T-cells Following T-Cell Depleted Allogeneic HCT for Prophylaxis Against Epstein Barr Virus, Adenovirus, And Cytomegalovirus	NCT01535885
Cytotoxic T Cells to Prevent Virus Infections	NCT01923766
Study Assessing the Effect of BK Specific CTL Lines Generated by ex vivo Expansion in Patients with BK Virus Infection and JC Virus Infection	NCT02479698
Antigen-specific Cytotoxic T Cells in the Treatment of Opportunistic Infections	NCT03159364
Virus Specific Cytotoxic T-Lymphocytes for Refractory Cytomegalovirus	NCT03266640
Allogeneic Virus-specific T Cell Lines	NCT02510417
Adoptive Cord Blood Immunotherapy for EBV, CMV, BKV and Adenovirus Reactivation/Infection or Prophylaxis	NCT03594981

    b. There have been reports of generation of EBV-specific CTLs resistant to calcineurin inhibitor tacrolimus by transduction with a calcineurin-mutated retroviral vector.

    c. Similarly, there are reports of EBV-specific T-cell resistance to both tacrolimus and cyclosporine.

    d. Phase I clinical studies are evaluating the safety and toxicity of CMV TCR-transduced donor-derived T cells post allogeneic HCT.

    e. Table 55.6 shows a list of selected clinical trials, exploring the role of cytotoxic T lymphocytes for viral infections.

T-Cell Receptor-Gene-Modified T cells for Cancer Treatment

T-cell-receptor-gene-modified T cells (TCR-modified T cells) involve the transfer of gene constructs encoding TCR α and β chains, which recognize 8–10 amino acid peptides processed from tumor-associated antigens (TAA) or tumor-specific target antigens (TSTA) and expressed by HLA molecules on the surface of target cells, generating therapeutic cellular products with a high level of tumor specificity, thus avoiding the toxicity of DLI, which is caused by the alloreactivity of the polyclonal T-cell receptor repertoire of infused donor T lymphocytes.

1. Mechanism of action

    a. TCR is a heterodimeric protein receptor, consisting of both α and β chains, expressed on the cell surface as part of a complex with CD3 peptides. TCR-modified T cells identify short tumor linear peptide epitopes presented by HLA class I (CD8 T cells) and II (CD4+ T cells) MHC antigens providing appropriate engagement and T-cell activation, which can elicit robust T-cell responses.

    b. TCR engagement is necessary but not sufficient for complete T-cell activation and triggering of effector function (i.e., proliferation, differentiation, survival,

and cytokine production) and a second signal is required, which is provided by costimulatory molecules, such as CD28 antigen.

c. TCR-modified T cells can target a much larger number of mutated proteins associated with cancers than CARs as the former can recognize intracellular mutated proteins while the latter target only transmembrane or extracellular antigens [52].

d. TCR-modified T cells have the major limitation of being HLA-dependent as it can only be used in a limited number of patients with the appropriate HLA alleles, for this reason the vast majority of TCR-modified T cells that are in clinical trials are restricted to HLA-A*0201, which is found commonly and is seen in approximately 45% of Caucasians.

2. Clinical experience with TCRs in cancer

a. In 2006, it was reported for the first time that patients with metastatic melanoma treated with TCR-modified T cells specific for a melanocyte-differentiating antigen (MART-1) showed long-term persistence of infused T cells and tumor regression in a small subset of patients [53].

b. Subsequent studies demonstrated that TCR-modified T cell therapy is safe, efficient in a proportion of patients, and can be associated with serious adverse events. Most of the TCR-modified T cell clinical trials were limited to MHC-I-restricted TCR-targeting peptides presented by HLA-A*0201.

c. A variety of tumor antigens are being targeted in clinical trials including cancer-testis antigen (CTS) family members (e.g., New York esophageal squamous cell carcinoma 1 (NY-ESO-1), melanoma-associated antigens (MAGE)-A3, MAGE-A4, and MAGE-A10), p53, gp100, p53, carcinoembryonic antigen (CEA), and viral protein family members.

d. In a clinical trial of multiple myelomas, the adoptive transfer of TCR-modified T cells specific for the cancer-testis antigens NY-ESO-1 and LAGE-1 was well tolerated without clinically apparent CRS, and showed an encouraging clinical response. NY-ESO-1-LAGE-1 TCR-modified T-cells were observed to migrate to the bone marrow and maintain durable persistence that was related to clinical activity against myeloma [54]. Table 55.7 features a summary of select current and past TCR-modified clinical trials.

TCR-Modified T-Cell-Associated Toxicities

Similar to the majority of other cellular therapies, the toxicity observed can be in general divided between three main categories: lymphodepleting preparative regimen, cytokine-related toxicity, and immune-related toxicity.

1. Lymphodepleting preparative regimen

a. As expected, the majority of the clinical protocol requires a conditioning regimen with cytotoxic lymphodepleting chemotherapy to facilitate engraftment,

Table 55.7 Selected past and present TCR-modified T cell therapy clinical trials

Target antigen	Target malignancy	Clinical phase	ClinicalTrials.gov identifier
P53	Metastatic cancer	Phase 2	NCT00393029
E7	HPV-associated cancers	Phase 1/2	NCT02858310
Gag	HIV	Phase 1/2	NCT00991224
AFP	Hepatocellular carcinoma	Phase 1	NCT03132792
HERV-E	Renal cell carcinoma	Phase 1	NCT03354390
KRAS G12V	Metastatic/unrespectable cancer	Phase 1/2	NCT03190941
NY-ESO-1	Melanoma	Phase 1/2	NCT01350401
NY-ESO-1	Multiple solid cancers	Phase 2	NCT00670748
MART-1	Melanoma	Phase 2	NCT00910650
Gp100	Melanoma	Phase 1	NCT01211262
NY-ESO-1	Multiple myeloma	Phase 1/2	NCT01352286
NY-ESO-1	Ovarian cancer	Phase 1/2	NCT01567891
Tyrosinase	Melanoma	Phase 1	NCT01586403
WT1	AML/CML	Phase 1/2	NCT01621724
WT1	Hematological malignancies	Phase 1/2	NCT01640301
MAGE-A4	Solid tumors	Phase 1	NCT01694472
NY-ESO-1	Solid tumors	Phase 2	NCT01697527
CEA	Adenocarcinoma	Phase 2	NCT01723306
NY-ESO-1	Multiple myeloma	Phase 1/2	NCT01892293
NY-ESO-1	Solid tumors	Phase 1	NCT02070406
MAGE-A4	Solid tumors	Phase 1	NCT02096614
NY-ESO-1	Solid tumors	Phase 1	NCT02366546
WT1	NSCLC/mesothelioma	Phase 1/2	NCT02408016
NY-ESO-1	Multiple solid tumors	Phase 1	NCT02457650
Gp100	Melanoma	Phase 1/2	NCT02535078
WT1	AML/MDS	Phase 1/2	NCT02550535
Gp100	Uveal melanoma	Phase 1	NCT02570308
NY-ESO-1	NSCLC	Phase 1/2	NCT02588612
MART-1	Melanoma	Phase 1/2	NCT02654821
HBV	HCC	Phase 1	NCT02686372
HBV	HCC	Phase 1/2	NCT02719782

expansion, activation, and persistence of TCR-modified T cells. There are inherent known toxicities related to the chemotherapy administered such as cytopenias, febrile neutropenia, and others.

2. Cytokine-related toxicities

   a. Cytokine-release syndrome (CRS) (see also Chap. 58) can range from fever to severe hypotension and respiratory failure and is due to highly proliferative TCR-modified T cells.

   b. Neurologic toxicities have been reported after TCR-modified T cell therapy in patients receiving MAGE-A3-specific TCR-modified T cells [55].

c. In general, CRS associated with TCR-modified T cells has been less severe than is observed with CAR T cells.

d. Treatment is in general supportive with the possibility of using IL-6 receptor antagonist Tocilizumab (Actemra®).

3. Immune-related toxicities

a. "off-tumor/on-target" side effects

   i. In many cases, tumor antigens (i.e., CTA, MART-1, and gp100) targeted by TCR-modified T cells can be expressed physiologically on normal cells, therefore triggering an undesirable immune response against normal organs such on normal melanocytes in the skin and inner ear. One example is the toxic effect on the melanocyte-rich tissues caused by TCR-modified T cells specific for the melanocyte differentiation antigen MART-1 [56].

      • In a trial using MART-1 and gp100-specific TCR-modified T cells, 29 of the 36 patients exhibited a widespread erythematous skin rash; in addition, some patients developed hearing loss and anterior uveitis [57].

      • In a clinical trial including metastatic colorectal cancer patients who received carcinoembryonic antigen (CEA) TCR-modified T cells, these patients developed severe inflammatory colitis; it was thought to be an on-target toxicity as a result of modified T cells recognizing the CEA expressed in normal colonic cells [58].

      • There was also a case report of fatal reaction from multiorgan failure and irreversible neurologic damage after MART-1-specific TCR administration thought to be due to on-target cytokine release [59].

b. "off-tumor/off-target" side effect.

   i. An example was reported by Linette et al. [60] of a patient who died from a cardiogenic shock after being treated with MAGE-A3 TCRs. At autopsy, there was extensive myocardial necrosis with a striking CD3+ lymphoid cellular infiltration in the myocardium; a similar infiltration was not observed in the skeletal muscle or other examined organs.

   ii. Elegant post-severe adverse events (SAEs) in vitro studies using an alanine-scanning methodology to delineate critical TCR-binding residues in the MAGE-A3 peptide EVDPIGHLY ultimately identified a peptide (ESDPIVAQY) derived from the very large (3-megadalton) cardiac muscle protein titin as the likely target of off-tumor, off-target TCR cross-reactivity.

4. Ongoing Challenges and Future Directions

a. Manufacturing:

   i. One of the most important challenges in cell therapy in general and in TCR-modified T cells in particular is the development of a manufacturing process that is dependable, rigorous, efficient, and reproducible.

    ii. The ideal product should exhibit a robust durable immune response, resist exhaustion, and be able to be suppressed relatively easily in case of toxicity.

   iii. Production of TCR-modified T cells goes through multiple steps from peripheral blood mononuclear cells collection, T-cell activation with microbeads conjugated with anti-CD3 and anti-CD28 antibodies, transduction with retroviral vector, microbeads washing, culturing of the cells, cryopreservation, quality control testing, and certification before release for infusion; all of the above steps are not yet universally standardized.

b. Reducing toxicity

    i. Few strategies are being tested.

    ii. One strategy is apoptosis induction as a safety switch, such as incorporating caspase 9 as a "suicide gene" into the transgene [61].

c. Neutralizing the tumor microenvironment inhibitory effect

    i. Tumor thrives on the immune inhibition by the microenvironment through cell–cell signaling and/or release of cytokines that inhibits endogenous and TCR-modified T cells.

    ii. Immune checkpoint molecules inhibitors (i.e., ipilimumab [Yervoy®], nivolumab [Opdivo®], pembrolizumab [Keytruda®]) counteract this inhibitory immune effect and have been combined with CAR-T cells to attempt to enhance the efficacy of CAR-T therapy.

   iii. Similar strategies of incorporation of checkpoint blockade and TCR-modified T cells are currently being tested in clinical trials for multiple myeloma and non-small-cell lung cancer incorporating pembrolizumab and TCR-modified T cell strategy.

d. Tumor-specific target identification

    i. Enhancing this strategy will not only improve the efficacy of TCR-modified T-cell therapy but will also perhaps reduce the risk of "off-tumor/on-target" toxicity.

    ii. One method is to identify and target neoantigens that are specific for tumor cells.

e. Addressing the inherent problem of HLA restriction of TCRs-modified T cells: By offering a wider range of HLA molecules beyond the traditional and common targets of HLA-A*02:01.

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Chapter 56
Dendritic Cell Vaccines

Levanto Schachter

Introduction

Dendritic cell vaccines have included non-specific products pulsed with whole-cell tumor lysate to antigen-specific targeted vaccines. The only currently Food and Drug Administration (FDA)-approved DC therapy is sipuleucel-T (Provenge®) for the treatment of castrate-resistant prostate cancer. Overall, the responses have been modest, but the phase III study in minimally symptomatic castrate-resistant prostate cancer demonstrated a statistically significant median survival advantage of 4.1 months [3].

While sipuleucel-T is the only approved DC vaccine therapy, there are a number of trials with promising results in a variety of malignancies. Bol, et al., reported on adjuvant treatment in melanoma using DCs targeting gp100 and tyrosinase [4]. The administration was shown to be safe and associated with demonstration of antitumor immunity and improved overall survival (OS) in those who received the vaccine. In acute myeloid leukemia, Anguille et al., reported on a WT1 directed DC vaccine in first complete remission after chemotherapy with noted favorable results compared to historical controls [5]. In addition, DC vaccines are being studied as an adjuvant treatment in autologous and allogeneic stem cell transplant (see Table 56.1).

As the prime APCs of the immune system, DCs are central to the activation and expansion of the effector cells of the immune system to target antigens, and particularly critical for the generation of antiviral immunity. In the tumor immunology sphere, suppression of DC function is one way for tumors to evade immune elimination, while their activation can improve the overall immune response against transformed tumor cells. DCs represent a diverse subset of leukocytes; as such, substantial clinical challenges persist in how to harness their potential and best integrate them into the sequence of antitumor therapies.

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Table 56.1 Dendritic cell vaccine trials currently active, recruiting, or completed in conjunction with transplant from clinicaltrials.gov as of March 2019

NCT Number	Phase	DC Source	Peptide delivery	Targets	Other intervention	Diseases	Post-transplant
NCT03679650	Phase 1	Mo-DC	PEG fusion	Any tumor antigens	Decitabine	AML	Allo
NCT00923910	Phase 1/2	Allogeneic donor DCs	Pulsed DCs	WT1	Given with DLI and must be HLA-A2	AML, ALL, MDS, CML, and NHL	Allo
NCT00186316	Phase 1/2	Allogeneic donor DCs	Idiotype-pulsed	Tumor-specific clonal immune Globulin	Specifically post non-myeloablative allogeneic	MM	Allo
NCT01067287	Phase 2	Mo-DC	PEG fusion	Any tumor antigens	CT-011-(anti-PD-1 mAb)	MM	Auto
NCT02728102	Phase 2	Mo-DC	PEG fusion	Any tumor antigens		MM	Auto
NCT00458653	Phase 1	Mo-DC	PEG fusion	Any tumor antigens		MM	Auto
NCT01995708	Phase 1	Langerhans cells	Electro-porated	CT7, MAGE-A3 and WT1		MM	Auto
NCT02851056	Early Phase 1	Autologous DCs from leuke-pheresis	Trans-fection with adenovirus	Survivin	G-CSF and Prevnar	MM	Auto

Mo-DC monocyte-derived dendritic cells, *AML* acute myeloid leukemia, *allo* allogeneic, *DCs* dendritic cells, *DLI* donor leukocyte infusion, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndrome, *CML* chronic myeloid leukemia, *NHL* non-Hodgkin lymphoma, *MM* multiple myeloma, *PEG* polyethylene glycol, *G-CSF* granulocyte colony stimulating factor

Dendritic Cells (DCs)

DCs were discovered in the 1970s initially as specialized cells residing in peripheral lymphoid organs in mice. Since then, DCs have been identified in many tissues. Their function and phenotypes vary depending on their tissue of residence and cell of origin.

1. Structure

   a. DCs are professional APCs with projections or dendrites giving them a distinctive microscopic appearance.
   b. They first were identified as a small subpopulation of glass-adherent cells isolated from murine lymphoid organs, but more detailed investigations led to

their identification as resident cells in a variety of tissues with varying phenotypes.

2. Phenotypes, classes, and functions of DCs

a. Classical dendritic cells (cDCs) are derived from common DC progenitors (CDPs) and express myeloid antigens CD11c, CD33, CD11b, or CD13. There are two major subsets: [6, 7]

   i. cDC1 which are CD141 expressing cells and are generally lymph node resident. These cells have the capacity for antigen cross-presentation and have the responsibility of activation of CD8+ T Cells.

   ii. cDC2 are CD1c expressing cells which are migratory and can activate CD4+ T cells.

b. Plasmacytoid dendritic cells (pDC) do not express myeloid antigens but instead express CD123 and CD45RA. Their major physiologic function is the production of type I interferon. Hematopoietic stem cells (HSCs), or myeloid progenitors, can also be driven to mature into either classical or plasmacytoid dendritic cell lineages; in contrast, lymphoid progenitors were shown to also be capable of maturation into plasmacytoid dendritic cells with the same surface phenotype, but with less APC function and more type 1 interferon production [5, 7, 8]. These cells do not depend on the growth factor, GM-CSF, for differentiation but respond to the cytokines, IL-3, and Fms-like tyrosine kinase ligand (FTL3L) [9].

c. Langerhans cells inhabit stratified squamous epithelium including the basal epidermis and have a unique function and phenotype. While cDC2s are also found in the skin, they are distinguished from Langerhans cells by higher CD11c and CD11b expression and lower CD1a and CD207 (langerin). As with other migratory DCs, once activated with antigen, these cells can migrate and home to lymphoid tissues and have functional antigen cross-presentation ability.

d. Monocyte-derived dendritic cells (Mo-DCs) are, as the name indicates, derived from CD14+ circulating monocytes and are resident in tissues, but are identified at a higher concentration at sites of inflammation. They retain myeloid markers including CD33, CD11b, and CD11c as well as frequently retaining CD14.

e. Nonclassical monocytes, which are CD16+, are considered DCs by some authors and include SLAN+ DC and DC4, but their function and origin are not well defined.

f. Thymic DCs, unlike most other DCs, mediate the negative selection of T cells during T-cell development and are central to the development of self-tolerance. The source of these cells appears to be a lymphoid-derived precursor in the thymus itself. Phenotypes vary and have been described in 3 subgroups: CD8α^+ conventional DC (cDC), signal regulatory protein α^+ (SIRPα^+) cDC, and plasmacytoid DC (pDC), but with a more mature phenotype than seen in the periphery [10, 11].

The Exploitation of Dendritic Cell Biology and Generation of Dendritic Cell Vaccines

1. The clinical application of dendritic cell vaccines generally involves administration of DCs cultured with target antigen to stimulate an in vivo T-cell response to viral or tumor-associated antigens.
2. Targeted vaccines involve loading cultured dendritic cells with specified antigens such as prostatic acid phosphatase (PAP) used for creating sipuleucel-T clinical product, or gp100, often as a melanoma-specific antigen. Methods used for the generation of antigen-specific DC include pulsing directly cultured DCs with antigen, transfection, and electroporation of genes encoding the target antigen, and culturing with mRNA encoding antigen.
3. Nontargeted vaccines involve loading DCs or exposing DCs to the entire repertoire of possible antigens within the tumor cells. Osmotic lysis, oxidizing the tumor cells, and radiation-induced apoptosis have been used to damage the malignant cells prior to being cultured with DCs for the generation of the tumor vaccines. In this setting, one is capitalizing on having the natural physiologic functions of the DC to metabolize the tumor lysate and to use its own proteolytic pathways to select the major histocompatibility complex (MHC) restricted, tumor-specific peptides that would generate the antitumor immune response.
4. Another method includes cell fusion, utilizing polyethylene glycol (PEG) to fuse malignant cells directly with host, expanded DCs. This approach is being validated currently in a multicenter study in which the fusion DC: myeloma cell partners from individual patients is performed locally, rather than using central manufacture, then administered as adjuvant therapy, post-autologous HCT (BMT CTN 1401 NCT02728102) [7, 12, 13].

Dendritic Cell Vaccines Currently in Use or Late Clinical Trials

1. The only FDA- approved dendritic cell vaccine is sipuleucel-T (Provenge®) for prostate cancer, where PAP peptide is cocultured with GM-CSF to activate APCs. Results have been modest as a single agent therapy, but an OS benefit was shown. Clinical trials are currently underway combining this therapy with various immune-modulating therapies including checkpoint inhibition.
2. DC vaccines have been evaluated in several studies in melanoma dating back over many years.

   a. In 2006, a phase III trial was conducted evaluating dacarbazine versus a peptide-loaded DC vaccine. This study showed no improvement over chemotherapy. There were however subsets of patients who appeared to derive more

benefit than others, which is discussed further below in section "Challenges in Implementation and Efficacy" (3).

b. A number of phase I and II trials have been conducted to improve the selection of patients, methods of delivery, and adjuvant therapies either with coadministration of or bound to costimulatory molecules [3, 14, 15].

Challenges in Implementation and Efficacy

1. The optimal source of DCs is unknown. Various cell sources have been utilized in trials across a variety of malignancies.

   a. MoDCs created by collecting circulating monocytes and then exposing them to cytokines such as GM-CSF and IL-4 to transform them into monocyte-derived dendritic cells. These cells are relatively easy to collect, however, there is evidence that these cells are not as apt at immune activation as pDCs or cDCs derived from common dendritic progenitors (CDPs) and often need further manipulation to achieve maturity of function [16, 17].

   b. cDCs or pDCs can be collected from the blood or tissues. Typically, these APC populations make up only 0.1% of marrow cells, therefore, simple physical harvesting would not yield enough cells for adequate manufacture.

      i. They can be cultured and expanded, but the source and the culture medium result in differing functions.

      ii. Given the variety of functions of DCs based on source and maturation, the DCs used for a vaccine have a significant impact on efficacy. Further refinement in this area is being explored [15, 18, 19].

   c. Langerhans cells matured from CD34+ HSCs can be derived from marrow or cord blood. They may be the most efficient APCs, and there is evidence that they may have an advantage over MoDCs for inducing an antigen-specific cytotoxic T-cell response [20, 21]. Early trials using Langerhans cells in melanoma show promise [20] and are being explored in multiple myeloma (see Table 56.1).

2. Antigen selection

   a. Targeting one or more broadly identified specific tumor-associated antigens (TAA) such as WT1, NYESO, Survivin, MAGEA3, PRAME, PAP as in prostate cancer, or others has the advantage of using antigens known to stimulate a response. However, if the antigens are not expressed by the patient's malignancy, there may be limited or no clinical response.

   b. The use of specific tumor lysate to release all tumor antigens has the advantage of allowing expression of a comprehensive repertoire of antigens including neoantigens from the tumor, but at the expense of diluting the most effective antigens with many which will not incite a significant T-cell response.

3. Human Leukocyte Antigen (HLA) Limitations

    a. Unique HLA expression may be critical for optimal vaccination. As observed in the phase III trial comparing dacarbazine to DC vaccination in melanoma, there was a significant (P = 0.01) difference in OS between patients with and without HLA A2+/B44-; patients with A2+/B44- had better OS. This advantage in HLA-A2 is being explored in a variety of settings including post-allogeneic HCT (NCT00923910).

4. Delivery of dendritic cell vaccines in trials has been primarily direct intradermal or intranodal injections.

    a. With an intradermal injection, the expectation is that the expanded cells will migrate via normal physiologic trafficking pathways to various lymphoid areas and activate a T-cell response. The process of migration though is incompletely understood and some vaccines in trial may have suboptimal results due to a failure in this migration system.

    b. Direct intranodal delivery bypasses the need for the initial cell migration, but may ultimately limit the extent of the effectiveness [7].

    c. IV administration, usually in conjunction with intradermal injection, has also been used in trials, though none of these methods have been tested head-to-head in larger trials.

Combination Dendritic Cell Vaccines

1. Given that a DC vaccine relies on activation of a T-cell-mediated immune response, there has been a recent focus on combinations of DC vaccines with checkpoint molecule blockade antibody therapy or other interventions which may provide a synergistic effect.

    a. Low-dose chemotherapy has been combined with DC vaccines.

        i. Combining the infusion of antigen-loaded DCs in combination with tumor-infiltrating lymphocytes (TILs) was reported in treating stage IV melanoma in a Phase I trial.

        ii. Cyclophosphamide was administered prior to the infusion of the DCs and then again prior to the infusion of the TILs. This approach is predicated on the theory that the chemotherapy would make "space" for the infused T cells and increase their cytokine exposure (i.e., homeostatic expansion), and eliminate Tregs which may suppress the immune effect of the cells [22].

    b. Use as adjuvant therapy to stimulate an immune response in the setting of either minimal residual disease (MRD) positive or negative disease continues to be a significant area of research.

    i. DC vaccines given after consolidation chemotherapy in AML have a positive signal of efficacy.

    ii. DC vaccines post-allogeneic or autologous HCT as an adjuvant treatment is also an area of active research.

- BMT CTN 1401 is an example of the development of a functioning post autologous HCT DC vaccine.
- In the allogeneic setting, DC vaccines are under evaluation for enhancing the GvL effect without inciting further GvHD and have been shown to be potent activators of tumor-specific T cells and NK cells [19].

c. Cytokines and toll-like receptor (TLR) agonists including TNFα, IL1β, IL6, IFNα, TLR-4 agonists, TLR-3 agonists are used in developing and expanding DCs. The specific "cytokine cocktail" is vital to the DC vaccine success [7]. In addition to being used in maturation designs, cytokines have also been given in conjunction with the DC vaccine or bound to the antigen such as GM-CSF in sipuleucel-T.

d. Checkpoint blockade and costimulation are also being studied in conjunction with DC vaccines.

    i. TriMix is an mRNA mix electroporated into DCs to deliver CD40L, CD70, and caTLR4 as activating and costimulatory signals [23]. TriMix-DC vaccine has been evaluated in conjunction with ipilimumab (Yervoy®; NCT01302496), a CTLA-4 inhibitor, in unresectable melanoma though results of this study are pending at the time of publication.

    ii. Sipuleucel-T has also been combined with ipilimumab (NCT01832870) and PD1 blockade (NCT01420965) in patients with prostate cancer.

    iii. Other targets being evaluated for combinations with DC vaccines are TIM3, LAG3, and indoleamine 2,3-dioxygenase (IDO) inhibitors among others.

Role in Infectious Disease

1. DC vaccines have shown some promise in the treatment and prophylaxis of cytomegalovirus (CMV). A small study of post-allogeneic HCT recipients with CMV infection infused with T cells and intradermal CMV peptide-pulsed dendritic cells demonstrated feasibility and in vitro CMV-specific T-cell activation could be detected [24].

2. Epstein-Barr virus (EBV)-DC vaccines targeting EBV-LMP2 and with adjuvant CD40L showed promise in nasopharyngeal cancer [25]. Given that EBV is a driver behind a number of hematologic malignancies, this area of study is of particular interest to the HCT community.

3. Human immunodeficiency virus (HIV) therapy with DC vaccines is under development, and early trials demonstrate increased T-cell activation and decreased viral load in patients who received vaccine therapy [26].

Potential Role in Graft-Versus-Host Disease (GvHD)

1. While DCs are generally considered APCs with the intent of stimulating an immune response, they are also a vital part of learning self-tolerance in the thymus. Early trials indicate the ability of DCs to modulate the immune system in the treatment or prevention of GvHD.

   a. Vitamin D has been shown to be a modulator of adaptive immunity, to promote a tolerogenic profile in DCs, and appear to upregulate Tregs. In a mouse model infusion of calcitriol, DCs appeared to delay GvHD development [27, 28].
   b. Studies in murine models indicate that modified DCs cultured with T cells can be used to generate a GvL effect in the absence of GvHD [29].
   c. In an animal model of autoimmune glomerulonephritis, a DC vaccine targeting CD40 DNA was shown to suppress Th17 (also involved in GvHD) and inhibit progression of the disease [30, 31].

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Chapter 57
BiTEs, DARTs, and Peri-Transplant Minimal Residual Disease

Jessica Leonard

Introduction

Bispecific antibody (BiTE) and dual-affinity retargeting (DART) therapies currently represent a novel therapeutic treatment modality for patients with acute leukemias. The first and to date only Food and Drug Administration (FDA)-approved BiTE is blinatumomab (Blincyto®), a bispecific T-cell engager that brings CD3+ T cells in proximity with CD19+ blasts. In addition to its usage for relapsed disease, blinatumomab also carries FDA approval for the treatment of minimal residual disease (MRD), a novel indication for drug approval. There are multiple other bispecific antibodies in early phase clinical trials to treat other hematologic malignancies; however, data at this time are limited. In the context of hematopoietic cell transplant (HCT), BiTE therapy has two potential roles. Treatment could occur prior to transplant to eradicate MRD, thus allowing patients to enter transplant in an MRD-negative state. However, the optimal method to eliminate MRD is unclear and whether converting an MRD-positive patient to an MRD-negative state will improve overall survival after allogeneic HCT remains unproven. Alternatively, BiTE therapy could be used in the post-transplant setting, either for overt relapsed disease or for re-emergence of MRD. Both strategies hold potential benefits; yet, data supporting their usage in these roles to date are limited. Similar opportunities may emerge if and when DART therapies earn FDA approval. Herein, the author will describe the various BiTE and DART constructs currently in development, as well as the clinical data available to date regarding their efficacy. In addition, the data supporting their usage in HCT will be discussed, along with future directions and challenges.

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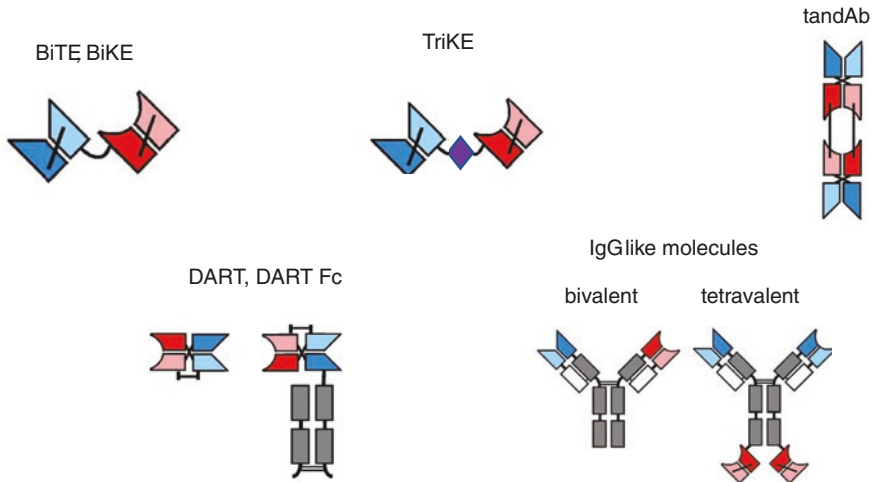
Fig. 57.1 Selection of bispecific antibody constructs. (Figures adapted with permission from Kontermann and Brinkmann [10]. Abbreviations: BiTE - bispecific T-cell engager; TriKE—trispecific killer cell engagers; DART— dual-affinity retargeting; tandAb—tandem antibodies)

Definitions (See Fig. 57.1 for Schematic Representation of Different Bispecific Antibody Constructs)

1. Bispecific T-cell engagers (BiTEs):

   a. Design: BiTEs are composed of two single-chain variable fragments (Fv) derived from the Fab portion of an antibody molecule combined via a peptide linker. One Fv targets a T cell-specific antigen (generally CD3), while the second targets a tumor-associated antigen [1, 2].

   b. Mechanism of Action: Brings target cells (T cells, NK cells, or macrophages) in close proximity to malignant cells, thus transiently forming a cytolytic synapse and allowing for lysis of target cells. Activated T cells secrete perforin and granzymes which lead to apoptosis of the target cells [3]. Activated T cells also produce cytokines that lead to additional T-cell recruitment, activation, and expansion [4].

      i. Binding is to the invariate region of CD3, thus effectively engaging and activating all cytotoxic T cells against tumor cells [5].
      ii. Response is independent of T-cell receptor (TCR) specificity and independent of MHC class I peptide presentation [5].
      iii. T cells are only activated when target cells present the BiTE antibody to T cells; blinatumomab administered without binding to tumor antigen is incapable of activating T cells through the TCR [5].

   c. Pharmacokinetics: BiTEs in general have a short serum half-life with that of Blinatumomab being 2–3 hours [6, 7].

    i. Requires infusion via a continuous infusion pump.

    ii. The current dosing scheme is 4 weeks on, 2 weeks off.

2. Dual-Affinity Retargeting Therapies

   a. Design: DARTs are composed of two variable fragments (Fv) composed of variable region light (V_L) and heavy (V_H) chains specific for two different antigens, arranged in a VLA – VHB + VLB – VHA configuration. Additional stability is provided through a C-terminal disulfide bridge [8, 9].

   b. Mechanism of Action: Similar to BiTEs, DARTs bring effector cells in close proximity to tumor cells. The lack of a linker chain is thought to make the association of the construct more like that of an IgG molecule, allowing maintenance of contact between cells. One in vitro study suggests that the DART construct is more potent than the BiTE construct, without increasing nonspecific T-cell activation or killing of nontarget cells [8].

   c. Pharmacokinetics: Similar to BiTEs, DARTs have a short serum half-life. This can be extended if DARTs are constructed with an Fc portion present [10].

3. Other bispecific antibody constructs [11]:

   a. Bispecific Killer Engagers (BiKEs), Trispecific Killer Engagers (TriKEs): These constructs direct NK cells to tumor cells to trigger antibody-mediated cellular cytotoxicity (ADCC). The construct is similar to BiTEs; however, CD16 on NK cells is targeted rather than CD3. TriKEs additionally sandwich IL-15 into the design to further stimulate NK cell expansion.

   b. Tandem Diabodies: This bispecific antibody format contains two binding sites for each antigen, providing a larger molecule which avoids first-pass renal clearance. This allows for a longer half-life than the BiTEs or DARTs.

   c. Bispecific Monoclonal Antibodies (bsmAb): This structure retains the format of a monoclonal antibody with an Fc fragment and two Fab fragments; however, each Fab fragment targets a different antigen. As the Fc fragment is retained in this construct, ADCC occurs via effector cells that have Fc receptors.

BiTEs and DARTs That Are FDA Approved or Have Preliminary Results from Clinical Trials (See Table 57.1)

1. BiTEs

   a. Blinatumomab (Blincyto®): Targets CD3 and CD19. Currently FDA approved for the treatment of relapsed / refractory B-cell acute lymphoblastic leukemia (ALL) (Philadelphia chromosome-positive [Ph+] and negative [Ph-]) or B-cell ALL with MRD (see section "Clinical Efficacy of Blinatumomab (Blincyto®)")

Table 57.1 Current clinical trials of bispecific antibodies in hematologic malignancies

Study	Drug	ClinicalTrials.gov number
Safety Study of MGD006 in Relapsed/Refractory Acute Myeloid Leukemia (AML) or Intermediate-2/High Risk MDS	Flotetuzumab (CD3-CD123 DART)	NCT02152956
A phase 1 study of AMG 330 in subjects with relapsed/refractory acute myeloid leukemia	AMG 330 (CD3-CD33 BiTE)	NCT02520427
A Study of JNJ-67571244 in Participants With Relapsed or Refractory Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)	JNJ-67571244 (Cd3-CD33 bispecific antibody)	NCT03915379
Dose-escalating Phase I Trial With GEM333 in Patients With Acute Myeloid Leukemia	GEM333 (CD3-CD33 bispecific antibody)	NCT03516760
MCLA-117 in Acute Myelogenous Leukemia	MCLA-117 (CD3-CLEC12A bispecific IgG antibody)	NCT03038230
AFM13 in relapsed/refractory cutaneous lymphomas	AFM13 (CD16A-CD30 bispecific tetravalent antibody)	NCT03192202
Study of TG-1801 in subjects with B-cell lymphoma	TG-1801 (CD47-CD19 bispecific antibody)	NCT03804996
Assess the anti-tumor activity and safety of REGN1979 in patients with relapsed or refractory follicular lymphoma	REGN1979 (CD3-CD20 bispecific antibody)	NCT03888105
Study of Cemiplimab and REGN1979 in patients with lymphoma	REGN1979 (CD3-CD20 bispecific antibody) Cemiplimab (anti PD-1 antibody)	NCT02651662
First in human (FIH) study of REGN5459 in patients with relapsed or refractory multiple myeloma (MM)	REGN5459 (CD3-BCMA bispecific antibody)	NCT04083534
First in human (FIH) study of REGN5458 in patients with relapsed or refractory multiple myeloma	REGN5458 (CD-BCMA bispecific antibody)	NCT03761108
Study of GBR 1342, a CD38/CD3 Bispecific Antibody, in Subjects With Previously Treated Multiple Myeloma	GBR 1342 (CD3-CD38 bispecific antibody)	NCT03309111
Phase 1 study of PF-06863135, A BCMA- CD3 bispecific ab, in relapse/ refractory multiple myeloma	PF-06863135 (CD3-BCMA bispecific antibody)	NCT03269136

    b. AMG420: Targets CD3 and BCMA. Currently in Phase I trials for relapsed / refractory multiple myeloma [12]

    c. AMG330: Targets CD3 and CD33. Currently in Phase I trials for relapsed / refractory acute myeloid leukemia (AML) [13]

    d. REGN1979: Targets CD3 and CD20. Currently in Phase I trials for relapsed / refractory follicular lymphoma [14]

2. DARTs

    a. Flotetuzumab (MGD006): Targets CD3 and CD123. In phase 1 trials for relapsed / refractory AML [15]

    b. Duvortuxizumab: Targets CD3 and CD19. Development halted in the context of FDA approval for blinatumomab

Clinical Efficacy of Blinatumomab (Blincyto®)

1. TOWER Study: Prospective, randomized, phase III trial comparing the outcomes of patients with relapsed/refractory ALL treated with standard of care chemotherapy vs blinatumomab. The primary endpoint was overall survival (OS); secondary endpoints included achievement of complete remission (CR), complete remission with partial hematologic recovery (CRh), or complete remission with incomplete hematologic recovery (CRi) within 12 weeks of treatment, and event-free survival (EFS) [16].

    a. Study Population: 405 patients randomly assigned to blinatumomab ($n = 271$) vs standard of care chemotherapy ($n = 134$).

    b. Major Finding: The median OS was 7.7 months in the blinatumomab group vs 4.0 months in the chemotherapy group (hazard ratio [HR] for blinatumomab vs chemotherapy 0.71, 95% confidence interval [CI] 0.55 – 0.93, $p = 0.01$).

    c. The rate of CR/CRh/CRi for blinatumomab was 44% vs 25% in the chemotherapy group, $p < 0.001$.

    d. 6 month EFS was 31% with blinatumomab vs 12% for chemotherapy (HR0.55, 95% CI 0.43 – 0.71 $p < 0.001$).

2. Blinatumomab for MRD: Open-label, single-arm phase-2 study to evaluate the efficacy of blinatumomab in treating patients with MRD. The primary endpoint was the rate of complete MRD response after 1 cycle of therapy [17].

    a. Study Population: 116 patients >18 yrs. of age in complete hematologic remission but MRD $> 10^{-3}$ present. MRD assessed via reverse transcription-polymerase chain reaction (RT-PCR).

    b. Major Finding: 88 of 113 evaluable patients (78%) achieved MRD negativity after one cycle. Relapse-free survival (RFS) at 18 months was 54% and median OS was 36.5 months.

    c. Outcomes significantly improved in patients who became MRD negative after treatment: RFS was 23.6 months in responders vs 5.7 months in nonresponders, $p = 0.002$, and OS was 38.9 months in responders vs 12.5 months in nonresponders, $p = 0.002$.

    d. Patients treated in CR1 vs ≥CR2 had improved RFS of 24.6 vs 11.0 months as well as improved OS.

3. ALCANTRA Study: Open-label phase-2 study evaluating the efficacy of blina-tumomab in treating patients with relapsed Ph + ALL. The primary objective was CR / CRh during the first two cycles [18].

   a. Study Population: Forty-five patients >18 years of age with relapsed Ph + ALL. Patients had to be refractory to at least one second-generation or later tyrosine kinase inhibitor (TKI) or intolerant of second-generation or later TKIs.
   b. Major Finding: Sixteen of 45 patients (36%) achieved a CR/CRh during the first two cycles. Of the patients who attained a CR/CRh, 88% achieved a complete MRD negative response.
   c. Median RFS was 6.7 months and median OS was 7.1 months.
   d. Results were similar to those of Ph- patients reported in the TOWER trial.

Addressing Pre-Transplant MRD with Bispecific Antibody Therapy

1. MRD positivity prior to transplant is one of the most highly significant predic-tors of disease relapse [19–21].

   a. Allogeneic HCT offers improved outcomes in adults with Ph-negative B-ALL with detectable MRD, with a longer RFS (HR 0.59, CI 0.41 – 0.84) and dura-tion of response (DOR) (HR 0.43, CI), as well as a trend toward improved OS (HR 0.72, CI 0.50 – 1.05) as compared to adults who do not undergo trans-plant. However, the percentage of MRD correlated with the outcome [19, 22].
   b. The level of MRD positivity strongly correlates with the failure of allogeneic HCT as a curative option with MRD levels of $>10^{-3}$ being highly predictive of poor outcome [20].

2. Evidence for Treatment of MRD with Blinatumomab Pre-Transplant

   a. Retrospective analysis of 15 pediatric patients aged 0-21 with B-ALL treated at 5 institutions, referred for allogeneic HCT due to persistent MRD after consolidation (range 0.01–2.2%) [23]

      i. Fourteen of 15 (93.3%) became MRD negative prior to transplant, cumu-lative incidence of relapse at 1 year was 27.8% at a median of 355 days, and 1 year OS was 93.3%.
      ii. Graft-versus-host disease (GvHD): Two of 14 patients (14.3%) had grade II or III acute GvHD and 3 of 14 developed chronic extensive GvHD (27.8%).

   b. Blinatumomab for MRD in Adults

      i. A subset of adults treated on the MRD study proceeded to allogeneic HCT, $n = 74$, 55 in CR1, 19 in CR2. 36 of 74 (49%) remained in remission at 24 months. There were 20 deaths in CR secondary to nonrelapse mortality (NRM) [17].

Re-Emergence of Leukemia Post-HCT

1. Blinatumomab as a Single Agent:

    a. Single-arm phase-II study to evaluate the efficacy and safety of blinatumomab in 64 patients with relapsed B-ALL after allogeneic HCT [24]

        i. Twenty-nine of 64 patients (45%) attained a CR/CRh with 19 of the 29 responders becoming MRD negative. Seven of the 19 who became MRD-negative underwent subsequent allogeneic HCT in remission; three proceeded to subsequent allogeneic HCT after relapse.

        ii. Median RFS in the patients who achieved a CR/CRh was 7.6 months and 11.4 months for those treated in first relapse vs. 6.2 months for those treated in second relapse. Median OS for those who achieved CR/CRh was 23.1 months.

        iii. Seven patients developed GvHD, 6 after receiving blinatumomab and one after subsequent allogeneic HCT. For the six who developed GvHD after blinatumomab, all GvHD events were grade I–3 and did not result in discontinuation of blinatumomab. The patient who developed GvHD after subsequent allogeneic HCT died of grade IV acute GvHD. Seventeen of 19 patients who had GvHD prior to the study did not experience reactivation of their GvHD after blinatumomab.

2. Blinatumomab + Donor Leukocyte Infusion (DLI)

    a. Case series of four patients treated with blinatumomab + DLI for relapse after allogeneic HCT [25]

        i. Two patients had disease relapse, two with return of MRD only. Of the patients with relapsed disease, one did not respond (had primarily extramedullary disease) and one responded for 6 months before developing extramedullary disease. Both patients who had MRD relapse only remain in remission at 7 and 12 months postinitiation of blinatumomab.

        ii. Three of the 4 patients were on low-dose tacrolimus at the time of blinatumomab treatment. Of these, one patient developed grade I GvHD of the skin treated with topical steroids alone. One patient developed grade 3 GvHD of the GI and skin which responded to corticosteroids and increase in tacrolimus dose.

3. Blinatumomab for Post-Transplant MRD

    a. There is no literature reporting the usage or outcomes of patients who have been treated with blinatumomab for the re-emergence of MRD post-transplant. Anecdotally, this strategy is being used in several transplant centers.

Future Directions and Challenges

1. Pre-Transplant Treatment of MRD

   a. Given that blinatumomab already carries an FDA-approved indication for MRD, it is highly unlikely that a prospective, randomized clinical trial assessing the efficacy of blinatumomab vs. control on transplant outcomes, EFS and OS will be forthcoming.

      i. Many centers are already using blinatumomab in this fashion.
      ii. As the poor prognostic significance of MRD in the pretransplant setting is well established, some would question whether it would be ethical to design such a trial.
      iii. A propensity analysis of outcomes of patients treated for MRD pretransplant as compared to a historic cohort of patients who went directly to transplant with MRD could provide an estimation of blinatumomab's efficacy in this setting.

   b. As bispecific antibodies are designed for other disease states including AML, it will be interesting to see if they are equally as effective at eradicating MRD, and whether they could also be used to address pretransplant MRD positivity.

      i. To date, there are no universally accepted assays for MRD in AML.
      ii. Trials of bispecific antibodies for AML are only in phase I trials therefore their efficacy is yet to be determined.

2. Post-Transplant Treatment of Re-Emergent MRD

   a. Blinatumomab has demonstrated efficacy in the treatment of ALL relapsed after allogeneic HCT; however, long-term outcomes remain elusive.
   b. Treating re-emergence of MRD after HCT as opposed to waiting for fulminant relapse may provide a higher response rate and potentially even longer durations of response, but data to date are lacking.
   c. Given FDA approval for the use of blinatumomab for the treatment of MRD, transplant centers are using blinatumomab in this context, and as such, a prospective randomized trial is unlikely to occur.

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Chapter 58
CAR T Toxicity Management: Cytokine Release Syndrome and Neurotoxicity

Craig W. Freyer and David L. Porter

Introduction

The development of chimeric antigen receptor (CAR) T cell therapy for various hematologic malignancies has brought unprecedented single-agent efficacy to patient populations with historically poor outcomes. With a novel mechanism of action comes novel toxicities that substantially differ from those observed with conventional therapies. Two of the most notable and clinically significant adverse effects (AE) associated with CAR T include cytokine release syndrome (CRS) and neurotoxicity (see Chap. 52 for a detailed description of CAR T therapies). Definitions, grading, and management of these toxicities are rapidly changing. To realize the maximal potential of cellular immunotherapy, a comprehensive understanding of, and effective management of these toxicities is necessary.

Cytokine Release Syndrome (CRS)

1. CRS is characterized by supraphysiologic immune system activation following activation and expansion of CAR T cells interacting with their target antigen (Fig. 58.1). Release of proinflammatory cytokines activates CAR T, endogenous T cells, and other immune effector cells (e.g., macrophages) in CRS [1–3].

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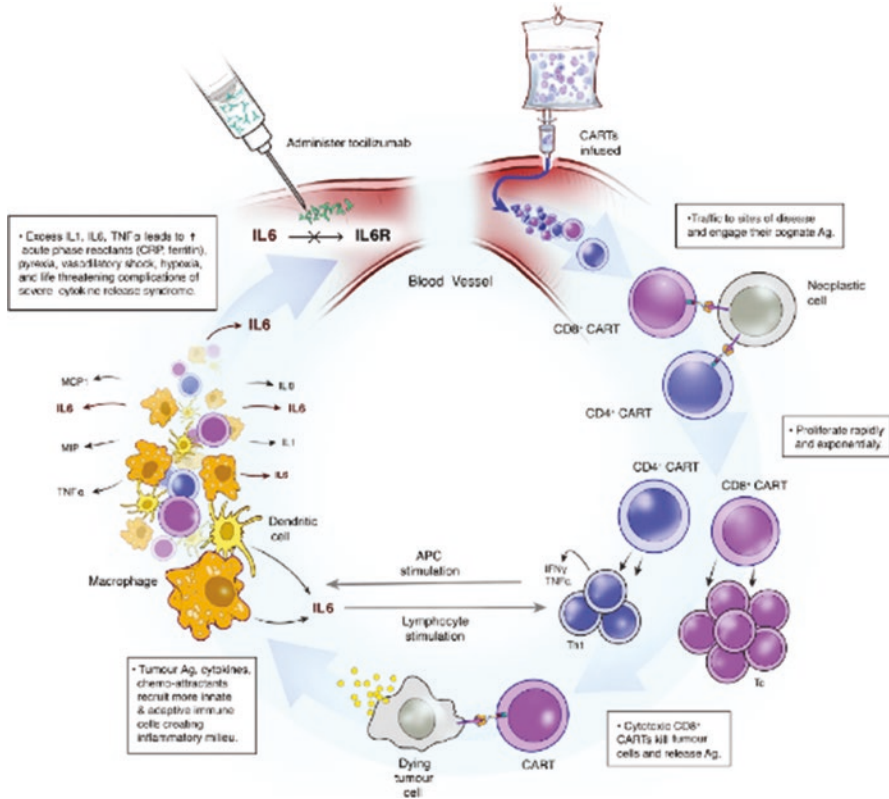
Fig. 58.1 A potential road to cytokine release syndrome [34]

2. Risk factors for CRS

    a. The incidence of CRS varies depending on the specific CAR T construct (CD28 vs. 4-1BB costimulatory domain) as well as the malignancy treated. In general, CRS is more common and more severe in patients with acute lymphoblastic leukemia (ALL) compared to patients with non-Hodgkin lymphoma (NHL) [4–6].

    b. Risk factors for severe CRS include high tumor burden, the addition of fludarabine to cyclophosphamide-based lymphodepleting chemotherapy (which enhances CAR T expansion), and higher CAR T cell dose [2, 3]. Further identification of risk factors will emerge detailed analyses of the expanded utilization across multiple disease types and patient populations.

    c. The incidence and severity of CRS appear similar in elderly and younger patients [7].

3. Grading of CRS

    a. Until recently, there has not been a standardized grading system for CRS. The National Cancer Institute Common Terminology Criteria for Adverse Events

(CTCAE) grading scale is inappropriate for CAR T; for instance, the need for infusion interruption is considered in grading and not feasible after CAR T cell infusion [8]. During CAR T clinical trials, various groups formulated their own grading scales, such as the PENN grading scale [9], Lee criteria [1], and MSKCC grading scale [10]. CRS grade assigned may vary between each grading system, limiting the ability to compare CRS severities across clinical trials and CAR T constructs.

b. In 2019, a consensus statement from the American Society of Transplant and Cellular Therapy (ASTCT) proposed a standardized CRS grading system (see Table 58.1) [11]. In the ASTCT scale, any vasopressor use is sufficient for a classification of grade 3 CRS, while some previous grading systems used vasopressor dose (high vs. low) to determine grade 2 vs. 3 CRS. The need for oxygen supplementation determines the grade based on the mode of delivery (i.e., low flow vs high flow). Additionally, the severity of end-organ toxicity is no longer considered for CRS grading which was used in earlier grading scales.

4. Clinical presentation of CRS [1–3]

a. Virtually all cases of CRS present with fever; temperatures ≥105 °F (40.5 °C) can be observed.
b. Common symptoms are similar to influenza-like symptoms and include myalgias, arthralgias, nausea, anorexia, headaches, tachycardia, and tachypnea.
c. Severe CRS-associated signs and symptoms can include hypoxia, hypotension, capillary leak, hypoalbuminemia, disseminated intravascular coagulation, and decreased ejection fraction.

Table 58.1 ASTCT Grading scale for cytokine release syndrome [11]

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)

d. The severity of coagulopathy and the need for transfusion support correlate with the severity of CRS. Many patients required cryoprecipitate and fresh frozen plasma to correct coagulopathy [12].

e. The majority of cases occur within 7 days of CAR T infusion. CRS tends to occur earlier with CD28-containing CAR T compared to 4-1BB CAR T. The median time to onset of CRS in NHL is 2 days for axicabtagene ciloleucel (axi-cel; Yescarta®) and 3 days for tisagenlecleucel (tisa-cel; Kymriah®) [5, 6].

f. Patients who ultimately develop severe CRS typically do not initially present with severe symptoms; rather symptoms can progress gradually over hours but more typically over a few days.

g. CRS can affect any organ system. Laboratory markers of generalized inflammation and hypotension include elevations in C-reactive protein (CRP), ferritin, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, lactate dehydrogenase, creatine phosphokinase, and serum creatinine.

5. Pathophysiology of CRS

a. During CRS, inflammatory cytokines may originate from CAR T cells themselves, other activated T cells, or macrophages.

b. The primary driver of CRS is thought to be interleukin (IL)-6. Beyond IL-6, the general cytokine profile observed during CRS can include elevations in IL-1, IL-2, tumor necrosis factor (TNF) α, interferon (IFN) γ, IL-8, IL-10, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1α (MIP-1 α). Detailed biochemical analyses of CRS following various CAR-T products have been reported, with minor differences observed in the cytokine profile of each [2, 3].

c. Unfortunately, in-depth cytokine analysis, such as that described above, is not available in real time at most institutions, limiting the clinical utility of such data in patient care decisions.

d. CRP and ferritin are commonly elevated during CRS. These assays are readily available at most centers and can be trended over time as a marker of generalized inflammation and response to therapeutic interventions.

e. IL-6 stimulates CRP synthesis from the liver, thus elevation in CRP may serve as a delayed onset surrogate marker for IL-6. CRP changes typically lag behind clinical changes in CRS by at least 12 hours.

f. CRS results from intense immune activation, and many patients with severe CRS meet diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS), which include fever, splenomegaly, cytopenias, hypofibrinogenemia, elevated serum ferritin (≥3000 mcg/L), elevated soluble IL-2 receptor, and hypertriglyceridemia. Ferritin levels >500,000 mcg/L have been noted [2, 3].

i. HLH/MAS is self-limited and manifestations resolve with resolution or successful treatment of CRS.

g. CRS is a clinical diagnosis. Cytokine profiles and biochemical profiles are useful confirmatory tests for the diagnosis of CRS, but are not considered in grading or clinical management decisions.

6. Treatment of CRS

a. Many cases of CRS are self-limiting and only require supportive care. Even severe CRS typically starts with mild–moderate symptoms that progress gradually and may not require immediate intervention.

b. General guidelines for the management of CRS have been published in addition to recommendations within the US Food and Drug Administration (FDA)-labeled package inserts for tisa-cel [13] and axi-cel [14]. Many institutions develop their own CRS management algorithms taking into consideration these guidelines and previous clinical experience. The optimal management algorithm for CRS is unclear and may differ based on the CAR T product, patient risk factors, and the malignancy being treated.

c. After supportive care measures, tocilizumab (Actemra®, RoActemra®) is the primary medical intervention for CRS.

   i. Tocilizumab is an IL-6 receptor antagonist monoclonal antibody that received FDA approval for severe CRS at the same time as the FDA approval of tisa-cel (for ALL) based on dramatic improvements in CRS in CAR T clinical trials.

   ii. Decreased oxygen and vasopressor requirements can be observed within hours following administration of tocilizumab, while organ dysfunction is often slower to resolve. The median time to CRS resolution following the initial dose of tocilizumab is 4 days.

   iii. The standard dose is 8 mg/kg (capped at 800 mg) or 12 mg/kg in patients <30 kg, and may be repeated in as soon as 6 hours in the case of inadequate improvement.

   iv. An overall response rate (ORR) of 70% was observed with 1–2 doses of tocilizumab in a combined analysis of trials with tisa-cel and axi-cel. In NHL trials, more patients received tocilizumab with axi-cel (43%) vs. tisa-cel (14%); however, direct comparisons of CRS grading were complicated by the use of different scales [15].

d. Grade 1 CRS is managed with supportive care, such as antipyretics (acetaminophen; avoid NSAIDs if thrombocytopenic), antiemetics, and IV hydration. Broad-spectrum antibacterials should be started if the patient is neutropenic according to institutional guidelines for febrile neutropenia [11].

e. Grade 2 CRS is characterized by the presence of hypotension or requirement of low-flow supplemental oxygen per the ASTCT grading scale [11]. IV hydration with crystalloid is advised; however, early consideration for vasopressors may be prudent given the potential for subsequent capillary leak and resultant pulmonary edema, which may be exacerbated by fluid overload. Some guidelines, including the package insert for axi-cel, advice initiating tocilizumab for grade 2 CRS prior to initiation of vasopressors [14]. The

tisa-cel package insert advises low dose vasopressors (now grade 3 CRS per ASTCT) prior to escalating therapy to tocilizumab [13].

    i. Early and limited data suggest that administration of tocilizumab does not impair subsequent CAR T cell expansion or response. Therefore, it may be reasonable to intervene with tocilizumab prior to escalating therapy with pressors or other intensive interventions.

f. The benefit of ≥3 doses of tocilizumab remains unclear; most investigators consider addition of other cytokine directed therapies if the response is inadequate to 2 doses of tocilizumab. The package inserts for tisa-cel and axi-cel advise a maximum of 4 doses of tocilizumab in total [13, 14]. No AE related to tocilizumab have been reported in the management of CRS, perhaps due to the short duration of therapy [15].

g. Tocilizumab is recommended for grade 2 CRS in addition to vasopressors to manage hypotension [11]. Corticosteroids have been used to manage CRS either concurrently with tocilizumab or in patients with suboptimal response to tocilizumab. There is no standard practice in terms of when to initiate steroids and what dose/duration of steroid is optimal. Researchers were initially hesitant to use steroids given the potential for toxicity to CAR T cells as steroids are lymphotoxic. The dose and duration of steroids at which CAR T persistence is impaired remain to be determined. Currently, there are some preliminary data that tocilizumab and steroids do not impair the efficacy of CAR T; however, comparative data are not available [16]. In general, steroids should be used at the lowest effective dose for the shortest time possible to avoid any potential for adverse effects on CAR T persistence.

h. Grade 3 CRS is characterized by the requirement of vasopressors to maintain blood pressure and/or high flow supplemental oxygen as per the ASTCT grading scale and is typically treated with tocilizumab with or without corticosteroids [11].

    i. CAR T package inserts advise a total daily dose of methylprednisolone 2 mg/kg for grade 3 CRS with escalation to 1000 mg daily × 3 days advised for grade 4 CRS in the axi-cel package insert [14]. Steroids should be gradually tapered as tolerated based on clinical improvement.

i. Grade 4 CRS is characterized by the use of multiple pressors and/or positive pressure oxygenation and is managed with tocilizumab +/− corticosteroids as above [11].

j. Other anti-cytokine or anti-inflammatory therapies have been considered to treat or prevent CRS but little data for approaches other than tocilizumab and/or steroids are available.

    i. Siltuximab (Sylvant®) is an anti-IL-6 monoclonal antibody that directly binds IL-6 and has been used after inadequate response to tocilizumab in CRS at a dose of 11 mg/kg. Some authors have suggested the use of siltuximab instead of tocilizumab in the presence of concurrent neurotoxicity;

however, this is controversial and the experience remains anecdotal [17]. Siltuximab has not been formally studied as an initial therapy for CRS and is not FDA approved for this indication.

ii. The IL-1 receptor antagonist anakinra (Kineret®) and the JAK1/2 inhibitor ruxolitinib (Jakafi®) may be helpful salvage agents in CRS given documented activity in HLH/MAS; however, experience remains anecdotal and requires further investigation [18–20].

iii. Dasatinib (Sprycel®) inhibits lymphocyte-specific protein tyrosine kinase (LCK), resulting in rapid and complete CAR T inhibition that is fully reversible in vitro and in animal models [21, 22]. Future studies should assess the clinical efficacy of dasatinib as a CAR T modulating agent to treat severe CRS.

iv. Additional agents with limited anecdotal experience for refractory CRS include cyclophosphamide, alemtuzumab (Campath®), and antithymocyte globulin given the anti-T cell activity of these agents.

7. Interventions to decrease the risk of CRS

a. Fractionated administration (ex: 10% of the total dose administered on day 1, 30% on day 2, remaining 60% on day 3) allows intra patient dose modification in the setting of early CRS. Doses can be held or delayed if the patient develops a fever early following cell infusion [23].

b. Risk-adapted dosing based on disease burden (e.g., marrow blast percentage) has been used to limit the risk of CRS, particularly in patients with ALL [10, 24].

c. Prophylactic administration of tocilizumab is being studied to prevent or limit CRS [25].

d. The combination of infection and CRS has led to fatalities in CAR T trials [23]. Patients with active infections should not receive CAR T. Prophylactic antimicrobials could indirectly reduce the risk of severe CRS by reducing infection risk.

Neurotoxicity

1. Neurotoxicity is the other unique and clinically significant AE from CAR T. The recent ASTCT consensus statement proposed the term "immune effector cell-associated neurotoxicity syndrome" (ICANS) for neurotoxicity following CAR T [11]. Earlier references may use the term CAR T-related encephalopathy syndrome (CRES). [17] Early descriptions often linked CRS and ICANS together; however, additional research has identified important differences in the pathophysiology and management of these conditions. ICANS is now considered a distinct entity, separate from CRS.

2. Risk factors for ICANS

a. The incidence of ICANS varies depending on the specific CAR T construct and appears higher with CARs containing a CD28 co-stimulatory domain compared to a 4-1BB costimulatory domain [4–6].

b. The incidence of ICANS may be related to the malignancy being treated. In general, ICANS is more common and more severe in patients with ALL than NHL [4, 5].

c. In addition to the CAR T construct being used, higher grade CRS is the most significant risk factor for severe ICANS. Additional risk factors include a prior history of neurologic comorbidity, higher disease burden, greater CAR T cell dose, greater CAR T expansion, and prior fludarabine-containing lymphodepletion [26–29]. Elderly patients may be at greater risk of ICANS than younger patients [7].

d. Predictive models based on fever and levels of inflammatory cytokines have been proposed; however, it is unclear if models for one CAR T product can be extrapolated to others. Fever develops earlier in patients who develop severe ICANS compared to patients who develop lower severity ICANS.

e. The presence of central nervous system (CNS) involvement of leukemia or lymphoma does not appear to increase the risk of ICANS [4, 30].

f. For unclear reasons, ICANS appears to be less common and less severe with BCMA and CD22 targeted CAR T compared to CD19 CAR T [31, 32].

3. Grading of ICANS

a. ICANS has been previously graded according to CTCAE with criteria and descriptions that were mostly applicable to antibody therapies (such as the requirement to interrupt the infusion) [8]. In 2019, the ASTCT released a consensus grading statement for ICANS in addition to the immune effector cell-associated encephalopathy (ICE) assessment tool (see Tables 58.2 and 58.3) [11].

Table 58.2 ASTCT ICE assessment tool for encephalopathy in adults [11]

Orientation	Orientation to year, month, city, hospital: 4 points
Naming	Ability to name 3 objects: 3 points
Following Commands	Ability to follow simple commands: 1 point
Writing	Ability to write a standard sentence: 1 point
Attention	Ability to count backwards from 100 by 10: 1 point
Grading by score	Grade 1: 7–9 points Grade 2: 3–6 points Grade 3: 0–2 points Grade 4: unarousable, unable to complete assessment

Neurologic assessment for children younger than 12 years of age should be conducted using the Cornell Assessment of Pediatric Delirium

Table 58.3 ASTCT ICANS consensus grading for adults [11]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2	0 (unable to perform)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable, requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure that resolves rapidly or nonconvulsive seizures on EEG that resolve without intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intracranial pressure/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

4. Clinical presentation of ICANS [26–29]

   a. ICANS typically occurs after the peak of CRS (often 3 days later or more), but rarely occurs without antecedent CRS (the latter is typically mild and self-limiting).

   b. The onset of ICANS symptoms of any grade is 4–5 days post-CAR T infusion, while the time to severe neurotoxicity was 5–9 days.

   c. Neurotoxicity may occur earlier and last longer with products using a CD28 costimulatory domain vs. a 4-1BB costimulatory domain. In a study assessing ICANS following a CD19 CAR T with a CD28 costimulatory domain, mild ICANS was present for a median of 10 days (range 1–14), while severe ICANS persisted for a median of 11 days (range 2–92 days) [27]. In a separate study with a 4-1BB CAR T product, the median duration of reversible ICANS was 5 days (range 1–70) [28].

   d. Most cases of ICANS are fully reversible within 4 weeks of symptom onset; however, a detailed analysis of long-term neurologic function post-CAR T has not yet been reported.

   e. ICANS typically manifests as encephalopathy with symptoms that include dysphasia, aphasia, confusion, or delirium. Expressive aphasia is found in up to 85% of patients who later develop severe ICANS.

   f. Other common symptoms of ICANS may include short-term memory loss, dysgraphia, impaired attention, language disturbances, disorientation, tremor,

confusion, agitation, somnolence, obtundation, global aphasia, and seizures (either tonic–clonic or focal). Symptoms often wax and wane, especially in the earlier stages. Focal deficits and ataxia are uncommon findings.

g. The severity of ICANS correlates with levels of CRP, ferritin, and several proinflammatory cytokines.

h. Fatal cerebral edema has rarely been reported with some CD19 CAR T constructs. Fatal cerebral edema has not been reported with tisa-cel, while a single case has been reported with axi-cel [17]. Clinicians should be vigilant when assessing patients for this potentially fatal neurotoxicity.

5. Pathophysiology of ICANS

a. There are a number of similarities in the pathogenesis of CRS and ICANS, which may explain their association and the correlation between severe antecedent CRS and severe ICANS.

b. In a study characterizing ICANS after tisa-cel, patients had higher serum levels of IL-2, IL-15, soluble IL-4, and hepatocyte growth factor compared to patients with isolated CRS [26].

c. Patients with biochemical evidence of endothelial activation (elevated Ang2:Ang1 ratio) prior to lymphodepletion have a greater risk of severe ICANS [28]. Elevated baseline levels of soluble TNF receptor-1 and low soluble CD30 may predict patients who will ultimately develop ICANS [26].

d. While the pathophysiology of ICANS is not completely understood, studies suggest it is mediated by inflammatory cytokines and not direct CAR T cell-mediated toxicity to neuronal or glial cells [26–29].

i. In ICANS, inflammatory cytokines cause endothelial activation, leading to a loss of integrity within the vasculature and the blood–brain barrier (BBB). Inflammatory cytokines, CAR T, and normal leukocytes infiltrate into the cerebrospinal fluid (CSF).

ii. Excitatory neurotoxins such as glutamate and quinolinic acid are elevated in the CSF of patients with ICANS, which may explain the risk of seizures.

iii. Patients with severe ICANS frequently have evidence of disseminated intravascular coagulation with elevations in prothrombin time, activated partial thromboplastin time, d-dimer, and hypofibrinogenemia.

6. Treatment of ICANS

a. While there is no consensus on the optimal management of ICANS, tocilizumab does not appear to be effective. In addition to optimal supportive care, corticosteroids are the mainstay of therapy [11].

b. Treatment is based on anecdotal data and clinical experience within CAR T cell trials. The package insert for axi-cel contains guidance for ICANS management based on the grade and presence of concurrent CRS [14]. Recommendations for one CAR T product or patient population may not be optimal for another product or population. Many institutions develop their

own ICANS management algorithms taking into consideration package insert recommendations and previous clinical experience.

c. Corticosteroids (typically dexamethasone due to improved BBB penetration) are frequently used despite lack of convincing evidence of efficacy. There does not appear to be a difference in efficacy in short course vs. long course steroids for ICANS. In fact, prolonged steroid courses (>10 days) have been associated with shortened overall survival (though this may reflect the severity of symptoms) as does the presence of grade 3–4 ICANS [29].

d. Prophylactic anti-epileptic therapy is often considered for patients who develop ICANS [17].

e. Patients experiencing seizures should receive appropriate anti-epileptic drugs as guided by an experienced neurologist.

f. ICANS management recommendations derived from the axi-cel package insert are listed below: [14]

   i. Grade 1: supportive care and monitoring only.

   ii. Grade 2: dexamethasone 10 mg IV every 6 hours, continued until grade 1 or less, then taper over 3 days. Consider starting anti-seizure prophylaxis if not started already. If concurrent CRS, administration of tocilizumab is advised, and dexamethasone started only if no improvement within 24 hours of tocilizumab.

   iii. Grade 3: same dexamethasone recommendation for grade 2. If concurrent CRS, start tocilizumab and dexamethasone concurrently.

   iv. Grade 4: methylprednisolone 1 g IV daily × 3 days. If improvement observed, manage as above. If concurrent CRS, start tocilizumab and methylprednisolone concurrently.

g. A safety expansion cohort of the ZUMA-1 study of patients with relapsed/refractory NHL assessed the benefit of earlier steroids (for grade 1 ICANS) following axi-cel. There was no apparent detriment in efficacy (ORR 76%, 48% complete remission rate) while the incidence of grade ≥3 ICANS was 10%, compared to 32% in the overall study [16]. The benefit and potential risks of earlier steroid intervention should be assessed in a larger trial before becoming standard practice.

h. As mentioned above, patients with concurrent CRS should receive tocilizumab, when appropriate based on the grade of CRS. Tocilizumab itself is ineffective at managing ICANS.

   i. Lack of efficacy of tocilizumab for ICANS is supported by the observation that the peak ICANS grade occurs after tocilizumab administration in more than 50% of patients [27, 28]. Blood levels of IL-6 increase following tocilizumab due to a higher affinity of the drug for the IL-6 receptor. Displaced IL-6 may enter the CSF and perhaps propagate ICANS. By this mechanism, some authors have hypothesized that tocilizumab may actually worsen ICANS [17].

   i. CNS imaging (MRI preferred) is advised to rule out cerebral edema or other causes of neurologic toxicity (e.g., hemorrhage); however, imaging is often negative. An electroencephalogram (EEG) often shows diffuse slowing during ICANS, but may pick up early seizure activity.

   j. Spinal fluid examination may be necessary to rule out infectious meningitis, particularly in patients with fevers, neutropenia, and new mental status changes.

   k. Spinal fluid examination may also be necessary to rule out malignant meningitis, particularly in patients with aggressive leukemia and lymphoma who develop new mental status changes.

   l. Novel interventions for ICANS have been considered and several are in preclinical or clinical development.

      i. Lenzilumab, a GM-CSF antagonist, may treat or prevent neurotoxicity while enhancing the antitumor effect of CAR T as suggested by animal studies [33].

      ii. The IL-1 antagonist anakinra (Kineret®) has anecdotally been used for severe ICANS, which is supported by animal data [18]. Future studies in human subjects are needed before routine use of anakinra for ICANS.

      iii. As mentioned above, dasatinib (Sprycel®) can act as a reversible CAR T-modulating agent that could be used to manage severe ICANS; however, additional research is needed [21, 22].

7. Prophylaxis against ICANS

   a. There is no consensus on the optimal prevention strategy for ICANS. As CRS grade correlates with the severity of ICANS, strategies listed above to limit CRS may also result in a decreased risk of ICANS.

   b. Levetiracetam (Keppra®) 500–750 mg every 12 hours is recommended for CAR T products associated with ICANS, but has mainly been used in clinical trials of axi-cel [17]. This agent has been used based on its favorable tolerability and lack of clinically significant drug interactions. The absolute clinical benefit of levetiracetam prophylaxis is unclear, as the recommendation for utilization is not based on randomized data. Levetiracetam has failed to prevent EEG changes and seizures in patients with ICANS [27].

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Chapter 59
Molecular Testing for Post-transplant Disease Surveillance

Ying Wang and Richard Press

Introduction

Allogeneic hematopoietic cell transplant (alloHCT) is the treatment of choice for a diverse range of inherited hematological disorders or acquired hematological malignancies and solid tumors [1–3]. When donor hematopoietic stem cells begin to successfully engraft in the host, the host becomes a genetic chimera with circulating hematopoietic cells derived from two genetically different individuals. The subsequent goal of achieving complete donor chimerism occurs when 100% of bone marrow and blood cells are of donor origin. Mixed or partial chimerism means that both donor and host cells are simultaneously present (in quantitatively heterogeneous mixtures, depending on the clinical scenario) [4].

The scientific basis for all post-transplant molecular chimerism testing is the detection and quantitation, by DNA diagnostic methods, of highly polymorphic genetic loci (within the human population) that differ between the host and his/her transplant donor. Decades ago, before the advent of polymerase chain reaction (PCR), post-HCT chimerism analysis was performed in most molecular diagnostic labs using restriction fragment length polymorphism (RFLP) and Southern blotting [5]. In this now obsolete multi-day method, polymorphic variable number of tandem repeat (VNTR) loci was distinguished using sequence-specific restriction enzyme digestion and separation of resultant genomic DNA

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fragments by gel electrophoresis and locus-specific Southern blot probes. In the modern era, PCR-based assays to amplify highly polymorphic short tandem repeat (STR) regions are most commonly used for this purpose. In this method, the genetic "profile" (or "fingerprint") of multiple STR loci, defined as stable (heritable) genetic loci with highly polymorphic (in number of tandem repeats) di- or tri-nucleotide repeat sequences, can be used to both "identify" cells derived from a particular individual and definitively distinguish those cells from cells derived from any other individual. These STR assays are essentially identity tests and the same PCR-based STR methodology is commonly used for forensic testing, paternity testing, and identification of maternal cell contamination in fetal samples [6, 7]. The most modern (and comprehensive) method for the determination of person-specific "identity" (and post-transplant chimerism) uses next-generation (massively parallel) sequencing (NGS) to interrogate dozens/hundreds/thousands of highly polymorphic single-nucleotide polymorphisms (SNPs) scattered across the genome. These multi-gene NGS-based methods allow the simultaneous sequencing of millions/billions of nucleotides of DNA, often with improved analytical sensitivity (and lower per-nucleotide cost) compared to older "single gene" methods, thus permitting the detection of lower levels of both chimeric donor-host cell mixtures and, in the cancer patient, post-transplant minimal residual disease (MRD) [8].

The quantitative determination of donor-host chimerism at various time points after HCT provides valuable information on engraftment kinetics and function. Longitudinal monitoring of chimerism is important to assess graft rejection, graft-versus-host disease (GvHD), and/or recurrence of disease if the transplant was performed to treat hematological malignancies [9, 10]. Disease relapse after transplant is the major cause of treatment failure for HCT performed for hematologic malignancies. In chimerism analyses, this disease recurrence will manifest as an increase in host-derived cells in the blood or bone marrow, which, although not specific for malignant (vs reactive) host-derived cells, should always raise concern for relapse with some laboratories heightening the sensitivity of detection of myeloid relapse by performing the molecular chimerism analysis on CD34 selected bone marrow cells. In addition to serial chimerism analyses, post-transplant surveillance often also includes the laboratory assessment of known disease-specific phenotypic or genotypic abnormalities, i.e., MRD. MRD analysis, performed by flow cytometric, cytogenetic, or fluorescence in situ hybridization (FISH), or molecular diagnostic methods, is routinely used to detect early low-level disease in the absence of direct morphological evidence of relapse. Early detection of MRD post-HCT often predicts subsequent overt disease recurrence and may directly inform therapeutic decision-making to prevent or delay such relapse [11–14].

Molecular Markers for Post-transplant Surveillance

Short Tandem Repeats (STRs)

1. STRs, also known as microsatellites, are repetitive DNA sequences which account for about 3% of the entire human genome [15].
2. STRs are composed of 10–60 tandemly repeated units, in which each unit is 1–6 bases in length [16].
3. STRs occur in both coding and noncoding regions.
4. STRs are highly polymorphic (in the population), stably inherited (for family-specific tracking) and, when combined together into a multi-locus profile (or fingerprint), characteristic for each individual, which makes them excellent markers to distinguish individuals and assess post-transplant chimerism.

Single-Nucleotide Polymorphisms (SNPs)

1. SNP is the result of single-nucleotide differences between individuals at various locations in the genome [16].
2. SNPs represent the most widespread type of genetic variation among humans.
3. On average, SNPs occur once every 1000 nucleotides, and there are approximately 4–5 million SNPs in each individual genome.
4. Similar to STRs, SNPs occur in both coding and noncoding sequences.
5. SNPs are polymorphic in the population, variably prevalent in specific ethnic groups (stably heritable), and, when combined together into a multi-locus profile (or fingerprint), characteristic for each individual.

Somatic Tumor-Specific Mutations

1. If the transplant was performed to treat a hematopoietic malignancy, clone-specific, disease-associated somatic mutations present before HCT can serve as a sensitive biomarker to monitor MRD and disease recurrence.
2. Different types of somatic mutations are assessed by different molecular diagnostic techniques.
3. Point mutations and small insertions/deletions can be sensitively monitored by quantitative PCR or next-generation sequencing (NGS) [13, 17].
4. Tumor-specific fusion genes such as *BCR-ABL, RUNX1-RUNX1T1, CBFB-MYH11,* and *PML-RARA* can be sensitively followed by reverse transcription quantitative-PCR (RQ-PCR), FISH, or NGS [18, 19].

5. For hematopoietic malignancies with a unique immunophenotypic profile by flow cytometry (distinguishable from normal hematopoietic cells), flow cytometric methods have been shown to be a sensitive, prognostic post-transplant biomarker for monitoring disease recurrence and predicting subsequent overt relapse.

Sample Types for Post-transplant Surveillance

Donor

1. Peripheral blood, buccal swab, saliva, or skin biopsy are acceptable for generating intact genomic DNA for deriving the donor STR profile for chimerism testing.

Host

1. Pre-transplant sample (blood, bone marrow, buccal swab, saliva, skin) to generate intact genomic DNA for deriving the host STR profile.

    a. The pre-transplanted host sample for post-transplant chimerism testing should ideally not contain a high burden of leukemia cells, which may have a wildly altered genome compared to normal non-leukemic cells – and thus may yield aberrant DNA profiling at some loci.

2. Post-transplant sample:

    a. Unsorted peripheral blood or bone marrow aspirate.
    b. Lineage-specific hematopoietic cell population: flow cytometry sorted CD3+, CD33+, CD14+, CD56+, or CD19+ cells from peripheral blood or bone marrow – depending on the pre-transplant hematopoietic malignancy.
    c. Immunomagnetic beads can also be used to separate leukocytes into specific cellular subsets. The purity is usually lower than the cell populations derived by flow cytometric sorting.
    d. Samples for chimerism testing and MRD analysis are collected at the recommended intervals post-HCT [20], which differ in different transplant centers.

3. For patients who have transferred care, if there is no documented pre-transplant host baseline profile (or sample) for chimerism testing, a buccal swab or skin biopsy can be collected and tested.
4. For tumor-specific MRD testing, it is critical to know the exact mutation (or immunophenotype) that "marks" the malignant clone. If the original tumor has not been previously characterized, a sample of the untreated tumor should be

procured (from the original Pathology lab) and tested – to unambiguously define the disease-specific mutation profile for post-transplant MRD monitoring.

Whole Blood/Bone Marrow Chimerism Testing Versus Lineage-Specific Chimerism Testing

1. Lineage-specific (sorted cell) chimerism may identify low level mixed chimerism which cannot be detected in the whole leukocyte population.
2. Chimerism studies in different cell subsets increase assay sensitivity and specificity to detect low level host signals, especially for T lymphocytes [10].
3. If the original hematopoietic malignancy has a known flow cytometry-defined marker (e.g., CD33 in AML), the chimerism testing-defined detection of host-derived cells with that same marker may be an early biomarker for impending relapse. This marker may not be detectable in an unfractionated whole blood or bone marrow population.

Molecular Technologies for Post-transplant Surveillance

Quantitative PCR-Based STR Analysis to Assess Chimerism [6]

1. Genomic DNA extracted from host, donor, and post-transplant (sorted or unfractionated) samples.
2. PCR primers are widely available (commercially) targeting the DNA region flanking known STRs (usually performed as a multiplex PCR targeting several such loci).
3. One of the primers is typically labeled with a fluorescent dye so that the subsequent fluorescently labeled PCR products can be analyzed by capillary gel electrophoresis for PCR fragment size and quantity.
4. The size of the PCR product from each targeted STR locus is variable depending on the number of tandem repeats present on the two alleles of the donor, host, and post-transplant samples (Fig. 59.1 and Table 59.1).
5. Informative alleles (resolvable PCR fragment sizes) that differ between the host and donor can be quantitated (peak area) and used to calculate the percentage of host-derived cells.
6. Sibling transplants will (by definition) have many alleles (50% on average) that are shared between donor and host – that are not informative for post-transplant chimerism monitoring.
7. To ensure the analysis of several informative alleles, most labs will use multiplex PCR to amplify more than 10 (often 15) STR loci, commonly with commercially available reagents and software.
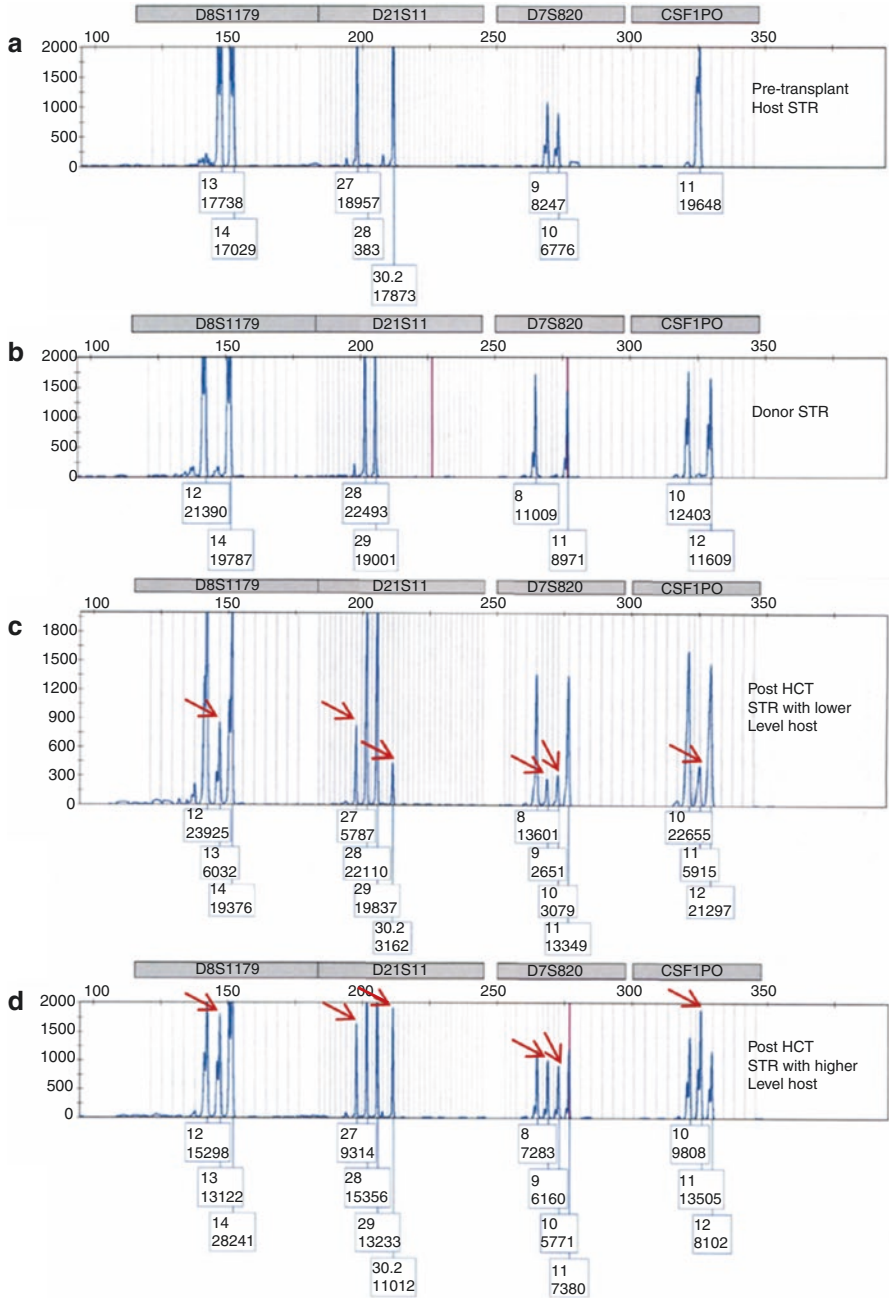
Fig. 59.1 STR PCR to monitor post-transplant chimerism. Capillary electrophoresis traces are shown for four representative STR loci D8S1179, D21S11, D7S820, and CSF1PO. (**a**) Pre-transplant host sample. (**b**) Donor sample. (**c**) Post-HCT sample with low level host alleles detected (red arrows). (**d**) Post-HCT sample with higher level host cells

Table 59.1 Percent host cells calculation for four STR loci shown in Fig. 59.1

	Pre-transplant host alleles (A)		Donor alleles (B)		Post-transplant host				% host	
					Donor alleles		Host alleles		(C)	(D)
D8S1179	13	14	12	14	12	14	13	14	20%	46%
D21S11	27	30.2	28	29	28	29	27	30.2	18%	42%
D7S820	9	10	8	11	8	11	9	10	18%	45%
CSF1PO	11		10	12	10	12	11		12%	43%
							% host (avg)		17%	44%
							% donor (avg)		83%	56%

8. The limit of detection (or analytical sensitivity) of the STR-based chimerism test is approximately 1–5% – with the variability due to heterogeneity between different STR loci.

Next-Generation Sequencing

1. Molecular minimal residual disease (MRD) by targeted NGS panels [12–14]

   a. Massive parallel sequencing (NGS) can assess a panel of genes of interest (dozens up to hundreds) at a low per-gene cost, simultaneously.

   b. Amplicon based or hybridization-capture NGS library preparations are used to prepare the DNA for subsequent sequencing, typically on an Ion Torrent or Illumina sequencing instrument.

   c. Bioinformatics tools and expertise are necessary for sequence alignment and detection/classification of mutations/variants.

   d. Quantitative allele burden for each mutation can be directly visualized (and/or determined by bioinformatics software) as the percentage of NGS reads of mutant (versus wild type) sequence (Fig. 59.2).

   e. Longitudinal post-treatment monitoring of the allele burden of each known disease-specific somatic mutation can determine early molecular relapse or disease persistence and guide therapeutic decision-making.

   f. In AML patients undergoing transplant, post-treatment NGS-defined MRD is significantly prognostic for subsequent overt relapse [14, 21, 22].

   g. Single-nucleotide variants and small insertion-deletions are sensitively detected by NGS (typically down to detection limit of 0.5–5%). Larger insertions or deletions can be missed, depending on the technical and bioinformatics details of the assay.

2. SNP NGS to assess chimerism

   a. Recently described method with fewer laboratories currently use it for routine chimerism analysis [8].
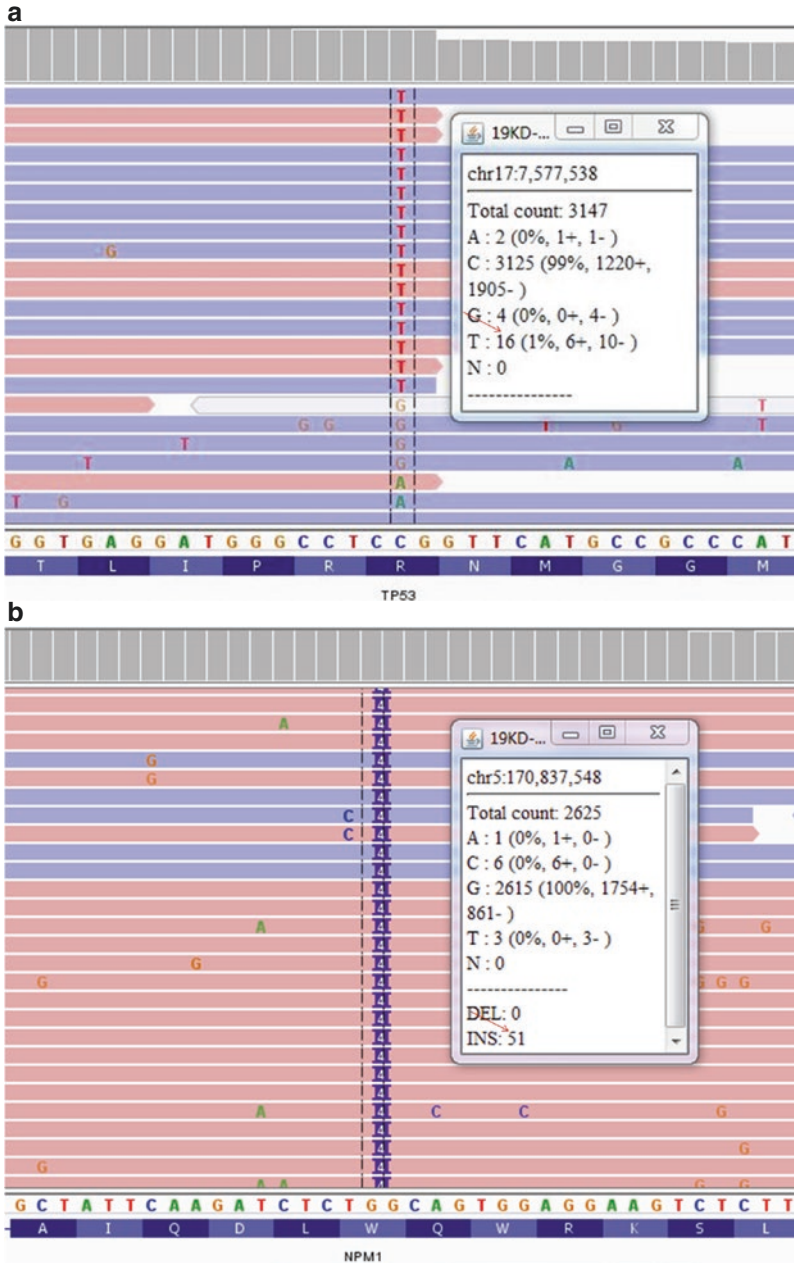
Fig. 59.2 NGS targeted panel for post-HCT MRD surveillance. NGS data is shown in the Integrative Genomics Viewer (IGV), which displays each individual DNA molecule sequenced by NGS as a horizontal "read," aligned to the expected wild type sequence. (**a**) Persistent low level *TP53* mutation (c.743G > A, p.R248Q) at 0.5% allele frequency detected after HCT. (**b**) Persistent low level 4 base pair insertion in *NPM1* gene (c.859_860insTCTG, p.W288fs*12) detected post-HCT (2% mutant allele frequency)

b. Uses NGS to compare (dozens/hundreds) of polymorphic SNP loci among samples from the pre-transplant host, donor, and post-transplant host [23].

c. SNPs are biallelic (compared to multi-allelic STRs) which requires the analysis of more individual loci for defining informative alleles – which is easily accomplished with NGS methods.

d. High concordance with conventional PCR STR assay.

e. Can often be more sensitive (down to below 1%) than PCR-based STR assays.

Other Commonly Utilized Laboratory Technologies

1. FISH

   a. FISH involves hybridization of fluorescently labeled (visualizable) gene-specific probes with the target sequence in interphase cells dispersed onto a microscope slide.

   b. For sex-mismatched transplants, FISH analysis of X and Y chromosomes is a valuable tool for chimerism analysis [4].

   c. Commonly utilized to assess aberrant chromosomal translocation/gene fusion events including *BCR-ABL RUNX1-RUNX1T1, CBFB-MYH11,* and *PML-RARA.*

   d. The level of detection (LOD) is approximately 1–5% (depending on the methodologic details).

2. Reverse-transcription quantitative PCR (RQ-PCR) of individual tumor-specific gene mutations/gene fusions

   a. Useful for mutations that are absolutely specific for the tumor cell (i.e., gene fusion/translocation events such as BCR-ABL, PML-RARA, etc.) in hematopoietic malignancies.

   b. Sequential quantitative measurements of fusion gene transcripts can inform the efficacy of treatment, the kinetics of treatment responses, and sensitively quantitate MRD.

   c. The detection limit can be as low as 10^{-4} to 10^{-5}.

3. Multiparameter flow cytometry (MFC)

   a. MFC is a commonly used, informative option to detect MRD following HCT [24].

   b. 8- to 10-color flow cytometry can identify leukemia-associated immunophenotypes that can then be sensitively monitored post-treatment, for MRD.

   c. Most flow cytometry laboratories are able to detect aberrant immunophenotypic cells with a sensitivity of 10^{-2} to 10^{-4} (in some labs, even better than molecular methods).

d. Immunophenotype shifts after treatment can be seen in up to 10–15% of leu-
kemia patients, thus obviating the practical utility of flow cytometry for MRD
monitoring.

Clinical Utility and Limitations

Post-HCT Chimerism Analysis

1. Conventional PCR STR assay:

    a. Quantitative results are reported as percent cells of donor or host origin
    (Fig. 59.1 and Table 59.1).
    b. For lineage-specific (sorted cell) chimerism, guidelines recommend reporting
    the purity of the cell population along with the chimerism assessment [4].
    c. Requires multiple informative loci between donor and host for accurate quan-
    titative assessments (usually the mean of multiple loci).
    d. The STR assay cannot directly distinguish whether host-specific signals are
    generated from neoplastic hematopoietic cells or normal host hematopoi-
    etic cells.
    e. The LOD is 1–5%; therefore, this method is suboptimal for MRD monitoring,
    due to limited sensitivity.

2. NGS SNP assay:

    a. Improved sensitivity relative to STR methods; the LOD can reach 0.1%.
    b. Can combine the post-transplant chimerism analysis (by SNPs) and MRD
    detection (of tumor-specific mutations) in a single assay; a cost-effective
    choice for many labs.
    c. At present, the cost of NGS-based tests remains high compared with standard
    STR-based assays. However the cost of NGS has been continuously declining.

3. Chimerism analysis is best interpreted in the context of multiple longitudinal
follow-up samples [9]

    a. When interpreting chimerism results, pre-transplant diagnosis, conditioning
    regimen, preparation of stem cells, post-transplant immunosuppressive ther-
    apy, the time elapsed since transplant, and previous chimerism results are all
    factors to be considered.
    b. Any given single chimerism result is best interpreted in the context of these
    multiple variables.
    c. Most (but not all) data suggest that in some hematologic malignancies, per-
    sisting post-transplant host-derived T cells may portend a poor outcome (and
    may indicate a consideration for preemptive chemo- or immunotherapy).

Post Solid Organ Transplant Chimerism Analysis

1. GVHD has been occasionally reported post solid organ transplant, usually after liver transplant. Detection of circulating donor-derived cells may assist the diagnosis.
2. Conventional PCR STR assays can be used to detect donor-derived cells in peripheral blood or bone marrow samples and/or tissue samples at sites of suspected GvHD (skin or GI tract) [25].

Post-HCT MRD Analysis

1. MRD detection allows robust post-HCT surveillance and improves risk stratification.
2. Post-HCT MRD positivity has been consistently shown to correlate with inferior outcome [13, 26].
3. European LeukemiaNet (ELN) guidelines suggest that a molecular MRD platform should be able to detect leukemic cells to a level of 0.1% (1 in 1000 cells) [11].
4. Cumulative evidence has also shown that the presence of pre-transplant MRD is associated with inferior post-HCT outcome in AML [14, 27].
5. Use of NGS in pre- and post-HCT MRD monitoring is an active area of research.
6. Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS):

   a. Persistent presence of *NPM1* mutations or fusion mutations (*RUNX1-RUNX1T1, CBFB-MYH11,* or *PML-RARA)* is a strong predictor of leukemia relapse [28–30].
   b. However, persistent *DNMT3A*, *ASXL1,* and/or *TET2* (pre-leukemic) mutations after AML therapy have been reported (in some studies) to not correlate with an increased relapse risk [12].
   c. Excluding *DNMT3A*, *ASXL1*, and *TET2* mutations, detection of molecular MRD is associated with a significantly higher relapse rate.
   d. The NGS-based detection of persisting gene mutations in post-transplant MDS patients has also been shown to be a significant predictor of poor outcomes [31].

7. Acute lymphoblastic leukemia (ALL)

   a. Leukemia cells from the founder B- or T-cell clone have been shown to share the same B- or T-cell gene rearrangement.
   b. MRD assessment of rearrangements in immunoglobulin (Ig) and T-cell receptor (TCR) genes has been shown to be a sensitive method for detecting prognostically relevant early relapse clones.
   c. NGS assay methods can improve analytic sensitivity for detecting low-level T- or B-cell clones with leukemia-specific antigen receptor gene rearrange-

ments. MRD $> 10^{-4}$ has been proven to be associated with a higher relapse rate [32, 33].

8. Chronic myeloid leukemia (CML)

   a. HCT procedures have declined in the era of tyrosine kinase inhibitors (TKIs).
   b. Serial monitoring of BCR-ABL fusion RNA is the gold standard paradigm for quantitative MRD monitoring and relapse prediction – with continued clinical relevance in the TKI era.
   c. CML patients with increasing or persistently high BCR-ABL transcript have a higher probability of disease progression [34].

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Chapter 60
Management of Immune Compromised Transplant and Immune Effector Cell Treated Patients in the Setting of the COVID-19 Viral Pandemic: The OHSU Experience

Richard T. Maziarz and Brandon Hayes-Lattin

Introduction

The year 2020 is unlike any years in the past several decades. The world is currently experiencing a viral pandemic with the COVID-19 (SARS-CoV-2) virus that as of May 30, 2020, has infected 5,952,145 individuals worldwide of which 365,437 people have died with mortality attributed to the infection. On the same date, the United States has reported 1,786,171 cases with 104,235 deaths attributed to COVID-19. Elderly patients and those individuals with comorbidities and immune-suppressed states have been particularly targeted. As such, all centers have required innovative interventions to decrease the risk of exposure to both individuals as well as treating staff and all supportive team members. Based on the community COVID-19 virus prevalence and the available resources within that community, whether it be at an individual hospital, city, region, or country level, the management will be different. Described below are the institutional guidelines established at Oregon Health & Science University and represent the Best Practice Guidelines that were implemented, based on local, regional, and national recommendations. This information is shared not to indicate that these are the optimal guidelines, but they were the guidelines that were established within our community based on the impact of the viral pandemic. Every transplant and cell therapy center has needed

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and will continue the need to develop and evolve their own best practice guidelines and will look for direction from our societies. Certainly, the guidance from the American Society of Transplant & Cell Therapy (ASTCT) and the European Group for Blood and Marrow Transplantation (EBMT) has been invaluable to our program and inevitably has saved lives.

Patient Selection

Recognizing that at an institutional level we faced substantial uncertainty regarding the viral pandemic and its potential impact on the entire local health system, we created guidelines to determine patient eligibility for treatment. This approach was established as standard operation with the general considerations that there could be:

1. Limitations of intensive care unit beds for critically ill patients
2. Limitations on availability of blood products if the blood donor pool was diminished
3. Limitations on available supportive medications such as tocilizumab (Actemra®)
4. Potential impact on supply chain for the delivery of unrelated hematopoietic cell or immune effector cell products
5. Limitations of housing for patients and families in need of relocation for cell therapy services
6. Limitations of available healthcare professionals for delivery of care to the transplant or immune effector cell recipient, recognizing the specialty training needed to provide the services and that the pandemic could potentially deplete our provider pool

Autologous Hematopoietic Cell Transplant Procedures

At the onset of the COVID-19 pandemic, our hospital, like many others across the country and around the world, made the administrative decision to limit medical and surgical elective procedures. This mandate required restrictions on planned transplant and immune therapy procedures and led to a set of programmatic guidelines.

Regarding decision-making on standard vs deferred transplant operations:

1. Multiple myeloma

    a. Defer primary therapy consolidation transplant procedures unless exceptional circumstance. *Justification*: awaiting data from sponsored national randomized trial assessing whether autologous hematopoietic cell transplant (HCT) is optimally performed as consolidation of first induction therapy versus utilized at time of first progression.

b. If decision is to also defer collection after primary therapy, consider bortezomib (Velcade®) maintenance until time of mobilization to avoid lenalidomide (Revlimid®)-associated toxicity on the stem cell pool.

c. Collect for two transplant procedures only (minimize unnecessary extra days of collection)

2. Autoimmune disorders/multiple sclerosis

a. Defer all patients at present recognizing that acceptable standard of care therapies remain active and that the National Institutes of Health funded phase 3 trial comparing autologous transplant to the standard of care has had a hold placed on a national level.

3. Low-grade lymphoma/mantle cell lymphoma

a. Defer; consider rituximab (Rituxan®) maintenance therapy as appropriate.

4. Aggressive lymphomas (e.g., relapsed diffuse large B cell; T-cell; refractory Hodgkin)

a. Proceed per standard guidelines.

Allogeneic Hematopoietic Cell Transplant Procedures

At the onset of the pandemic extension outside of China to Europe and the United States, the National Marrow Donor Program/Be the Match™, with ASTCT and EBMT, made recommendations for ensuring the safety of subjects undergoing transplant and cell therapy procedures. Our institution immediately adopted the recommended guidelines including preferential consideration of cryopreserved products for HCT recipients. This approach would ensure that the needed cell product would be collected and stored within the cell therapy laboratory before transplant conditioning was initiated. This maneuver would overcome the potential risk of prolonged marrow aplasia if the conditioning process had started and the supply chain delivery that ensures transport of products was disrupted.

Regarding decision-making on standard vs deferred transplant operations:

1. Myelodysplastic syndrome (MDS)

a. For patients with intermediate-grade MDS who are stable on a hypomethylating agent (HMA), continue HMA treatment and utilize transfusion support as needed.

b. For patients with higher grade MDS, primarily defined by higher blast count with failure of marrow suppressive therapy, proceed directly to HCT.

2. Myelofibrosis

   a. Consider deferral of HCT and maintain standard therapy.
   b. Patients in blast phase should proceed to transplant.

3. Non-malignant diseases (e.g. primarily aplastic anemia, dyskeratosis)

   a. Defer and continue supportive care.

4. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)

   a. Patients with high-risk acute leukemia defined by cytogenetics or next-generation sequencing, patients in second complete remission, or with primary induction failure should proceed with transplant
   b. Patients with intermediate-risk AML, defer unless outstanding circumstances

Immune Effector Cell/Chimeric Antigen Receptor–T Cell Therapy

1. For patients with relapsed, refractory diffuse large B-cell lymphoma (DLBCL)

   a. Recommend proceeding directly to treatment with commercial products. Patient's disease state as well as likelihood of toxicities necessitating prolonged hospital stay will be considered for product selection and utilization.
   b. Clinical trial participation for patients with relapsed, refractory DLBCL will likely be deferred given institutional restrictions on the performance of clinical research, limiting hospital access of all non-essential personnel, as well as limiting availability of staff to obtain all trial specific study specimens.

2. Recognizing that at the time of this pandemic, no commercially available immune effector cell products have been approved by regulatory bodies for treatment of multiple myeloma patients. As such, we elected to maintain considerations for participation in phase II clinical trials for relapsed/refractory advanced myeloma patients with limited alternative options.

Inpatient Care Management

The care of the inpatient undergoing HCT or immune effector cell therapy or the individual who has experienced complications of these treatments is focused on the safety of the patient and those involved in their care.

1. Isolation policies remain in place with patients restricted to the rooms to ensure social distancing and to ensure limited encounters with any other individual.

2. A strict no visitation policy was enacted. The only exceptions were for patients with cognitive defects or who may be entering the terminal hours to days of life.
3. All patients require COVID viral screening before entering the inpatient ward. Current screening allows for routine testing with turnaround in 24 hours or urgent testing with turnaround in 1 hour.

   a. Screening can be initiated in the outpatient setting and must take place within 72 hours of the planned hospitalization for those being admitted electively.
   b. For all patients requiring urgent admission, viral testing can be performed in the clinic or emergency room before decision is made for location of their hospitalization.
   c. Patients who test positive for COVID-19 are admitted into neutral or negative pressure rooms and/or cohorted on a specialty isolation ward. Patients who are viral test negative continue to be admitted to the transplantation and cell therapy ward.
   d. Routine COVID-19 screening tests are done on a weekly basis for all patients experiencing prolonged hospital stays.

4. All encounters with patients require masking and appropriate hand-care hygiene. When possible, patient examinations are done with the fewest people entering the room. Social work support, discharge planning, counseling, spiritual guidance visits are performed virtually or over the phone.

Outpatient Care Management

The care of the outpatient actively undergoing HCT or cell therapy care or patients receiving follow-up care has also focused on the safety of the patient and the provider as well as in maintaining social distancing.

1. There has been an increased emphasis on decreasing the volume of patients physically seen in the outpatient setting. An increasing effort has been made to either establish telephone consultations and visits as well as virtual visits with visual telecommunication tools.
2. All patients with any upper or lower respiratory symptoms consistent with potential COVID-19 infection are directed to a COVID-19 isolation outpatient area, established as a means to limit any exposure of the general patient population. Within that area, they are isolated and undergo viral screening.
3. A strict no visitation policy is in place; no caregivers are permitted. Caregiver contact and support are provided virtually. An appeal system has been established for specific review of those patients with cognitive deficits for whom information delivery in the outpatient setting is not assured to be effectively recorded. In that setting, a multidisciplinary group reviews circumstances and reaches consensus regarding allowing companion participation for that outpatient visit.

4. Patients requiring infusion support of blood products, fluids and electrolytes, or chemotherapy, receive their care performed by a specialized team, maximizing social isolation with individual patients assigned to private rooms.

Clinical Trials

Clinical investigation and research efforts are under the mandate of the institutional guidelines for all laboratory and clinical studies. The decision has been made at our institution to halt many research activities following established national biosafety level (BSL) practices. This restriction was applied to all research, not just studies of infectious biohazards, with the intent of achieving maximal, state government-mandated social isolation. Thus, research teams that normally could collect specimens, perform questionnaire reviews, send samples to central laboratories, and interact with patients directly were restricted by these rulings. As such, programmatic consensus agreements were established to halt accruals to any study that required multiple direct patient encounters that were not directly related to the safety of the patient. This action was in concordance with many industry-sponsored trials which were requested to be halted during the COVID-19 pandemic.

A limited number of trials anticipated to provide any clinical benefit were maintained to offer treatment options to patients with no other available standard therapies. This action was viewed as a safety intervention. However, this decision required an appeal to the institutional research governing team and endorsement of approval by this independent body.

Personnel Management

The safety of all patients is best ensured with a fully functioning healthcare team.

1. All healthcare personnel with any symptoms of respiratory illness or findings that could be consistent with COVID-19 viral infection were restricted from entering campus in any public space.
2. Institutional occupational health kiosks were established for drive-through viral screening. Employees tested in this manner were to return directly to home and await contact from Occupational Health before being allowed to return to work.
3. Only individuals deemed as "essential" for the ongoing direct care of patients were permitted to enter campus. All nonessential healthcare personnel were instructed to socially isolate and perform their work activities from home.
4. Any encounter with a patient suspected of or confirmed to have a COVID-19 viral infection required strict adherence to hospital guidelines for the donning of personal protection equipment (N95 mask, gloves, gown, face shield, or goggles) and for either disposal or recycling of that equipment.

5. All face-to-face meetings, either administrative or educational, were changed to virtual group meetings or chat rooms.
6. At the institutional level, a central command team was formed to determine all COVID-19-related policies and disseminate communication of policies daily. At a programmatic level, a multidisciplinary team comprised of representatives from nursing, social work, hematology and medical oncology physicians, advanced practice providers, and palliative care was established to ensure the appropriate dissemination of information across the clinical team.

Recommended Readings

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Appendix 1: The Vocabulary of Transplant

AA: Aplastic anemia

aGvHD: Acute graft-versus-host disease

AIHA: Autoimmune hemolytic anemia

AKI: Acute kidney injury

ALL: Acute lymphoblastic leukemia

Allele: Molecular variants of a single gene

Allogeneic: Cells derived or obtained from another individual

AML: Acute myeloid leukemia

APC: Antigen presenting cell

APL: Acute prolymphocytic leukemia

ANC: Absolute neutrophil count

Antigen: Any molecule that is recognized and bound by immunoglobulin or T-cell receptors; in immunogenetics, this term is often interchangeably used to describe a particular HLA molecule

Antigenic determinant/epitope: The specific part of an antigen bound by immunoglobulin or T-cell receptor

ARDS: Adult respiratory distress syndrome

ASBMT: American Society for Blood and Marrow Transplantation, now known as ASTCT.

ASTCT: American Society for Transplantation and Cellular Therapy. An international professional association that promotes the blood and marrow transplantation and cellular therapy fields. www.astct.org

ATG: Antithymocyte globulin

AUC: Area under the curve

Autologous: Cells derived or obtained from the afflicted individual

BAL: Bronchoalveolar lavage

BiTe: Bispecific antibody

BMI: Body mass index

BMT: Bone marrow transplant

BMT CTN: Blood and Marrow Transplant Clinical Trial Network. National Heart, Lung, and Blood Institute (NHLBI) and National Cancer Institute (NCI)-sponsored intergroup focused on the development of clinical trials in the hematopoietic cell transplantation arena. www.emmes.com

Bone marrow harvest: The procedure through which donor stem cells are collected directly from the bone marrow cavity

BOOP: Bronchiolitis obliterans organizing pneumonia, now known as COP

BOS: Bronchiolitis obliterans syndrome

BSA: Body surface area

CAR-T: Chimeric antigen receptor T-cell therapy

CARTOX: Immune effector cell Therapy Toxicity Assessment and Management scoring system

CBU: Cord blood unit

CD34: A surface marker of the earliest progenitors and stem cell pools. Clinical exploitation has been achieved using this molecule in determining if adequate numbers of transplantable stem cells are obtained prior to a procedure

CDC: Center for Disease Control and Prevention (United States organization)

cGvHD: Chronic graft-versus-host disease

Chimerism: The establishment of donor cells within another recipient; can be partial or complete

CHIP: Clonal hematopoiesis of indeterminate potential

CI: Comorbidity index

CIBMTR: Center for International Blood and Marrow Transplant Registry, the registry of > 400 transplant centers worldwide that contribute outcomes data to a central data repository for analysis. www.cibmtr.org

CKD: Chronic kidney disease

CLL: Chronic lymphocytic leukemia

CML: Chronic myeloid leukemia

CMML: Chronic myelomonocytic leukemia

CMV: Cytomegalovirus

CNI: Calcineurin inhibitor

CNS: Central nervous system

COP: Cryptogenic organizing pneumonia

Conditioning: The euphemistic term for the chemotherapy or radiation based preparation of the host prior to the transplant, the goals of which include immune suppression and myelosuppression.

CR: Complete remission/response

CRS: Cytokine release syndrome

CSA: Cyclosporine A

CSF: Cerebrospinal fluid

CVC: Central venous catheter

DAH: Diffuse alveolar hemorrhage

DART: Dual affinity retargeting

DC: Dendritic cell

DEXA: Dual-energy X-ray absorptiometry

DFS: Disease-free survival

DIC: Disseminated intravascular coagulation

DLBCL: Diffuse large B-cell lymphoma

DLCO: Diffusion capacity of lung for carbon monoxide

DLI: Donor lymphocyte infusion

DLT: Dose-limiting toxicity

DSA: Donor-specific antibody

DTaP: Diphtheria, tetanus, and full-dose pertussis vaccine

EBMT: The European Society for Blood and Marrow Transplantation. An organization based in Europe that promotes cooperative studies and collects transplant outcome data from multiple European and Eurasian countries. www.ebmt.org

EBV: Epstein Barr virus

ECOG: Eastern Cooperative Oncology Group performance scale

ECP: Extracorporeal photopheresis

EFS: Event-free survival

ET: Essential thrombocythemia

FA: Fanconi anemia

FACT: Foundation for the Accreditation of Cell Therapy

FDA: United States Food and Drug Administration

FEV1: Forced expiratory volume in 1 second

FISH: Fluorescence in situ hybridization

FLC: Free light chains (includes Kappa and Lambda)

FVC: Forced vital capacity

G-CSF: Granulocyte-stimulating factor

GF: Graft failure

GFR: Glomerular filtration rate

GM-CSF: Granulocyte macrophage-stimulating factor

GvHD: Graft-versus-host disease

GVL: Graft-versus-leukemia

HAV: Hepatitis A virus

Haplotype: The location of a linked set of polymorphic HLA genes on a single chromosome; all cells, other than the germ cells of an individual, express two haplotypes, each inherited from a single parent

Haploidentical: The circumstance in transplantation in which there is a partial or complete mismatch at a single HLA locus between two individuals

HBV: Hepatitis B virus

HCT-CI: Hematopoietic cell transplantation comorbidity index

HCV: Hepatitis C virus

HDL: High-density lipoprotein

HEPA: High- efficiency particulate air

HepBcAb: Hepatitis B core antibody

HepBsAb: Hepatitis B surface antibody

HepBsAg: Hepatitis B surface antigen; a.k.a. Australia antigen

Hematopoietic stem cell: A bone marrow derived stem cell with the capacity for self-renewal and the ability to generate downstream mature products of red cells, white blood cells and platelets. By definition, a transplantable product.

HiB: Haemophilus influenzae vaccine

HIV: Human immunodeficiency virus

HL: Hodgkin lymphoma

HLA: Human leukocyte antigen

HLA Class I: Gene products of HLA A, B, C, E, and G, universally expressed on the surface of all cells of an individual (with some specific exceptions, e.g., trophoblast tissue); the class of histocompatibility molecules that present cellular peptides to CD8 T-cell effectors

HLA Class II: Gene products of HLA DR, DP, DQ, limited cell surface expression on lymphohematopoietic tissues; inducible cell surface expression on many tissues after inflammatory cytokine exposure; the class of histocompatibility molecules that present cellular peptides to CD4 T-cell effectors.

HLH: Hemophagocytic lymphohistiocytosis

HPV: Human papilloma virus

HRSA: United States Health Resources and Services Administration

HRT: Hormone replacement therapy

HCT: Hematopoietic cell transplant

HSV: Herpes simplex virus

HUS: Hemolytic uremic syndrome

HVG: Host-versus-graft

IBW: Ideal body weight

ICANS: Immune effector cell-associated neurotoxicity syndrome

ICE: Immune effector cell-associated encephalopathy

IDM: Infectious disease markers

IEC: Immune effector cell

IFI: Invasive fungal infection

IPI: International prognostic index

IPS: Interstitial pneumonitis

IPV: Inactivated poliovirus vaccine

ISCT: International Society for Cell Therapy

IST: Immune suppressive therapy

JACIE: Joint Accreditation Committee of ISCT-Europe and EBMT

KIR: Killer immunoglobulin-like receptor

KPS: Karnofsky Performance Score

LDL: Low-density lipoprotein

LFS: Leukemia-free survival

LVEF: Left ventricular ejection fraction

M protein: Monoclonal protein

MA: Myeloablative

MAC: Myeloablative conditioning

MAHA: Microangiopathic hemolytic anemia

MCL: Mantle cell lymphoma

MDS: Myelodysplastic syndrome

MF: Myelofibrosis

MHC: Major histocompatibility complex. The collection of genes located on human chromosome 6 that encode the polymorphic proteins involved in antigen presentation to T-cells; the regulators of the cellular immune response

MM: Multiple myeloma

MMF: Mycophenolic acid

MMR: Measles, mumps, and rubella vaccine

Mobilization: The act of enhancing the movement of stem cells from their microenvironment niche into circulation; usually performed with growth factor or growth factor plus chemotherapy exposure

MOF: Multi-organ failure

MPN: Myeloproliferative neoplasm

MRD: Minimal residual disease; also matched related donor

MSC: Mesenchymal stromal cell

MTX: Methotrexate

MUD: Matched unrelated donor; see also URD

Myeloablative: Conditioning regimens designed to eliminate all host stem cells

NCCN: National Comprehensive Cancer Network

NCI: National Cancer Institute; a United States organization

NCI CTC: National Cancer Institute Common Toxicity Criteria. Widely accepted criteria for assessing severity of adverse events. Its utilization allows for overcoming institutional variation in reporting and for comparative outcomes research to be performed.

NGS: Next-generation sequencing

NHL: Non-Hodgkin lymphoma

NIH: National Institutes of Health

NK: Natural killer cell

NMA: Non-myeloablative

NMDP: National Marrow Donor Program. An American organization focused on facilitating unrelated donor and cord blood transplant procedures. www.bethematch.org

Non-myeloablative: Conditioning focused on immune suppression and establishment of donor chimerism without dose intensity enough to destroy all residual host stem cells

NRM: Non-relapse mortality

OS: Overall survival

PAM score: Pretransplant Assessment of Mortality

PBSC: Peripheral blood stem cells

PBSC collection (apheresis): The procedure by which stem cells are mobilized directly into the blood of the donor for harvesting by leukapheresis

PCR: Polymerase chain reaction

PCV13: 13-valent pneumococcal vaccine

PET: Positron emission tomography

PFS: Progression-free survival

PFT: Pulmonary function tests

PICC: Peripherally inserted central catheter

PID: Primary immunodeficiency

PJP: *Pneumocystis jiroveci* pneumonia, formerly known as *Pneumocystis carinii* pneumonia (PCP)

PNH: Paroxysmal nocturnal hemoglobinuria

PPSV23: 23-valent Pneumococcal polyscaccharide vaccine

PR: Partial remission/response

PRES: Posterior reversible encephalopathy syndrome

PTCy: Post-transplant cyclophosphamide

PTCL: Peripheral T-cell lymphoma

PTLD: Post-transplant lymphoproliferative disorder

PUVA: Psoralen and ultraviolet A therapy

QOL: Quality of life

RA: Refractory anemia

RAEB: Refractory anemia with excess blasts

Reduced intensity transplantation: A blanket term for any degree of conditioning that is less intense than traditionally defined maximal myeloablative conditioning

REMS: Risk evaluation and mitigation strategy

RFS: Relapse-free survival

RIC: Reduced intensity conditioning

RRT: Regimen-related toxicity

RSV: Respiratory syncytial virus

RT-PCR: Real-time polymerase chain reaction

RV: Residual volume

SAA: Severe aplastic anemia

SCD: Sickle cell disease

SCID: Severe combined immunodeficiency

SCTOD: Stem Cell Transplant Outcome Database

SITC: Society for Immunotherapy of Cancer

SNP: Single-nucleotide polymorphism

SOS: Sinusoidal obstructive syndrome, formerly known as veno-occlusive disease (VOD)

Syngeneic: Cells derived or obtained from an identical twin

TA-GvHD: Transfusion-associated graft-versus-host disease

tAML: Treatment-related acute myeloid leukemia

Targeted therapy: Biologic and pharmaceutical therapies directed at biologic pathways in the neoplastic cell rather than widespread cellular toxic therapies (AKA precision oncology)

TA-TMA: Transplant-associated thrombotic microangiopathy

TBI: Total body irradiation

Td: Tetanus, diphtheria vaccine

TKI: Tyrosine kinase inhibitor: a class of pharmaceuticals targeting intracellular kinase activation pathways such as imatinib, ibrutinib, sorafenib, etc.

TLC: Total lung capacity

TLS: Tumor lysis syndrome

tMDS: Treatment-related MDS

TNF: Tumor necrosis factor

TPN: Total parenteral nutrition

TRALI: Transfusion-related acute lung injury

T-reg: Regulatory T cells characterized by surface high CD25 expression and FOXP3 positive status

TRM: Treatment-related mortality

TSH: Thyroid-stimulating hormone

TTP: Thrombotic thrombocytopenia purpura

TwinRix: Combined hepatitis A and hepatitis B vaccine

UCB: Umbilical cord blood

URD: Unrelated donor

VGPR: Very good partial remission/response

VOD: Veno-occlusive disease, see also SOS

VRE: Vancomycin-resistant Enterococcus

VZIg: Varicella zoster immune globulin

VZV: Varicella zoster virus

WBMT: Worldwide Network for Blood & Marrow Transplantation

WHO: World Health Organization

WMDA: The World Marrow Donor Foundation. An international organization focused on donor safety, stem cell accessibility, and generation of standard practices for the exchange of hematopoietic stem cells for clinical transplantation worldwide. www.wmda.info

Appendix 2: Procedure – Bone Marrow Aspirate and Biopsy

Indication Evaluate marrow for disease involvement; restaging; evaluate post-transplant chimerisms; evaluate cytopenias.

Procedure
1. Contact the Bone Marrow Bench to schedule a technician for the procedure.
2. Complete all appropriate requisitions or electronic orders as outlined below.
3. Identify the patient and complete TEAM PAUSE documentation.
4. Obtain written consent. If patient requests medication for anxiolysis or sedation, indicate this on the consent form and ascertain that the patient *is accompanied by a driver*.
5. Obtain a bone marrow biopsy tray. This should contain an 11g 4" aspirate needle and a 11g 4" biopsy needle, a 30-mL luer lock syringe, a 10-mL syringe with 21-g, 20-g, and 25-g needles, 10-mL lidocaine 1%, scalpel, paper drapes, Betadine swabsticks or alternative skin prep, 4 × 4 gauze sponges and an adhesive bandage. Also obtain sterile gloves.
6. Position the patient in the prone position and prepare your supplies.
7. Identify the iliac crest. Prepare the biopsy site with Betadine, put on your sterile gloves, and drape the area.
8. Administer local anesthesia using lidocaine 1%. Begin by forming a wheal on the skin. Continue to numb the area with lidocaine through the fatty layer down to the bone. Administer lidocaine in a widening circular area over the surface of the bone completely infiltrating the periosteum.
9. Prepare your syringes to obtain aspirate specimens. The bone marrow technician will provide additional sterile syringes and sodium heparin to use during the procedure.
10. Using the scalpel, make a single cutaneous incision to the hub of the scalpel to allow easy passage of the aspirate needle.
11. Insert the aspirate needle through the skin incision until contact with the bone is made. Using gentle, steady, rotating pressure, continue until the needle is firmly seated in the marrow space.

a. The first aspirate should be a quick pull into an unheparinized syringe (1–2 ml). Slides should be made from this specimen if spicules are present. The remainder of the specimen should be sent for morphology.

b. If same-sex chimerisms are required, the second specimen should be sent for VNTR in an unheparinized syringe.

c. Specimens which should be sent in a heparinized syringe include flow cytometry, cytogenetics, and FISH studies along with samples for appropriate research studies.

d. Any additional specimens should be sent per lab guidelines.

e. Please keep in mind that collection methods and sample collection vary from institution to institution. Your institution's guidelines should be followed to ensure adequate interpretation of the sample.

12. Once the aspirates have been collected, remove the aspirate needle. Insert the biopsy needle through the skin incision until contact with the bone is made. Using gentle, steady, rotating pressure, introduce the needle through the cortex slightly into the marrow space. Remove the trochar and continue to advance the needle further into the marrow space to obtain a core biopsy. Using the trochar, measure the approximate length of the core by inserting it back through the biopsy needle. Once the core measures at least 2 cm, break the core biopsy off by rotating the biopsy needle multiple times.

13. Remove the biopsy needle and attach the needle guard to the bottom of the biopsy needle. Insert the shepherd's hook through the bottom of the needle to dislodge the core onto a sterile gauze or slide provided by the bone marrow technician.

14. Once adequate specimens have been obtained, hold pressure to the biopsy site until bleeding has stopped and apply a clean bandage.

15. Assist the patient to the supine position and observe for 10–15 minutes for signs of bleeding. The patient may require longer observation if anxiolysis or sedation was administered.

16. Instruct the patient to keep the bandage clean and dry for 24 hours. The bandage may then be removed. Also instruct the patient to call should any signs of infection develop.

17. Document the procedure in the patient's medical record.

Standard Tests for Marrow Studies

For most malignancies, standardized testing includes morphology, flow cytometry, cytogenetics, and a disease-specific FISH panel. Additionally, a next-generation sequencing panel should be obtained for myeloid malignancies.

Additional disease-specific testing may also include the following:

1. AML

    a. FISH for t(15;17) or PCR for PML/RAR to r/o acute promyelocytic leukemia

2. ALL

    a. FISH for t(9;22) or PCR for BCR/abl to evaluate for the presence of the Philadelphia chromosome

    b. ClonoSEQ® if available; this is an FDA-cleared in vitro diagnostic test service provided by Adaptive Biotechnologies for use in acute lymphoblastic leukemia and multiple myeloma patients to detect minimal residual disease

3. CML

    a. PCR for BCR/abl is not indicated as peripheral blood sensitivity is adequate

4. CLL

    a. FISH to include abnormalities of chromosomes 11, 13, and 17

5. MDS

    a. FISH to include abnormalities of chromosomes 5 and 7

6. Non-Hodgkin lymphoma

    a. For mantle cell lymphoma, FISH for t(11;14)

    b. For follicular lymphoma, FISH for t(14;18)

7. Multiple myeloma

    a. FISH to include abnormalities of chromosome 1, t(11;14), t(4;14), t(14;16), 17p, 13, ploidy

    b. Congo red stain to r/o amyloid involvement

8. Post-transplant samples to determine chimerisms

    a. Same sex donors: VNTR or sorted cell chimerism studies

    b. Mismatched sex donors: FISH for XY

Appendix 3: Procedure – Lumbar Puncture

Indications:
- Diagnostic: r/o CNS leukemia/lymphoma, r/o infection
- Therapeutic: instillation of intrathecal chemotherapy

Procedure:
1. Review lab studies to verify patient's platelet count is >50,000/mm^3. If platelet count is <50,000/mm^3, transfuse one single-donor irradiated platelet product and check a post-platelet count. Continue to transfuse single-donor irradiated platelet products to achieve a platelet count >50,000/mm^3.
2. If chemotherapy will be administered during the procedure, submit the orders to pharmacy for mixing. All intrathecal chemotherapy should be mixed in preservative-free normal saline only. Chemotherapy should be checked prior to administration according to institutional policy.
3. Place the orders for CSF studies in the patient's chart or electronic medical record. These typically include the following:

    a. Tube 1: protein, glucose
    b. Tube 2: cell count and differential
    c. Tube 3: flow cytometry and cytology
    d. Tube 4: cultures for diagnostic studies, if indicated

4. Identify the patient and complete TEAM PAUSE documentation.
5. Obtain written consent. If patient requests medication for anxiolysis, indicate this on the consent form and ascertain that the patient *is accompanied by a driver*.
6. Obtain lumbar puncture tray. This should contain a 20g 3½" needle with stylet, a 3-mL syringe with 25-g and 22-g needles, 2-mL lidocaine 1%, four numbered specimen vials, gauze pads, Betadine swabsticks, paper drapes, and an adhesive bandage. Also obtain sterile gloves.
7. Place the patient in the lateral decubitus position, curled into the fetal position or upright and bent forward, supported by stable bedside table/pillow. Prepare your supplies.

8. Locate the sacral promontory. The end of this structure coincides with the L5-S1 interspace. Use this reference to locate the L4–L5 interspace.
9. Using sterile technique, prep the skin over L4–L5 with betadine and drape the area.
10. Administer local anesthesia using lidocaine 1%. Begin by forming a wheal on the skin. Continue to numb the deeper tissue with lidocaine, positioning the needle toward the umbilicus.
11. Insert the spinal needle bevel up through the skin and into the deeper tissue. Aim the needle toward the umbilicus. A slight pop will be felt when the dura is punctured.
12. Once inside the dura, remove the stylet. If fluid does not flow, reinsert the stylet and attempt to enter the dura again. This may require slight advancement or partial withdrawal and repositioning.
13. Once CSF flows, collect the appropriate specimens in the numbered tubes.
14. If chemotherapy is to be administered during the procedure, attach the chemotherapy syringe to the hub of the spinal needle once fluid collection is completed, keeping one hand sterile.
15. Slowly inject the chemotherapy over a period of 2–3 minutes, checking for flow every 2–3 mL.
16. Once fluid collection and chemotherapy administration are completed, withdraw the needle and apply gentle pressure to the insertion site. Apply a clean bandage.
17. Instruct the patient to lie flat for 1–4 hours to avoid post-procedure headache.
18. Label the CSF-containing tubes with the patient's identifying data prior to transport to the lab.
19. Document the procedure in the patient's medical record.

Appendix 4: Procedure – Ommaya Reservoir Tap

Indications:
- Diagnostic: r/o CNS leukemia/lymphoma, r/o infection
- Therapeutic: instillation of intrathecal chemotherapy

Procedure:
1. If chemotherapy will be administered during the procedure, submit the orders to pharmacy for mixing. All intrathecal chemotherapy should be mixed in preservative-free normal saline only. Chemotherapy should be checked prior to administration per institutional policy.
2. Place the orders for CSF studies in the patient's chart or electronic medical record. These typically include the following:

    a. Protein, glucose
    b. Cell count and differential
    c. Flow cytometry and cytology
    d. Cultures for diagnostic studies, if indicated

3. Identify the patient and complete TEAM PAUSE documentation.
4. Obtain written consent. If patient requests medication for anxiolysis, indicate this on the consent form and ascertain that the patient *is accompanied by a driver*.
5. Obtain supplies including the following: 10-mL luer-lock syringe, 25-g butterfly needle, Betadine swabsticks, sterile 2 × 2-gauze pads, and an adhesive bandage. Also obtain sterile gloves.
6. Place the patient in the supine position with the head of bed elevated approximately 30º. Locate the Ommaya reservoir and pump the port gently three times to ensure flow.
7. Using sterile technique, prep the skin over the port.
8. Insert the needle into the center of the port until the needle strikes the back of the port. Observe for flow of CSF.
9. Attach the sterile syringe to the butterfly needle and slowly withdraw 6 mL of CSF.

10. Once the specimen has been collected, attach the syringe containing chemo-therapy and slowly inject the chemotherapy over a period of 2–3 minutes, checking for flow after every 2–3 mL.
11. Remove the needle from the Ommaya and hold gentle pressure to the site until the bleeding has stopped. Apply a clean bandage.
12. Seal the syringe containing CSF with a sterile cap and label the syringe with the patient's identifying data.
13. Document the procedure in the patient's medical record.

Appendix 5: Procedure – Skin Biopsy

Indication: Evaluation of rash or other skin lesion; r/o GvHD, infection, etc.

Procedure:

1. Identify the patient's affected areas of skin to be biopsied and mark those areas.
2. Obtain topical anesthetic, either topical anesthetic spray (e.g., Flori-Methane) or Elamax cream. If using Elamax cream, apply 2.5 gms (approximately 1/2 of a 5-gm tube) in a thick layer over the site to be biopsied. Cover with an occlusive dressing (Op-Site/Tegaderm). Note the time of application on the dressing. A minimum of 1 hour is necessary to obtain analgesic effect. If using anesthetic spray, spray area to be biopsied for 3–5 seconds at a distance of approximately 12 inches. Do not frost the skin. Note: Intradermal injections of lidocaine may distort the histologic architecture, so the use of Elamax cream or anesthetic spray is encouraged.
3. Obtain supplies including a 3–4 mm biopsy punch, scalpel, scissors, forceps, needle driver, cloth/paper drapes, betadine swabsticks, alcohol wipes, 4 × 4 gauze sponges, 5-0 nylon suture material, and a specimen container with formalin. A syringe, 1% Lidocaine, and sterile gloves should also be available. A suture removal kit may be used to obtain some of the supplies.
4. After a minimum of one-hour application of the Elamax cream, remove the occlusive dressing and wipe off the Elamax cream. Prepare and lay out required supplies. Using sterile technique, prepare the biopsy sites with Betadine, put on gloves, and apply drape if necessary. Apply anesthetic spray, if using.
5. Place the biopsy punch on the skin and exert moderate downward pressure. Rotate the punch until the entire blade is within the skin, and then remove the instrument.
6. Using forceps, gently pull the punch from the skin which will leave the base of tissue attached to the subcutaneous layer of tissue. Using scissors, cut the base of the biopsy and lift it free from the surrounding tissue.
7. Place the specimen in the formalin solution and label the container with the patient's identifying data.

8. Blot or apply pressure briefly to the biopsy site with gauze, then suture or steri-strip site as needed. If the patient experiences discomfort at the biopsy site during suturing, intradermal Lidocaine should be used at this time.
9. Apply a small amount antibacterial ointment to biopsy site and cover with occlusive dressing. Instruct patient to leave dressing in place for 24 hours. After 24 hours, remove the dressing. Apply small amount of antibacterial ointment to biopsy site twice a day. Instruct the patient/caregiver to notify the nursing staff if redness, swelling, persistent or colored drainage, or discomfort occurs at the biopsy site.
10. Complete an appropriate requisition and send specimen to Dermatopathology per institutional guidelines.
11. Remove the sutures in 7–10 days.
12. Document the procedure in the patient's medical record.

Appendix 6: OHSU Food Safe Diet

Below is the food safe diet currently in use at Oregon Health & Science University. It is intended to be an example of one institution's practice.

This diet is intended for neutropenic patients and autologous peripheral blood stem cell transplant recipients until day +30 post-transplant.

Foods to be avoided:

- Raw seed and vegetable sprouts
- Raw or rare meat, fish, and poultry
- Foods from salad bars and buffets or fast food restaurants
- Foods with raw eggs (salad dressings, egg nog)
- Unpasteurized dairy products
- Unroasted nuts and nuts in the shell
- Unpasteurized juices and ciders
- Probiotics and probiotic containing foods such as Nancy's® yogurt, Dannon Activia®, kombucha, kefir, etc.

Appendix 7: OHSU Low-Bacteria Diet

Below is the low-bacteria diet currently in use at Oregon Health & Science University. It is intended to be an example of one institution's practice.

Inpatient

Certain whole, undamaged fresh fruit and vegetables are allowed as long as they are thoroughly washed with water by a RN, CNA, or family member. (*The ones denoted with asterisks will be provided by the dietary service.)

Allowed items that must be washed and peeled

*Apple	Melons	Lime	Cucumber
*Orange	Peach	Pineapple	Carrot
*Banana	Kiwi	Mango	Onion
Grapefruit	Avocado	Papaya	Squash
Cantaloupe	Lemon	Pear	Garlic

May be eaten unpeeled after stems and greens removed and washed

Plum	*Tomato	Cherry
Apricot	Celery	Green beans
Blueberry	Bell pepper	Grapes
Prunes	Radish	Raisins

Other packaged dried fruits

Not allowed unless cooked or processed

Strawberry	Broccoli	Spinach
Raspberry	Cauliflower	Leafy greens
Marionberry	Mushroom	Lettuce

| Blackberry | Cabbage | Bulk dried fruits |

- Pasteurized yogurt is allowed at all times. Avoid Nancy's, Stoneyfield, Dannon, Activia, etc.
- No unpasterized milk products; no aged cheeses (brie, bleu, sharp cheddar, etc.).
- Sodas should be in cans or bottles.
- Nuts allowed in cans or packets, no "bulk" foods.
- Meats should be cooked until well done; no smoked fish.
- No miso or tempeh.
- No moldy or outdated foods.
- No "fresh" salsa or salad dressings.
- No home canned foods or homemade freezer jams.

Outpatient

Above diet should be followed until day +100 for allogeneic patients (except those with active GvHD)

May go to restaurants at day +30 for autologous patients, day +60 for allogeneic patients.

Appendix 8: OHSU Graft-Versus-Host Disease Diet

Graft-versus-host disease (GvHD) of the gut may cause you to have excessive nausea, vomiting. and diarrhea. Your doctor may ask you to follow a bland diet to give the gut time to heal, which is the GvHD 1, GvHD2, and GvHD 3 diets. These diets will be advanced according to individual tolerance.

The following tips may help decrease symptoms:

- Smaller more frequent meals
- Low-fat, low-fiber, and low-lactose options
- Try to drink liquids between meals
- Eat slowly and chew food thoroughly
- Introduce one new food at a time
- If your symptoms worsen, inform your doctor or dietitian right away

Stage 1: Initiate oral diet with isotonic, low-residue, low-lactose beverages.

Food group	Allowed foods	Foods not allowed
Dairy	None	Milk Milkshakes
Beverages	Tap & bottled water, ice made from tap water Gatorade®, G2®, Propel® Herbal teas brewed from commercially packaged tea bags Diluted juices (½ juice to ½ water) Diet soda	Unboiled well water Mate tea Green tea Commercial supplements Regular soda
Soups	Broth	Cream based-soups
Desserts	Sugar-free gelatin Sugar-free popsicle	All others

Stage 2: As tolerated, advance to low-fiber, low-fat, and low-lactose solids.

Food group	Allowed foods	Foods not allowed
Dairy	Lactose-free milk Soy milk/rice milk	All others
Meats	Egg whites Low cholesterol eggs (such as Egg Beaters®)	All others
Fruits and Nuts	Canned fruit Ripe banana	All others Canned pineapple
Vegetables	Well-cooked green beans, carrots, squash, peas, smooth tomato sauce	All others
Beverages	Tap & bottled water, ice made from tap water Gatorade®, G2®, Propel® Herbal teas brewed from commercially packaged tea bags Diluted juices (½ juice to ½ water) Diet soda	Unboiled well water Mate tea Green tea Commercial supplements Regular soda
Fats	Margarine (1 tsp) Low-fat cream cheese Low-fat mayonnaise	All others
Starches	Plain white bagel White bread/roll English muffin White rice Pasta Baked potato, mashed potato Plain rice cake Flour tortilla Saltines, graham crackers Pretzels Dry cereal: Rice Krispies®, Rice Chex®, corn flakes	Whole wheat breads, pasta, etc. Flavored rice cakes French fries Potato chips Other starches with butter/gravies High-fiber or high-sugar cereals
Desserts	Sugar-free popsicle Sugar free gelatin Vanilla wafers Angel food cake Ginger snaps Sherbet	Regular popsicle Regular gelatin Pies, cakes, cheesecake Cookies make with nuts, fruits, chocolate or with frosting
Soups	Broth-based (chicken noodle, vegetable, etc.)	Cream-based soups

Stage 3: Slowly start adding in lean cuts of meat and other items as allowed by your provider or dietitian.

Food group	Allowed foods	Foods not allowed
Dairy	Lactose-free milk Soy/rice milk Additional items per recommendation of provider/dietitian	All others unless specified by provider/dietitian

Food group	Allowed foods	Foods not allowed
Meat and meat substitutes	Eggs whites Pasteurized egg substitutes (such as Egg Beaters®) 1–2 ounces of meats (chicken, fish, turkey, lean ham, etc.)	All others unless specified by provider/dietitian
Fruits and nuts	Canned fruit Ripe banana	All others Canned pineapple
Vegetables	Well-cooked vegetables	Fresh vegetables
Beverages	Tap & bottled water, ice made from tap water Gatorade® Herbal teas brewed from commercially packaged tea bags Juices Diet soda	Unboiled well water Mate tea Green tea Regular soda
Fats	Margarine Low-fat mayonnaise/low-fat salad dressing Low-fat cream cheese	Fresh salad dressings (stored in the grocer's refrigerated case) Lard
Other	Commercial pasteurized grade A honey	Raw honey; honey in the comb Miso products Home canned products Brewers yeast if uncooked See health-care provider about herbal and nutrient supplements
Starches	Plain bagel White bread/roll English muffin Rice Pasta Baked potato, mashed potato Rice cake Flour tortilla Saltines, graham crackers Pretzels Dry cereal: Rice Krispies®, Rice Chex®, corn flakes	Whole wheat breads, pasta, etc. French fries Potato chips Other starches with butter/gravies High-fiber or high-sugar cereals
Desserts	Sugar-free popsicle Sugar-free gelatin Vanilla wafers Angel food cake Ginger snaps Sherbet	Pies, cakes, cheesecake Cookies make with nuts, fruits, chocolate or with frosting Regular popsicle Regular gelatin
Soups	Broth-based (chicken noodle, vegetable, etc.)	Cream-based soups

Appendix 9: OHSU Vaccine Guidelines

A wide variety of post-transplant vaccination strategies exist and practices vary among institutions. While the recommended series of vaccines is generally agreed upon, the timing of administration after transplant remains a debated topic.

Below is OHSU's post-transplant vaccination protocol as an example of one institution's policy.

General Recommendations
1. Patients who undergo both autologous and allogeneic stem cell transplantation are likely to lose their immunity to vaccines received prior to transplant.
2. Current opinion suggests treating both autologous and allogeneic recipients as though they have never been vaccinated, recommending revaccination for both subsets of patients.
3. Vaccines should begin between 3 and 6 month post-transplant and >6 months after their last dose of anti-CD20 monoclonal antibody therapy. Exceptions include patients

    a. receiving chemotherapy
    b. with active graft-versus-host disease (GvHD)
    c. who are acutely ill

4. Vaccines have been shown to be safe and effective in patients received post-autologous transplant lenalidomide (Revlimid®).
5. Transplant recipients should avoid live vaccines (MMR, yellow fever, Zostavax®, and FluMist®) for at least two years following transplant and for at least one year after discontinuation of all immunosuppressive medications. Evaluation of patient's immune status (CD4 count, IgG) is recommended prior to administration of live-virus vaccines.
6. Patient's family members and close contacts are encouraged to remain up to date with their vaccinations.

    a. Family members may receive live-virus vaccines; however, they should avoid contact with the HCT recipient if they develop a fever and/or rash post-vaccination until symptoms have resolved.

b. For varicella zoster virus (VZV) seronegative caregivers or those with no history of VZV, it is recommended they receive the Varivax® vaccine. Isolation from the transplant patient is necessary if the recipient of the vaccine experiences a rash post vaccination; continue isolation until the rash resolves.

c. VZV seropositive caregivers and family members ≥ age 50 should receive the Shingrix® vaccine if they are not already vaccinated.

d. Family member and close contacts are recommended to receive the inactivated influenza vaccine annually. FluMist® should be avoided, as this is a live-virus vaccine and can be shed by the vaccine recipient.

e. HCT patients should avoid diaper changing of infants and children who receive the Rotavirus vaccine. If this is not possible, practice good hand hygiene.

    i. RV5 is dosed at 2, 4, and 6 months of age and is shed in the stool for up to 15 days after vaccination.

    ii. RV1 is dosed at 2 and 4 months of age and is shed in the stool for up to 30 days after vaccination.

7. Immunization-specific recommendations

  a. Polio

    i. Oral polio vaccine (OPV) is no longer available in the United States. Therefore, injectable polio vaccine (IPV) is utilized.

  b. Pneumococcal vaccine

    i. While timing of initiation of dosing remains controversial, early vaccination may be preferred, as it protects against both early and late pneumococcal infection, but may result in a shorter lasting antibody response.

    ii. PCV13 (Prevnar®) is the preferred vaccine for the first 3 doses. However, consider PPSV23 for the 4th dose to provide broader immune response.

  c. Diphtheria-tetanus vaccine

    i. DT is full-dose diphtheria toxoid while Td is reduced dose. The dose of tetanus toxoid is the same in both.

    ii. Full toxoid (T) vaccines should be used whenever possible.

    iii. DT vaccine is not currently approved for children > age 7 due to side effects. However, it is usually tolerated well in HCT recipients as they are similar to vaccine-naïve patients.

    iv. Diphtheria antibody levels after vaccination may be warranted in areas of increased risk of diphtheria.

  d. Pertussis vaccine

    i. HCT patients are more susceptible to complications from pertussis due to underlying pulmonary damage secondary to the conditioning regimen and/or GvHD.

    ii. Patients should receive full-dose acellular pertussis toxoid (DTaP); however, in the United States, this vaccine is not approved for patients >7 years old

   iii. The Tdap vaccine contains lower doses of diphtheria and pertussis proteins; preliminary data show poor response to Tdap in autologous and allogeneic HCT patients, regardless of timing of the dose

e. Influenza

    i. Lifelong seasonal vaccination is recommended.

   ii. If possible, the inactivated influenza vaccine should be given up to two weeks prior to admission to pre-transplant patients who have not yet been vaccinated if admission falls during flu season.

   iii. All transplant recipients should receive the inactivated influenza vaccine after day +120; however, consideration should be given for earlier dosing (day +90) in the setting of community outbreak.

- Mandatory consideration should be given for a second dose in allogeneic recipients 60 days after the initial injection if within flu season (as defined by Center for Disease Control criteria).

   iv. Use of the quadrivalent inactivated influenza vaccine is recommended, when available. The Trivalent egg-free vaccine should be used only for those patients with a documented egg allergy.

   v. High-dose vaccine should be used for patients ≥65 years old.

   vi. The live intranasal influenza vaccination (FluMist®) should never be administered in this patient population or their close contacts.

  vii. It is recommended that all caretakers and family members receive the inactivated influenza vaccine annually.

f. Varicella vaccines

    i. Varivax® (varicella zoster vaccine) should be administered only to VZV-seronegative patients.

   ii. Patients must meet institutional guidelines for live-virus vaccination prior to dosing.

g. Hepatitis A and B vaccines

    i. All patients should receive the Hepatitis A and Hepatitis B vaccines post-HCT

- These can be given as separate doses or in a combined preparation (e.g., TwinRix®).
- For HBsAg or HBcAg positive patients, vaccination should be given to prevent the risk of reverse seroconversion.
- For HBsAG or HBcAg-negative patients, vaccination should be given to prevent new acquisition of the virus.

- Assess the HBsAb 1–2 months after the last vaccination. If negative, repeat the series administering double-dose vaccines, then repeat the HBsAb; if negative, no additional vaccination is recommended.

h. Meningococcal vaccine

   i. There is a reasonable assumption that conjugated meningococcal vaccines give more stable immune responses than polysaccharide-based vaccines, although no comparative studies have been performed.
   ii. Meningococcal vaccination is typically recommended for individuals <25 years of age and those serving in the military or living in college dorms; however, vaccination may be considered for patients who are functionally immunodeficient.
   iii. Patients who proceed with immunization should receive two doses of both a serogroup A vaccine (e.g., Menactra®), and a serogroup B vaccine (e.g., Bexsero®).

i. MMR vaccine

   i. Measles, mumps, and rubella are typically given in a combination vaccine.
   ii. MMR is a live vaccine. Immunization should be considered in patients who are at least 2 years post-HCT, off all immune suppressive therapy for >1 year, and have not received an infusion of IVIG or plasma for at least 5 months. Additionally, minimal or no immune reactivation should be documented by an immune reconstitution panel.

j. Human Papillomavirus (HPV)

   i. Vaccination can be considered in both female and male patients between the ages of 9 and 45.

k. Shingrix®

   i. Vaccine was approved by the United States Food & Drug Administration for the prevention of shingles in adults ≥50 year of age on 10/13/17.
   ii. This is a recombinant vaccine and when compared with Zostavax®, appears to have a longer duration of efficacy and is more effective.
   iii. Two dose series with the second vaccine dosed 2–6 months after the first.
   iv. Prior vaccination with Zostavax® is not a contraindication to Shingrix® vaccination.

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OHSU recommendations for autologous and allogeneic transplant recipients not receiving post-transplant maintenance therapy*

Time post-transplant	Vaccine	Comments
3 months	Prevnar® 13	Pneumococcal vaccine
6 months	Prevnar® 13	Pneumococcal vaccine
12 months	Prevnar® 13	Pneumococcal vaccine
	Gardasil® 9	Human papilloma virus (HPV). For all females and males aged ≤ 26 years. Consider for patients age 27–45 if potential for new sexual partner.
	Twinrix®	Combined hepatitis A and hepatitis B vaccine
	IPV	Polio
	Tdap	Tetanus, diphtheria, and pertussis
	HiB	Haemophilus influenzae
	Shingrix®	Shingles. Must meet all criteria: VZV IgG+ pre-transplant, off all immune-suppressive therapy and not receiving chemotherapy
14 months	IPV	Polio
	Twinrix®	Combined hepatitis A and hepatitis B vaccine
	Td	Tetanus, diphtheria
	HiB	Haemophilus influenzae
	Shingrix®	Only if dosed at 12 months
	Gardasil® 9	Only if dosed at 12 months
	Menactra® + Bexsero®	Meningococcal vaccines; ONLY for patients with functional asplenia or chronic GvHD¥
18 months	Twinrix®	Hepatitis B antibody testing should be completed 1 month after the last Hepatitis B vaccine injection. If negative, repeat series with double doses at 1, 2 and 6 months.
	IPV	Polio
	Td	Tetanus, diphtheria

Time post-transplant	Vaccine	Comments
	HiB	Haemophilus influenzae
	Gardasil® 9	Only if dosed at 12 and 14 months
	Menactra® + Bexsero®	Only if dosed at 14 months
24 months	MMR	Measles/mumps/rubella. Must meet all criteria: At least 2 years after transplant, 1 year off all immune-suppressive medications, 8 months after last IVIG infusion, IgG > 300 and CD4 > 200
	PPSV23	Pneumococcal. Must meet all criteria: At least 2 years after transplant, 1 year off all immune suppressive medications, 8 months after last IVIG infusion, IgG > 300 and CD4 > 200. **Patient should receive an addition Prevnar 13 if criteria not met
	Varivax®	Chicken pox. Must meet all criteria: At least 2 years after transplant, 1 year off all immune suppressive medications, 8 months after last IVIG infusion, IgG > 300 and CD4 > 200. This should be given only to patients who do not have immunity to Varicella zoster (VZV IgG negative)
Annually	Inactivated influenza vaccine	Dose between days +90 and 120 after transplant; a second dose should be given at day +180 for allogeneic recipients if still within flu season

*Vaccines should be given at indicated time points to all autologous and allogeneic transplant recipients who are *not* receiving post-transplant maintenance therapy. *Exception: Patients receiving post-transplant TKIs or lenalidomide may proceed with attenuated vaccines as above if CD4 count > 200 and CD19 count > 20. These patients should not receive live-virus vaccines*

OHSU recommendations for autologous and allogeneic transplant recipients receiving post-transplant maintenance therapy*

Time post-transplant	Vaccine	Comments
3 months	Prevnar® 13	Pneumococcal vaccine
6 months	Prevnar® 13	Pneumococcal vaccine
12 months	Prevnar® 13	Pneumococcal vaccine
24 months	Prevnar® 13	Pneumococcal vaccine
Annually	Inactivated influenza vaccine	Dose between days +90 and 120 after transplant; a second dose should be given at day +180 for allogeneic recipients if still within flu season

*Vaccines should be given at indicated time points to all autologous and allogeneic transplant recipients receiving post-transplant maintenance therapy including bortezomib, azacitidine, etc. *Exceptions: 1. Patients receiving post-transplant TKIs or lenalidomide may proceed as per standard vaccine protocol; 2. Patients receiving post-transplant rituximab should not receive vaccines until at least 6 months after completion of therapy.* Patients may begin the full post-transplant vaccine schedule 3 months after completion of maintenance therapy with the *exception of patients receiving rituximab who should wait 6 months to begin additional vaccines*

Appendix 10: OHSU Donor and Stem Cell Source Selection in Allogeneic Hematopoietic Progenitor Cell Transplantation

Purpose

To ensure the appropriate cell source selection that will provide the best outcome for the patients undergoing allogeneic hematopoietic cell transplantation (HCT).

Policy

To ensure the appropriate cell source selection for patients undergoing allogeneic hematopoietic cell transplantation by following the requirements of this policy based on national published standards.

Definitions

BMDW: Bone Marrow Donors World Wide (registry)
CBU: Cord blood unit
HLA: Human leukocyte antigens
HPC: Hematopoietic progenitor cell
IRB: Investigational Review Board
NMDP: National Marrow Donor Program

Responsibilities

- *Transplant program physicians are responsible for compliance with this policy when selecting a donor for an allogeneic transplant procedure.*
- *Unrelated donor searchcoordinators are responsible for compliance with this policy when searching for donors for allogeneic transplant procedures.*

Policy Requirements

1. Consideration will be given to the following factors:

    a. Degree of HLA-match
    b. Immediacy of the need for transplant and timeliness of donor procurement
    c. CMV serology, gender, pregnancy history, ABO compatibility, age, and weight of the donor

2. All hematopoietic cell transplant procedures using allogeneic donor sources (related, unrelated, and haploidentical) will be performed under institutionally

approved standard treatment plans or IRB-approved research protocols, follow-
ing NMDP requirements. All treatment protocols must specify type of donor(s),
degree of HLA-matching, and cell sources allowed.

3. Algorithm for donor search and selection:

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                                    ▼
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                    │  Matched Related Donor Identified? │
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            │ Verification Typing│   │  Initial BMDW and NMDP       │
            │ of patient and     │   │  unrelated donor/cord search │
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                        │ Verification Typing │  │ Consider haplodentical│
                        │ of Patientt and     │  │ donor search or cord  │
                        │ Donor               │  │ blood (if not         │
                        └────────────────────┘  │ previously considered)│
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4. Initial patient (recipient) typing

   a. Patients considered for potential allogeneic HCT will undergo high-resolution
      typing for HLA-A, B, C, DRB, DQB1, and DPB1 typing.

5. Family donor search and selection

   a. HLA typing

      i. All full siblings should be typed. The first screening step will be interme-
         diate resolution for HLA-A and B. Donors matching at that level will then
         proceed to high-resolution typing for HLA-A, B, C, DRB, and DQB1.

    ii. If no matched siblings are identified, parents if available and of eligible age may also be typed as described in section 5a to aid with haplotype identification and facilitate alternative donor search if necessary.

   iii. Other relatives will be typed only if deemed necessary by the transplant physician, such as in the case of ethnicities or HLA-types with limited representation in the unrelated donor or cord blood pool.

   iv. In the rare event of an available sibling cord blood unit, typing of the unit will proceed as in section 8bii.

a. Donor selection

   i. HLA-matched (10/10) related donors when available will be the first choice for allogeneic transplantation.

   ii. If more than one matched related donor is identified, donor selection will be on the basis of (in order or preference): Donor age with younger donors preferred CMV status (CMV seronegative donor if recipient is CMV sero-negative) ABO compatibility

Recipient ABO	Donor ABO
O	O
A	A or O
B	B or O

    Gender and pregnancy history (if applicable) for male recipients, avoiding female donors with positive pregnancy history, if possible Medical/Health History of the donors Psychosocial factors: Suitability and willingness to donate based on initial donor assessment and parental opinion (for donors <18 years)

a. Stem cell source

   i. Acceptable graft types in the HLA-matched related setting will be marrow, peripheral blood stem cells or cord blood (when available).

   ii. Donors 18 years and older will be counseled by the transplant physician about donation options, including the method of donation preferred (if applicable).

   iii. For donors <18 years and/or <40 kg, peripheral blood stem cell donation will not be routinely allowed due to the risk associated with the need for central venous catheter placement and blood transfusion exposure expected with an apheresis procedure. Peripheral blood stem collection by apheresis in these young donors will only be considered under special circumstances as approved by the transplant physician or as specified by a research protocol.

   iv. A donor planning to donate peripheral blood stem cells must be deemed suitable for apheresis collection by the transplant physician and a member of the Apheresis Unit staff, in terms of venous access and ability to comply with the collection procedure.

    v. HLA-matched related cord blood units will be deemed acceptable if the cryopreserved total nucleated cell dose is $\geq 3 \times 10^7$ TNC/Kg of recipient's weight for a single cord blood unit transplant.

6. Alternative donor sources

    The search for alternative donors will be performed by the unrelated donor search coordinator in consultation with the transplant attending physician. After a review of the patient's disease, clinical condition and available HLA typing, the transplant physician will make a determination of acceptable alternative donor sources. Alternative donor sources include unrelated donors, unrelated cord blood units, and mismatched related/haploidentical donors.

7. Unrelated donor search and selection

    a. HLA typing

        i. If the patient does not have full siblings, or if the initial family typing does not reveal an HLA-identical or closely matched relative suitable for donation, an unrelated donor search will be initiated.

        ii. Potential donors will be screened and procured from the National Marrow Donor Program and associated donor registries. Final selection of an unrelated donor will be based upon results of high-resolution typing of HLA-A, B, C, DRB1, DQB1, and DPB1 alleles.

    b. Donor selection:

    c. Acceptable levels of HLA match/mismatch include the following:

        i. HLA-matched: 8/8 Allele-match for HLA-A, B, C, DRB1.

        ii. HLA-mismatched: (preferred in the following order)

        Avoid mismatches of allotypes with donor-specific antibodies.
        HLA-C mismatch 03:03 vs. 03:04 is acceptable.
        Minimize mismatches at HLA DRB3/4/5 and DQB1.
        Permissive single antigen disparity at HLA-DPB1.
        Non-permissive single antigen disparity at HLA-DPB1.
        Single allele/antigen disparity for HLA-A, B, C, DRB1.

    d. If applicable, select donor with single antigen mismatched at recipient's homozygous locus

        i. Other levels of mismatch will be restricted to research protocols and/or may be selected by BMT physician as appropriate.

        ii. If more than one matched unrelated donor is identified, donor selection will be on the basis of (in order of priority): Donor age with younger age preferred. CMV status (CMV seronegative donor if recipient is CMV seronegative) ABO compatibility.

Recipient ABO	Donor ABO
O	O
A	A or O
B	B or O

Gender and pregnancy history (if applicable) for male recipients, avoiding female donors with positive pregnancy history if possible Availabilityto donate in the requested timeframe

8. Unrelated cord blood selection

   a. Unrelated cord blood units will be considered for the following patients:

      i. No HLA-matched related donor or an acceptable alternative unrelated donor.

      ii. Timing of the transplant precludes the ability to conduct extensive unrelated volunteer donor searches.

      iii. Designated conditions where cord blood is the preferred stem cell source for transplant (as deemed by the transplant physician).

   b. HLA typing

      i. Potential cord blood units will be screened and procured from the National Cord Blood Inventory and associated cord blood registries. Use of FDA unlicensed cord blood units will adhere to current federal regulatory requirements for procurement.

      ii. The minimum criteria for typing will be intermediate resolution at HLA-A and B and high resolution at DRB1. The preferred level of typing for cord blood units will be high resolution of HLA-A, B, C, DRB1 alleles. Typing of HLA-DQB1 may be ordered upon special request by the transplant physician, or if mandated per IRB-approved research protocol.

   c. Cord blood unit selection: Cord units will be chosen based on their degree of HLA-match and the cryopreserved total nucleated cell dose. Acceptable cord blood units will be as follows:

      i. Matched at least at 4 of 6 loci for HLA-A, B and DRB1 by high resolution. HLA-C antigen/allele level typing, if available, may be used to optimize unit selection.

      ii. Single units must have a minimum cryopreserved (pre-freeze) cell dose of:

      $\geq 2.5 \times 10^7$ TNC/Kg recipient's weight
      $\geq 1.5 \times 10^5$ CD34/Kg recipient's weight

    iii. Selection of two UCB units is required if a single UCB unit will not provide a sufficient total nucleated cell dose. When two units are chosen, the following rules apply based on cryopreserved (pre-freeze) cell dose:

$\geq 1.5 \times 10^7$ TNC/Kg recipient's weight each
$\geq 1.0 \times 10^5$ CD34/Kg recipient's weight each

    iv. Other considerations for cord blood unit selection:

Select unit with the least HLA disparity with the recipient.
For units with equal degree of HLA matching, the unit containing the highest cell dose should be considered.
Units that are red cell depleted are preferred.
Units that are ABO compatible to the donor are preferred.

Recipient ABO	ABO of Units
O	O
A	A or O
B	B or O

Cord blood banks located in the United States or NMDP-affiliated are preferred. Accreditation or licensure should be considered. Units with total frozen volume ≤ 25 mls are preferred. Younger units are preferred. Avoid units for which recipient has donor-specific antibodies. Unit-to-unit HLA-matching is not required unless required per protocol.

9. Haploidentical donors

If the patient does not have HLA-matched related or acceptable unrelated donor/cord blood unit identified, haploidentical related donors will be considered. The decision to use a haploidentical donor will be made by the transplant physician after a careful review of the recipient's disease, need for transplant, and alternative donors available.

   a. HLA typing

    i. Potential haploidentical donors will undergo high-resolution typing for HLA-A, B, C, DRB, DQB1, and DPB1alleles.

   b. Donor selection

    i. Identified potential haploidentical donors will then be tested for the presence of anti-HLA antibodies against the recipient and vice versa. If the initial screen reveals the presence of HLA antibodies, further testing will be ordered to identify their HLA specificity.

    ii. If more than one haploidentical donor is identified, donor selection will be prioritized on the basis of:

T-cell *ex vivo* depleted graft	Non T-cell-depleted grafts
No DSAs (MFI < 1000)	No DSAs (MFI < 1000)
NK cell alloreactive donor (for malignancies)	Younger donor over older donor
Younger donor over older donor	Male donor for a male recipient
Male donor for a male recipient	Sibling or offspring donor over parent donor
First degree relative over second degree	Between parent donors, father is preferred over mother donor
HLA half-matched donor	ABO-matched is preferred to minor ABO mismatch to major ABO-mismatched donor
Between parent donors, mother is preferred over father	First-degree relative over second-degree HLA half-matched donor
ABO-matched donor	
CMV seropositive donor for CMV seropositive recipients	

10. Verification (confirmatory) typing

    a. The purpose of verification HLA typing is to verify the accuracy of previous typing and the identity of patient and donor samples.

    b. All recipients' related donors will have verification typing performed prior to initiation of transplant conditioning.

    c. All unrelated donors/cord blood units will have initial typing from their registry, and repeat confirmatory typing per NMDP guidelines.

    d. Samples will be obtained during pre-transplant and donor workup evaluations.

    e. The verification typing will be performed at one of our contracted immunogenetics laboratories. For unrelated donors, a sample run at other CLIA-certified laboratories may be allowed under special circumstances after discussion with the transplant physician. Cord blood unit verification typing can be performed at an NMDP-contracted laboratory or one of our contracted Immunogenetics laboratories.

11. Detection of recipient/donor allo-antibody:

    a. All recipients/selected donor pairs of matched unrelated donor or mismatched related/unrelated donor transplants will be screened for HLA sensitization by a Flow PRA assay. If anti-HLA antibody is detected, additional testing may be performed to characterize the HLA specificity.

    b. Cross match studies will be performed for the following patients-donor pairs:

        i. All patients with a positive HLA antibody screen

        ii. Recipients of mismatched related donor

        iii. Recipients of matched or mismatched unrelated donor

        iv. Patients undergoing a second allogeneic transplant

    c. HLA antibody testing on a recipient receiving a cord blood transplant, especially if receiving a mismatched cord blood unit may be ordered by the transplant physician on a case-by-case basis.

12. KIR typing
   a. KIR typing of a patient/donor in the setting of hematologic malignancies may be considered as indicated by the BMT physician.
   b. Donors with the most activating KIR genes may be the preferred donor for a patient with hematologic malignancies, if all other factors are equal when comparing donors.

13. Physician review/signature

A transplant physician must review and sign the patient/selected donor initial and verification HLA typing reports, and antibody/cross-match reports prior to the start of the recipient conditioning regimen.

Selected References

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