Advances and Controversies in Hematopoietic Transplantation and Cell Therapy
Series Editors: Syed A. Abutalib · James O. Armitage

Laura Finn
Alva R. Roche Green *Editors*

Supportive Care Strategies

Optimizing Transplant Care

Springer

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1 Introduction to First Edition: Progress in Supportive Care Medicine and Hematopoietic Cell Transplant and Cellular Therapy

Laura Finn and Alva Roche Green

Hematologists are tasked with treating and potentially curing patients with terminal cancers through the constantly evolving field of hematopoietic cell transplant. Transplant has progressed dramatically over the past decade(s) with an enduring increase in the number of hematopoietic cell transplants performed, an increase in patient populations offered transplant, and an expansion of the variety of sources of CD34+ cells donated for transplant. Patient outcomes during and after transplant have improved during this evolution through changes in patient selection and greater improvements in supportive care. Supportive care has improved through understanding and management of complications and side effects, immune suppression, and infection control, though the need for improvement remains in areas of mental health, patient and caregiver quality of life, management of refractory transplant complications, and long-term survivorship concerns. As the process of transplant continues to advance, hematopoietic cell transplant and cellular therapy programs have begun to foster relationships with palliative medicine to strengthen their comprehensive patient care and further improve the hematopoietic cell transplant trajectory. This relationship may seem counter-intuitive, but the affiliation upon appraisal is natural for both services and advantageous to patients and their families.

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Palliative medicine is specialized care of patients living with serious illness including advanced cancer focusing on alleviating the burden of disease, treating refractory symptoms, and improving patient quality of life. It is appropriate for any age and any stage of any serious illness and is ideally provided concurrently with curative and life-prolonging treatments including hematopoietic cell transplant (Center to Advance Palliative Care and National Palliative Care Research Center 2015). Palliative medicine specialists work alongside the patient's multidisciplinary team to provide symptom and communication expertise, emotional support, and assistance with medical decision making. Despite the obvious harmony between the hematopoietic cell transplant population and the goals of palliative medicine, frankly, palliative medicine is at present grossly under-utilized in the field of hematology and transplant.

A variety of barriers may antagonize the relationship between hematology and palliative medicine. There is a reported perception that hematologist/oncologists may be reluctant to access palliative medicine services due to the misconception that palliative medicine is associated with end-of-life care and lack of knowledge regarding the spectrum of palliative care services (Cherny 2009). One simple but effective measure to divest this stigma is simply adding "supportive care" to the name of palliative medicine practices (Roeland and Ku 2015). "Palliative Medicine and Supportive Care" teams have established connections with hematologists and hematopoietic cell transplant services. Another approach is direct education of hematologist and oncologists to improve awareness of the range of potential partnerships with palliative medicine and roles of primary and secondary palliative care providers (Selvaggi et al. 2014).

Hematologists are primary palliative care providers. During the hematopoietic cell transplant trajectory, hematologists provide the primary management of pain and non-pain symptoms, often from the time of cancer diagnosis, through cancer treatments including transplant, to the time of cancer survivorship. This primary palliative care involves the entire transplant team and sub-specialists. Palliative medicine experts deliver specialized secondary palliative care treating refractory symptoms and pain, addressing all forms of patient distress, deliver caregiver and family stewardship, and often provide an opportunity for patients to convey their goals for advance care planning (Hui 2014). Palliative medicine becomes an additional tier to the multidisciplinary transplant care team.

This guide to supportive care during hematopoietic cell transplant is the *first book* to discuss palliative medicine as a coexisting specialty with transplant. There is limited but expanding research on the involvement and delivery of palliative medicine during transplant. This volume explores that research and describes the experience of experts in the fields of palliative medicine and hematopoietic cell transplant and cellular therapy. The goal of this volume is to demystify the field of hematopoietic cell transplant for palliative medicine providers and to outline the opportunities for palliative medicine integration for hematologists.

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Palliative Care for the Hematopoietic Cell Transplant and Cellular Therapy Clinician

2

Winnie Wang, Eric Roeland, Thomas LeBlanc, and Areej El-Jawahri

2.1 Introduction

Palliative care is a multidisciplinary model of medical care that aims to improve quality of life for patients and families facing serious illness. Palliative care focuses on assessing and treating physical, psychosocial, and spiritual suffering. Following the 2010 study by Temel and colleagues that demonstrated its clear benefits for patients with advanced cancer, and other key randomized controlled trials (Temel et al. 2010; Bakitas et al. 2009), the American Society of Clinical Oncology (ASCO) released a provisional clinical opinion in 2012, recommending that palliative care be delivered concurrently with usual oncology care early in the course of illness for all patients with metastatic disease and/or in patients with high symptom burden (Smith et al. 2012). Based on subsequent studies, ASCO issued an updated provisional clinical opinion in 2016, extending the recommendation for early concurrent palliative care for all patients with advanced cancer and their caregivers—with

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advanced cancer more clearly defined as one that is life-limiting or late-stage, with distant metastasis, and/or a prognosis of 6–24 months (Ferrell et al. 2017). Despite evolving clinical guidelines and immense unmet symptomatic burden, patients with hematologic malignancies infrequently receive palliative care services (Manitta et al. 2011; Epstein et al. 2012). Yet, there are many reasons to think these patients stand to benefit. To inform oncologists' clinical practice in this regard, this chapter will review the evidence of unmet palliative care needs in hematology, describe and define the scope of palliative care, discuss the challenges to its integration in hematology, and provide a model for care moving forward.

2.2 Unmet Palliative Care Needs in Patients with Hematologic Malignancies

Hematologic malignancy patients experience a substantial symptom burden that is equal to or possibly greater than non-hematologic malignancies (Manitta et al. 2011; Fadul et al. 2008; LeBlanc et al. 2015a). This symptom burden is attributable to both disease and its treatments; however, little is known about how symptoms differ across disease types or specific treatment regimens (LeBlanc and Abernethy 2013). Frequent physical symptoms include pain, mucositis, dyspnea, depression, fatigue, nausea, constipation, diarrhea, anorexia, and delirium (Epstein et al. 2012; LeBlanc et al. 2015a; Roeland et al. 2010a). In a study of 180 patients with hematologic malignancies, patients reported a mean of 8.8 physical and psychological symptoms (Manitta et al. 2011). Risk factors for a higher number of symptoms included active treatment, poor performance status, hospitalization, and more advanced disease (Manitta et al. 2011).

Patients with hematologic malignancies often undergo hematopoietic cell transplant, a highly intensive and potentially curative therapy. There has been a recent rise in the use of transplant for the treatment of hematologic malignancies due to data demonstrating its efficacy for new disease indications and acceptable safety profile for older patients, particularly with the advent of reduced-intensity conditioning regimens. Hematologic malignancy patients undergoing transplant experience substantial physical symptoms due to chemotherapy-induced toxicities and early post-transplant complications. Studies show that 50–70% of patients who undergo transplant report moderate-to-severe nausea, vomiting, diarrhea, pain, insomnia, and fatigue. These symptoms, along with the physical isolation patients experience during their often-prolonged transplant hospitalization, contribute to a rapid and dramatic deterioration in their quality of life and mood (El-Jawahri et al. 2015a). Notably, 40% of patients report clinically significant depression and anxiety symptoms during their transplant hospitalization (El-Jawahri et al. 2015a).

The psychological impact of having a hematologic cancer is also daunting for patients and their caregivers and can persist for years regardless of the outcome (McGrath 2001, 2002; Nissim et al. 2013; Goetzmann et al. 2008). Psychosocial stressors include the disease itself, as well as related treatments and side effects,

worry about treatment success, financial burden, family-related stress, and difficulty understanding and processing information from clinicians (Heinonen et al. 2005; LeBlanc et al. 2017). Patients struggle with symptoms of depression, anxiety, grief/loss, demoralization, and anger while caregivers can experience decreased quality of life and increased depression (El-Jawahri et al. 2015a; Roeland et al. 2010b; Nipp et al. 2016a).

As increasing numbers of patients survive hematopoietic cell transplant, there is a growing recognition of survivorship needs of these patients and their caregivers (Bevans et al. 2017). Many consider these to be unmet palliative care needs. While the majority of patients return to pre-transplant conditions within the first year, a significant number of patients report residual physical and psychosocial distress after the first year of transplant. Notably, studies show 10–50% of patients have ongoing physical symptoms like pain, fatigue, sleep disturbance, physical debility, and sexual dysfunction, while 5–60% of patients have persistent psychological symptoms including emotional distress, depression, post-traumatic stress, and cognitive dysfunction (Mosher et al. 2009). Financial burden/toxicity is also substantial, impacting up to 73% of patients (Khera et al. 2014). Risk factors predicting residual effects and decrease in quality of life include poor pre-transplant health, history of depression, reduced social support, being female, and active chronic graft-versus-host disease, the latter of which is the strongest predictor of negative long-term outcomes (Syrjala et al. 2004; Fraser et al. 2006; Fiuza-Luces et al. 2016). Chronic graft-versus-host disease, which occurs when donor T lymphocytes attack the host cells of the immunocompromised recipient, is a relatively common complication of long-term transplant survivors, with an incidence of 40–70% (Socie et al. 2003). Graft-versus-host disease is a major and often lethal complication with a host of complex symptoms related to involved organ systems including the skin, liver, lungs, eyes, and gastrointestinal tract (Socie et al. 2003). As such, we contend that patients with chronic graft-versus-host disease have marked unmet palliative care needs.

In addition to the palliative care needs of patients during and after hematopoietic cell transplant, patients with hematologic malignancies have substantial unmet palliative care needs at the end of life. Symptom trajectory at the end of life in this population has been poorly studied. However, data suggest that hematologic malignancy patients may not receive high quality end-of-life care (Hui et al. 2014; El-Jawahri et al. 2015b; Mannis et al. 2016). In the last 30 days of life, these patients are more likely to receive active cancer treatment, to be hospitalized, and to die in the acute care setting (Hui et al. 2014; El-Jawahri et al. 2015b; Howell et al. 2011, 2013, 2017). Transplant clinicians also recognize that end-of-life discussions may be occurring too late, with many clinicians waiting until death is imminent before initiating advance care planning or end-of-life discussions (Odejide et al. 2016a; Wang et al. 2016a). Despite significant unmet palliative care needs, these patients rarely utilize palliative care and hospice services before death, or enroll in hospice too late to obtain meaningful benefit (El-Jawahri et al. 2015b; Howell et al. 2011; Odejide et al. 2016b; LeBlanc et al. 2015b).

2.3 Defining Palliative Care

Many health organizations, including the World Health Organization (WHO), National Comprehensive Cancer Network (NCCN), and Oncology Nursing Society (ONS), have published official definitions of palliative care. We prefer the iteration issued by the Center to Advance Palliative Care, as follows:

> Palliative care is specialized medical care for people with serious illness. This type of care is focused on providing patients with relief from the symptoms, pain, and stress of a serious illness—whatever the diagnosis. The goal is to improve quality of life for both the patient and the family. Palliative care is provided by a team of doctors, nurses, and other specialists who work with patients' other doctors to provide an extra layer of support. Palliative care is appropriate at any age and at any stage in a serious illness, and can be provided together with curative treatment (CAPC 2011).

This definition emphasizes that palliative care is prognosis independent. Although palliative care is frequently misunderstood by patients and blood cancer specialists as equivalent to end-of-life or hospice care (LeBlanc et al. 2015c; Odejide et al. 2014; Hui et al. 2015), palliative care is appropriate at any point, even concurrent with curative-intent treatment (Fig. 2.1) (Ferrell et al. 2017; El-Jawahri et al. 2016a). End-of-life care is just one aspect of palliative care, while hospice is just one type of end-of-life care (Fig. 2.2). The Center to Advance Palliative Care definition also highlights the multidisciplinary collaboration necessary between palliative care specialists and various medical specialties to provide comprehensive palliative care for all patients. Oncology clinicians often provide what is called "primary palliative care," by managing basic symptoms and engaging in discussions about prognosis and advanced care planning (Quill and Abernethy 2013). In cases where patients and families may need additional support in managing complex symptoms and psychosocial burden of illness, "secondary palliative care," also known as "specialist palliative care," offers an additional layer of support and expertise—just as an infectious disease specialist supports the hematopoietic cell transplant team in challenging cases of unusual or refractory infections (Quill and Abernethy 2013). Studies of early palliative care offered concurrently with active cancer therapy support this distinction, demonstrating that palliative care clinicians focus on different issues

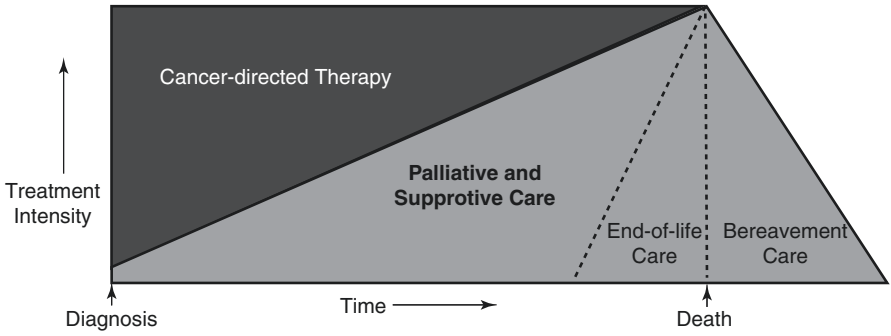

Fig. 2.1 Concurrent palliative care timeline

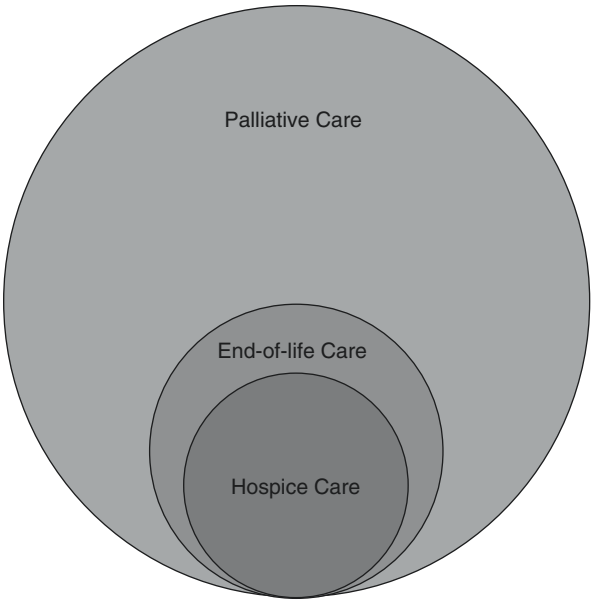

Fig. 2.2 Palliative care-related terms

than oncologists, thereby providing an extra layer of much needed support (Back et al. 2014; Yoong et al. 2013). Patients may focus on their cancer with their oncologist while they discuss their symptoms with palliative care specialists (LeBlanc and El-Jawahri 2015). Integrated palliative and oncology care collectively provides enhanced care and more support to patients and caregivers facing serious illness.

2.4 The Benefits of Palliative Care

The benefit of early palliative care integration is well established in solid tumor patients, as demonstrated in a series of well-designed randomized control trials (Table 2.1). In ENABLE II, the first of these studies, 322 patients with advanced solid tumors were randomized to a palliative care intervention versus usual oncology care (Bakitas et al. 2009). The intervention was a manualized, psychoeducational, telephone-based palliative care–focused intervention delivered by palliative care advanced practice nurse practitioners (with no integration of specialty palliative care clinicians otherwise). Intervention patients reported better quality of life and mood, with a trend toward less symptom burden. In a randomized control study by Temel and colleagues, 150 patients with newly diagnosed metastatic non-small-cell lung cancer were randomized to receive early integrated palliative and oncology care versus usual oncology care alone. The intervention entailed at least monthly outpatient palliative care visits from the time of diagnosis until death (Temel et al. 2010). Palliative care visits were not manualized or scripted, but they followed guidelines published by the National Consensus Project for Quality Palliative Care (Temel et al. 2010). Intervention patients reported better quality of life and mood and better prognostic awareness, and received less aggressive end-of-life care

Table 2.1 Key randomized controlled trials for benefits of early palliative care in solid tumors (LeBlanc and El-Jawahri 2015; Ferrell et al. 2017)

Reference	Setting	Population	Intervention	Control	Duration	Improved QOL/mood	Reduced healthcare utilization	Improved survival	Improved caregiver outcomes
Bakitas et al. (2009) ENABLE II study	Rural New Hampshire and Vermont at cancer centers, VA medical centers, community clinics	Patients with advanced stage solid tumor with prognosis 1 year	*n* = 161 Telephone-based, manualized, nursing-led multicomponent psychoeducational intervention	*n* = 161 Usual care	11/2003–12/2007	Yes	No	No	[a]
Temel et al. (2010)	Academic hospital	Patients with newly diagnosed metastatic lung cancer	*n* = 77 Early integrated PC with monthly outpatient PC clinic visits	*n* = 74 Usual care	6/2006–7/2009	Yes	Yes	Yes	[a]
Zimmermann et al. (2014)	Cluster RCT, Canadian comprehensive care center	Patients with stage III/IV lung, GI, GU, gynecologic cancer with prognosis 6–24 months	*n* = 228 PC consultation and at least monthly follow-up in PC clinic	*n* = 233 Usual care	12/2006–2/2011	Yes	Yes	[a]	[a]
Bakitas et al. (2015) ENABLE III study	Rural New Hampshire and Vermont at cancer centers, VA medical centers, community clinics	Patients with advanced stage solid tumor or hematologic malignancy (*n* = 10, 4.8%) with prognosis 6–24 months	*n* = 104 Early initiation of PC (within 30–60 days of diagnosis) Involving outpatient in-person PC consult, 6 weekly telephone coaching session by advanced practice nurse using manual	*n* = 103 Delayed initiation of PC (3 months of diagnosis)	10/2010–3/2013	No	No	One-year survival: Yes Overall survival: No	[a]

Dionne-Odom et al. (2015) ENABLE III study	Rural New Hampshire and Vermont at cancer centers, VA medical centers, community clinics	Caregivers of patients with new diagnosis, recurrence, or progression of advanced-stage solid tumor or hematologic malignancy (n = 7, 3.4%) with prognosis 6–24 months	n = 61 Early initiation of PC (within 30–60 days of diagnosis) Telephone-based, manualized, nursing-led coaching for caregiver	n = 61 Delayed initiation of PC (3 months of diagnosis)	10/2010–3/2013	[a]	[a]	[a]	Yes
Grudzen et al. (2016)	Urban, academic emergency department at a quaternary care referral center	Patients with advanced stage solid tumor	n = 69 PC consultation by inpatient team; refer to outpatient PC clinic if appropriate	n = 67 Usual care	6/2011–4/2014	Yes	No	No	*
El-Jawahri et al. (2016a, b)	Academic hospital	Caregivers of patients with new diagnosis of incurable lung or non-colorectal GI cancer	n = 137 PC visit for patient within 4 weeks of enrollment and at least monthly until death. Caregivers encouraged, but not required to attend	n = 138 Usual care	5/2011–7/2015	[a]	[a]	[a]	Week 12: Yes (improved caregivers' total distress, depression, but not anxiety or QOL) Week 24: No (no differences in caregivers' outcomes)

(continued)

Table 2.1 (continued)

Reference	Setting	Population	Intervention	Control	Duration	Improved QOL/mood	Reduced healthcare utilization	Improved survival	Improved caregiver outcomes
Temel et al. (2017)	Academic hospital	Patients with newly diagnosed incurable lung or noncolorectal GI cancer	*n* = 175 Early integrated PC with monthly outpatient PC clinic visits	*n* = 175 Usual care	5/2011–7/2015	(varied by cancer type) Lung cancer: Intervention patients with improved QOL and depression at 12 and 24 weeks, usual care patients reported deterioration GI cancer: Both study groups reported improvements in QOL and mood by week 12	[a]	[a]	[a]

QOL quality of life, *PC* palliative care
[a]Not studied

compared to those receiving usual oncology care. Aggressive end–of-life care was defined as receiving chemotherapy within 14 days of death, lack of hospice care, or admission to hospice within 3 days of death. Interestingly, patients randomized to palliative care also had a better overall survival compared to those receiving oncology care without palliative care. These two studies provided the rationale for ASCO's 2012 provisional clinical opinion recommending concurrent palliative care from the time of diagnosis for all patients with metastatic cancer and/or in patients with high symptom burden (Smith et al. 2012).

Subsequent studies have explored the effects of palliative care across different diseases, care settings, and delivery models and investigated the components of palliative care that impact patient outcomes. In a cluster randomized trial of 461 patients with advanced solid tumors and a prognosis of 6–24 months, Zimmerman and colleagues randomized patients to receive early palliative care versus usual oncology care (Zimmermann et al. 2014). Patients in the intervention arm, who received outpatient palliative care consultation and monthly follow-up, reported better quality of life and less symptom burden at 4 months. Although this data is promising, much more work is needed to understand which patients benefit most from concurrent palliative care. For example, a recent randomized control trial of early palliative care in patients with advanced lung or non-colorectal gastrointestinal cancers suggests there may be differential effects of early palliative care in different cancer populations (Temel et al. 2017). Palliative care has also been tested in the emergency department setting (Grudzen et al. 2016). In a randomized control trial by Grudzen and colleagues, 136 patients with advanced cancer presenting to the emergency department at an academic, urban care center were randomized to receive a palliative care consultation versus usual care (Grudzen et al. 2016). Patients in the intervention arm received palliative care consultation with comprehensive evaluation, daily follow-up upon admission, and outpatient follow-up upon discharge, if indicated. These patients reported improvement in their quality of life at 12 weeks, despite this relatively low "dosage" of palliative care intervention. Median survival increased, but this difference was not statistically significant. Rates of healthcare and hospice use were unchanged.

ENABLE III tested the timing of palliative care: 207 advanced cancer patients (including 4.8% patients with advance hematologic malignancies) were randomized to early versus delayed palliative care. While all patients received the ENABLE intervention, which involved one initial in-person palliative care consultation followed by nurse-led telephone coaching, patients were randomly assigned to receive the ENABLE intervention early (within 30–60 days of diagnosis) or delayed (3 months after diagnosis). Those randomized to early palliative care were more likely to live 1 year compared to patients that received delayed palliative care (Bakitas et al. 2015). Although this trial did not demonstrate a benefit in patient-reported outcomes, this study had limited power and half of the patients in the delayed group actually received palliative care consults earlier than what was specified in the protocol. Together these trials provide growing evidence that early palliative care improves quality of life, mood, symptoms, delivery of end-of-life care, and satisfaction with care, with no adverse outcomes reported.

Additionally, recent trials have studied the effects of palliative care on caregivers (i.e., family and close friends), with encouraging findings. As part of the ENABLE III study, caregivers of advanced cancer patients were randomly assigned to a caregiver-directed palliative care-based psychoeducational intervention consisting of early versus delayed telephone-based caregiver intervention. Caregivers who received the early intervention had improved mood and less stress (Dionne-Odom et al. 2015). Moreover, a recent randomized control trials of caregivers of patients with advanced lung and gastrointestinal cancers randomized to early subspecialty palliative care involvement reported improvement in caregiver psychological distress (El-Jawahri et al. 2016b), while a recent cluster-randomized study of caregivers of patients with advanced lung, gastrointestinal, genitourinary, breast, and gynecological cancers randomized to early palliative care reported increased caregiver satisfaction with care (McDonald et al. 2017). In light of these new studies, ASCO issued an updated provisional clinical opinion in 2016, extending the recommendation for early palliative care concurrent with treatment to all patients with advance cancer, and additional consideration for referring caregivers of patients with early or advance cancer to palliative care services (Ferrell et al. 2017).

Despite clear evidence of these benefits among patients with advance solid tumors, patients with hematologic malignancies have largely been excluded from these studies. The ENABLE III study is the only early palliative care trial that included any patients with hematologic malignancies, and there were only 10 such patients randomized, wherein 5 received early palliative care and 5 delayed palliative care (Bakitas et al. 2015). But new data suggest that the integration of palliative care concurrently with usual transplant care for hematologic malignancy patients may indeed improve their outcomes. In a recent single-center randomized control trial by El-Jawahri and colleagues, 160 patients with hematologic malignancies were randomized to early inpatient palliative care integrated with transplant care versus usual transplant care during hospitalization for hematopoietic cell transplant (El-Jawahri et al. 2016a). Recipients of the palliative care intervention were seen by palliative care clinicians at least twice a week during transplant hospitalization; the palliative intervention was focused on symptom management and psychological support. At week 2 of follow-up, intervention recipients reported better quality of life and less depression, anxiety, and symptom burden compared to controls. Three months after hematopoietic cell transplant, intervention recipients continued to report better quality of life, and less depression compared to controls. Additionally, they reported less post-traumatic stress symptoms at 3 months post-transplant, compared to those receiving usual care. Although this study was underpowered to examine caregiver outcomes, the palliative care intervention also led to improvements in caregivers' coping and depression symptoms at 2 weeks, suggesting that modifying patients' experiences during transplant may have positive effects on aspects of caregivers' well-being as well. This is the first randomized control trial to demonstrate feasibility and efficacy of early concurrent palliative care in patients with hematologic malignancies, and the first clinical trial to show benefit of palliative care in the curative setting. A similar multi-site randomized control trial of early concurrent palliative care is underway among patients with high-risk acute myeloid leukemia hospitalized for intensive induction chemotherapy (El-Jawahri 2016).

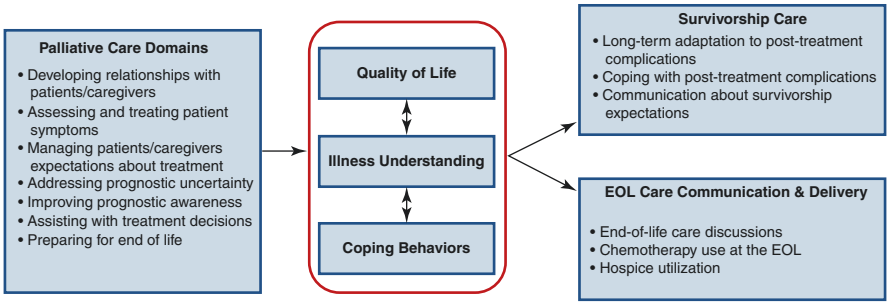

Fig. 2.3 Conceptual model of integrated palliative care's impact on patients with hematologic malignancies and their caregivers

2.5 Conceptual Model of Palliative Care in Hematologic Malignancies

Figure 2.3 depicts our conceptual model for palliative care integration in hematologic malignancies, which is adapted from our conceptual model for the early integration of outpatient palliative care for patients with solid tumors (Irwin et al. 2013). This model depicts the mechanism by which early integration of palliative and oncology care in patients with hematologic malignancies is thought to improve patients' and caregivers' quality of life, illness understanding, and coping behaviors. By enhancing patients' and caregivers' illness understanding and coping behaviors, the integrated palliative care in oncology model has the potential to improve both long-term adaptation to illness and survivorship care and end-of-life communication and delivery. Of note, the potential impact of palliative care integration may extend to all individuals interacting with palliative care and thus may impact outcomes among both patients and caregivers.

2.6 Barriers to Palliative Care Integration in Hematologic Malignancies

Despite the mounting evidence of palliative care's benefits in oncology, there remains a lack of integration of palliative care in neoplastic hematology, primarily due to illness-specific factors that are reinforced by misconceptions about the appropriate timing of palliative care consultation (Manitta et al. 2011; Epstein et al. 2012). Patients with hematologic malignancies have a unique set of care needs. Unlike the solid tumor setting, for example, where palliation is the main goal in advance disease, hematopoietic cell transplant offers the chance of cure for those with hematologic malignancies, even in advance stage of the disease. A short and rapid decline near death and the lack of a clear demarcation between curative and palliative stages of illness make it difficult to identify when a patient is approaching the end of life and when to stop treatment (Odejide et al. 2014; LeBlanc 2014). Prognostication is further confounded by recent studies demonstrating encouraging survival rates in

this patient population even when admitted to the intensive care unit (Azoulay et al. 2013, 2014; Pene et al. 2008). Thus, if hematologist-oncologists misunderstand palliative care as being only end–of-life care (LeBlanc et al. 2015c; Odejide et al. 2014; Hui et al. 2015), patients are then referred to palliative care when they are actively dying, when it is often too late for the patient to fully benefit from palliative care services, rather than facilitating upstream, concurrent palliative care independent of prognosis (LeBlanc 2014).

In addition, many clinicians are not aware of the benefits that palliative care can offer to their patients. In a recent survey of hematologic oncologists, the most commonly reported barrier to high-quality end-of-life care was "unrealistic patient expectations" (Odejide et al. 2016c). Palliative care specialists are trained to facilitate effective advance care planning discussions and prognostic communication, and can help patients gain improved understanding of their illness. However, many hematologists are perhaps unaware of this observation. In the same study, the second highest-ranked perceived barrier to end-of-life care was "clinician concern about taking away hope" (Odejide et al. 2016c). Although oncologists may feel that talking about poor prognosis or end-of-life issues will dash their patients' hopes, patients report desiring detailed, honest disclosure of their prognosis for better understanding and realistic planning (El-Jawahri et al. 2014, 2015c). In fact, studies suggest that early palliative care can facilitate better prognostic understanding without increasing anxiety or depression (Temel et al. 2010).

There are also system-based issues unique to hematologic malignancies that pose barriers for hospice access, further challenging the ability to provide high-quality end-of-life care for this population. Hospice agencies are currently ill-equipped to manage the complex symptom burden of patients with hematologic malignancies, including infections, bleeding, and graft-versus-host disease. For example, patients with hematologic malignancies frequently experience bleeding complications at end of life, sometimes necessitating palliative transfusions (Odejide et al. 2014). Because of the low per-diem reimbursement rate for a patient receiving hospice care, hospice agencies are frequently unable to provide blood transfusions due to their cost. Thus, patients and their clinicians are left to choose between hospice care and hospital care (LeBlanc 2014; Wang et al. 2016a, 2016b). Moving forward, we must develop hospice reimbursement models that account for and address the hematology population's unique needs at end of life. We also must study and more fully understand the unique needs faced by these patients, their caregivers, and their clinicians at end-of-life.

2.7 Strategies to Optimize Integration/Expert Point of View

While the recent trial of early integrated palliative care in hematopoietic cell transplant and cellular therapy offers encouraging evidence of the benefits of palliative care for patients with hematologic malignancies (El-Jawahri et al. 2016a), it also underscores the need for further research. There is a great need for rigorous studies that comprehensively assess the needs of patients with hematologic malignancies,

while fully acknowledging that these needs may differ across cancer type, disease risk, and illness trajectory. There is also a great need for studies of different modalities for providing palliative care to the hematology population. Since recent data suggest that the benefits of palliative care may differ across cancer populations (Temel et al. 2017), future palliative care intervention studies should target the specialized needs of particular populations with an eye toward better understanding of the expected trajectory of their patient-reported outcomes. This includes those with hematologic malignancies, among others.

Amid a workforce shortage in palliative care, future studies must also identify high-risk populations that may benefit from palliative care at particular points in their illness. Additionally, we must develop a more comprehensive understanding of the potential mediators and moderators of the effect of palliative care interventions, to better elucidate the benefits of the integrated care model and guide its implementation across different populations. This will allow for the development and dissemination of personalized integrated palliative care models that are best equipped to address the specialized and evolving needs of patients with hematologic malignancies. Lastly, we must develop and test primary palliative care models that address the unique needs of patients with hematologic malignancies within the cancer care team, separate from specialist involvement. Together, these strategize will help us enhance the quality of life and delivery of care for all patients with hematologic malignancies, and their families.

Promoting palliative care research and educational outreach is critical to overcome misperceptions about palliative care, and allowing for more successful integration with hematologic malignancies. These studies create opportunities for collaboration between palliative care and transplant clinicians, or non-transplant hematologists, thereby building trust while encouraging bidirectional education. While future palliative care research efforts should also focus on improving the delivery of end-of-life care for patients with hematologic malignancies, studies that focus on the potential benefits of palliative care for patients receiving curative therapy can help overcome the substantial misconceptions that exist in hematology, which equate palliative care with end-of-life care (LeBlanc et al. 2015c; Hui et al. 2015).

2.8 Future Directions

Amid growing evidence as to the many benefits of early, concurrent palliative care among patients with serious illness, now is the time to explore the integration of palliative care in hematology. Patients with blood cancers have unique needs, requiring unique approaches and necessitating further research in a few key areas (Temel et al. 2010): clarifying the role of early palliative care in hematology (Bakitas et al. 2009); identification of high-risk patients who would most benefit (Smith et al. 2012); and evaluating the specialized needs of these patients at key points in their illness trajectory. Just as solid tumor patients can have different palliative care needs depending on cancer type, age, and sex (Nipp et al. 2016b; Greer et al. 2016), it is likely that

patients with blood cancers have different needs depending on the type of malignancy, stage of disease, and/or treatment regimen. Ongoing palliative care research combined with continued education on the role of palliative care, and exposure to helpful palliative care specialists, will form a base for collaboration moving forward. Additional efforts are needed to improve available modalities for providing end-of-life care to patients with blood cancers, which will likely require reimbursement and policy solutions. Lastly, further studies are needed to improve understanding of the end-of-life trajectory of hematology patients, to enable us to best optimize end-of-life care outcomes by matching patients with available services. Innovative end-of-life care delivery models are sorely needed to target this patient population, given their unique end-of-life needs, including palliative transfusions, infectious complications, and graft-versus-host disease, which currently preclude most patients with blood cancers from receiving high-quality end-of-life care and access to hospice care services (Hui et al. 2014; El-Jawahri et al. 2015b; Mannis et al. 2016).

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3 Recognition and Management of Transplant-Related Aches and Pain Issues

Mary Callahan, Lucas Puttock, and Sonia Malhotra

3.1 Introduction

Pain is a global epidemic that has brought many organizations to the forefront to develop guidelines to address it including the World Health Organization (WHO), the American Pain Society, the European Association for Palliative Care, and the American Geriatrics Society. Pain is one of the most common and debilitating of symptoms described by patients with cancer. However, undertreatment of pain in patients with advanced illness, including cancer, continues to be an ongoing and highly prevalent problem. The prevalence of poorly controlled cancer-related pain is as high as nearly one third of patients with cancer and nearly half of advanced disease receiving inadequate treatment for their pain (Haumann 2017). Poorly controlled pain has significant consequences that have been associated with diminished quality of life due to functional impairment, anxiety, depression, and insomnia that affect patients and caregivers (Webb and LeBlanc 2018).

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3.2 General Assessment of a Patient with Pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Swarm et al. 2013). The definition highlights the integral connection between each individual's past and current experience in creating the subjective feeling of pain and its widely variable perception. The gold standard for assessing pain is obtaining a detailed, comprehensive history of the experienced pain that includes onset, precipitating or alleviating factors, quality, radiating locations, severity, and timing. Previous pain history and management from each patient are also critical to evaluate. There are various tools to assess pain severity that include the Numeric Pain Rating scale (0 means no pain and 10 means worst possible pain) and the Verbal Rating Scale ("mild," "moderate," or "severe") (Ripamonti et al. 2012; Swarm et al. 2013). More comprehensive assessment tools include the Edmonton Symptom Assessment Scale (ESAS) that is often utilized by palliative care clinicians when seeing patients. Regardless of which tool is utilized, it is crucial to assess pain with the same tool at each visit so the effectiveness of the treatment can be evaluated and whether adjustments can be made.

3.3 Types of Pain

The two main types of pain classified based on underlying pathophysiology are broadly categorized as nociceptive and neuropathic pain. The central nervous system (CNS) and peripheral nervous system (PNS) are involved in the mechanism and pathway of perceived pain. Identifying the type of pain the patient may be experiencing can help in determining the treatment plan. Patients may have multiple etiologies of pain ("mixed pain") where multimodal assessment and treatment approaches are needed.

3.3.1 Nociceptive Pain

Nociceptive pain is caused by the activation of pain receptors (nociceptors) as a result of actual tissue injury, potential tissue injury, or inflammation in response to a mechanical, thermal, or chemical stimulus. Nociceptive pain can be further classified based on the location of the pain receptors as either somatic (nociceptors on skin and deep tissue) or visceral (nociceptors on internal organs). Examples of somatic pain include sunburn, chemical or thermal burns, cuts, skin contusions, arthritis, and tendonitis. Examples of visceral pain include colic, appendicitis, pancreatitis, peptic ulcer disease, and bladder distention.

Nociceptive pain is part of the normal sensory (ascending) pathway that activates in response to noxious stimuli to warn or protect individuals from further tissue

damage. This pathway consists of nociceptors being activated and sending a signal via the peripheral sensory neuron that synapses with the dorsal horn (DH) neuron of the spinal cord activating the N-methyl-D-aspartate (NMDA) receptors. This activation results in the signal propagating from the DH to the brainstem and thalamus and eventually processed by the somatosensory cortex as perceived pain (Yam et al. 2018). However, not all signals are transmitted from the DH. The processing and response to the initial stimulus is heavily modulated by several variables including an inhibitory pathway that prevents the propagation of the signal from the dorsal horn. This inhibitory neuronal pathway originates within the brainstem and synapses with the DH neurons and releases inhibitory substances such as endogenous opioids, serotonin, norepinephrine, and GABA. The NMDA receptors on the DH ascending neuron play a significant role in overcoming the central inhibition. Positive reinforcement and continued activation of the NMDA receptors are critical to overcome central inhibition and transmission of the signal generated by the nociceptors to the somatosensory cortex. If there is a breakdown in this circuit where there is over-sensitization or spontaneous firing of the nociceptors, the patient may experience persistent nociceptive pain. Exogenous opioids are part of the therapeutic arsenal available to address this scenario to inhibit DH nociceptive transmission and adjuvant agents that regulate serotonin, norepinephrine, and GABA may help as well (Yam et al. 2018).

3.4 Pharmacologic Treatment of Pain

Once the type of pain has been clearly elucidated, the next step is determining the best management plan. Often treatment will include both pharmacologic and non-pharmacologic therapies, and multiple options exist and should be used in a multimodal approach. The World Health Organization's cancer pain ladder proposes a stepwise approach to treatment of cancer pain that can serve as a general guideline. This approach suggests starting as follows:

Step 1: For mild pain, non-opioid medications such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs).
Step 2: If pain persists or increases to mild–moderate to include initiation of weak opioids, such as codeine or tramadol.
Step 3: If pain remains poorly controlled or is moderate to severe, an upwards move to strong opioids including morphine, hydromorphone or fentanyl.

The ladder also includes thoughtful use of non-opioid adjuvant medications at each step. Although there is some debate on the utility of this framework, especially in regard to the use of weaker opioids in Step 2 of the ladder, the WHO guidelines have been shown to be useful for cancer pain relief (Carlson 2016; World Health Organization 1996).

3.5 Non-opioid Adjuvant Medications

Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for management of pain ranging from mild to severe. NSAIDs can be particularly helpful when managing inflammatory pain and pain related to bony metastatic disease. It is important to be aware of the adverse effects related to NSAID use including gastrointestinal bleeding, platelet dysfunction, and renal failure, Caution is advised with use of acetaminophen and NSAIDS during the early phase of transplant since they can mask fever. Topical NSAIDs such as diclofenac can useful for localized musculoskeletal pain and have little systemic absorption. Other topical agents include lidocaine and capsaicin cream which have limited data on efficacy and yet can provide some patients with relief. Non-opioid neuropathic adjuvant agents can also play a role in pharmacologic pain management and are discussed below.

3.5.1 Opioids

Opioids are the mainstay of treatment for the management of moderate-to-severe cancer pain. This class of medications includes morphine, oxycodone, hydrocodone, hydromorphone, and fentanyl. Opioids are not equianalgesic to each other but can be converted to equivalent doses (Table 3.1). No opioid has been shown to be superior to another. The medications differ in dose, dosing intervals, and available routes. The oral route is preferred if tolerated. If oral administration is not feasible, intravenous opioids are often used and have the advantage of rapid onset of action, typically 5–15 min after administration and doses can be rapidly titrated. Patient controlled analgesia (PCA) can be used for administering both continuous IV opioids, as well as frequent breakthrough doses, and is often used for management of severe acute pain episodes.

Morphine has highly excreted renal metabolites. Due to this, morphine should be avoided in patients with a creatinine clearance less than 30 mL/min who are not at the end-of-life and have prognoses that are greater than days to weeks.

Tramadol is considered a weak opioid and exerts its mechanism of action by binding to mu opioid receptors and weakly inhibiting norepinephrine and serotonin reuptake. The use of tramadol is often limited by side effects that include dizziness, nausea, vomiting, and constipation. Because tramadol affects serotonin metabolism, it can potentially lead to serotonin toxicity. Caution must be used when prescribing

Table 3.1 Opioid equianalgesia

Medication	Parenteral (mg)	Oral (mg)
Morphine	10	30
Oxycodone	–	20
Hydromorphone	1.5	7.5
Oxymorphone	1	10
Fentanyl	0.1	–

tramadol along with other serotonergic medications because of its ability to lower the seizure threshold. Additionally tramadol often has interactions with various chemotherapeutic agents.

Fentanyl is available as a transdermal patch which allows for extended release of the medication over 48–72 h. It can be useful if oral access is limited by the underlying disease, complications of treatment including nausea, vomiting, or mucositis. Fentanyl patches should only be used for patients with stable opioid requirements and should not be initiated in opioid-naïve patients. Fentanyl is considered to be one of the safest medications to use in patients with renal impairment; however, it is used with caution in liver insufficiency.

Methadone can also be useful in treating cancer-related pain. It binds to various opioid receptors and is also thought to have additional pharmacologic activity via NMDA receptor activity. Methadone has a long half-life that is variable based on individual differences in metabolism, and thus, close monitoring is required. Methadone should only be initiated by providers who have experience using it, only used in patients who are opioid tolerant and should be titrated upwards slowly to account for patient variability in metabolism (Good et al. 2014).

The first step in dosing opioids is to determine if the patient is opioid naïve or opioid tolerant. Opioid-naïve patients are those who have not been exposed to opioid medications. Opioid-tolerant patients have seen a certain amount of opioids continuously in their system leading to a level of tolerance. These patients can often handle larger doses of short-acting opioids and/or long-acting opioids.

Opioid-naïve patients should first be treated with the lowest dose of immediate release medications. Oral short-acting medications are typically dosed every 3–4 h as needed based on pharmacokinetics. The minimum recommended dose should be started and subsequently up-titrated to achieve adequate analgesia without unacceptable side effects. Once pain has stabilized at an acceptable level and a tolerable dose of medication is being given, the total daily dose in oral morphine equivalents (OME) can be calculated and used to guide dosing of long-acting opioids to provide around-the-clock relief (Table 3.2). The effective short-acting opioid dose is continued and can be used for breakthrough pain. Frequent re-evaluation of pain control is needed and opioid requirements should be checked to ensure appropriate dosing regimens (Fallon et al. 2018). State laws vary in requirements for opioid prescriptions and should be referenced to ensure delays do not occur with patients receiving their medications.

Table 3.2 Calculation of opioid doses

Pain level	Medication
Opioid naïve: Mild-to-moderate pain	Short-acting oral q3–4 h prn Example: MSIR 7.5 mg or oxycodone 5 mg
Opioid naïve or tolerant: Severe pain	Short-acting oral opioid q3–4 h prn + Long-acting opioid q8–12 h/long-acting opioid q72 h →Must calculate OME →1/2–2/3 of total OME should be in the long-acting opioid

3.6 Side Effects of Opioids

Many patients develop adverse effects from opioid use. Monitoring side effects is an important part of managing pain with opioids. Common side effects include constipation, nausea, vomiting, pruritis, urinary retention, and central nervous system toxicities such as sedation, confusion, agitation, myoclonic jerking, and opioid-induced hyperalgesia. Often clinicians are worried about respiratory depression which occurs when inappropriate doses of opioids are administered.

The most common side effect of opioid therapy is constipation. A bowel regimen should be routinely prescribed to patients taking opioids for prophylaxis and treatment of opioid-induced constipation. Commonly used classes of medications include stimulant and osmotic laxatives. Fiber bulking agents should be avoided as they can worsen constipation if there is not enough fluid to move stool along. Newer evidence suggests that opioid antagonists such as naloxone and methylnatrexone can be useful for the treatment of opioid-induced constipation and are often used for constipation that is refractory to traditional laxatives (Candy et al. 2011).

Nausea and vomiting are rare side effects that occur with initiation and often self-resolve. Pruritis also often occurs with opioid initiation and self-resolves. Low-dose naloxone or opioid rotation may be considered to alleviate opioid induced nausea, vomiting, or pruritus (Monitto et al. 2011). Sedation, confusion, and agitation often can occur with the initiation and increase of opioids. If these side effects persist, opioid doses should be checked and renal and hepatic function should be checked. Myoclonus and urinary retention are rare side effects that often occur with rapidly increasing doses of opioids and prolonged duration of use.

Opioid rotation is the process of switching between opioids when a given opioid agent fails to provide adequate pain relief or leads to intolerable side effects. When switching between medications or routes of administration, it is crucial to consult an equivalency table to ensure safe opioid conversion. The concept of cross-tolerance must be considered in opioid rotation. Cross-tolerance takes into account that tolerance developed to one opioid does not imply complete tolerance to another. In this process, the dose of the new opioid should be reduced by 25–50% (Indelicato and Portenoy 2002).

3.7 Neuropathic Pain

Neuropathic Pain is often thought of as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Neuropathic pain results from the damage to or disruption of the neurons within the signaling pathway in the peripheral, central, and autonomic nervous systems. Repetitive stimulation from a prolonged painful condition or state due to disruption or damage of the neurons can sensitize neurons in the dorsal horn of the spinal cord so that a lesser peripheral stimulus can invoke pain, often termed “allodynia.” Allodynia is commonly associated with neuropathic pain (Yam et al. 2018). Common causes of neuropathic pain include trauma, inflammation, metabolic disorders, infections, tumors, toxins,

primary neurological disorders, and some medications including certain chemotherapy agents such as Vincristine (Gewandter et al. 2017). Neuropathic pain can be persistent or episodic and can be perceived in many ways such as numbness and tingling, burning, pins-and-needles, and shooting pain.

3.8 Neuropathic Agents

If the characterization of pain suggests a neuropathic component, different classes of pharmacologic agents can be used. While neuropathic pain can be challenging to treat, there is evidence for the use of several medication options. The first-line agents for the treatment of neuropathic pain include serotonin-norephinephrine reuptake inhibitors such as duloxetine and venlafaxine, anticholinergics such as tricyclic antidepressants, and calcium channel mediators such as gabapentin or pregabalin. Second-line therapy includes topical medications such as capsaicin and lidocaine patches. There is limited evidence to suggest that opioids are effective for treating neuropathic pain. Due to the side effect profile and safety concern of opioids, they are generally considered third-line treatment (Finnerup et al. 2015). Opioids can be considered first-line in some instances, such as acute neuropathic pain and intractable pain.

It is generally recommended to start with monotherapy and give adequate time for patients to experience full medication effect, often 1–2 weeks at the maximum tolerated dose. If pain remains poorly controlled, it is important to consider combination therapy with another neuropathic agent with a different mechanism of action. The additive and synergistic effects of combined neuropathic pain medications can lead to improved pain control (Freynhagen and Bennett 2009).

3.9 Non-pharmacological Treatments

Physical pain often has variable perceptions and response to treatment due to other factors including psychosocial and spiritual aspects. Although pharmacologic treatments are the primary modalities utilized for treatment, particularly in cancer patients, optimal individualized treatment often includes nondrug therapies that are categorized as physical, psychosocial-spiritual, interventional, complementary, and integrative approaches. Physical measures like acupuncture and mindfulness have been gaining more widespread acceptance recently.

Acupuncture is an essential component of traditional Chinese medicine that consists of inserting small needles into selected points at a specified depth with manipulation that may include physical forces, heat or electrical stimuli to promote balance in the body's energy. There is an increasing level of evidence that acupuncture is effective for the treatment of many conditions including nausea and vomiting, especially post-chemotherapy (Ezzo et al. 2005), and perioperative and postoperative pain (Poulain et al. 1997; Kotani et al. 2001) with potential in chronic cancer-related pain. A Cochrane review in 2015 found acupuncture benefit for cancer pain to be

inconclusive due to small sample sizes and variable methodologies (Paley et al. 2015). A short course of acupuncture may be beneficial for patients with intractable pain that are experiencing challenges with pharmacotherapy.

Transcutaneous electrical stimulation (TENS) is an inexpensive nonpharmacological intervention that activates a complex neuronal network via a cutaneous electrode that sends an electrical current to the perceived painful region to help reduce pain. The evidence for TENS efficacy is conflicting and lacks guidelines on dosing. A recent Cochrane review completed in 2012 reviewing cancer pain was inconclusive due to the limited number of randomized control trials (Hurlow et al. 2012). There is emerging evidence that suggests TENS may be of some benefit to patients with fibromyalgia, complex regional syndrome, diabetic neuropathy, osteoarthritis, and postoperative pain (Vance et al. 2014).

Yoga is a mind–body intervention that comprises a wide range of techniques aimed to harmonize the body and the mind. Yoga has many known benefits and has been studied in a variety of scenarios with benefits that include improvement of pain in cancer patients as well in chemotherapy-induced nausea and vomiting (Agarwal and Maroko-Afek 2018; Cramer et al. 2017; Raghavendra et al. 2007). A plethora of noted benefits include improved mood states related to reduction in stress hormones, improved parasympathetic function, improved perceived control over situations, and improvement in quality of life (Vadiraja et al. 2009; Carlson et al. 2004). Of note, no studies have addressed side effects with regard to yoga, but consideration must be made for patients with long bone metastasis and pulmonary involvement or complications due to breathing techniques utilized with yoga. Much of these studies for cancer patients have been completed in patients with breast cancer, and further studies are needed to evaluate the effects of yoga and mindfulness interventions on other malignancies such as those patients with solid, blood, lung, and head and neck cancers (Rao et al. 2017).

Integrating pharmacological and non-pharmacological approaches individualized to the experience of pain ultimately helps improve overall comfort and quality of life. There are numerous non-pharmacological options that the National Comprehensive Cancer Network (NCCN) lists as interventions that can be offered to patients. The above discussion only encompasses a small sample of what is available.

3.10 Careful Considerations in Transplant Recipients

Treating pain in patients who underwent hematopoietic cell transplantation (HCT) requires thoughtful management and consideration of unique factors. One such important consideration is the availability of routes of administration. HCT can be complicated by oral mucositis or delirium that can limit the ability of medications to be administered orally. Additionally, rectal administration is often avoided in neutropenia due to the risk of bacterial translocation. Severe diarrhea secondary to graft-versus-host disease (GVHD) or enteritis may also lead to decreased drug absorption (Ma et al. 2018).

It is important to consider medication contraindications that may pertain to HCT patients. For example, NSAIDs may be contraindicated in patients as a result of renal impairment or thrombocytopenia. Caution is advised with use of acetaminophen and NSAIDS during the early phase of transplant. As always, it is important to consider drug–drug interactions before starting new medications, and HCT patients often are on multiple immunosuppressant and anti-infective agents which may interact with medications used to treat pain. Notable in the opioid and non-opioid classes that interact with immunosuppressant and anti-infective agents is Methadone and TCAs, respectively.

Given the potential for high symptom burden, utilization of early palliative care to assist with pain and symptom management can be helpful for HCT patients.

3.11 Expert Recommendations

Pain is a common symptom that many cancer patients experience at some point during their treatment course either as a result of the underlying cancer or treatments related to it. Recommendations for pain control are based on evidence-based guidelines, consensus, and expert opinion. Clinicians should identify tools to assess pain and have approaches to its management. Additionally, dosing and side effects of various pharmacologic therapies should be well understood. Multimodal approaches to different types of pain should be considered and should include pharmacologic and non-pharmacologic therapies.

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Transplant-Related Non-pain Issues: Prevention, Intervention, and Limitations

4

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4.1 Introduction

Hematopoietic stem cell transplant (HCT) involves the use of high-dose chemotherapy, radiation, and immunosuppressive medications which affect every organ system. Diligent monitoring and multidisciplinary supportive care during and after HCT are important for successful outcomes. Prolonged immunocompromised status and donor–host immune interactions can give rise to complications that significantly affect patient quality of life. This chapter covers the diagnosis and management of different non-pain ailments associated with hematopoietic stem cell transplant focusing on gastrointestinal complications, anorexia, fatigue, and delirium. Here we provide a comprehensive review of management strategies for providers taking care of transplant patients in hospital and clinic settings. Transplant-related complications can start immediately after conditioning therapy utilizing high doses of chemotherapy and radiation treatments. The post-transplant recovery period varies widely among patients and can span from months to years. Nausea, vomiting, and mucositis are early complications which can lead to anorexia and malnutrition if left

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untreated. Diarrhea can be a side effect of chemotherapy-related mucosal injury, medications, infection, or graft-versus-host disease (GVHD). Polypharmacy, infection, and electrolyte disturbances may cause confusion and delirium in the post-transplant period which can be a source of significant distress for patients and caregivers. Generalized deconditioning and disability from transplant can impair patient and caregiver quality of life. These complications are also the main elements of increasing resource utilization and health care costs related to HCT (Khera et al. 2012). Supportive care during transplant may involve palliative care specialists and multiple medical specialties including nurses, nutrition services, physical therapists, and social workers. Supportive care should continuously overlap with the overall transplant course and should adjust accordingly to interim complications such as infections, disease relapse, or graft-versus-host disease. Our discussion below describes different transplant related non-pain symptoms, risk factors, diagnosis, treatments, and prevention strategies.

4.2 Fatigue

Cancer-related fatigue is one of the most common symptoms of cancer, cancer treatment, and HCT. Cancer fatigue may be defined as the persistent subjective perception of unusual tiredness that varies in pattern and severity and impairs ability to function in patients with cancer and cancer survivors (Mock et al. 2007). Cancer fatigue is multidimensional with both physical components of weakness and cognitive elements of tiredness. This symptom may be constant or have a waxing/waning pattern marked by flares of fatigue (Radbruch et al. 2008). In the setting of HCT, the white blood cell count nadir has been associated with a peak in cancer-related fatigue (Anderson et al. 2007). Even for cancer and transplant survivors, fatigue can chronically impact their quality of life (Shi et al. 2011; Bower et al. 2014). Fatigue rarely presents as an isolated symptom and often accompanies other severe symptoms such a pain, depression, poor nutrition, or sleep disturbances (Chang et al. 2000). Fatigue may be compounded by co-existing comorbidities such as pulmonary or cardiac disease, diabetes, thyroid dysfunction, etc.

4.2.1 Measuring Cancer-Related Fatigue

Fatigue is a patient-reported outcome which is difficult to measure objectively; therefore a variety of patient reported measurement tools exist to quantify fatigue. One example is the Brief Fatigue Inventory created for the rapid assessment of fatigue and validated in multiple cultures and patient populations. This is a simple-language 9-item fatigue scale that helps differentiate non-severe fatigue from severe fatigue (Mendoza et al. 1999). It is also interchangeable with the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) (Dittner et al. 2004). Another well-known, validated, and easy to administer assessment is the Fatigue Severity Scale (Dittner et al. 2004; Stone et al. 2000). The Fatigue Severity Scale is a 10-item

survey also written in easy language and measures the impact of fatigue on motivation and daily activities (Stone et al. 2000). The use of a subjective fatigue measurement system is important for clinical practice as treatment guidelines direct interventions by the severity of the symptom on a scale of mild, moderate, or severe (Berger et al. 2015).

4.2.2 Causes of Fatigue and Interventions

Fatigue may be considered primary, directly related to the patient's underlying cancer, or it may be secondary, related to a non-disease factor and more easily reversible (Dittner et al. 2004). Identifying the type of fatigue helps guide treatment which is important to improve patient quality of life and because increasing fatigue is associated with decreased survival in cancer patients (Hwang et al. 2002). Examples of secondary causes of fatigue are found in Table 4.1. When a secondary cause of fatigue cannot be identified or once the secondary cause has been treated but severe fatigue persists, additional therapy should be considered. Standard therapy for

Table 4.1 Secondary causes of fatigue, assessment, and treatment

Secondary cause	Assessment	Treatment
Anemia	CBC with differential Ferritin, vitamin B12, folate Erythropoietin	Transfusion Iron, vitamin B12, folate levels Erythropoietic agents
Poor nutrition	Diet assessment Pre-albumin/albumin Electrolyte evaluation	Nutrition consultation Nutritional supplements Replace electrolytes
Dehydration	Blood pressure/orthostatic Renal function Serum sodium	Oral and intravenous hydration
Sleep disturbances	Contributing symptom Sleep hygiene assessment Sleep study if needed	Treat underlying cause Sleep hygiene counseling CPAP Hypnotic/sleeping medication(s)
Depression	Psychiatry/psychology evaluation	Counseling Anti-depressants Cognitive behavioral therapy Psychoeducational therapy
Infection	Blood and urine cultures Appropriate imaging	ID consultation Antibiotic therapy
Pain medications/ polypharmacy	Medication evaluation for side effects, interactions, recent changes, and doses	Discontinue offending agents Dose-reduce offending agents

Table 4.2 Treatment of primary fatigue therapy

Non-pharmacologic interventions		
Physical activity (Bower et al. 2014; Schmitz et al. 2005; Wiskemann et al. 2011)	Initiate/maintain 150 min of moderate aerobic exercise weekly (walking, cycling)	
	Initiate/maintain 2 strength training sessions weekly (light weight lifting)	
	Patients with severe fatigue should be referred to a physical therapist or rehabilitation medicine	
Mindfulness activities (Bower et al. 2014)	Yoga	
	Massage therapy	
	Acupuncture	
Pharmacologic interventions		
Treatment	**Dosing**	**Comments**
Methylphenidate (Minton et al. 2011; Breitbart and Alici 2010)	Initiate at low dose 2.5–5 mg and titrate to 10–20 mg daily as needed	Usually well tolerated
		Side effect of insomnia and nervousness may be dose limiting factors
		Avoid inpatients with the history of arrhythmias
Modafinil (Blackhall et al. 2009)	Initiate at 100 mg daily and titrate to 200 mg daily as needed	It improves daytime fatigue
		Administer in the morning
		Do not exceed 100 mg in liver failure Assess liver function
Corticosteroids (Yennurajalingam et al. 2013)	Dexamethasone 4 mg twice daily for 14 days	Only consider for short-term use
		Administer doses morning and early afternoon to decrease insomnia
Ginseng (Yennurajalingam et al. 2015)	Panax Ginseng (Asian ginseng) 800 mg daily	Minimal adverse side effects
		Patients also report improved pain, appetite, and quality-of-life

primary cancer–related fatigue or refractory fatigue has not been established but includes both pharmacologic and non-pharmacologic interventions as seen in Table 4.2 (Bower et al. 2014; Minton et al. 2011).

4.3 Delirium

Delirium is an acquired acute change in mental status that has an underlying physiologic cause and is prevalent in hospitalized patients with serious illness (American Psychiatric Association 1999). In the setting of a serious illness such

as hematologic malignancy requiring transplant, the cause of delirium can usually be identified and potentially reversed. Identifying and reversing delirium is extremely important as studies have shown that the onset of delirium at any point after transplant is highly predictive of increased mortality (Beglinger et al. 2006). Delirium during transplant can also result in prolonged neurocognitive impairment (Fann et al. 2007). Common causes of delirium include fluid and electrolyte imbalances, medication toxicity or interactions, infections, hypoxia, renal or liver failure, arrhythmias, and anemia (Gaudreau et al. 2005; Gaudreau et al. 2007). Delirium is diagnosed by the review of clinical history, complete mental and physical examination, careful review of medications, observation of a patient's behavior, and diagnostic evaluation for a reversible etiology including a complete blood panel, comprehensive metabolic panel, and evaluation for infection (Weckmann et al. 2012; Fann et al. 2011). Delirium may be described as hyperactive involving agitation and hypervigilance or as hypoactive characterized by somnolence. Behavioral symptoms associated with delirium include rapid onset of altered mental status, disorientation, altered levels of consciousness, unintentional cognitive or motor activity, hallucinations, and/or fluctuations in symptoms (American Psychiatric Association 1999). The history provided by a delirious patient is not reliable; and support staff, family, and caregivers become a vital resource in establishing the diagnostic criteria of delirium (see Table 4.3). It is important to differentiate the signs and symptoms of delirium from an alternative diagnosis such as depression, dementia, or psychiatric disorders; and mental health professionals should be consulted in complex situations to minimize patient and caregiver distress.

4.3.1 Intervention: Non-Pharmacologic

Non-pharmacologic intervention is the preferred first-line therapy for all patients with delirium and may begin with treatment or reversal of any metabolic disturbances, electrolyte abnormalities, and anemia. The patient environment should be modified to promote comfort and safety including limiting fall risks, adjusting sources of noise (television, music, medical device monitors, IV infusion pumps), and dimming bright lights to avoid over-stimulation and to avoid day/night confusion and sleep disturbances. If patients have visual or auditory disabilities, their eyeglasses, hearing aids, and any other assistive devices should be available to optimize sensory input. Medical personnel interacting with the patient should be limited

Table 4.3 Diagnostic criteria of delirium (American Psychiatric Association and American Psychiatric Association 2013)

Attention	Reduced ability to direct, sustain, or shift mental focus
Cognition	New memory deficit, perceptual and/or language disturbance
Onset	Symptom development over hours to days with fluctuations throughout the day
Etiology	Physiologic consequence of a medical condition, intoxication, or medication

to avoid confusion and should introduce themselves and describe their role at every patient encounter (Cole et al. 2002; Pitkala et al. 2008). Patients with delirium should not be left unattended; and as such family members, caregivers, and sitters should be recruited as attendants to help monitor and reorient the patient as needed. Nutrition and hydration status should be monitored closely along with bowel and bladder activity (Dalal and Bruera 2004). Temporary physical restraints should only be a last resort to maintain patient safety after less restrictive measures have been exhausted (Inouye et al. 2007). Family and caregivers will need orientation, education, and counseling to cope with the distress of caring for a loved one with delirium (Gagnon et al. 2002).

4.3.2 Intervention: Pharmacologic

The first pharmacologic intervention for delirium should be a thorough medication review to identify any drug toxicity, drug interactions, or withdrawal syndromes. Pharmacy consultation may be needed for assistance with complex polypharmacy and prolonged hospital courses. Opioid agents may need to be substituted, dose-reduced, or discontinued. Benzodiazepines, steroids, anticholinergic agents, antisecretory drugs, and anti-epileptics may need to be weaned or stopped. Medication administration records should be reviewed for any benzodiazepines, antidepressants, or steroids that were stopped abruptly. Medications may also need to be dose adjusted for liver or renal dysfunction.

There are currently few published randomized control trials to guide recommendations for the pharmacologic treatment of delirium; therefore, there are no Federal Drug Administration (FDA)–approved medications available for delirium. The American Psychiatric Association recommends against the first-line use of benzodiazepines in the treatment of delirium as they can worsen symptoms or result in withdrawal symptoms (American Psychiatric Association 1999; CADTH Rapid Response Reports 2016). Opioids have no role in the treatment of delirium (American Psychiatric Association 1999). Guidelines recommend the use of first-generation antipsychotics as the treatment of choice for delirium; and haloperidol is usually the preferred agent as it is available in oral and intravenous forms, has few anticholinergic side effects, and has a low risk of hypotension though high doses may be required to treat delirium (American Psychiatric Association and American Psychiatric Association 2013; Sipahimalani and Masand 1998; Agar et al. 2017). Pharmacologic treatment of delirium is further outlined in Table 4.4. It is important to note that the FDA has issued a black box waning about the increased risk of death with the use of first- and second-generation antipsychotics in elderly patients with dementia which does not directly address the short-term use of pharmacologic therapy in delirium. Pharmacologic therapy for delirium should be reserved for management of severe symptoms (Campbell et al. 2009).

Table 4.4 Pharmacologic agents for delirium treatment (Campbell et al. 2009)

Medication	Dosing	Comments
Haloperidol	1–2 mg orally/IV/SC daily or twice daily	Preferred agent for first-line treatment of delirium
	Maximum dose is 100 mg/day	
Chlorpromazine	25–50 mg orally/IV/SC/PR daily or twice daily	Can cause hypotension Avoid per rectum administration in immunosuppressed transplant recipients
	Maximum dose is 2000 mg/day	
Risperidone	0.25–0.5 mg orally daily or twice daily	Not superior to first-line haloperidol
	Maximum dose is 6 mg/day	
Olanzapine	2.5–5 mg orally/SC daily or twice daily	Not superior to first line haloperidol
	Maximum dose is 30 mg/day	
Quetiapine	25–50 mg orally daily to three times daily	Not superior to first-line haloperidol
	Maximum dose is 1200 mg/day	
Methyphenidate	2.5–5 mg orally twice daily	Consider for hypoactive delirium Avoid in tachycardia or arrhythmias
	Maximum dose is 60 mg/day	

SC subcutaneous, IV intravenous, PR per rectal

4.4 Malnutrition/Anorexia

Cancer malnutrition and cachexia are different than simple malnutrition. The presence of a negative caloric and energy balance combined with skeletal muscle loss marks the presence of cancer malnutrition. The reduced caloric intake and metabolic derangements are in part aggravated by systemic illness, inflammation, and catabolic demand (Arends et al. 2017). Malnutrition and poor appetite often precede stem cell transplant with onset at the time of the underlying hematologic cancer diagnosis. A study by the University of Washington identified poor caloric intake in patients at the time of admission for allogeneic stem cell transplant, a baseline median intake of 56% of basal caloric requirements quickly declined to a median of 3% after the first dose of transplant conditioning chemotherapy. At the end of the month-long study period, median basal caloric intake was still only 25% (Malone et al. 2007). It is has been found that 50% of patients have nutritional deficits even at 1 year after transplant (Iestra et al. 2002). Cancer malnutrition during the acute transplant phase (induction chemotherapy to engraftment) is due to primary anorexia compounded by clinical symptoms of secondary anorexia including mucositis, nausea, dysgeusia, diarrhea, and constipation that further decrease calorie intake

(Arends et al. 2017). Patients with a body mass index (BMI) less than 28 and loss of 15% or more of their baseline weight have lost significant muscle mass which greatly increases their mortality (Aoyama et al. 2017). Patients with mild caloric deficits also have a poorer prognosis as studies have demonstrated weight loss during transplant even with normal or increased caloric intake (Arends et al. 2017; Aoyama et al. 2017; August and Huhmann 2009).

4.4.1 Management of Cancer Malnutrition

Because of the complex nature of cancer malnutrition, nutritional supplementation only provides partial clinical improvement, though it does have a role in the hematopoietic stem cell transplant population (Jatoi Jr. and Loprinzi 2001). Due to the combination of anorexia and altered metabolism including altered protein turnover, insulin resistance, and impaired glucose tolerance, treatment of malnutrition requires a collective approach of nutrition therapy, medical management, and physical therapy (Arends et al. 2017). Aerobic exercise and muscle training has been shown to expedite recovery during the acute phase of transplant and is recommended before, during, and after transplant and should be continued even after hospital discharge with moderate activity for 10–60 min at least three times weekly (Arends et al. 2017; Knols et al. 2011). Oral supplements are effective at improving nutrition and patient quality of life (Baldwin et al. 2012). Tolerance for supplements should be monitored as taste changes during cancer therapy (IJapma et al. 2016). Both the American and European Societies for Parenteral and Enteral Nutrition guidelines recommend nutritional support therapy for transplant patients who are malnourished with anticipated inability to ingest or absorb oral intake for a prolonged period of time, defined as 7–14 days (Arends et al. 2017; August and Huhmann 2009). Nutritional support therapy is defined as bypassing oral intake to treat cancer-related anorexia. This may include the use of parenteral nutrition which may help weight gain, increase body fat, and improve nitrogen balance with minimal effect on lean body mass or enteral nutrition that may improve weight gain and nitrogen balance with minimal effect on body fat (August and Huhmann 2009). Guidelines prefer the use of enteral nutrition and studies suggest faster engraftment, decreased transfusion requirements, and less clinical complications using enteral nutrition; but common transplant complications of neutropenia, mucositis, malabsorption, nausea, diarrhea, and graft versus host disease often contraindicate its use (Arends et al. 2017; August and Huhmann 2009; Seguy et al. 2012). Studies suggest increased morbidity with total parenteral nutrition (TPN), and patients recover oral intake sooner with intravenous fluid support alone (Charuhas et al. 1997). When TPN is provided, it should be discontinued as soon as oral intake is adequate.

If cancer malnutrition persists despite treatment of secondary anorexia, nutrition counseling, oral supplementation, and a trial of enteral and/or parenteral nutrition a trial medical therapy for anorexia should be considered. Table 4.5 outlines the potential evaluation and treatment of secondary anorexia. Agents with evidence of efficacy include progesterone agents such as megestrol 160–1600 mg daily, which

Table 4.5 Treatment of secondary anorexia

Secondary cause	Treatment	Comments
Mucositis	Topical mouth rinses, opioids, palifermin	Side effects of palifermin may cause/worsen anorexia
Nausea/vomiting	Antiemetics	Mirtazapine and olanzapine may help treat both nausea and depression
Constipation	Laxatives	Appropriate hydration is required if bulk-forming fiber agents are provided; avoid suppositories and enemas during neutropenia
Diarrhea	Check and treat for clostridium difficile, anti-diarrheal medications	Consider treating for constipation for leakage diarrhea
Dry mouth	Artificial saliva	Maintain hydration; maintain oral hygiene to avoid cavities; monitor use of diuretics
Pain	Opioids, anti-inflammatory agents, supportive care consultation, pain management consultation	Opioids may cause nausea or constipation
Depression	Psychology/psychiatry consultation, antidepressants	Selective serotonin reuptake inhibitors (SSRI) may decrease appetite; avoid bupropion

may improve body weight by gain of fat rather than lean body weight and possibly improve fatigue and nausea, improving overall quality of life (Lesniak et al. 2008; Berenstein and Ortiz 2005; Pascual Lopez et al. 2004). The potential benefit of megestrol needs to be weighed against the risk of fluid retention, hypertension, hyperglycemia, and thromboembolism. Melatonin 20 mg daily has shown some value in preventing weight loss during cancer therapy with few side effects (Lissoni 2002). There is mixed evidence for fish oil 1.5–2.2 mg daily supporting skeletal muscle mass (Murphy et al. 2011; Ries et al. 2012). Current American and European nutritional guidelines for cancer patients do not recommend cannabinoids to treat anorexia in cancer patients due lack of research and evidence at this time (Arends et al. 2017; August and Huhmann 2009). Treatment approach for primary anorexia is outlined in Table 4.6.

4.5 Mucositis

Mucositis includes any mucosal damage secondary to cancer therapy (chemotherapy or radiation) primarily involving oral cavity, pharyngeal, and laryngeal regions; however it can involve any part of the gastrointestinal tract. Oral Mucositis is a common early complication in patients undergoing transplant. The degree of severity varies based on conditioning regimen and patient characteristics. The use of myeloablative conditioning therapy using total body irradiation (TBI), methotrexate for graft-versus-host disease prophylaxis, and poor performance status are associated with increased risk for oral mucositis. In one study, BMI $\geq$ 25 and presence of

Table 4.6 Approach and treatment of primary anorexia

Treatment	Comments	
Nutrition consultation	Thorough evaluation should include measurements of weight, body mass index, and muscle mass. Recommendations should include expected total energy expenditure and daily calorie and protein intake	
Oral supplements	Increases nutritional intake and improves quality of life. Be aware of taste changes during therapy that may require altering oral supplements	
Physical therapy	10–60 min of moderate aerobic exercise three times weekly recommended. Daily activity improves outcomes during inpatient transplant setting (Arends et al. 2017; Knols et al. 2011)	
Artificial nutrition	Enteral nutrition is preferred. Parenteral nutrition should be discontinued as soon as possible (Arends et al. 2017; August and Huhmann 2009)	
Drug therapy		
Drug	**Dosing**	**Comments**
Megestrol	160–1600 mg daily	Side effects of fluid retention, hypertension, hyperglycemia, and thromboembolism
Melatonin	20 mg daily	Few side effects
Fish oil	1.5–2.2 mg daily	May improve skeletal muscles. Taste may be barrier to therapy

methylenetetrahydrofolate reductase 677TT genotype were associated with increased oral mucositis risk in the patients undergoing allogeneic transplant with myeloablative conditioning therapy for chronic myelogenous leukemia (CML) (Wardley et al. 2000; Robien et al. 2004; Fanning et al. 2006; Blijlevens et al. 2008). Mucositis can cause pain, discomfort with swallowing and speech, localized bleeding, impaired nutrition, and increased infection risk. Severe mucositis can even adversely affect overall prognosis of the patients undergoing HCT (Fanning et al. 2006).

The exact pathogenesis behind mucositis is complex, but direct cellular damage from chemotherapy or radiation therapy is often the inciting event. Release of pro-inflammatory cytokines, reactive oxygen species, secondary infection, and cellular immune cells play a key role in mucosal damage and the healing process (Al-Dasooqi et al. 2013). Clinical assessment for mucositis on a daily basis is important during the pre-engraftment period in transplant patients. Different clinical instruments are available for grading and evaluating the treatment response: national cancer institute common toxicity criteria (CTCAE v.4.0), Oral Mucositis Index (OMI), Oral Mucositis Assessment Scale (OMAS), Nijmegen Nursing Mucositis Scoring System (NNMSS), and Visual Analogue Scale (VAS) (NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data file 2009; Potting et al. 2006). Patients may require swab cultures to rule out herpes simplex virus–associated mucosal lesions if clinical suspicion is high. Oropharyngeal candidiasis is a clinical diagnosis based on direct visualization of white plaques on the buccal mucosa, palate, tongue, or the oropharynx. Endoscopic evaluation is necessary in the cases involving the esophagus, small bowel, and colorectal mucosa. It can be difficult to differentiate simple mucositis from oral manifestations of acute graft-versus-host disease without tissue

biopsy in the early transplant period. Persistence of oral lesions more than 3 weeks after transplant should be investigated for graft-versus-host disease.

4.5.1 Prevention and Treatment of Oral Mucositis

An interdisciplinary approach to oral care involving the nurse, physician, dentist, dental hygienist, dietician, and pharmacist is important to the prevention of oral mucositis. Routine oral care in transplant patients is important for the prevention of mucositis. Regular brushing and oral rinses are recommended by MASCC (Lalla et al. 2014). There is no clear data to favor saline, sodium bicarbonate, mixed medication mouthwashes, calcium phosphate, or chlorhexidine for oral rinse.

Palifermin, a recombinant human keratinocyte growth factor, is the only drug approved by the U.S. FDA for oral mucositis. It is beneficial in reducing the duration and severity of mucositis in patients undergoing autologous transplant for hematological malignancies (Spielberger et al. 2004). Retrospective studies suggested a benefit in reduction of intestinal mucositis and risk of infection with prophylactic use of palifermin (Tsirigotis et al. 2008). The American Society of Clinical Oncology recommends its use for mucositis prevention in autologous transplant patients receiving myeloablative conditioning with TBI (Hensley et al. 2009). It is administered by intravenous bolus for 3 days prior to myelotoxic therapy and additional 3 doses after the completion of the conditioning regimen (total 6 doses).

Amifostine is a phosphorylated aminothiol with cytoprotective effects from radiation and alkylating agents. In a retrospective study, amifostine was given to patients undergoing melphalan-based transplant conditioning therapy. Amifostine use was associated with reduced grade 3–4 mucositis (21 versus 53%) (Capelli et al. 2000). No prospective study is available to confirm these findings. Benzydamine hydrochloride is a nonsteroidal anti-inflammatory agent which inhibits the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1b and prevents mucosal inflammation (Rastogi et al. 2017). It is commonly used with patients with head and neck cancer undergoing concurrent chemotherapy and radiation therapy. There is insufficient evidence to support the routine use of zinc, glutamine, pilocarpine, pentoxyfylline, misoprostol, allopurinol, bethanechol, chewing gum, propantheline, or tetrachlorodecaoxide for the prevention or treatment of oral mucositis.

Cryotherapy can cause local vasoconstriction and reduce alkylating drug exposure and prevent mucositis. Placing ice on the oral mucosa during melphalan infusion was associated with reduced grade 3–4 oral mucositis, the use of narcotics, and the use of TPN in a randomized clinical study in autologous transplant patients (Lilleby et al. 2006). Low level laser therapy (LLLT) is thought to have a variety of biological effects and has been studied for the prevention of oral mucositis. Two different wavelengths of LLLT were compared with placebo in a study involving patients undergoing autologous and allogeneic transplant. LLLT was associated with reduced severity of oral mucositis and pain scores (Schubert et al. 2007).

4.5.2 Pain Control

Pain control is an important aspect of management of mucositis which helps maintain adequate oral intake. Patient controlled anesthesia (PCA) is favored by MASCC guidelines for improved patient comfort. Various topical anesthetic agents are used widely, usually in a combination oral rinse with mucosal coating, anti-inflammatory, and anti-microbial agents (i.e., sucralfate, diphenhydramine, lidocaine, nystatin). Data supporting the efficacy of these agents is limited, and they usually provide only transient relief. Interestingly, topical use of tricyclic anti-depressants like nortriptyline and doxepine can provide pain relief in the setting of oral mucositis (Epstein et al. 2001).

4.5.3 Nutritional Support

Oral mucositis can severely impair patients' nutritional status. Early involvement of professional nutritional service is important for baseline evaluation and ongoing monitoring of transplant patients for timely interventions. TPN can be used in severe oral mucositis patients who cannot tolerate any oral intake. Continued use of TPN should be weighed against the risk of infection and electrolyte disturbances on a daily basis. Data does not support the routine use of TPN as first-line therapy in the setting of severe mucositis, and it should be reserved for those patients who are unable to tolerate enteral feedings (Arfons and Lazarus 2005). An oral elemental diet contains mixture of liquid nutrients which are easily absorbed. A single Japanese study evaluated its role for transplant patients, and it showed reduced severity of oral mucositis and length of hospitalization. Larger studies are needed to establish its routine use (Morishita et al. 2016).

4.6 Nausea and Vomiting

Chemotherapy-induced nausea and vomiting is a common complaint of patients undergoing transplant. Nausea and vomiting may occur early in the transplant course secondary to effects of conditioning regimens. Risk of nausea and vomiting is significantly increased with higher doses of chemotherapy, consecutive-day administrations, concurrent radiation or TBI, and other medications used during the early transplant period. A single-institute study by Adel et al. analyzed the rate of nausea and vomiting in patients undergoing hematopoietic stem cell transplant. The study found that allogeneic transplant (79%), the use of radiation therapy (51%), and diagnosis of leukemia (85%) were associated with higher incidence of nausea and vomiting (Adel et al. 2016). Nausea and vomiting can lead to significant distress and impair a patient's nutrition and quality of life.

Chemotherapy-induced nausea and vomiting has three distinct types: acute, delayed, and anticipatory. It is imperative to distinguish between these types as it has implications for prevention and management.

1. *Acute emesis:* It occurs within the first 1–2 h up to 24 h after chemotherapy administration. Most clinical studies are done in this setting by using different anti-emetics for prophylaxis of acute emesis. 5-Hydroxytryptamine receptor 3 (5-HT3) inhibitors such as ondansetron are very helpful in preventing acute emesis.
2. *Delayed emesis*: Emesis occurring after 24 h of chemotherapy is classified as delayed. It is generally less responsive to currently available anti-emetics compared to acute emesis. Neurokinin-1 receptor (NK1R) inhibitors such as aprepitant are particularly effective in this setting.
3. *Anticipatory emesis:* It is the result of negative conditioning due to nausea and vomiting during previous cycles of chemotherapy. It can be an issue in transplant patients as most have received multiple cycles of chemotherapy prior to transplant. Benzodiazepines can be helpful controlling anticipatory emesis.

The establishment of the degree of chemotherapy-induced nausea and vomiting is important in clinical and research settings. NCI Common Terminology Criteria for Adverse Events (CTCAE) and Multinational Association for Supportive Care in Cancer (MASCC) antiemetic tool (MAT) are commonly used tools (Molassiotis et al. 2007). In one clinical study, MAT had a higher discriminant power than CTCAE in assessing the intensity of nausea in patients receiving allogeneic transplantation (Yeh et al. 2014). The Functional Living Index-Emesis (FLIE) and Visual Analog Scale (VAS) are also used in clinical studies (Lindley et al. 1992; Grunberg et al. 1996).

The precise mechanisms behind chemotherapy-related nausea and vomiting are not completely understood; however, current understanding points toward two main pathways, peripheral and central pathways. The peripheral pathway is mediated by the release of 5-hydroxytryptamine (5-HT) from the enterochromaffin cells of the small intestine stimulated by the chemotherapy agent and its metabolites. 5-HT via 5-HT3 receptor sends afferent vagal stimulus to the area postrema and nucleus tractus solitaries in the mid brain. The final vomiting reflex is generated by the central pattern generator in the medulla by signals from the area postrema and nucleus tractus solitaries. The peripheral pathway is thought to be the central mediator of acute emesis. The central pathway is mediated by substance P released by afferent vagal stimulus and NK1 receptors and is located primarily in the brain. It is mainly associated with delayed chemotherapy-induced nausea and vomiting (Hesketh 2008; Navari and Aapro 2016).

Significant progress has been made in the management of chemotherapy-induced nausea and vomiting since the introduction of 5-HT3 and NK1R inhibitors. The American Society of Clinical Oncology (ASCO) and MASCC have established evidence-based guidelines for the management of chemotherapy-induced nausea and vomiting (Roila et al. 2016; Hesketh et al. 2016). There are a limited number of randomized trials specifically studying the issue of emesis in the high-dose chemotherapy setting, and those involving hematopoietic stem cell transplant are summarized in Table 4.7.

Table 4.7 Summary of clinical trials of anti-emetic agents in hematopoietic stem cell transplant patients

Drugs studied	Patient no. (*n*)	Trial settings	Complete/major control of vomiting
Granisetron versus ondansetron (Orchard et al. 1999)	197	Autologous, allogeneic	63% versus 61% ($p = 0.68$)
Granisetron versus ondansetron (Walsh et al. 2004)	96	Autologous, allogeneic	50% versus 46% ($p = 0.16$)
Palonsetron and Dexamethasone (Giralt et al. 2017)	73	Autologous	41–44%
Tropisetron and dexamethasone (Giralt et al. 2017)	31	Autologous	71–83%
Aprepitant, granisetron, dexamethasone versus granisetron, dexamethasone (Schmitt et al. 2014)	362	Autologous	78% versus 65% ($p = 0.0036$)
Aprepitant, ondansetron, dexamethasone versus ondansetron, dexamethasone (Stiff et al. 2013)	179	Autologous, allogeneic	73% versus. 23% ($p = 0.001$)

4.6.1 5-HT3 Inhibitors

Early studies comparing 5-HT3 inhibitors (ondansetron, granisetron) versus dopaminergic receptors (D1, D2) blockers (prochlorperazine, metoclopramide) have established superior efficacy and improved safety profile of these drugs in the setting of high-dose chemotherapy (HDT) during conditioning. (Bosi et al. 1993; Okamoto et al. 1996) Subsequent studies have confirmed improved control of chemotherapy induced nausea and vomiting with 5-HT3 inhibitors and dexamethasone combination compared to 5-HT3 inhibitors alone (Yeh et al. 2014; Barbounis et al. 1999; Abbott et al. 1999).

4.6.2 NK1R Inhibitors

NK1R inhibitor (aprepitant) was investigated with 5-HT3 inhibitor and dexamethasone in two phase III studies of transplant patients. The addition of aprepitant leads to complete absence of emesis in 73% and 78% of the study participants, respectively (Schmitt et al. 2014; Stiff et al. 2013). Fosaprepitant is an intravenous form of aprepitant which is approved by the FDA for single day use. Netupitant is single dose oral NK1 inhibitor with comparable efficacy to aprepitant (Gralla et al. 2014). Both aprepitant and netupitant are CYP3A4 inhibitors which will impair metabolism of certain co-administered drugs. The dose of dexamethasone should be reduced appropriately when used in conjunction with these medications. Rolapitant is a new oral NK1R inhibitor with a longer plasma half-life (approximately 7 days) and no CYP3A4 inhibition. It was tested in two phase III studies in combination with 5-HT3 inhibitor and dexamethasone in patients receiving highly and

moderately emetogenic chemotherapy. It showed improved control of chemotherapy-induced nausea and vomiting in both studies with no safety concerns (Schwartzberg et al. 2015; Rapoport et al. 2015). Netupitant and rolapitant have not been specifically studied in hematopoietic stem cell transplant populations, and there is no study comparing rolapitant with currently available NK1R inhibitors.

4.6.3 Glucocorticoids

Glucocorticoids, as a single agent, have limited therapeutic anti-emetic efficacy; however, they are highly effective when combined with 5-HT3 inhibitors and/or NK1R inhibitors. Dexamethasone is the most commonly used and extensively studied glucocorticoid for chemotherapy induced nausea and vomiting. The antiemetic efficacy of 5-HT3 inhibitors is greatly enhanced with dexamethasone, and this has been demonstrated with multiple phase 3 clinical studies (Ioannidis et al. 2000).

4.6.4 Olanzapine

Olanzapine is a second-generation antipsychotic which blocks 5HT2 and dopamine D2 receptors. It is effective in preventing acute as well as delayed nausea and vomiting. Prophylactic regimens containing the combination of olanzapine with dexamethasone and a 5-HT3 inhibitor were effective in the prevention of acute and delayed chemotherapy–induced nausea and vomiting (Chiu et al. 2016). In a randomized phase 3 study, olanzapine was compared with aprepitant in combination with palonosetron and dexamethasone. There was better control of delated nausea and vomiting in the olanzapine arm and no difference in control of acute nausea and vomiting among both groups (Navari et al. 2011).

4.6.5 Other Agents

Other antiemetics like promethazine, metoclopramide, and prochlorperazine are dopaminergic antagonists with increased side effects due to anticholinergic effects. Cannabinoids such as dronabinol (tetrahydrocannabinol) are partial agonists of cannabinoid receptors (CB1, CB2) in the central nervous system. They have limited therapeutic efficacy and data supporting their use is limited (Smith et al. 2015). These drugs can be used in refractory nausea and vomiting after the use of conventional antiemetics, and further studies are needed to establish efficacy.

In summary, for the patient undergoing HCT and receiving HDT and radiation therapy as a part of their conditioning regimen, we recommend a combination of dexamethasone, 5-HT3 receptor antagonist, and NK1R antagonist. Olanzapine may be added for patients receiving myeloablative doses of chemotherapy and TBI.

4.7 Diarrhea

Diarrhea in patients undergoing transplant has a broad differential which includes mucositis secondary to the effect of conditioning regimens, infection, medications, and graft versus host disease. Neutropenic enterocolitis, cord colitis syndrome, and post-transplant lymphoproliferative disease (PTLD) involving the gastrointestinal tract are uncommon causes of diarrhea in transplant patients. In a single-institute study, 79% of allogeneic and 47% of autologous transplant patients have acute diarrhea within the first 100 days of transplant. (van Kraaij et al. 2000) Uncontrolled diarrhea can lead to significant electrolyte disturbances and impaired nutritional status. The diagnostic workup and management of diarrhea varies according to its etiology and severity. Initial workup usually includes clinical assessment, measurement of blood electrolyte levels, and testing the stool for infectious etiologies. Further radiological studies and endoscopic exams may be necessary in selected cases.

4.7.1 Graft-Versus-Host Disease

Acute graft-versus-host disease (aGVHD) involving the gut can cause severe profuse watery diarrhea within the first 3 months of transplant. It is one of the most common and serious etiologies of acute diarrhea in the allogeneic HCT patient. The diagnostic workup includes ruling out infectious organisms and histological confirmation of aGVHD by endoscopic biopsy. Detailed management of aGVHD is discussed in Chap. 6.

4.7.2 Non-oral Mucositis

Chemotherapy and radiation therapy conditioning regimens can directly damage intestinal mucosa. Diarrhea often occurs within the first 2 weeks of the conditioning therapy. Management is usually conservative with loperamide once infectious etiologies have been ruled out. Patients may require bowel rest and nutritional support. Infrequently, severe mucositis and prolonged neutropenia can case intestinal wall necrosis and bacterial overgrowth, leading to neutropenic enterocolitis which usually presents with increasing abdominal pain and fever.

4.7.3 Infections

Infection-related acute diarrhea is relatively uncommon; however, timely diagnosis is important for appropriate treatment decisions (van Kraaij et al. 2000). Microbiological examination of the stool specimen is quite helpful for the diagnosis of bacterial and parasitic infection–associated diarrhea (i.e., *Clostridium difficile* and Giardia); however, endoscopic examination and tissue biopsy are imperative for the diagnosis of viral colitis. *C. difficile*-associated diarrhea is quite common in the

post-transplant period and can lead to significant morbidity. From a single-institute study, *C. difficile* was associated with 15% of diarrhea cases in autologous transplant patients (Arango et al. 2006). Gastrointestinal graft-versus-host disease is also a strong risk factor for recurrent *C. difficile* infection (Alonso et al. 2012). The symptoms *C. difficile* infection varies from mild abdominal pain, fever, and diarrhea to pseudomembranous colitis with intestinal ileus and colonic perforation. Diagnosis is usually straightforward with stool testing for A and B toxins by enzyme immunoassay or PCR testing for *C. difficile* DNA for the corresponding toxins. *Salmonella, Shigella, Yersiania*, and *Camphylobacter* are uncommon etiologies for bacterial diarrhea (0–2.8%) (Kamboj et al. 2007).

Cytomegalovirus (CMV) is the most common cause of viral diarrhea in transplant patients. Transplantation from an unrelated or HLA-mismatched donor, umbilical cord blood transplantation, and the use of antithymocyte globulin (ATG) for graft-versus-host disease (GVHD) prophylaxis are common risk factors for CMV infection. Isolated CMV colitis and the absence of detectable CMV viral copies in the blood are possible. Endoscopic exam and tissue biopsy staining for anti-CMV antibody are important for the diagnosis. Adenovirus, coxsackie, echovirus, rotavirus, and norovirus are uncommon viral etiologies of infectious diarrhea after transplant. Diarrhea secondary to parasitic infection is relatively uncommon. *Cryptosporidiosis* can mimic gut GVHD and requires stool microscopy for diagnosis. In a report by Legrand et al., *cryptosporidiosis* was detected in 9.6% of allogeneic transplant patients with diarrhea (Legrand et al. 2011). The management of infectious diarrhea is pathogen-specific antiviral or antibacterial therapy with supportive care. Reduction in immunosuppressive therapy may be required in serious cases.

4.7.4 Neutropenic Enterocolitis (Typhlitis)

Neutropenic enterocolitis is a serious complication in transplant patients with prolonged neutropenia and mucositis (Rodrigues et al. 2017). It presents with fever, abdominal pain, and watery or bloody diarrhea. Peritoneal signs and hemodynamic shock are signs of interstitial perforation. Computed tomography (CT) scans are usually diagnostic for this condition. Patients should also have blood and stool cultures and a *C. difficile* toxin stool assay. Colonoscopy is relatively contraindicated due to risk of iatrogenic perforation. Conservative management with bowel rest, IV fluids, and broad spectrum antibiotics is recommended; however, timely surgical intervention is necessary in cases with bowel perforation and hemodynamic instability.

4.7.5 Cord Colitis Syndrome

Cord colitis syndrome is culture-negative, antibiotic-responsive diarrhea specifically described in patients undergoing cord blood transplant (Herrera et al. 2011). *Bradyrhizobium enterica* is a newly discovered bacteria attributed as a causative

organism for this condition (Bhatt et al. 2013). Common presenting symptoms are persistent watery, non-bloody diarrhea. It is a diagnosis of exclusion, where graft-versus-host disease and other infectious etiologies have been ruled out. CT scan may show focal or diffuse colonic wall thickening. The endoscopic biopsies are consistent with chronic active colitis and frequently associated with granulomatous, neutrophilic cryptitis, and mild cryptic epithelial apoptosis. Excellent response to antibacterial treatment is the norm in cord colitis syndrome. Commonly used antibiotics are metronidazole with or without a fluoroquinolone.

4.8 Constipation

Constipation is a common gastrointestinal complaint encountered by providers of transplant patients in both inpatient and outpatient settings. Common etiologies are medications (narcotics, antiemetics), inadequate liquid intake, low fiber diet, and limited physical mobility. It can lead to significant mental/physical distress and reduce oral intake. Straining during defecation can cause exacerbation of hemorrhoids and anal mucosal tears. In neutropenic patients, this can lead to perirectal abscess formation and become a source of bacteremia. Diagnosis is usually clinical; however, radiography may be required to rule out intestinal obstruction or ileus.

4.8.1 Laxatives

Choice of laxative should be individualized based on the patient's history, potential drug interactions and side effects. Bulk forming laxatives like psyllium and methylcellulose can increase fecal mass. There are very few high-quality studies supporting their clinical use (American College of Gastroenterology Chronic Constipation Task Force 2005). Polyethylene glycol (PEG), lactulose, and sorbitol are osmotic laxatives. They act by increasing stool water content and are relatively well-tolerated. At higher doses, they can lead to abdominal cramping, diarrhea, and electrolyte disturbances. Stimulant laxatives include components containing senna or bisacodyl. They directly enhance colonic peristalsis by direct simulation of the gastrointestinal nerves. These drugs are used for refractory cases; however long-term use is not advisable due to the risk of melanosis coli.

4.8.2 Opioid Antagonists

Methylnaltrexone (Relistor©) is a peripherally acting mu receptor antagonist with no central nervous system effects. It has been shown to be effective in opioid-induced constipation (Michna et al. 2011). It is available as a subcutaneous injection and oral tablet forms. Alvimopan is the other agent in the same drug class. It is only approved for short-term hospital use, and it carries a potential risk for myocardial infarction with long-term use.

Rectal enemas are generally contraindicated in neutropenic patients due to potential risk for bacterial translocation and mucosal injury. Endoscopic disimpaction is generally reserved for refractory cases where medical therapy has failed.

4.9 Summary

The conditioning chemotherapy and radiation treatments, in addition to prophylactic and immune suppressive medications, may have many toxic side effects during and after transplant. Vigilance in monitoring patients for non-pain-related transplant side effects is a task for the entire multidisciplinary transplant care team. Identification of symptom etiology early leads to early intervention, relief of symptoms, and improved patient quality of life.

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Pre-transplant Comorbidities: Influence on Decision-Making and Outcomes

5

Shirali Agarwal, Jennifer E. Nyland, Ahmed H. Rashad, and Mohamed L. Sorror

5.1 Introduction

The quality of life is more important than life itself—Alexis Carrel

Hematopoietic cell transplantation (HCT) is a transcendent invention providing potential cures to a large number of malignant and non-malignant hematological disorders. Initially, allogeneic hematopoietic cell transplant (allo-HCT) was generally offered to young and relatively healthy patients believed to be fit enough to withstand the toxicity of high-dose conditioning regimens. With the development of reduced intensity conditioning (RIC) and non-myeloablative (NMA) conditioning regimens, it has now become possible to offer allo-HCT to older patients. Chronological age is usually considered a hypothetical barrier, thus excluding elderly patients from a variety of treatment and clinical trial options. According to various reports, age alone should not be considered as a contraindication to HCT (Sorror et al. 2011a; McClune et al. 2010; Federmann et al. 2015). Comorbidities

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and functional status influence the outcomes of cancer patients more than age alone (Wedding et al. 2007; Extermann et al. 1998). Feinstein defined comorbidity as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the [primary] index disease under study" (Feinstein 1970). In simple terms, it refers to the simultaneous occurrence of two or more chronic conditions in an individual. As the age of cancer patients increases, the burden of comorbidities tends to increase (Extermann 2000). This, combined with the peak incidence of hematological malignancies occurring in patients above 60 years of age, made it imperative to design a model to calculate the impact of comorbidities on HCT outcomes. HCT should be appropriately offered to those who would benefit from it rather than using vague exclusion criteria such as age. Cancer patients with comorbidities are often treated less aggressively, presumed to develop more post-treatment toxicities and poor quality of life. Therefore, an objective system of measuring and weighing the risks of comorbidities is essential for accurate pre-transplant assessments to guide potential treatment options.

One caveat of the curative benefits associated with allo-HCT is the potential increased risk of adverse impacts on organ systems and non-relapse mortality (NRM). These may result from (a) direct organ toxicities from myeloablative or NMA conditioning regimens (Gyurkocza and Sandmaier 2014); (b) infections due to a compromised immune system (Junghanss and Marr 2002); (c) acute and chronic graft-versus-host-disease (GVHD) caused by donor T and B cells (Nassereddine et al. 2017; Socié and Ritz 2014); and (d) long-term morbidities and secondary malignancies due to transplant regimens (Tichelli et al. 2008; Lowe et al. 2007). Overall, these impacts become a hindrance to the desired goal of HCT.

In attempts to overcome these barriers and achieve better overall survival and quality of life, there have been various breakthrough developments. Among them is the development of various risk assessment models, including comorbidity indices that can capture the burden of multiple medical problems before transplant and provide insight regarding the prediction of outcomes after HCT. This enables physicians to determine who will benefit from HCT, and to what extent they will benefit.

In this chapter, we will discuss the impact of comorbidities on HCT outcomes, development of prediction models to accommodate multiple comorbidities into a single validated score, other composite models, their application to guide decision-making in various diseases, and future directions to refine strategies of predicting HCT outcomes.

5.2 Historical Efforts to Correlate Comorbidities with Transplant Outcomes

Allo-HCT exposes patients to serious treatment-related risks associated with chemo-radiotherapy and immunosuppression as well as side effects such as GVHD. As such, adequate organ function is necessary to tolerate the burden of allo-HCT. Early studies investigating correlations between pre-transplant organ

comorbidities and post-transplant morbidity and mortality focused on single organ systems including pulmonary, cardiac, renal, and hepatic systems.

Compromised lung function as demonstrated by abnormal pulmonary function tests—measured by diffusion capacity of carbon monoxide (DLCO) and forced expiratory volume in one second (FEV_1)—has consistently demonstrated a correlation with post-transplant pulmonary function worsening and mortality (Parimon et al. 2005; Savani et al. 2006). Low pre-transplant DLCO and increased alveolar-arterial gradient ($A\text{-}aO_2$) were found to be associated with post-HCT death; however, not all mortalities in this cohort were entirely due to respiratory failure (Crawford and Fisher 1992). Further, low FEV_1 was identified as a risk factor for cytomegalovirus-associated interstitial pneumonitis (Horak et al. 1992).

Cardiac dysfunction, as indicated by decreased left ventricular ejection fraction (LVEF), has also been assessed as a predictor of post-HCT outcomes; however, historically there have been conflicting results correlating decreased LVEF to severe post-transplant cardiac toxicities. Reduced pre-transplant LVEF failed to demonstrate severe and life-threatening post-HCT cardiac toxicities in one study (Hertenstein et al. 1994), while another study found patients with reduced LVEF before HCT were at significant risk of severe cardiac toxicity, but no information on mortality was given (Fujimaki et al. 2001).

Studies have also examined correlations between abnormal laboratory test results for renal and liver function and post-transplant outcomes (Goldberg et al. 1998). Elevated pre-transplant levels of transaminases and chronic hepatitis have been demonstrated to be predictive of post-transplant sinusoidal obstruction syndrome and liver injury (McDonald et al. 1993; Ozdogan et al. 2003). Additionally, elevated pre-transplant levels of serum creatinine were identified as risk factors for post-transplant acute renal failure and mortality (Goldberg et al. 1998; Gruss et al. 1995). Yet, there were no substantial efforts toward combining the impacts of single organ comorbidities into a prognostic model specific for HCT.

As it is unlikely that a single organ comorbidity would affect post-transplant outcomes in isolation, there was a need for a prognostic model that incorporated multiple comorbidity variables to predict post-transplant outcomes for any given individual. One index commonly used for predicting mortality risk for various medical conditions as well as solid organ malignancies is the Charlson comorbidity index (CCI). The CCI was originally developed by assigning weights to 19 chronic conditions according to their association with 1-year mortality in a study comprising 559 patients with general medical conditions (Charlson et al. 1987). The scores were stratified into four categories: 0, 1–2, 3–4, and ≥5, with the corresponding 1-year mortality rates of 12%, 26%, 52%, and 85%, respectively. Initially, investigators at the Fred Hutchinson Cancer Research Center (Fred Hutch) used the CCI to evaluate associations between comorbidities and HCT outcomes (Sorror et al. 2004). In patients undergoing unrelated donor HCT after NMA ($n = 60$) and ablative conditioning ($n = 74$), CCI scores were calculated as 0, 1–2, and ≥3. For non-ablative patients, the 1-year NRM was 16% for patients with scores of 0–2 and 36% for those with scores ≥3. This was comparable to patients receiving ablative conditioning who had NRM rates of 28% for patients

with a score of 0, and 67% for those with scores of 1–2 (there were no patients with scores ≥3 in this category). The incidence of grade III and IV toxicities as well as grade III and IV acute GVHD was lower for non-ablative patients despite their higher comorbidity score. The 2-year overall survival for NMA patients with a score of 0–2 versus those with a score ≥3 was 50% and 9%, respectively. The 2-year survival rates for ablative patients with scores of 0 versus 1–2 were 63% and 22%, respectively. The 1-year NRM rate was 20% in NMA patients compared with 32% in ablative patients. Overall, high CCI scores were effective in predicting increased NRM and toxicities in these patients. CCI scores also proved to be effective for predicting NRM in a similar study of hematopoietic cell transplants from related donors, but with a weaker magnitude of association (Diaconescu et al. 2004). One follow-up study confirmed these findings among patients with chronic lymphocytic leukemia (CLL) treated with NMA and allo-HCT (Sorror et al. 2005a). This study reported that patients with CCI scores of 0, 1, or ≥2 were found to experience 2-year NRM incidences of 7%, 31%, and 46%, with survival rates of 78%, 49%, and 33%, respectively. There were several limitations of the CCI in the prediction of outcomes following HCT, as some of the comorbidities defined in it had crude definitions, particularly for hepatic and pulmonary comorbidities. Further, it did not include comorbidities relevant to the HCT setting, such as recurrent infection, obesity, and psychiatric disturbances. This model identified comorbidities in only 35% of patients and was even lower in patients undergoing ablative HCT (12% in unrelated (Sorror et al. 2004) and 22% in related ablative recipients (Diaconescu et al. 2004). Therefore, the CCI had limited sensitivity for patients undergoing HCT; hence, there was a need for a tailored index specific to the HCT setting.

5.3 Development of the HCT-Specific Comorbidity Index

The hematopoietic cell transplantation comorbidity index (HCT-CI) is a tool that captures the burden of influential comorbidities prior to HCT to allow accurate risk assessment for post-HCT outcomes. With desirable success using NMA regimens and better supportive care, HCT is offered to more patients despite comorbidities, hence making the age cutoff obsolete. The HCT-CI score enables a predictive assessment of the impact of comorbidities on NRM and overall survival. The HCT-CI was developed in 2005 (Sorror et al. 2005b) by modifying the CCI with the following adjustments:

1. Inclusion of tests for pulmonary function (DLCO and FEV_1), cardiac function (LVEF), and hepatic function (bilirubin and hepatic transaminases) in the assessments of pulmonary, cardiac, and hepatic comorbidities, respectively.
2. Inclusion of all comorbidities encountered in the cohort of the study population.
3. Development of new adjusted hazard ratios (HR) for the impact of comorbidities on NRM.

This study included 1055 patients who had undergone allo-HCT (after myeloablative or NMA conditioning) for different hematological diseases (Sorror et al. 2005b). They were randomly divided into two cohorts: a training set (n = 708), to develop the scoring weight, and a validation set (n = 347). Adjusted HRs for NRM were calculated for each comorbidity over the first 2 years following transplant. Adjusted HRs for any comorbidity exceeding 1.2 were converted into integer weights (comorbidities with a HR 1.3–2.0 were assigned a weight of 1; 2.1–3.0 were assigned a weight of 2; and 3.1 and above were assigned a weight of 3). The HCT-CI score was generated by addition of these weights. The HCT-CI was divided into three risk groups based on these scores: low (0), intermediate (1–2), and high (≥3). The validation set was then used to confirm the predictive power of the model. The HCT-CI model significantly predicted 2-year NRM as 14%, 21%, and 41%, with overall survival of 71%, 60%, and 34%, for the three groups, respectively (Table 5.1). The HCT-CI was compared with the CCI, which was also divided into low (0), intermediate (Sorror et al. 2011a), and high risk (≥2). The corresponding NRM for these groups was 23%, 29%, and 25% and overall survival was 59%, 49%, and 17%, respectively. Risk groups according to the HCT-CI were more evenly distributed than those in the CCI model (Fig. 5.1). Further, the HCT-CI was able to capture more pre-transplant comorbidities, provide better discriminative power for NRM, and had a higher overall predictive value for survival compared with the CCI. Overall, the HCT-CI had higher c-statistics for 1-year NRM (0.69 versus 0.55) and overall survival (0.66 versus 0.56) than the CCI, respectively.

5.3.1 Validation

A large number of studies have validated the HCT-CI, both retrospectively and prospectively, at various centers focusing on either a single disease or a spectrum of hematological disorders. So far, 25 studies have consistently validated the predictive ability of the HCT-CI on transplant outcomes (Sorror et al. 2007a, b, 2008a, b, 2015a; Elsawy et al. 2014a, 2015; Raimondi et al. 2012; Maruyama et al. 2007; Kerbauy et al. 2005, 2007; Majhail et al. 2008; Artz et al. 2008; Farina et al. 2009; Kataoka et al. 2010; Lim et al. 2010; Barba et al. 2010; Smith et al. 2011; Bokhari et al. 2012; Mo et al. 2013; Le et al. 2013; Ratan et al. 2013; Hashmi et al. 2013; Bayraktar et al. 2013; Chemnitz et al. 2014). Three of the largest studies were conducted on 19,767 (Sorror et al. 2015a), 2523 (ElSawy et al. 2015), and 1937 (Raimondi et al. 2012) patients. All of these studies calculated NRM and overall

Table 5.1 HCT-CI score and risk group showing the percentage of 2-year NRM and overall survival

HCT-CI score	Risk group	NRM at 2 years (%)	Overall survival at 2 years (%)
0	Low	14	71
1–2	Intermediate	21	60
≥3	High	41	34

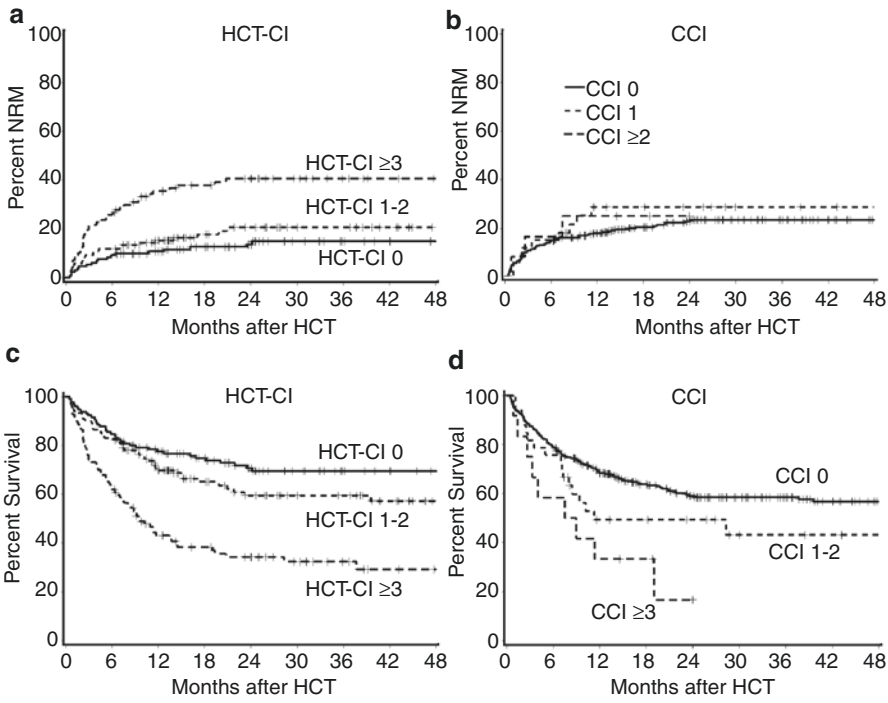

Fig. 5.1 The HCT-CI compared with the CCI. Cumulative incidences of NRM as stratified by (**a**) the HCT-CI compared with (**b**) the original CCI. Kaplan–Meier estimates of survival as stratified by (**c**) the HCT-CI compared with (**d**) the original CCI. Only 13% of patients had scores of 1 or more when scored by the original CCI, while 62% had scores of 1 or more when scored by the HCT-CI. This research was originally published in Blood. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912–9. © The American Society of Hematology

survival as the measured outcomes. Two of these studies used c-statistics estimates for comparison and to measure the discriminative power of the HCT-CI (ElSawy et al. 2015; Raimondi et al. 2012). One study was a multicenter prospective trial in which 11,652 out of 19,767 patients had autologous transplantation, confirming the predictive power in an autologous setting as well (Sorror et al. 2015a). Overall, the HCT-CI provides a comprehensive model with comorbidities relevant to transplant candidates and consistent results regarding outcomes. This model accommodates the results from historical studies on single organ comorbidities and circumvents the limitations of the CCI. While the HCT-CI has proven useful in various settings, the model is not without its limitations. Eight studies failed to validate the model; however a small sample size may be the reason for this discrepancy (Xhaard et al. 2008; Terwey et al. 2010; Defor et al. 2010; Birninger et al. 2011; Castagna et al. 2011; Williams et al. 2012; Guilfoyle et al. 2009; Nakaya et al. 2014). Another limitation of the HCT-CI was a variation in inter-rater agreement of comorbidity coding when

calculating the HCT-CI score. To ensure adequate consistency and precision, a systematic method was developed for reviewing medical charts and guidelines for comorbidity coding (Sorror 2013). There were concerns regarding improving the model performance, and investigators attempted to recalibrate the score by replacing integer weights with exact hazard ratios for different comorbidities (Defor et al. 2010). However, this model could not be validated, and the original HCT-CI score was agreed to be more appropriate (Sorror et al. 2011b).

5.4 How to Implement the HCT-CI Model

Familiarization with adapting the HCT-CI score in routine practice is simple and effortless. It takes approximately 15 minutes to complete the evaluation and generate a score. It can be done by transplant physicians or other members of the clinical care team. The scheme of the model is depicted in Fig. 5.2 (Sorror 2013).

First, a date is selected on or before which all of the relevant medical details, laboratory, and organ function tests need to be collected; this is termed the landmark date. For retrospective analyses, the landmark date is 10 days prior to transplant (D −10), as most of the conditioning regimens for patients through which the HCT-CI was developed started after D −10. If conditioning starts before D −10, the day before the start of conditioning can be taken as the landmark date. In prospective analyses and utilization of the HCT-CI for risk-benefit assessment, the date of consultation with the transplant physician could be used as the landmark date. For general purposes, any date prior to D −10 should suffice. All relevant data should be taken as close as possible to the landmark date (Sorror 2013). A readily accessible, free web-based calculator (www.hctci.org) is also available for accurate calculation of scores. The definition of the 17 comorbidities and the corresponding HCT-CI score has been summarized in Table 5.2.

The following steps should be followed for evaluation (Sorror 2013):

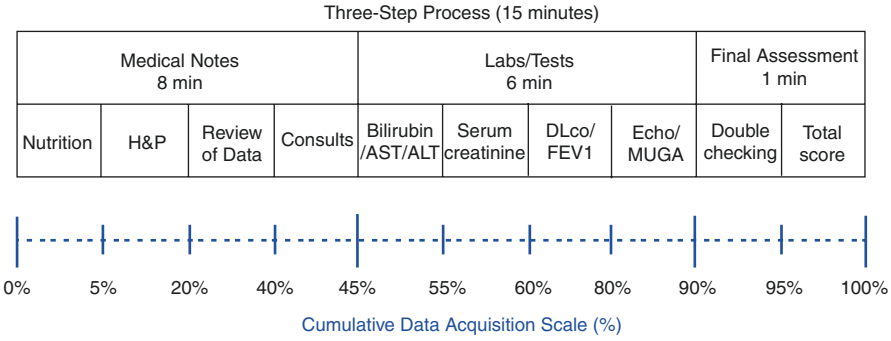

Fig. 5.2 Three-step methodology for comorbidity coding. This research was originally published in Blood. Sorror M. How I assess comorbidities prior to hematopoietic cell transplantation. Blood. 2013;121(15):2854–63. © The American Society of Hematology

Table 5.2 Definitions of comorbidities included in the HCT-CI and their corresponding scores

Comorbidity	Definition	Score
Arrhythmia	Any type of arrhythmia that has necessitated the delivery of a specific anti-arrhythmia treatment at any time point in the patient's past medical history	1
Cardiac	Coronary artery disease,[a] congestive heart failure, myocardial infarction, or EF ≤50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis requiring treatment at any time point in the patient's past medical history	1
Diabetes or steroid-induced hyperglycemia	Requiring treatment with insulin or oral hypoglycemic agents continuously for 4 weeks before the start of conditioning	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Any disorder requiring continuous treatments for 4 weeks before the start of conditioning	1
Hepatic, mild	Chronic hepatitis, bilirubin >upper limit of normal (ULN) to 1.5× ULN or AST/ALT > ULN to 2.5× ULN; at least two values of each within 2 or 4 weeks before the start of conditioning	1
Obesity	Patients with a BMI > 35 kg/m^2 for patients >18 years or a BMI for age of ≥95th percentile for patients of ≤18 years of age	1
Infection	Requiring antimicrobial treatment starting from before conditioning and continued beyond day 0	1
Rheumatologic	Requiring specific treatment at any time point in the patient's past medical history	2
Peptic ulcer	On the basis of prior endoscopic or radiologic diagnosis	2
Moderate/severe renal	Serum creatinine >2 mg/dL (at least two values within 2 or 4 weeks before the start of conditioning), on dialysis or prior renal transplantation	2
Moderate pulmonary	Corrected DLCO (via Dinakara equation) and/or FEV_1 of 66–80% or dyspnea on slight activity	2
Prior malignancy	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer	3
Heart valve disease	Of at least moderate severity, prosthetic valve or symptomatic mitral valve prolapse as detected by echocardiogram	3
Severe pulmonary	Corrected DLCO (via Dinakara equation) and/or $FEV_1 \leq 65\%$ or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin >1.5 × ULN or AST/ALT >2.5 × ULN; at least two values of each within 2 or 4 weeks before the start of conditioning	3

Adapted from Sorror et al. (2005b)

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

1. Review of medical records:
   (a) Calculate the body mass index (BMI) based on weight and height closest to landmark date.
   (b) Assess the history and physical examination (H&P) note. It should comprise evaluation of the patient's present, past, social and family history; physical examination; and a review of the organ systems. Specific attention should be

directed to any medical history pointing towards recent or remote organ dysfunction and all current medications, as it may help detect any comorbidity missed during history evaluation. The final assessment summary should be reviewed for a quick overview of the information, as well as to assess any scheduled follow-up consultations.

(c) Review the note that summarizes pre-transplant evaluation by the transplant physician. This can give valuable information on the current status of the disease, recent laboratory and organ function test results, and the final recommendations of the planned consultations.

2. Review laboratory and organ function tests: review reports closest to the landmark date.
   (a) Pulmonary function test (PFT) results for:
      - Percentage of measured-to-predicted forced expiratory volume in 1 s (FEV_1).
      - Percentage of measured-to-predicted diffusion capacity of carbon monoxide (DLCO) after correction for hemoglobin.
   (b) Echocardiogram or multi-gated acquisition (MUGA) scan report result for:
      - Percentage of ejection fraction (EF) for adults or shortening fraction (SF) for children.
      - Presence and magnitude of severity for any valvular abnormality.
      - Other cardiac comorbidities (e.g., dilated cardiomyopathy).
   (c) Diagnosis of infection with Hepatitis B or C or proven diagnosis of cirrhosis at any point prior to conditioning should be recorded. Assess liver function tests between days −24 and −10 (or between days −40 and −10 if only a single value is reported between days −24 and −10) before HCT; for elevated values of total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).
   (d) Assess serum creatinine values between days −24 and −10 (or between days −40 and −10 if only a single value is reported between days −24 and −10) before HCT.
3. Summary and final assessment:
   (a) Collect all relevant data and enter the positive findings either on a note pad, excel sheet or directly into the web-based calculator.
   (b) Double-check the findings entered on the calculator or the sheet and make corrections if required. It is extremely important that the information entered is accurate.
   (c) Calculate a total score for the patient.

5.5 Impact of HCT-CI and Comorbidities on Transplant Outcomes

The HCT-CI is a clinically meaningful tool to predict post-transplant complications; organ toxicities; acute and chronic GVHD; and transplant outcomes like morbidity, mortality, and quality of life. In a multi-center study involving retrospective analyses of 2985 patients who underwent allo-HCT, higher HCT-CI scores predicted increased risk of grades III and IV acute GVHD (Table 5.3) (Sorror et al. 2014a).

Table 5.3 Association between HCT-CI scores and development of acute GVHD

HCT-CI score	Incidence of grade III–IV acute GVHD (%)
0	13
1–4	18
≥5	24
$P < 0.001$	

This research was originally published in Blood. Sorror ML, Martin PJ, Storb R, Bhatia S, Maziarz RT, Pulsipher MA, et al. Pretransplant comorbidities predict severity of acute graft-versus-host disease and subsequent mortality. Blood. 2014;124(2):287–95. © The American Society of Hematology

Incidences of grades III and IV acute GVHD were 13%, 18%, and 24% for patients with HCT-CI scores of 0, 1–4, and ≥5, respectively. There was a 2.63-fold higher risk of mortality in patients whose HCT-CI scores were ≥3 and who developed grades III or IV acute GVHD than those with scores of 0–2 and did not develop acute GVHD. Another multi-institutional study investigated the role of the HCT-CI to predict chronic GVHD development and mortality from 2909 patients treated with allo-HCT for various malignant and non-malignant hematological conditions (Vaughn et al. 2015a). They concluded that, though the HCT-CI scores did not significantly correlate with the development of chronic GVHD, increasing HCT-CI scores were associated with an increased risk of NRM (HR 1.29, $P < 0.0001$) as well as overall mortality (HR 1.25, $P < 0.001$) after the development of chronic GVHD. Further, there is evidence to suggest that pre-transplant comorbidities have an influence on post-HCT organ toxicities. Cumulative incidences of grade III and IV non-hematologic toxicities (as graded by Common Toxicology Criteria) are higher with increasing CCI and HCT-CI scores (Sorror et al. 2004, 2008a).

Any comorbidity scored by the CCI or HCT-CI (score > 0) was correlated to an increased number of serious organ system toxicities and an increased length of hospital stay after autologous HCT (Labonté et al. 2008). Comorbidities are associated with a higher rate of NRM, organ toxicity, and GVHD, which can heavily impact resources and financial burden. A recent study found HCT-CI scores to be associated with resource utilization (RU) after allo-HCT, concluding that HCT-CI scores >1 were associated with higher RU (Decook et al. 2017). This retrospective study of 328 patients undergoing allo-HCT examined the impact of comorbidities as indicated by HCT-CI scores on RU in terms of readmissions, length of hospital stay (LOS), and days out of hospital alive (DOHA) in the first 100 days and at 1 year. Patients with HCT-CI scores >1 were found to have increased LOS and lesser DOHA compared to those with HCT-CI scores of ≤1 at both 100 days and at 1 year post-HCT. The number of readmissions were also higher in the first 100 days for patients with HCT-CI scores >1 ($P < 0.05$), but readmissions were not significantly different at 1 year ($P = 0.13$). It is therefore worthwhile to identify factors which can influence health care cost for patients undergoing allo-HCT so that appropriate steps can be taken to minimize cost. A study on CLL/lymphoma patients found that those with no comorbidities had a lower median number of inpatient days after NMA conditioning (Sorror et al. 2008b). Investigators determined that the presence

of at least one of the seven pre-transplant cardiac risk factors (past history of smoking, hypertension, hyperlipidemia, coronary artery disease, arrhythmia, prior myocardial infarction, and congestive heart failure) was associated with a higher cardiac complication rate (Qazilbash et al. 2009).

HCT-CI scores can be used as an indicator of post-transplant complications, allowing appropriate preventative measures to be taken. One study on adult long-term survivors (3–18 years) following allo-HCT found that higher HCT-CI scores were associated with impaired physical health, increased depression, increased distress from cancer or its treatment, diminished social support, and a higher comorbidity burden (Sorror et al. 2013). The HCT-CI could be used to guide management of comorbidities prior to transplant; however, further studies are needed to determine the impact this would have on post-transplant outcomes. Finally, the HCT-CI could also prove useful in guiding intervention studies to improve the quality of life of long-term survivors, arguably the most important aspect of any treatment offered.

5.6 Expansion of the HCT-CI

The predictive power of the HCT-CI may be amplified by the addition of patient- and/or disease-specific risk factors. Further, the HCT-CI model may be expanded by analyzing its utility in conjunction with other available indices to capture outcomes. Several available models are as follows:

- Augmented HCT-CI score (Vaughn et al. 2015b).
- Composite comorbidity/age index (Sorror et al. 2014b).
- Composite HCT-CI score and Karnofsky performance status (Sorror et al. 2008a).
- Composite HCT-CI score and European Society for Blood and Marrow Transplantation (EBMT) risk score (Elsawy et al. 2014b).
- Combined HCT-CI score and the Instrumental Activities of Daily Living (IADL) for HCT recipients 50 years of age or older (Muffly et al. 2014).
- Combined comorbidity/relapse model (Sorror et al. 2011a).

5.6.1 Augmented HCT-CI Score

The augmented HCT-CI is a composite score that takes into consideration pre-transplant levels of ferritin, albumin, and platelet counts, along with comorbidities scored by the HCT-CI for predicting outcomes after allo-HCT. It is the sum of the score assigned to the HCT-CI plus that assigned to each biomarker value. Independently, these laboratory values are predictive of NRM and overall mortality after allo-HCT (Vaughn et al. 2015b). These laboratory values were assigned weights and combined with the original HCT-CI to develop an augmented HCT-CI score (Table 5.4). The augmented HCT-CI has been shown to further refine the discriminative capacity of the HCT-CI for transplant outcomes. It divides patients into four risk groups, with scores 0, 1–2, 3–4, and ≥5. It has a higher c-statistic estimate

Table 5.4 Augmented HCT-CI score

All HCT-CI comorbidities plus		
High ferritin	Values ≥2500 as measured the closest before the start of conditioning	1
Thrombocytopenia	Values of <100,000 as measured the closest before the start of conditioning	1
Mild hypoalbuminemia	Values of <3.5–3.0 as measured the closest before the start of conditioning	1
Moderate hypoalbuminemia	Values of <3.0 as measured the closest before the start of conditioning	2

Adapted from (Vaughn et al. 2015b)

Table 5.5 Composite comorbidity/age index (Sorror et al. 2014b)

	Outcome at 2 years		
	HCT-CI/age	NRM (%)	Overall survival (%)
Comorbidity/age score (NMA and RIC)	0	5–12	81–87
	1–2	9–18	66–67
	3–4	17–36	47–54
	≥5	35–41	34–35

(0.61) for prediction of NRM compared with the HCT-CI alone (0.58) when measured as a continuous variable. Future studies may consider specific interventions to improve conditions resulting in these poor laboratory values before HCT in an effort to improve overall survival.

5.6.2 Composite Comorbidity/Age Index

The HCT-CI/age index was developed using data from 3033 patients who underwent allo-HCT in an attempt to determine if age and comorbidities could collectively guide decision-making for HCT referral (Sorror et al. 2014b). In the training set, patient age ≥40 years showed an impact on NRM that was equivalent to a single comorbidity with a weight of 1. Hence, patients ≥40 years of age were accredited with a score of 1 added to the HCT-CI to constitute this index (Table 5.5). The HCT-CI/age index stratifies patients according to four distinct risk groups with scores of 0, 1–2, 3–4, ≥5. In the validation set, the HCT-CI/age index had a significantly higher c-statistic estimate compared with age alone for the prediction of NRM (0.66 versus 0.56; $P < 0.001$) and survival (0.68 versus 0.56; $P < 0.001$), respectively. Therefore, it is recommended that patients should be evaluated with the HCT-CI/age composite index which integrates both comorbidities and age instead of age alone in order to select the most effective transplantation strategy.

The results from this study also suggested that patients with low (<3) HCT-CI/age score had comparable survival rates regardless of the conditioning regimens (RIC, NMA, and myeloablative) (Sorror et al. 2014b). Patients with scores ≥3 had better survival if given NMA (but not RIC) rather than high intensity conditioning.

The HCT-CI/age index could therefore be used for randomizing patients with a low burden of comorbidities (scores <3) into clinical trials for comparing the effectiveness and differences between conditioning regimens on outcomes. Patients with high comorbidity risk could be appropriate candidates for novel RIC regimens that could potentially provide better overall survival and less NRM.

5.6.3 Composite HCT-CI Score and Karnofsky Performance Status

As more medically infirm and elderly patients are being offered NMA HCT, researchers are attempting to better understand the impact of health status on HCT outcomes. In one study, the HCT-CI index was compared with the Karnofsky performance status (KPS), a widely used measure of health status and functional impairment, to analyze their predictive value on outcomes post-NMA HCT (Sorror et al. 2008a). In this study, both the HCT-CI and KPS scores independently correlated with post-HCT outcomes, while multivariate analyses indicated that the HCT-CI had greater predictive power for toxicities, NRM, and overall mortality compared with the KPS. The two models weakly correlated with one another, as they captured different aspects and levels of patient health status. It is critical to assess both of them simultaneously prior to HCT. Consequently, patients with HCT-CI scores of 0–2 or ≥3 were further stratified based on KPS percentages (>80% versus ≤80%) (Table 5.6). The combination of these two scores stratified patients into four risk groups: low comorbidities/high KPS; low comorbidities/low KPS; high comorbidities/high KPS; high comorbidities/low KPS. The 2-year NRM for these risk groups were 16%, 17%, 30%, and 39%, respectively. An increasing score was associated with worse outcomes, and 2-year survival was 68%, 58%, 41%, and 32% in the four groups, respectively. Therefore, integrating the two scoring systems refined the risk stratification model for post-HCT outcomes.

5.6.4 Composite HCT-CI and European Society for Blood and Marrow Transplantation Score

The EBMT score was one of the earliest models developed to predict outcomes after HCT by combining disease- and patient-specific risk factors. After analyzing

Table 5.6 Composite HCT-CI score and Karnofsky performance status (Sorror et al. 2008a)

Comorbidity/PS score	HCT-CI	KPS (%)	NRM at 2 years (%)	Overall survival at 2 years (%)
Group I	0–2	>80	16	68
Group II	0–2	≤80	17	58
Group III	≥3	>80	30	41
Group IV	≥3	≤80	39	32

numerous variables from a cohort of 3142 patients diagnosed with chronic myeloid leukemia (CML), investigators identified five factors associated with post-HCT outcomes (Gratwohl et al. 1998). The factors included in the EBMT score are: age of patient, disease stage, time from diagnosis to transplant, donor type, and donor/recipient sex combination. The EBMT combination score ranges from 0 (best) to 7 (worst) and is predictive of overall survival and transplant-related mortality (TRM). The EBMT was further validated for other hematological diseases as well and is now widely used (Passweg et al. 2004; Gratwohl 2012).

The simplicity of this model makes its widespread use easy; however, there are certain limitations such as the lack of age categorization beyond 40 years, superficial disease stage categorization, non-inclusion of factors such as comorbidities and performance status, and modest discriminative capacity (Gratwohl 2012). Investigators have proposed that a combination of EBMT and HCT-CI scores allows for better stratification of high-risk patients undergoing allo-HCT. Accordingly, a composite model was created, dividing patients into six risk groups based on HCT-CI score (0, 1–2, ≥3) and EBMT score (<4 and ≥4) to predict NRM and overall survival (Barba et al. 2014). This model was later validated by investigators from Fred Hutch in a study comprising a relatively larger and more diverse cohort of HCT recipients (Table 5.7) (Elsawy et al. 2014b). The composite model resulted in a significant improvement in c-statistic estimates for NRM and survival compared with the HCT-CI alone. This integrated index is a beneficial tool that can be used as an aid to determine selection of better conditioning regimens, predict outcomes, and counsel patients about transplantation.

5.6.5 Combined HCT-CI Score and the Instrumental Activities of Daily Living Assessment

In older patients, geriatric assessment (GA) variables across domains of functional status, frailty, comorbidity, mental health, nutritional status, and degree of inflammation may be predictive of HCT outcomes (Muffly et al. 2014). The IADL

Table 5.7 Composite HCT-CI and EBMT index

HCT-CI/EBMT score	HCT-CI	EBMT	4-year NRM (%)	4-year overall survival (%)
Group 1	0	<4	11	72
Group 2	0	≥4	19	61
Group 3	1–2	<4	16	63
Group 4	1–2	≥4	28	48
Group 5	≥3	<4	31	40
Group 6	≥3	≥4	41	30

This research was originally published in Biology of Blood and Marrow Transplantation. Sorror (Elsawy et al. 2014b) © The American Society for Blood and Marrow Transplantation

measures patients' functional status and ranges from 0 to 14, with higher scores corresponding to more independence (Lawton and Brody 1969). A simplified score was derived by combining assessments of comorbidities as measured by the HCT-CI with the most prognostic GA measure (i.e. the IADL) (Muffly et al. 2014). One point was given each to a HCT-CI score of ≥3 or IADL score <14, grouping patients into three categories with 0, 1, or 2 points. Amongst these groups, the 2-year overall survival was 62%, 44%, and 13%, respectively. This demonstrates the prognostic value of combining assessments of comorbidities with geriatric variables in older HCT patients.

5.6.6 Combined Comorbidity/Relapse Model

Investigators at the Fred Hutch, while studying long-term outcomes of older patients (> 60 years of age) post-NMA HCT, demonstrated that comorbidity and disease relapse risk were the most influential factors for overall survival (Sorror et al. 2011a). They found that major ABO-mismatch and higher HCT-CI scores had higher HRs for NRM, while the higher relapse risk score was associated with increased progression and relapse. The patients' outcomes were stratified based on HCT-CI and relapse risk score, as both were independently associated with overall and progression free survival (PFS) (Table 5.8). High comorbidity burden (HCT-CI > 0) and standard to high relapse risk of the disease were associated with inferior survival rates compared with no comorbidity burden and low relapse risk. The overall survival rate was 69% versus 23% in patients with low comorbidity burden and low relapse risk compared with patients with a high comorbidity burden and high relapse risk, respectively.

Table 5.8 Comorbidity relapse score

0HCT-CI	Relapse risk score	5-year overall survival (%)
0	Low	69
0	Standard	45
0	High	41
1–2	Low	56
1–2	Standard	44
1–2	High	15
≥3	Low	56
≥3	Standard	23
≥3	High	23

5.7 Application of HCT-CI in Decision-Making for Specific Malignancies

Integration of patients' comorbidities into an index like the HCT-CI has been helpful to guide decision-making and optimize treatment selection for various hematological disorders. Specifically, it has been possible to consolidate this index with other disease-specific risk factors to enable better prognostication. We will briefly discuss several seminal studies here.

5.7.1 Acute Myeloid Leukemia and Myelodysplastic Syndromes

In order to refine risk stratification for outcomes in patients prior to HCT, a retrospective study was conducted on 577 patients diagnosed with acute myeloid leukemia (AML, $n = 391$) and myelodysplastic syndromes (MDS, $n = 186$) who received either myeloablative ($n = 452$) or NMA ($n = 125$) conditioning prior to allo-HCT (Sorror et al. 2007b). Comorbidities were assessed based on HCT-CI, and disease morphology was determined by the French-American-British classification as low, intermediate, and high risk. Patients were stratified into four groups characterized as: Group I, having HCT-CI scores of 0–2 and low disease risk; Group II, consisting of HCT-CI scores of 0–2 and intermediate or high disease risk; Group III, with HCT-CI scores ≥3 and low disease risk; and Group IV, with HCT-CI scores ≥3 and intermediate or high disease risk (Table 5.9). The relapse rates were lower in low-risk disease groups (Groups I and III) compared with intermediate- or high-risk groups. Overall, Group I had the most favorable outcome in terms of overall survival and relapse-free survival (RFS) rates, while Group IV had the poorest survival, and Groups II and III had intermediate rates. Higher disease risk and increasing HCT-CI score were associated with increasing mortality. Regardless of disease risk, 2-year NRM and 2-year overall survival were comparable between patients with an HCT-CI score of 0–2, irrespective of whether they received myeloablative (overall survival 78%) or NMA conditioning (overall survival 70%). Thus, it was proposed that patients with low comorbidity scores can be prospectively randomized to receive either NMA versus myeloablative conditioning. Patients with HCT-CI scores ≥3 and high disease risk showed higher rates of NRM following

Table 5.9 Non-relapse mortality and overall survival in AML and MDS patients ($n = 577$) after myeloablative and non-myeloablative conditioning (Sorror et al. 2007b)

			2-year NRM and overall survival (%)			
			Myeloablative		NMA	
Group	HCT-CI score	Disease risk	NRM	Survival	NRM	Survival
I	0–2	Low	11	78	4	70
II	0–2	Intermediate and high	24	51	3	57
III	≥3	Low	32	45	27	41
IV	≥3	Intermediate and high	46	24	29	29

myeloablative versus NMA conditioning. Therefore, it would be worthwhile to try novel RIC or NMA conditioning regimens with target agents within this group of patients to minimize toxicity and achieve improved survival.

A retrospective study analyzing the impact of pre-transplant comorbidities on alemtuzumab-based RIC allo-HCT for AML/MDS showed a 3-year overall survival of 69%, 39%, and 32% among 128 patients with HCT-CI scores of 0, 1–2, and ≥3, respectively (Lim et al. 2010). Both the disease status at the time of transplant and HCT-CI score were predictors of poor outcomes. In another study correlating the HCT-CI and NRM for AML patients in first remission after various RIC regimens, 2-year NRM rates of 9%, 15%, 18%, and 31% were reported for patients with HCT-CI scores of 0, 1, 2, and ≥3, respectively (Mohty et al. 2009). Inferior survival of MDS and CML patients undergoing allo-HCT with a higher HCT-CI score was also shown in studies by Boehm et al. (2008) and Kerbauy et al. (2005). Recently, investigators from China concluded that the HCT-CI score can be used as an evaluation criterion to guide the selection of treatment for elderly AML patients (Zhang et al. 2017). They observed that patients benefited more from chemotherapy than supportive therapy, as demonstrated by median survival times of 840 days and 150 days ($P < 0.01$) in patients with HCT-CI scores of 0–1, and 210 and 60 days ($P < 0.01$) in patients with HCT-CI scores of 2–3, respectively. While in patients with HCT-CI scores ≥4, there was no significant difference in survival time amongst patients receiving either supportive therapy (90 days) or chemotherapy (130 days).

Recently, investigators from New York evaluated the association between the HCT-CI and HCT-CI/age index with outcomes in a homogenous cohort of patients undergoing allo-HCT with CD34-selected grafts for AML and MDS (Barba et al. 2017). NRM according to HCT-CI was lower in patients with the score of 0–2 versus ≥3. The cumulative incidence of NRM at 3 years was 7%, 14%, 25%, and 37%, and the rates for 1-year chronic GVHD relapse-free survival were 87%, 75%, 67%, and 59% for patients with HCT-CI/age scores of 0, 1–2, 3–4, and ≥5, respectively ($P < 0.001$). The 3-year overall survival showed a decreasing trend in the four risk groups according to HCT-CI/age index (ranging from 86 to 45%). The c-statistic estimate for measuring NRM was 0.62 and 0.65 according to HCT-CI and HCT-CI/age scores, respectively. Overall, increasing scores in both models were associated with higher NRM, lower overall survival, and lower chronic GVHD relapse-free survival. Thus, this model could be efficiently utilized in selecting appropriate patients to propose treatment with CD34-selected grafts.

From the above studies, it can be concluded that comorbidities have a valuable contribution in predicting outcomes. It is worthwhile randomizing patients to receive either myeloablative or NMA/RIC regimens if they have low-risk comorbidities, while those with high comorbidities might benefit more from conditioning regimens that cause less toxicity. Potentially, this index can be used for guiding the selection of conditioning regimens. For example, in a clinical trial (NCT00322101), HCT-CI scores <3 were used as a stratification criterion to randomize patients with AML or MDS between high-dose versus RIC regimens prior to allo-HCT.

5.7.2 Chronic Lymphocytic Leukemia

In a retrospective analysis of 82 patients with CLL who received NMA conditioning, comorbidities and lymph node size were found to be the two most important predictors of overall survival in a risk stratification model (Sorror et al. 2008c). Patients with comorbidities (HCT-CI score ≥1) or without comorbidities (HCT-CI score of 0) who had a lymph node size <5 cm achieved a 5-year overall survival of 60% and 78%, respectively. In comparison, those with a lymph node size of ≥5 cm had an overall survival of 27% and 43%, respectively. Another retrospective study reviewed patient outcomes after NMA versus myeloablative conditioning in 220 patients with lymphoma and CLL (Sorror et al. 2008b). This study concluded that patients without comorbidities (HCT-CI score of 0) tolerated both conditioning regimens equally well, with 3-year NRM rates of 15% and 18% and 3-year overall survival rates of 60% and 68% after myeloablative versus NMA conditioning, respectively. In patients with comorbidities (HCT-CI score ≥1), the 3-year NRM rates were 50% and 28%, and 3-year overall survival rates were 35% and 47% after myeloablative and NMA conditioning, respectively. Overall, the results indicate that patients with CLL had significantly better outcomes after NMA than myeloablative conditioning if comorbidities were present.

5.7.3 Chronic Myeloid Leukemia

Pavlu et al. (2010) investigated the role of comorbidities and pre-transplant C-reactive protein (CRP) values as prognostic indicators in 271 patients with imatinib-resistant CML in chronic phase who underwent myeloablative HCT. HCT-CI scores ≥1 and CRP levels greater than 9 mg/dL were predictors of inferior survival (5-year overall survival of 56% and 40%, respectively). The 5-year NRM was 19% versus 5% with HCT-CI score ≥1 and 0, respectively. Predicted outcomes are better in patients with low HCT-CI scores (HCT-CI score of 0) and low CRP values (<9 mg/dL), and such patients are better candidates for early HCT after imatinib failure, while patients with higher HCT-CI scores and CRP values might benefit from second-line tyrosine kinase inhibitors.

5.7.4 Lymphoma

Investigators from Italy retrospectively analyzed a cohort of 203 patients with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and multiple myeloma (MM) who were treated with either a RIC regimen (Flu-Cy) or a 2-Gy total body irradiation-based NMA regimen to determine the association of HCT-CI and KPS scores with patient outcomes (Farina et al. 2009). Overall, HCT-CI scores of 0, 1–2, and ≥3 predicted an overall survival of 87%, 51%, and 49%, respectively. HCT-CI scores predicted NRM, overall survival, and progression-free survival (PFS), while

KPS was also significantly associated with overall survival and NRM. The type of conditioning did not affect patient outcome after stratification by HCT-CI. Therefore, it is feasible to offer a wide variety of conditioning regimens (RIC, NMA) irrespective of patient age and the number of comorbidities. It was suggested that the HCT-CI should be a routine part of the pre-transplant work-up to identify transplant outcomes.

5.7.5 Pediatric Transplant

Comorbidities can influence the outcome of transplant in children, adolescents, and young adult patients as well. Though HCT-CI as a tool is acceptable in categorizing adult patients, its utility in pediatric patients needs to be validated. Smith et al. (2011) describe findings indicating that increasing HCT-CI scores are associated with higher 1-year NRM and lower overall survival in a study of 252 pediatric patients at four Centers. In this study, patients were divided into three groups based on HCT-CI score (0, 1–2, ≥3) with 1-year NRM rates of 10%, 14%, and 28%, and 1-year overall survival rates of 88%, 67%, and 62%, respectively. In another study, investigators from Argentina retrospectively analyzed 140 pediatric patients and found TRM rates of 14%, 44% and 53% among patients with a HCT-CI score of 0, 1–2, and >3, respectively (Figueroa Turienzo et al. 2016). Results also showed significant differences in survival curves among these groups. In an additional study on adolescents and young adults, the HCT-CI was predictive of overall survival (Wood et al. 2011). Though these studies demonstrate adequate power to predict TRM and overall survival, more prospective research is required to validate this score in pediatric populations.

5.7.6 Non-malignant Diseases

Comorbidities also impact outcomes of patients undergoing allo-HCT for non-malignant diseases. However, the literature lacks sufficient evidence demonstrating an association. Recently, investigators analyzed the impact of comorbidities on 4083 patients (Center of International Blood and Marrow Transplantation Research (CIBMTR) database) between 2004 and 2014 who received allo-HCT for the treatment of a variety of non-malignant disorders such as acquired aplastic anemia, immune deficiencies, hemoglobinopathies, bone marrow failure, histiocytic disorders, metabolic diseases, and autoimmune disease (Broglie et al. 2018). Results show that patients with an HCT-CI score >3 were at an increased risk for poor survival (score 3–4: HR 1.33, $P < 0.01$; score ≥5: HR 2.31, $P < 0.0001$). The 2-year overall survival for patients with HCT-CI scores of 0, 1–2, 3–4 and ≥5 was 83%, 80%, 74% and 56%, respectively. They concluded that HCT-CI scores ≥3 are associated with decreased survival in patients regardless of the conditioning regimen. This provides evidence that the HCT-CI is beneficial in prospective risk assessment for patients undergoing HCT for non-malignant disease.

5.8 Application of the HCT-CI in Autologous Transplants

5.8.1 Multiple Myeloma

Recent studies have demonstrated the utility of the HCT-CI in predicting outcomes in the autologous HCT (AHCT) setting. In 2014, a multi-institutional study was conducted with 1156 MM patients who underwent AHCT and received high-dose melphalan as a conditioning regimen (Saad et al. 2014). Comorbidities were assessed at the time of AHCT, and both HCT-CI and KPS scores were generated to assess the impact of comorbidities and functional status on NRM and survival. Results found that a HCT-CI score greater than 0 was associated with inferior survival (3-year overall survival rate of 71%) compared with a HCT-CI of 0 (overall survival rate of 76%). Of note, the HCT-CI was not associated with NRM in this particular study as the cumulative incidence of NRM was only 2%. However, a previous study on a smaller cohort (n = 126) found that comorbidities scored by either the HCT-CI or CCI were associated with increased organ toxicities and prolonged hospitalization after HCT (Labonté et al. 2008).

5.8.2 Lymphomas

AHCT after high-dose chemotherapy is an extensively accepted treatment for relapsed/refractory HL and NHL. Several studies have analyzed the influence of comorbidities on AHCT outcomes. In a study of patients with relapsed NHL, comorbidities as calculated by the CCI predicted higher treatment-related mortality and lower overall survival (Wildes et al. 2008). In this study, patients over 60 years of age experienced similar toxicities and survival when compared with a younger cohort of patients, indicating that comorbidities, rather than age, significantly influenced survival. In another study of 121 patients above 50 years of age with relapsed/refractory HL, those patients with HCT-CI scores greater than 1 and CCI scores greater than 1 were more likely to have poor overall survival and low PFS (Martinez et al. 2017). HCT-CI scores >1 were associated with a higher risk of grade III and IV extra-hematological toxicities post-AHCT. There was no difference in outcome for patients aged 50–60 years compared with those above 60 years. Overall survival rates at 5 years were 62%, 30%, and 17% for transplanted patients with comorbidity scores of 0, 1–2, and ≥3, respectively. These studies show that AHCT can be performed in patients irrespective of age with acceptable outcomes based on comorbidities.

As with allo-HCT, comorbidities play an important role in AHCT when determining treatment options. One study reviewed the importance of comorbidities for assessing prognostic information on 273 patients treated with AHCT for HL and NHL (Sorror et al. 2007c). Compared with patients with HCT-CI scores of 0, those with scores of 1–2 had similar 2-year NRM (rates of 3% versus 8%, respectively) and overall survival (rates of 80% versus 78%, respectively). While patients with scores ≥3 had a 2-year NRM rate of 19% and an overall survival rate of 52%, scores

≥5 had far worse outcomes with a 2-year NRM rates of 57% and an overall survival rate of 25%. This indicates similar tolerability to high-dose conditioning regimens amongst patients with HCT-CI scores of 0–2, and increasing mortality with scores ≥3. It might be suitable to avoid AHCT in patients with HCT-CI scores ≥5. In this study, HCT-CI scores independently predicted NRM and, combined with lactate dehydrogenase (LDH) and chemo sensitivity, predicted overall survival and RFS in multivariate analyses. Patients with HCT-CI scores ≥3, high LDH, and chemo-resistance at HCT had a median overall survival of 7.8 months and were independently associated with increased mortality. Overall, the HCT-CI is a predictable tool for patients undergoing AHCT and can be informative to prospectively determine treatment options.

5.9 Future Directions

Parameters which can enhance the strength of objectivity in diagnosing pre-HCT comorbidities to predict post-HCT outcomes such as NRM are a future potential area of research. The mechanism and underlying biological processes that associate post-HCT outcomes with pre-transplant comorbidities remain to be explored. Development of novel biomarkers that can enhance the predictive power of our assessment for post-HCT outcomes seems to be a promising method. The evolution and application of molecular techniques, such as whole–genome sequencing, gene expression profiling (Wilson et al. 2006), expression of micro-ribonucleic acid (microRNA) (Schwind et al. 2010), single-nucleotide polymorphisms (Bochud et al. 2008), and non-human leukocyte antigen (HLA) genetic variants (Petersdorf et al. 2012) has led to advances in this direction.

In 2015, investigators analyzed the association between microRNA and comorbidities in predicting mortality risk in patients undergoing allo-HCT for acute leukemias (Sorror et al. 2015b). Results identified a set of seven microRNAs that were diagnostic biomarkers for pre-transplant comorbidities and prognostic markers for post-transplant mortality. Additionally, there have been consistent attempts to assess the role of biomarkers for acute and chronic GVHD (Ali et al. 2016; Pidala et al. 2017). Further, there are ongoing efforts to validate and compare the predictive power of the clinical comorbidity index with a combined model including these biomarkers and identification of associated genes (Sorror et al. 2015b). The identification of more precise, objective markers will provide more individualized prognostic assessments for patients considering HCT therapy.

Another approach to improve our predictability in the future could assess differences in the impacts of comorbidities based on the type of hematological disease and/or the influence of comorbidities at various time points of the HCT course. In addition, there is a scarcity of available data regarding the management of comorbidities both pre- and post-transplant and the difference it could make in improving outcomes. There is an urgent need for further trials to incorporate the management of comorbidities as well, and analyze the impact managing comorbidities might have on patient outcomes.

Furthermore, emerging data suggests including data obtained from patient-reported methods is valuable for risk-stratification (Wood et al. 2016). This includes quality of life surveys and geriatric assessments examining physical functioning, frailty, and fatigue, and measuring resilience. Early decreases in physical function were associated with higher overall and treatment-related mortality. Functional assessments have also shown that physical well-being was significant for overall mortality, and functional well-being was significant in reducing risk of relapse (Hamilton et al. 2015). Geriatric assessment measures confer independent prognostic utility in older allo-HCT recipients. It might be beneficial to perform a comprehensive geriatric assessment that summarizes the influence of comorbidities, physical function, nutritional, cognitive, and other social factors on treatment planning and evaluation (Brunello et al. 2009). Emotional support before HCT and patient-reported resilience is associated with longer survival post-transplant, improved health, and psychosocial outcomes (Ehrlich et al. 2016; Rosenberg et al. 2015).

It is critical to investigate the predictive utility of patient characteristics in parallel with other aspects of risk assessment to improve decision-making, inform trial design, and identify appropriate supportive care interventions. An integrated evaluation would be the most beneficial method in predicting HCT outcomes. The present indices, along with future directives, can be used to customize decision-making to attain the most favorable outcome for each patient.

5.10 Summary and Conclusions

The decision to recommend allo-HCT, which promises hope and potential cure for advanced hematological malignancies, must be scrutinized against the risk of relapse, NRM, and toxicities before being offered to patients. An accurate balance between the risks and benefits of the procedure must be achieved to ensure optimum results.

Of all the efforts to incorporate comorbidities into predictive models of transplant outcomes, the HCT-CI has emerged as a valuable tool. It is an essential model to predict post-transplant outcomes and complications, as well as for comparing conditioning regimens and treatment decision-making. In addition, the various composite models that combine age or laboratory tests such as the composite age/comorbidity and augmented HCT-CI have added to the power of this model. Combining the EBMT with the HCT-CI has also proven to be beneficial to enhance survival prediction. Accordingly, the HCT-CI is currently used worldwide for decision-making, designing new HCT clinical trials, and for determining severity-adjusted outcomes for the purpose of public reporting by the Center of International Blood and Marrow Transplantation Research (CIBMTR).

This is just the beginning of our understanding of how comorbidities can influence overall patient outcomes. Age alone should not be a barrier for denying HCT to patients. Comorbidities coupled with disease- and patient-specific risk factors widely affect mortality and morbidity. Further refinement of the decision-making

processes by investigating these factors and managing them appropriately is still in preliminary stages, and much research is yet required to address this comprehensively. Future studies should focus on (1) objectively developing and optimizing methods to stratify risks and clinical grading systems and (2) seeking ways to alleviate the burden of comorbidities on morbidity and mortality after allo-HCT. Ultimately, the aim is to provide HCT as a treatment option to all those who need it, while achieving the most favorable results and providing a better quality of life.

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Graft-Versus-Host Disease and Quality of Life: Can We Make a Difference?

6

Nandita Khera and Navneet S. Majhail

6.1 Introduction

Acute and chronic graft-versus-host disease (GVHD) are immune-mediated complications that occur after allogeneic hematopoietic cell transplantation (HCT) and contribute to the mortality and morbidity of the procedure. The clinical syndrome of GVHD is considered acute or chronic based on clinical features and not the temporal relationship to HCT (Filipovich et al. 2005). The incidence of acute GVHD ranges from 35 to 60% and that of chronic GVHD from 30 to 70% and is dependent on risk factors such as stem cell source, patient and donor age, conditioning, GVHD prophylaxis used, and prior acute GVHD specifically for chronic GVHD (Jacobsohn and Vogelsang 2007; Lee and Flowers 2008; Jagasia et al. 2012).

Both acute and chronic GVHD (chronic more than acute) have been shown in multiple studies to be associated with poor quality of life (QOL), impaired functional status, adverse psychological outcomes, and delayed recovery from HCT (Lee et al. 2006; Kiss et al. 2002; Hjermstad et al. 1999; Syrjala et al. 2004; Fraser et al. 2006; Sun et al. 2011). In the last few years, studies from chronic GVHD consortium have helped elucidate quite well the impact of chronic GVHD on patient reported outcomes (PROs).

This chapter provides an overview of the current literature on QOL associated with GVHD, specifically summarizing studies from Chronic GVHD Consortium. We briefly describe the considerations in developing endpoints and response

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measures that incorporate QOL aspects to test the efficacy of interventions used for prevention and treatment of GVHD. We conclude by describing interventions to help improve QOL in patients with GVHD, exploring the lacunae in the state of our current knowledge and outlining research priorities in the area.

6.2 Impact of Acute GVHD on QOL

In one of the earlier studies, Lee et al. reported grades II and IV acute and chronic GVHD to be associated with worse QOL after allogeneic HCT as measured by the Trial Outcome Index of the FACT-BMT (Lee et al. 2006). Acute GVHD led to a measurable decline in the QOL of patients who developed it, unlike those with no acute GVHD who had stable QOL over the first 6 months after HCT. Williams et al. have reported grade I–IV acute GVHD to be associated with greater symptom burden during 100 days after HCT than no acute GVHD (Williams et al. 2009).

6.3 Impact of Chronic GVHD on QOL

The impact of chronic GVHD on QOL is more profound and has been described by many more studies than for acute GVHD. Chiodi et al. examined the QOL in 244 patients undergoing an allogeneic HCT and found chronic GVHD to be one of the predictors for poor QOL (Chiodi et al. 2000). The BMT Survivor Study, a collaborative effort between City of Hope and University of Minnesota, reported that patients with active chronic GVHD were more likely to report adverse general health, mental health, functional impairments, activity limitation, and pain than were those with no history or those who had been optimally treated with the resolution of chronic GVHD (Fraser et al. 2006). Additionally patients with chronic GVHD have been reported to exhibit other poor psychosocial outcomes such as worse psychological, social, and spiritual well-being, higher depression, higher somatic distress, and lower likelihood of returning to work (Syrjala et al. 2004; Sun et al. 2011; Wong et al. 2010). In a large European Society for Blood and Marrow Transplantation (EBMT) registry study, chronic GVHD was an important predictor for a higher risk of committing suicide after allogeneic HCT (Tichelli et al. 2013).

6.4 Studies from Chronic GVHD Consortium

The Chronic GVHD Consortium is an integrated group of academic medical centers, patient support organizations, and clinical research resources that conducts clinical research in immune-mediated disorders after allogeneic HCT with the goal of improving the care and limiting the disability of patients affected by these disorders. Studies from the consortium have provided extensive information about impact of chronic GVHD on PROs. These studies are based on a cohort of allogeneic HCT recipients with chronic GVHD requiring systemic immunosuppressive therapy that was prospectively assembled in a multicenter observational study. Information

about symptoms, global ratings and perceptions of change, quality of life, and functional status was collected from the enrolled patients using the following well-validated instruments: SF-36, FACT-BMT trial outcome index, chronic GVHD symptom scale, and Human Activities Profile.

In one of the first studies from the consortium, Pidala et al. examined baseline QOL of HCT patients with chronic GVHD at the time of enrollment in the Chronic GVHD Consortium (Pidala et al. 2011a). They reported moderate and severe GVHD as defined by NIH global severity scoring system to be associated with poor patient-reported QOL, particularly in the physical domain, similar to some other systemic autoimmune diseases. In another analysis that compared the impact of overlap subtype and classic chronic GVHD, overlap subtype was associated not only with inferior clinical outcomes but also higher functional impairment and symptom burden (Pidala et al. 2012). Other consortium studies which have helped describe the influence of moderating factors such as age, the site of GVHD involvement and socioeconomic status on QOL in chronic GVHD patients are summarized in Table 6.1.

6.5 Consideration of QOL and Other PROs in Treatment and Prevention of GVHD

The use of PROs such as QOL, functional status, and symptom burden has been recognized as important for the drug approval process for products developed to treat chronic disabling conditions where the intent is not curative but to ameliorate symptoms, facilitate functioning, or improve QOL (Gnanasakthy et al. 2012). Challenges of including PRO end points in trials for acute GVHD include lack of instruments validated specifically for GVHD population, inability to tease out the impact of concurrent complications on QOL in a patient with severe acute GVHD, and patient burden associated with frequency and timing of data collection (Lee and Williams 2010).

Clinical Trials Working Group of 2014 NIH Consensus Conference on Chronic GVHD has proposed SWOPI (survival without progressive impairment) as a primary endpoint in chronic GVHD treatment trials (Martin et al. 2015). They also felt that PRO assessment might be reasonable to consider as a key secondary or co-primary endpoint to measure the core disease-related symptoms of chronic GVHD.

6.6 Use of QOL Endpoints in Treatment/Intervention Trials

QOL was examined as a secondary endpoint in a randomized trial of T-cell depleted bone marrow transplantation versus unmodified transplantation for unrelated transplants (Altmaier et al. 2006). Even though the incidence of acute GVHD was slightly higher in the unmodified arm, T-cell depletion did not have a differential impact on QOL at 1 year after transplantation indicating that acute GVHD may not have a notable impact on QOL. An ongoing multicenter trial that is evaluating the Outcomes of Second-line Therapy in Acute Graft-versus-Host Study including

Table 6.1 Summary of studies from chronic GVHD consortium

Author; number of patients	Aims of the study	Results
Pidala et al. (2011a) *N* = 298	• Examine association between cGVHD severity and QOL • Compare cGVHD cohort members' SF-36 mean scores to age- and gender-matched US population • Compare cGVHD cohort members' SF-36 mean scores to other chronic health conditions	• cGVHD severity was independently associated with QOL, adjusting for age • Compared with population normative data, SF-36 scores were lower for some domains but comparable for others • Moderate-to-severe cGVHD associated with significant compromise in multiple QOL domains, comparable to those for SS, SLE, and MS, but greater impairment compared with several common chronic health conditions including chronic lung disease, hypertension, diabetes, and arthritis
Pidala et al. (2011b) N = 336	• Examine association between changes in cGVHD severity over 6 months as assessed by NIH severity scale, clinicians, and patients with changes in patient-reported QOL	• No association between change in cGVHD severity evaluated by NIH criteria and change in QOL • Clinician-reported changes in severity were associated with changes in some QOL measures • Patient-reported changes in the severity of cGVHD were strongly associated with changes in all QOL measures
Inamoto et al. (2012) *N* = 283	• Assess correlation of the calculated response based on the provisional algorithm with symptom burden, QOL, and survival outcomes	• Clinical response at 6 months correlated with changes in symptom burden in patients with newly diagnosed cGVHD, but not with changes in quality of life or survival outcomes
Pidala et al. (2012) *N* = 427	• Examine clinical, functional, or prognostic significance of overlap subtype cGVHD	• Overlap syndrome (vs. classic cGVHD) was associated with: – Higher degrees of functional impairment – Higher symptom burden – Worse social functioning – Lower overall survival and higher non-relapse mortality rates
Pidala et al. (2013a) *N* = 567	• Examine whether the site of GI (esophageal, upper GI, lower GI) and type of hepatic (bilirubin, AP), ALT) involvement are associated with overall survival and non-relapse mortality, symptoms, QOL, and functional status measures	• Any esophageal involvement and NIH GI score greater than zero were associated with both symptoms and QOL • Elevated bilirubin was associated with QOL • No evidence that upper GI involvement, AP, ALT, or NIH liver score was associated with survival, overall symptom burden, or QOL

Table 6.1 (continued)

Author; number of patients	Aims of the study	Results
Pidala et al. (2013b) *N* = 584	• Examine relationship between hand grip strength (HGS) and 2-minute walk test (2 MWT) with patient-reported measures, cGVHD global severity, calculated and clinician-reported cGVHD response, and mortality	• Shorter 2MWT: – Associated with higher symptom burden, lower QOL, functional disability • Lower HGS: – Associated with lower QOL and functional disability
Inamoto et al. (2014)	• Evaluate 3 joint assessment scales and 10 other scales that assess symptoms, QOL, and physical functions • Examine longitudinal joint responses according to the validated scales and associations of joint/fascia manifestations with subsequent mortality	• Joint and fascia manifestations were associated with higher symptom burden, lower QOL
El-Jawahri et al. (2014) *N* = 522	• Examine the relationship between age group and QOL, physical functioning, functional status, non-relapse mortality, and overall survival	• More physical limitations in older patients with worse functional status relative to adolescent young adults (AYA) and middle-aged patients • Overall better QOL in older patients compared with middle-aged patients and similar to AYA patients
Palmer et al. (2014) *N* = 496	• Association of pulmonary measures with non-relapse mortality, overall survival, and patient-reported outcomes	• NIH symptom-based lung score was associated with non-relapse mortality and overall survival, patient-reported symptoms, and functional status
Sun et al. (2015) *N* = 342	• Describe the impact of ocular involvement in QOL	• Patients with ocular GVHD had worse QOL, and greater cGVHD symptom burden, compared with patients without ocular GVHD
Hamilton et al. (Abstract submitted to BMT Tandem Meetings 2017) *N* = 421	• Examine the association of SES parameters (income, education and work status) with survival and patient-reported outcomes	• Higher income was significantly associated with lower symptom burden • Ability to return to work was associated with lower symptom burden, better activity, and QOL • No association of SES with survival after cGVHD

Abbreviations: *cGVHD* chronic graft-vs.-host disease, *QOL* quality of life, *SS* systemic sclerosis, *SLE* systemic lupus erythematosus, *MS* multiple sclerosis, *NIH* National Institutes of Health, *AP* alkaline phosphatase, *ALT* alanine aminotransferase, *GI* gastrointestinal, *SES* socioeconomic status

extra corporeal photopheresis plans to examine the differences in QOL with different treatments (Personal communication: Madan Jagasia; PI of POSTAGE STUDY).

CBMTG 0801 was a randomized, multicenter study that examined whether the addition of Thymoglobulin (TG) to preparative regimens resulted in a decrease in the use of immunosuppression for chronic GVHD, leading to improvements in

QOL (Walker et al. 2014). Life Happiness was higher and chronic GVHD symptoms were lower in the TG group as compared to the no TG group ($p = 0.014$ and 0.017 respectively). The long-term follow-up data from BMT CTN 0201 study (peripheral blood vs. bone marrow for unrelated donor HCT) was recently published and showed better psychological well-being, less burdensome chronic GVHD symptoms, and increased likelihood of return to work for bone marrow recipients as compared to peripheral blood at 5 years after HCT (Lee et al. 2016).

QOL endpoints have recently been used in the case of treatment of organ-specific chronic GVHD. In a phase II trial of bandage contact lenses for ocular GVHD, eye symptoms were primary endpoint (Inamoto et al. 2015). All measures including the Lee eye subscale, ocular surface disease index, and 11-point eye symptom ratings showed statistically significant and clinically meaningful improvement in symptoms after the placement of these lenses. A prospective, multicenter, randomized, two-arm phase II crossover trial of imatinib or rituximab for the treatment of sclerotic chronic GVHD examined the correlation of changes in patient-reported outcomes (SHAQ standard disability index, Lee skin symptom scale, SF-36, FACT-BMT, or HAP) with significant clinical response as a secondary endpoint (Arai et al. 2016). Patients on imatinib arm showed a median 10-point decrease for the Lee skin symptom scale and a response to imatinib was associated with improvement in the SF-36 vitality score and the Lee lung symptom score. There were no differences in the other patient-reported measures, including skin bother, and no differences correlated with rituximab treatment successes. Williams et al. recently reported on the use of Fluticasone propionate, azithromycin, and montelukast (FAM therapy) with steroid pulse to be associated with stable lung function and improved functional and patient-reported outcomes (SF 36 social functioning score and mental component score, FACT emotional well-being, and Lee symptom scores in lung, skin, mouth, and the overall summary score) for newly diagnosed patients with bronchiolitis obliterans syndrome (Williams et al. 2016).

The BMT CTN 0801 was a phase II/III randomized, multicenter trial comparing sirolimus plus prednisone, and sirolimus/calcineurin inhibitor plus prednisone for the treatment of chronic GVHD. The trial examined the severity of chronic GVHD symptoms as reported by patients and QOL utilizing the FACT-BMT, SF-36, etc., as secondary endpoints and results of these secondary analyses are awaited.

6.7 Non-pharmacologic Interventions to Improve QOL in GVHD Patients

Interventions such as exercise, cognitive behavioral therapy, mindfulness-based practices for developing positive emotions, and educational efforts have been tried in HCT generally to help improve QOL (Baumann et al. 2009; DeFor et al. 2007; DuHamel et al. 2010; Jacobsen et al. 2014). The proportion of patients with GVHD in these studies is either not described optimally or very small to be able to make definitive conclusions about their benefits for chronic GVHD patients. While there have been some preclinical studies showing the benefits of exercise on survival,

clinical severity, physical fitness, and cytokine profile in a murine model, there is a paucity of clinical studies that have assessed the impact of exercise interventions on ameliorating the detrimental effects of both acute and chronic GVHD in humans (Fiuza-Luces et al. 2016). In a small retrospective study, pulmonary rehabilitation led to improvement in 6-minute walk distance, subjective symptoms of dyspnea, and exercise tolerance in ten patients with bronchiolitis obliterans syndrome (Tran et al. 2012). It is intuitive that aggressive physical therapy and a home-based exercise program, along with the provision of resources for regular strength training and aerobics, can help address the functional impairments due to fasciitis, contractures, and steroid myopathy commonly seen in chronic GVHD patients but have not been tested in a study or reported widely. Despite this, the Ancillary Therapy and Supportive Care Working Group of 2014 National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD recommends more frequent screening for such issues and appropriate referrals for physical medicine and rehabilitation for intensive physical therapy, cognitive, behavioral interventions, or psychiatry assessment if indicated (Carpenter et al. 2015).

6.8 Gaps in Research and Recommendations

Survivors with acute and chronic GVHD have a different spectrum of issues that impact QOL. While acute GVHD is mostly about symptoms such as pain, diarrhea and itching, factors such as prolonged hospitalization, concurrent complications such as infections, and need for higher doses of immunosuppressive medications may contribute to the decline in QOL. Prospective collection of QOL and other PRO information in the context of large BMT CTN studies may provide us with better insights into the impact of different transplant strategies on the incidence and QOL impact of acute GVHD, though some of the challenges around measuring QOL in these patients such as intrinsic measurement variability and higher mortality/sicker patients leading to more missing data may influence the quality of such information. In that case, the hope will be that interventions directed toward decreasing the incidence and mortality associated with acute GVHD will have positive impact on QOL as well.

The psychological, functional, or adjustment difficulties have been much better characterized for chronic GVHD. The extensive work done by Chronic GVHD Consortium has contributed to our understanding of the PRO as endpoints and their sensitivity to clinical change in patients with chronic GVHD. One of the other areas that has recently been highlighted in HCT is the concept of financial toxicity and its impact on other psychosocial outcomes after HCT (Majhail et al. 2013; Khera et al. 2014; Hamilton et al. 2013; Abel et al. 2016). It is likely that chronic GVHD can result in increased financial burden for HCT patients even after a long time from HCT because of the need for intense medical follow-up/treatments and impaired functional status preventing return to work. Interestingly while chronic GVHD was shown to be associated with delayed return to work in one of the studies (Syrjala et al. 2004), it has not emerged as a predictor for return to work or overt financial

hardship in others (Khera et al. 2014; Abel et al. 2016; Kirchhoff et al. 2010). This is likely due to small sample size for patients with chronic GVHD in the overall study population. An ongoing Chronic GVHD Consortium study is examining financial burden and its determinants in chronic GVHD patients and will study the association of financial burden with quality of life as measured by FACT-BMT and SF-36.

6.9 Conclusion

There is a need to apply the knowledge that has been gathered in the area of QOL in chronic GVHD to start including validated measures of QOL in prevention/treatment trials for chronic GVHD. In addition to therapeutic trials for this disease, we must design and test non-medical interventions to help improve QOL for these patients while working toward decreasing its psychosocial and financial burden and increasing the social and professional reintegration of these patients. While advances are being made in the understanding of the pathobiology and targeted treatments for GVHD, it is important to include assessments of patient outcomes and experiences when testing approaches to contain this difficult complication of allogeneic HCT to be able to meet the goal of optimum patient centered care.

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Special Aspects of ICU Care: Is There an Art to It?

7

Ann C. Long

7.1 Introduction

Intensive care unit (ICU) admission is common following hematopoietic cell transplant (HCT) (Saillard et al. 2016; Bayraktar and Nates 2016), and despite advances in both critical care and transplant processes, patients who develop critical illness following transplant continue to experience high mortality (Bayraktar and Nates 2016; Saillard et al. 2016). Many of these individuals will receive aggressive interventions, dying in the ICU after the terminal withdrawal of mechanical ventilation or discontinuation of other life-sustaining measures. For those who survive, the sequelae of critical illness, including physical impairment and symptoms of psychological distress, may follow the patient long after discharge from the ICU (Brummel et al., 2017; Hashem et al. 2016). Given the significant ramifications of critical illness for these patients and their family members, the importance of pursuing high-quality supportive care cannot be overstated. The key components of supportive care—high-quality communication, symptom control, and emotional and spiritual support—are no different for these patients than for other critically ill patients; however, there are special aspects to supportive care for critically ill patients undergoing HCT that warrant consideration.

For patients undergoing transplant, critical illness often occurs against a backdrop of pre-existing physical dysfunction, symptoms from transplant-related complications, and psychological distress (Pallua et al. 2010; Bevans et al. 2014; Chaudhry et al. 2016; Mosher et al. 2009; Cohen et al. 2012; El-Jawahri et al. 2016b). Although most intensivists possess a core set of supportive care skills and

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are adept at providing primary supportive care, the management of severe pain and complex psychosocial symptoms may exceed their capabilities. In addition to these challenges, intensivists must also help patients and their family members navigate the tenuous balance between hope for a lasting cure of the patient's underlying disease process and the real possibility of death in the ICU. This balancing act must occur in close concert with the patient's hematologists, who bring specific expertise to the table and in many instances have long-standing relationships with the patient and their family.

The provision of excellent supportive care to critically ill patients and their family members requires dedicated attention to several aspects of ICU care. First, high-quality communication between providers of different disciplines must be considered as essential as communication with the patient and family. Second, specialty supportive care providers should be introduced early during a patient's ICU stay, particularly when symptom management or psychosocial concerns are prominent or the risk of death is very high. Finally, for patients who will not survive their ICU admission, providers should consider several end-of-life care issues unique to this population, including the support of patients and family members as they cope with a major shift in the focus of care, challenges related to maintaining social support networks, and the need to foster closure of the therapeutic relationship with outpatient providers. This chapter will focus on these specific aspects of ICU care for patients undergoing HCT.

7.2 Importance of Interdisciplinary Shared Decision-Making for Patients in the ICU

Early during the assessment and management of a critically ill patient, ICU providers are primarily focused on addressing the life-threatening physiologic derangements that led to ICU admission. As the patient stabilizes, the ICU team begins to develop an understanding of the patient's overall trajectory, and for many critically ill patients, the intensivist has all of the expertise he or she needs to provide prognostic information to patients and their family members. Patients who have undergone HCT, however, present unique challenges for ICU providers who may not have a complete understanding of the patient's underlying disease process or how it relates to overall prognosis. For this reason, hematologists should be considered essential members of the critical care team to ensure that intensivists have all of the information they need to provide appropriate care. The intensivist needs key details about the disease process that led to transplant, the post-transplant course to date, and any estimates of projected disease-free survival in the event that the critical illness is overcome. The hematologist, on the other hand, should respect the intensivist's experience managing critically ill patients, as many conditions managed in the ICU, such as acute respiratory distress syndrome or septic shock, carry their own prognostic implications. All involved parties must acknowledge that an ICU admission for a patient following HCT is a critical transition in a patient's course that may dramatically affect the patient's overall trajectory (Mayer et al. 2017; Platon et al. 2016). Residual prognostic uncertainty can set the stage for discord among various providers, often specifically related to the application of aggressive, life-sustaining

therapies. When such situations arise, it is imperative that all involved providers find common ground, in order to present clear and consistent communication about prognosis and treatment goals to patients and their family members. Conflicting information may generate confusion and frustration for patients and family members and also contribute to difficulties with decision-making (Iverson et al. 2014; Reeves et al. 2015; McNeese et al. 2016).

Although many providers may feel that they collaborate well with other members of the healthcare team, there is evidence to suggest that much of the decision-making that occurs in the ICU takes places independently (DeKeyser Ganz et al. 2016). Following HCT, independent decision-making by intensivists or hematologists about prognosis or treatment options may thwart efforts to engage in primary supportive care or may delay the involvement of specialty supportive care providers. In the ICU, interdisciplinary shared decision-making should be viewed as an essential component of supportive care in transplant. Although there is no standard approach to interdisciplinary care in the ICU, there are many different ways in which providers can improve the current processes in place at their institutions. One potential method involves daily multidisciplinary meetings between critical care providers and hematology team members. Multidisciplinary care has been championed in the ICU environment in the form of multidisciplinary rounds (Durbin 2006; Kim et al. 2010), but these interactions are typically confined to members of the ICU team, including nurses, pharmacists, respiratory therapists, advanced care practitioners, and physicians. There is limited information about the impact of multidisciplinary meetings that specifically involve the patient's critical care team and other subspecialty providers involved in the patient's care; however, the potential benefits of these meetings seem readily apparent. Multidisciplinary meetings provide an opportunity for providers who may have very different impressions of the patient's clinical condition to develop a shared perspective about the patient's disease process and overall prognosis. Based upon these conversations, a consistent message about the treatment plan can be shared with the patient and family. Although these meetings may not completely mitigate the provision of inconsistent information to patients or their family members, they are certainly a step in the right direction. Furthermore, multidisciplinary meetings offer healthcare providers an opportunity to address intra- and inter-team conflicts, including concerns that the care being provided is not concordant with the patient's expressed values and preferences. Efforts to improve communication between providers may attenuate disagreement, resolving conflicts that have the potential to negatively impact patient care and provider well-being (Azoulay et al. 2009; Danjoux Meth et al. 2009; Fassier and Azoulay 2010; Martins Pereira et al. 2016).

7.3 Early Involvement of Specialty Supportive Care in the ICU

Specialty supportive care has been shown to attenuate decrements in quality of life for patients with hematologic malignancies hospitalized for hematopoietic stem cell transplant (El-Jawahri et al. 2016a). Although there is little to no evidence assessing the effects of specialty supportive care on patient-centered

outcomes for these patients in the ICU, benefits from specialty supportive care for those who are not critically ill supports the concept that specialty supportive care could also improve outcomes for critically ill patients. However, barriers to the introduction of specialty supportive care in transplant still exist (Roeland and Ku 2015). HCT is an intense process, which carries significant risk for the patient but also the potential for a sustainable cure of what might otherwise be a terminal disease process. Patients consent to the receipt of toxic therapies and may experience significant pain and suffering in the pursuit of long-term survival. In some ways, HCT may seem at odds with the goals of supportive care, which is largely focused on quality of life, not necessarily quantity of life. However, there are many circumstances in which a patient can receive care directed at sustaining both quantity *and* quality of life. For example, a patient with septic shock can receive fluid resuscitation, undergo placement of central venous access, and begin vasopressor support to maintain mean arterial pressure, all while receiving supportive therapies intended to control severe oral pain from mucositis or manage the anxiety associated with a period of clinical deterioration. Supportive care is not at odds with the management of a patient who has elected to pursue aggressive interventions in the ICU. Rather, patients who have already dealt with significant pain and suffering prior to ICU admission should be expected to have even more of a need for supportive care once critically ill. The case can be made that any patient admitted to the ICU following HCT should be evaluated by specialty supportive care. However, the reality is that there are a limited number of specialty supportive care providers available to care for the growing number of patients undergoing HCT (Lupu 2010; Kamal et al. 2017). There is a clear need to increase the available workforce of specialty supportive care providers, but until this need can be met, critical care providers can take the patient's symptom burden and overall prognosis into consideration to help ensure that the benefits of specialty supportive care are realized by patients and family members most in need.

Among patients who face critical illness in the setting of transplant, several subpopulations should receive strong consideration for early involvement of specialty supportive care. Patients with severe symptoms or complex psychosocial needs should be considered a priority for specialty supportive care consultation. For patients admitted to the ICU with severe symptoms related to the transplant process, including pain, nausea, mucositis, or diarrhea, specialty supportive care can provide tremendous assistance by helping the critical care team develop a treatment plan that will be effective in the context of new physiologic derangements (Roeland et al. 2010a). Psychosocial symptoms may also be a significant concern, and specialty supportive care providers can help patients and family members cope with illness, recognize, and treat symptoms of psychological distress, and process grief and loss (Roeland et al. 2010b). Furthermore, for many patients in the ICU, ongoing prognostic assessments allow patients and their family members to reassess their willingness to focus on quantity of life when it may actually interfere with the relief of pain and suffering, for instance, when mechanical ventilation is involved. Specialty supportive care providers can dedicate their

time and expertise to helping the patient and family understand the role of comfort care measures in the ICU as they consider the process of terminal withdrawal of life-sustaining therapies.

Another group of patients who should be high priority for specialty supportive care referral includes individuals whose overall prognosis is grim. For patients who have undergone HCT, several factors have been consistently associated with a poor prognosis following ICU admission. These include the need for mechanical ventilation (Paz et al. 1993; Price et al. 1998; Kroschinsky et al. 2002; Afessa et al. 2003; Soubani et al. 2004; Pene et al. 2006; Scales et al. 2008; Huynh et al. 2009; Trinkaus et al. 2009; Townsend et al. 2013; Lengline et al. 2015; Mokart et al. 2015; Faucher et al. 2016; Platon et al. 2016; Mayer et al. 2017), the presence of multi-organ failure (Soubani et al. 2004; Pene et al. 2006; Trinkaus et al. 2009; Agarwal et al. 2012; Benz et al. 2014), and the need for vasopressor support (Kew et al. 2006; Huynh et al. 2009; Trinkaus et al. 2009; Boyaci et al. 2014; Mayer et al. 2017). Other special populations who may also be at high risk for mortality include patients experiencing early relapse, particularly with high-risk hematologic malignancies (Mielcarek et al. 2007), patients with active or acute graft versus host disease (Pene et al. 2006; Bayraktar et al. 2013; Lengline et al. 2015; Escobar et al. 2015; Platon et al. 2016), and patients who develop idiopathic pneumonia syndrome (Crawford and Hackman 1993; Kantrow et al. 1997; Afessa et al. 2001; Yanik et al. 2014). The impetus for involving specialty supportive care providers for patients with these risk factors is not only related to the significant potential for death in the ICU, but also related to poor prognosis among those who survive to ICU discharge. Patients with these risk factors may survive their ICU stay but then experience death within the coming weeks to months. Specialty supportive care providers can be introduced in the ICU and then supportive care can be continued outside of the critical care setting for those who survive. In many ways, an ICU admission for respiratory failure, multi-organ failure, or shock should serve as a clear signal to the healthcare team that specialty supportive care may be indicated, particularly when prognostic uncertainty may have curtailed previous discussions about supportive or end-of-life care (Odejide et al. 2014). Involvement of specialty supportive care providers should occur early for these patients, as late referrals may make it difficult for consultants to adequately address symptom burden, explore psychosocial needs, or assist in the transition from full, aggressive measures to a comfort-focused approach (Button et al. 2014).

7.4 End-of-Life Care for Patients Undergoing Hematopoietic Cell Transplant and Their Family Members in the ICU

For patients undergoing HCT, critical illness often leads to death (Saillard et al. 2016; Bayraktar and Nates 2016). Key elements of end-of-life care for these patients are identical to those recommended for other critically ill patients, and should include a focus on shared decision-making with patients and their family members,

high-quality communication about the dying process, and a well-planned approach to symptom control and the withdrawal of life-sustaining therapies (Truog et al. 2008). In addition to providing these core elements of care at the end of life, intensivists should also consider aspects of care that may be unique to these patients and their families. Specific issues include the support of patients and family members as they cope with a major shift in the focus of care, challenges related to maintaining social support networks, and the need to foster closure of the therapeutic relationship with outpatient providers.

Transitioning from the pursuit of life-sustaining therapies to a focus on comfort is often a major shift in care for patients following HCT. Transplantation is typically undertaken with the central objective of curing an underlying malignancy and sustaining life, and when it becomes apparent that this objective will not be met, the patient and their family members may feel completely overwhelmed. When this realization occurs hours or days prior to the patient's death, which is often the case in the ICU, patients and their family members have little time to process a complex array of emotions. Compared to bereaved family of patients who have not undergone transplant, family of patients who have undergone HCT may experience higher levels of psychological distress following the patient's death (Drew et al. 2005; Jalmsell et al. 2011). This seemingly abrupt transition in treatment goals may contribute to these symptoms of psychological distress, making bereavement and support services an especially important element of end-of-life care for these patients and their family members. The potential for such emotional upheaval is yet another reason why patients at high risk of death in the ICU may benefit from the early involvement of specialty supportive care providers who can help patients and family members cope with this sense of loss and grief.

Another aspect of end-of-life care that may require special attention for patients following transplant relates to the presence of social support from friends and family members. Many patients have travelled far from their homes to receive care at specialized transplant centers. For these individuals, their support system in the ICU may only consist of a small number of immediate family members, with the majority of their social support network left in the patient's hometown. The healthcare team should make efforts to facilitate patient interaction with loved ones who cannot be near and also support the family in their desire to make the ICU feel as much like home as possible for the patient. Following death, social workers can play an integral role in helping the family coordinate funeral arrangements, especially for those who plan to transport the decedent to another state.

Finally, the role of the patient's outpatient transplant team cannot be forgotten during the end-of-life process. There is often a long-standing relationship between the patient and family and the providers who have guided them through the transplant process. In some circumstances, providers from the outpatient setting also provide inpatient services and may be very familiar with the patient's ICU course. However, in other situations, the outpatient provider may not be aware of the course of events that led to ICU admission or the patient's severity of illness. In these cases, it is reasonable for the critical care team to update the outpatient

hematologist and also explain any plans regarding the patient's end-of-life care. Concerns about loss of continuity and abandonment at the end of life are very real for patients and their family members (Back et al. 2009), and the critical care team can play an important role in helping to maintain the link between the outpatient and inpatient realms. In addition, this kind of communication allows the patient's primary hematologist to engage in the grieving process with the family and gives them an opportunity to seek closure of the patient-family-clinician therapeutic relationship.

7.5 Expert Opinion

ICU admission is common among patients undergoing HCT, and the development of critical illness is often a major event influencing a patient's overall trajectory. Many of these patients will die following ICU admission. For those who survive critical illness, physical disability and symptoms of psychological distress may affect quality of life long after discharge from the ICU. Importantly, caregivers for these patients must also cope with the burden imposed by critical illness. Supportive care is essential for critically ill patients and their family members, and should include high-quality communication between providers of different disciplines and early involvement of specialty supportive care providers, particularly when symptom management or psychosocial concerns are prominent or the risk of death is very high. For those patients who will not survive their ICU admission, end-of-life care must address issues unique to this patient population, including the support of patients and family members as they cope with a major shift in the focus of care, challenges related to maintaining social support networks, and the need to foster closure of the therapeutic relationship with outpatient providers.

7.6 Future Directions

There is a paucity of evidence to inform the best approach to providing high-quality supportive care for patients who develop critical illness following hematopoietic stem cell transplant. Rigorous study of the role of supportive care in the ICU is necessary, and particular attention should be paid to addressing outcomes that matter most to patients and their family members. Strategies to improve existing supportive care practices in the ICU include interventions to enhance interdisciplinary shared decision-making and efforts to promote early involvement of specialty supportive care. Future research should also focus on the potential role of intensivists and specialty supportive care providers outside of the ICU, specifically in the decision-making processes that occur immediately prior to ICU admission. Additionally, there is a need to develop a better understanding of the experiences of family members of patients who die in the ICU following HCT, in order to ensure that their supportive care needs are met.

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Mental Health: Assessment, Treatment, and Outcomes

8

Mary Callahan and Sonia Malhotra

8.1 Prevlance Precedes Screening and Diagnosis

Approximately 47% of patients with cancer, including all types and stages, meet diagnostic criteria for a psychiatric disorder (Derogatis et al. 1983). Rates of depression vary widely depending on the diagnostic method of screening and specific patient population (Valente et al. 1994). It has been reported that up to 58% of patients with cancer have symptoms of depression and up to 20–25% of patients meet diagnostic criteria for major depressive disorder at some point in their illness (Hotopf et al. 2002). Prevalence rates appear to increase as disease progresses. Additionally, nearly 70% of patients with serious medical illness endorse symptoms of anxiety, especially those with a diagnosis of cancer (Portenoy et al. 1994).

8.2 Screening and Diagnosis

The American Society of Clinical Oncology (ASCO) recommends that all patients with cancer as well as cancer survivors be evaluated for symptoms of depression and anxiety at their initial visit and at any point when there are changes in disease or treatment status including transition to end-of-life care or as otherwise clinically indicated (Andersen et al. 2014). It is recommended that hematopoietic cell

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transplant (HCT) patients be assessed throughout the transplant recovery period, at 6 months post-transplant and at least yearly thereafter (Majhail et al. 2012).

In HCT patients, it is important to keep in mind that the variety of emotions felt on a daily basis can be a normal way of responding and coping with their complex disease and the nearly constant outpouring of information and test results. However, when feelings of sadness or anxiety cause significant distress or dysfunction in social or occupational settings, psychiatric illness may be contributing. It is also important to remember that organic causes must be excluded before a primary psychiatric diagnosis can be made. General medical conditions such as thyroid dysfunction can present with anxiety or depression. Other considerations should include vitamin deficiencies, electrolyte disturbances, medication side effects, and substance use. When an underlying medical condition is at the root of symptoms, the best treatment is to treat the underlying condition rather than treatment with antidepressants or anxiolytics.

While physicians tend to be attuned to the well-being of patients, there is a tendency for physicians to underestimate the degree of depressive symptoms in patients who are more depressed (Barata et al. 2017; Passik et al. 1998). Thus, the use of diagnostic criteria and screening tools are a necessary part of evaluating the mental health of HCT patients (Kathol et al. 1990).

The most widely used diagnostic criteria for the diagnosis of psychiatric illness comes from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (American Psychiatric Association 2013). Some of the most prevalent disorders seen in the HCT population are major depressive disorder (MDD), generalized anxiety disorder (GAD), and adjustment disorders (Tables 8.1 and 8.2).

Screening questionnaires are available, though they have not been incorporated widely into practice. Another limiting factor of many screening tools is the inability to distinguish between symptoms that are due to disease and/or treatment versus those due to depression or anxiety. The Functional Assessment of Cancer Therapy-Bone Marrow Transplantation (FACT-BMT), a validated measure of quality of life in HCT patients, includes a section on emotional well-being (Table 8.3) (McQuellon et al. 1997). Depression and anxiety symptoms can also be assessed using the Patient Health Questionnaire-9 (PHQ-9) and the GAD-7 Anxiety Severity score which are more cumbersome to administer and include questions that often screen positive due to the underlying disease and/or treatment. One of the most effective and easiest to use tools is the following series of 2 questions (Chochinov et al. 1997):

1. Have you felt depressed or hopeless for most of the time over the last 2 weeks?
2. Have you found that little brings you pleasure or joy over the last 2 weeks?

8.3 Diagnostic Dilemmas

The diagnosis of clinically significant depression and anxiety in HCT transplant patients is obscured by multiple factors. First, there is significant overlap of symptoms between physiologic illness and mental health. Some can be attributed to

Table 8.1 DSM V diagnostic criteria: major depressive disorder

• Five (or more) of the following symptoms have been present during the same 2 week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
  • Note: Do not include symptoms that are clearly attributable to another medical condition.
  • Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (note: in children and adolescents, can be irritable mood)
  • Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
  • Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (note: in children, consider failure to make expected weight gain.)
  • Insomnia or hypersomnia nearly every day.
  • Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
  • Fatigue or loss of energy nearly every day.
  • Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
  • Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
  • Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
• The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
• The episode is not attributable to the physiological effects of a substance or another medical condition.
 	
4. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
 	
5. There has never been a manic episode or a hypomanic episode.		

serious medical illness such as weight loss, fatigue, loss of energy, and changes in sleep. In regard to anxiety, there are several different physiologic causes of anxiety, such as dyspnea, pain, alterations of self-image secondary to weight loss or surgery, and worry stemming from the status of the cancer. On the other hand, mental illness often presents with somatic complaints and it can be difficult to distinguish between the two (Kroenke 2003). Physical manifestations of the cancer itself may lead to anhedonia and malaise or pain may prevent patients from participating in enjoyable activities. Transient feelings of sadness, hopelessness, anxiety, and even passive suicidal ideation can be common amongst patients with serious illness and can be on the

Table 8.2 DSM V diagnostic criteria: generalized anxiety disorder

• Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
• The individual finds it difficult to control the worry.
• The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
  • Note: Only one item is required in children.
  • Restlessness or feeling keyed up or on edge.
  • Being easily fatigued.
  • Difficulty concentrating or mind going blank.
  • Irritability.
  • Muscle tension.
  • Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
• The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
• The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
• The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).		

Table 8.3 Fact-BMT

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

spectrum of normal coping. Lack of involvement in social activities or those once enjoyable for patients out of proportion to physical hindrance from the chronic disease may be the best way to identify depression in these patients (Wilson et al. 2007).

Some clinicians prefer using the more cognitive symptoms, such as irritability and social withdrawal when diagnosing major depressive disorder in patients with serious illness. The more traditional diagnostic approach may lend itself to overdiagnosing depression and anxiety in patients with severe medical illness. This risk, however, is much lower than the risk of undertreating these patients. Ultimately, when diagnostic uncertainty remains, treatment should be highly considered. Patients whose depression is not accurately classified tend to report higher levels of pain and have higher levels of disability (Passik et al. 1998).

8.4 Treatment

For patients diagnosed with major depressive disorder, the gold standard of treatment includes patient and family education, supportive psychotherapy, and antidepressant medication. As with all supportive care, the best care is delivered with an interdisciplinary approach, including physicians, nurses, psychologists, and spiritual counselors (Spiegel et al. 2011). In patients with advanced cancer, cognitive behavioral therapy has been shown to offer significant benefits. Group supportive therapy has also been shown to be a very positive experience for patients (Miller et al. 2005).

The mainstay of pharmacologic treatment of depression in patients with cancer is use of selective serotonin reuptake inhibitors (SSRIs) and psychostimulants. There have been several randomized, controlled trials comparing antidepressants with placebo for the treatment of depression in patients with cancer and have suggested a benefit to treatment overall (Theobald et al. 2003). Notably, it is important to keep in mind that SSRIs typically require 8 weeks of therapy to demonstrate a benefit, as demonstrated in the STAR*D trial (Rush et al. 2004). Thus, SSRIs may not be appropriate to initiate in patients with a prognosis of less than 6 months.

Stimulants, such as methylphenidate and dextroamphetamine, are particularly effective for treatment of depression at the end of life given their rapid onset (Escalante et al. 2014; Rozans et al. 2002). A therapeutic response is generally seen within 24–48 h of initiating therapy. Additionally, psychostimulants have evidence for use in cancer-related fatigue (Bruera et al. 2006).

Additional options include buproprion, an activating antidepressant that can help patients with low energy levels. Venlafaxine, an serotonin and norepinephrine reuptake inhibitor (SNRI), can be energizing and assist patients with neuropathic pain issues. Mirtazapine is another effective antidepressant that tends to be sedating at lower doses and helpful for insomnia while also providing appetite-stimulating effects. Tricyclic antidepressants are not as well tolerated as other antidepressants due to sedating effects and are not used as first line therapies for depression in patients with cancer (Table 8.4). When first-line therapies are ineffective, patients have suicidal ideation, or there is diagnostic uncertainty, patients should be referred to a psychiatrist. As with all medications used for supportive care, consultation with

Table 8.4 Therapeutic considerations in pharmacologic treatment of depression and anxiety

Class	Mechanism of action	Benefits	Adverse side effects
Tricyclic antidepressants	Inhibition of 5-HT and NA reuptake; anti-muscarinic, antihistaminic, anti-alpha 1	Decreased pain, improved sleep	Constipation, dry mouth, urinary retention, drowsiness, hypotension
Selective serotonin reuptake inhibitors	Inhibitions of 5-HT reuptake	Increased sedation	Sexual dysfunction, nausea, vomiting, diarrhea
Selective noradrenaline reuptake inhibitors	Inhibition of NA reuptake, slight anti-muscarinic	Improved drive, improved cognition	Hypotension, dizziness, dry mouth, urinary retention
Selective serotonin and noradrenaline reuptake inhibitors	Inhibition of 5-HT and NA reuptake	Decreased pain	Hypertension
Selective dopamine and noradrenaline reuptake inhibitors	Inhibition of dopamine and NA reuptake	Improved concentration and attention, decreased fatigue	Anxiety, psychomotor activation
Noradrenergic and specific serotonergic antidepressants *Serotonin antagonist and reuptake inhibitors*	Increase 5-HT and NA activity, antihistaminic Increase 5-HT activity	Improved sleep, increased appetite, weight gain Improved sleep, decreased pain	Drowsiness Drowsiness
Psychostimulants *Benzodiazepines*	Increase dopamine activity Binds to benzodiazepine receptors; enhances GABA effects	Increased energy, improved concentration, decreased pain Reduced acute anxiety or agitation; reduced anticipatory nausea	Restlessness, agitation, insomnia, psychosis, anorexia, tachycardia, hypertension, seizures Sedation, dizziness, increased agitation

Adapted from Jordan et al. (2015)

a HCT pharmacologist should occur to ensure there are no adverse interactions between medications. HCT patients are on a wide variety of medications that need to be cross checked to ensure they do not interfere with therapeutic levels of immunosuppressants and/or anti-rejection agents.

Treatment of anxiety in patients with life-limiting illness involves a multidisciplinary approach, as well. Many effective nonpharmacologic interventions, such as psychotherapy, relaxation training, acupuncture, meditation, music therapy, art therapy, pet therapy and aromatherapy, have shown promise for treatment of anxiety in patients undergoing supportive care (Traeger et al. 2012). The most studied psychosocial intervention for anxiety is psychotherapy, which has shown modest effects for preventing or reducing anxiety in patients with cancer (Sheard and Maguire 1999). Other modalities represent an exciting opportunity for further research.

Medications such as trazodone can be used for treatment of anxiety while assisting patients with sleep issues which often are a source of anxiety. SSRIs remain the drugs of choice for chronic anxiety, but their effects take time and use can be limited by life expectancy. Benzodiazepines can be used for relief of acute anxiety, though should be used with caution as they can worsen or induce delirium.

8.5 Conclusion

Mental health is of utmost importance when it comes to quality of life in the HCT patient population. Depression and anxiety are common, and unfortunately, underrecognized and undertreated. All patients should be routinely screened for depression and anxiety. There are multiple challenges to diagnose mental health issues in this patient population, however this should not defer clinicians from evaluating and treating patients. Supportive care in an interdisciplinary setting, along with pharmacologic therapy, can decrease suffering for both patients and their family members.

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9 Spirituality and Acknowledgement of Cultural Diversity: Who Said It Is Important?

Laura Finn, Rev. Estrella Valino, and Rev. Anthony De Conciliis

Our most cruel failure in how we treat the sick is the failure to recognize that they have priorities beyond merely being safe and living longer.

Atul Gawande, Being Mortal (Atul 2014)

9.1 Introduction

Does spirituality play a "healing" role as a person faces illness and hospitalization with the attending thoughts and feeling of vulnerability? Spirituality is the result of the personal search for meaning and purpose in life, a connection with the transcendent dimension of existence, and the experiences and feelings associated with that search for connection (Peterman et al. 2002). Indeed, this personal search is enhanced

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by illness. Spirituality is a living reality that opens patients to the reverence of life and the transcendent experience that transforms the way people think about life and death. The nature of spirituality challenges us in all facets of life including concerns about life and death. Our response to these challenges is highly dependent on the awareness and depth of one's religious and spiritual ways of thinking, feeling, and believing. These become part of the healing process understood as making one whole again. The truth is that healing can occur even when there is no cure. Side by side the medical treatments, the strength of one's spirituality helps patients because "they attend to their inner world of suffering illness and physical challenges" (Hilsman 2016).

As cancer treatments evolve, cure of disease often replaces the goal of healing the sick and may be incorrectly considered separate processes. The term healing and its consideration as an endpoint of treatment nearly disappeared from medical literature until its revival by Palliative Medicine (Egnew 2005). Psychology conceives healing as reordering an individual's position in the universe, as the process of making one whole again. The practices of Palliative Medicine, psychology, and spiritual counseling are proofs, healing can occur even when there is no cure (Comfort 1978; Gordon 1979). The complex process of healing requires addressing a patient and his/her illness from several different perspectives, including the spiritual perspective. Spirituality enhances the way a patient faces the ultimate questions.

An assessment of spirituality is crucial in order to create a reciprocal relationship between the patients and provider which in turn allows for complete, whole person healing. It is important to respect the intent of "do no harm" and uphold the patients' right to autonomy and freedom to have and express their thoughts and beliefs (Anandarajah and Hight 2001; Post et al. 2000). The origins of medicine, nursing, and spiritual guidance arise from the foundation of compassion and these practices share a common goal of healing (Hilsman 2017). The primary measure of spiritual care asks how well a patient's cultural, religious, and spiritual needs are being met by his/her healthcare community when a patient is dealing with illness. Spiritual need is the unpleasant or painful experience of being unable finding meaning and purpose relative to what we cannot control. The National Cancer Care Network defines spiritual distress as "common, normal feelings of vulnerability, sadness, and fear to problems that become disabling such as depression, anxiety, despair, and existential spiritual crises" (Holland et al. 2003). To address spiritual needs we must recognize the role of spiritual care, address disruptions to spirituality that impact patient healing, and utilize the tools around us to treat spiritual distress. In the next section, we will introduce a definition of spirituality and its connection to this new understanding of healing.

9.2 Defining Spirituality

Spirituality is a domain of health, in addition to the physical, emotional, and social domains (Herdman and Kamitsuru 2017). Spirituality may involve religion but is not defined by religion. A global, consensus definition of spirituality is "a dynamic and intrinsic aspect of humanity through which persons seek ultimate meaning,

Table 9.1 Primary spiritual areas (Hilsman 2017)

Personal: *Developing self-worth*	Interpersonal: *Relationships*	Transcendent: *Beyond mortality*	Communal: *Sense of belonging*
Self-care	Romance	Nature	Family
Sexuality	Parenting	Religion	Heritage
Ageing	Friendships	Birth/death	Neighborhood
Occupation	Elders	Art	Church
Mindfulness	Teaching	Universe	Nation
Materiality	Mentorship	Loss	Peers
Hobbies	Giving/getting help	Music	Community

purpose, and transcendence, and experience relationship to self, family, others, community, society, nature, and the significant or sacred. Spirituality is expressed through beliefs, values, traditions, and practices" (Puchalski et al. 2009). The enormous scope of spirituality is "all that people have learned to do, believe, ponder, and practice in order to cope with and enjoy what human beings cannot control" (Fitchett 2002). All human experiences contain an aspect of spirituality, see Table 9.1.

Clearly defining spiritual needs and the goal to address them is included in Palliative Medicine's practice of defining "goals of care" with patients (Puchalski et al. 2019). Spiritual providers, as members of multidisciplinary primary care teams or Palliative Medicine teams are specialists in the area of supportive spiritual care. All healthcare professionals can provide primary palliative care by recognizing and inquiring about their patients' spiritual needs or performing structured spiritual assessments, see Table 9.2. Palliative Medicine and chaplain services are specialists in the treatment of spiritual pain and addressing spiritual crises. Practices have described inclusion of chaplain services on routine, daily multidisciplinary inpatient oncology unit rounds as beneficial to their patients' satisfaction and quality of life (Kao et al. 2017; Sinclair and Chochinov 2012; Sinclair et al. 2009).

9.3 Why Is a Spiritual Assessment Necessary?

Ninety-four percent of hospitalized patients consider spiritual health as important as their physical health, 77% of patients want their physicians to inquire about and consider their spiritual needs, and 40% use their faith to cope with illness (King and Bushwick 1994; Koenig 1998). At the time of terminal illness and dying, 79% of patients want their physicians to know their beliefs (MacLean et al. 2003). Despite their desire for spiritual assessment, most patients in both outpatient and inpatient settings report never being asked about their spiritual needs, even though up to 90% of physicians admit they should be aware of their patients' spirituality (Maugans and Wadland 1991; Monroe et al. 2003; Luckhaupt et al. 2005). The Joint Commission requires spiritual assessment at hospital admission. The Joint Commission recommends that patients are asked about their cultural and spiritual beliefs and how they may impact their preferences for care. These spiritual and cultural preferences may include requests for privacy and modesty, use of

Table 9.2 Spiritual assessment framework (Hilsman 2017)

Foundational questions	Source of spiritual need
What does the patient need emotionally?	Shock Fear/anxiety Anger/hostility Sadness/despair Deep hurt Empowerment
What has the patient lost?	Current loss Past loss Dying Life adjustment Estrangement
How does patient maintain their human spirit?	Religion Meditation Spiritual validation Spiritual counseling Relief of regrets Mentoring/instructing
What are the patient's referral needs?	Medical ethics Addiction counseling Mental health professional Pain management Advocacy Family counselor

complementary medical practices, need for spiritual services, request for a place to pray, or impacts on choice of treatments (The Joint Commission 2010).

The most common barriers to the spiritual assessment cited by physicians are similar to the barriers cited for not having other difficult conversations such as advance care planning and goals of care discussions. These barriers include lack of time, lack of training, and experience with the assessment, inability to identify the patients who desire assessment, and opinion that spiritual assessment is outside their scope of care (Ellis et al. 1999, 2002). Questions regarding death and fear of death are the most common spiritual topic discussed with patients. Spirituality has been linked to improved outcomes in many medical conditions including less hospital admissions and improved survival in patients with cardiovascular disease, less symptoms in patients with cancer, and decreased depression, anxiety, and pain that should prompt spiritual assessment in all patient populations (Koenig et al. 1999; Luskin 2000; O'Laoire 1997).

To address these barriers and objections to the spiritual assessment, there are tools and literature available to improve physician efficiency and comfort with the exam. Prior to conducting a spiritual assessment, providers should consider their own spirituality, faith beliefs, and experiences and the impact of these factors in one's ability to discuss spirituality with frankness and ease. Models of spiritual assessment are described in the following sections. All the models provide sample

questions and prompts to start the conversation for the spiritual assessment. The common requirement of the provider to use each model effectively is the need to be a compassionate and empathetic listener. Willingness to allow a patient to describe this very personal aspect of his/her beliefs is sometimes all the spiritual support a patient needs.

9.4 Models of Spiritual Assessment

There is increasing recognition of positive associations between spirituality and health (Peteet and Balboni 2013). A 2018 systematic review of spiritual distress in hospitalized patients with advanced cancer found that 96% of patients experience spiritual pain and spiritual distress can vary widely from 16 to 63% of patients studied (Roze des Ordons et al. 2018). The presence of spiritual distress is associated with worse patient reported physical health outcomes (Jim et al. 2015). Most oncology patients never receive spiritual care from their providers, nurses, or physicians, yet 77.9% of patients believe spiritual care is important to their health outcomes (Balboni et al. 2013a; Phelps et al. 2012).

The incorporation of spirituality to medical practice remains a challenge. The barriers to inclusion of spirituality include the variety of cultures and beliefs that are encountered, the time constraints providers attribute to the spiritual interview, and the sensitivity of beliefs held by both providers and patients (Phelps et al. 2012; Balboni et al. 2014). Performance of a spiritual assessment is recommended in primary care practice but remains underrecognized and underutilized in specialty practice (Levin et al. 1997). Specialists and inpatient providers are more likely to encounter a patient at the point of spiritual distress and the spiritual assessment allows providers to address spiritual themes of healing. Physicians and nurses cite lack of training in spiritual care as their primary barrier in recognizing and treating spiritual pain and distress (Balboni et al. 2013a).

The spiritual assessment usually involves four parts: identification of a patient's relationship to the holy (by their own definition), determining whether a person has a sense of community, identification of a person's sense of hopefulness, and determining whether a person has spiritual distress (Anandavajah 2005). The goal of interrogating these domains is deeper understanding of the patient and action is not required after inquiry. Possible outcomes after a spiritual assessment include allowing the patient opportunity to express their concerns and beliefs with no further action, incorporate their beliefs into their care plan (i.e., consider alternative to transfusion for a Jehovah's witness), or directly address their spiritual needs or spiritual pain by consulting chaplain services. The spiritual assessment is an important step in addressing the mental health and well-being of patients (Anandarajah and Hight 2001; Hilsman 2017; Phelps et al. 2012). The following sections are examples of spiritual assessment models available to all providers, nurses, and physicians, to apply in the spiritual interview.

9.4.1 FICA Model

The FICA (faith, importance, community, address in care) model of spiritual assessment has three main components: the clinician–patient relationship and the clinical assessment and treatment of spiritual distress, see Table 9.3. The FICA model allows for a broad approach to spirituality. This model is a validated assessment and can serve as a guide for providers to incorporate open-ended questions about spirituality into the medical interview (Borneman et al. 2010).

9.4.2 AMA HOPE Questions

The American Medical Association (AMA) suggests using the HOPE questions, four domains of questions to assess spiritual needs, see Table 9.4. The HOPE questions were developed as a teaching tool for both physicians in practice and in

Table 9.3 FICA spiritual history tool (Borneman et al. 2010)

Domain	Questions	Follow-up
F—Faith and belief	Is spirituality something important to you? Are you spiritual or religious?	If "no," ask what gives your life meaning?
I—Importance	What importance does spirituality have in your life?	Address influence on health care decisions including advance directives and treatment
C—Community	Are you part of a spiritual community? Is there a group of people most important to you?	Identify and include these support systems which may include churches, group of friends, family, etc.
A—Address in care	How would you like me to address your spirituality in healthcare?	Refer patients to chaplain, clergy, and spiritual care providers

Table 9.4 The HOPE questions for spiritual assessment (Anandarajah and Hight 2001)

Categories	Sample questions	Effect, examples
H—Sources of hope	What is your source of hope? What do you turn to in difficult times?	1. No further action, be present, and offer compassion 2. Include spirituality in preventive care and wellness using meditation, yoga, etc. 3. Incorporate spirituality into adjuvant care, recommend reflection or prayer prior to medications or surgery 4. Modify the treatment plan, stopping or continuing chemotherapy and/or consider referral to chaplain services
O—Organized religion	Are you part of a religious community? How does your religion help you?	
P—Personal spirituality	How would you describe your spirituality? How do you practice your spirituality?	
E—Effects on medical care	Are you worried about conflicts between your spirituality and your medical care? Would you like to speak with a chaplain	

training to incorporate the spiritual assessment into the medical interview. Though not validated by research, the open-ended format of the questions allows for easy evaluation of a patient's spiritual needs and resources. The HOPE questions do not focus on using the words spirituality or religion, decreasing barriers across patient population to conversations regarding these topics (Anandarajah and Hight 2001).

9.4.3 7 × 7 Model

The 7 × 7 model of spiritual assessment was developed as a collaboration between nursing and chaplain services at Rush University in Chicago as a tool for nurses to perform spiritual assessments (Farran et al. 1989). The 7 × 7 model of spiritual assessment has two major subdivisions each containing seven dimensions, see Table 9.5. The model's intent is to explore how people find meaning in life and then further describe the content of a person's spiritual life including relationships, beliefs, and practices. The model includes a psychosocial assessment as a functional approach to spirituality. The Holistic Division of the model allows a

Table 9.5 7 × 7 model of spiritual assessment (Farran et al. 1989)

Dimension		Dimension	
Holistic	Content	Spiritual	Content
Medical	Medical diagnosis and history Reason for admission to hospital	Beliefs/meaning	Sources of meaning and purpose
Psychological	Mental health Major psychiatric illness	Vocation/ consequences	Duties and obligations, one feels they must fulfill
Psychosocial	Place of birth and circumstances of upbringing Level of education Current living situation Occupation	Experience/ emotion	Direct encounters with the divine and demonic Core spiritual experience
Family system	Impact of relationships	Courage/growth	Reactions to challenges in one's beliefs Tolerance to spiritual doubts
Ethnic/cultural	Race and ethnic background	Ritual/practice	Activities that express a person's sense of meaning, purpose, and beliefs
Societal issues	Impact of oppressive social and cultural systems Populations at risk for disadvantages	Community	A formal or informal community of shared beliefs and meaning
Spiritual	Wholeness, how a person expresses their spiritual self	Authority/ guidance	External and/or internal sources of support for life challenges

provider to use psychosocial aspects of a patient's life to ease in spiritual questioning. This may be appealing to providers who are beginning to incorporate the spiritual assessment into their routine practice. This model also provides an approach to societal impacts on spirituality and health (Fitchett 2002; Farran et al. 1989). Societal influences on the spirituality of certain patient populations can be profound. For example, consider the societal bias during the HIV/AIDs epidemic or the current opioid epidemic.

9.4.4 The North American Nursing Association Diagnostic Model

The profession of nursing has a longstanding interest in the whole-person treatment of patients, including their spiritual needs (Caldeira et al. 2016). Nursing literature provides a breadth of publications related to spiritual assessments and recognition of spiritual pain. Accordingly, the North American Nursing Diagnosis Association (NANDA) developed its own model of spiritual assessment. All nursing diagnoses contain three components: the definition, related factors, and defining characteristics (Herdman and Kamitsuru 2017). The NANDA definition of spiritual distress is "disruption in the life principle that pervades a person's entire being and that integrates and transcends one's biological and psychological nature" (Caldeira et al. 2017a, b) (see Table 9.6). The intent of a nursing diagnoses is to teach recognition, then allow for assessment and treatment (Fitchett 2002).

Table 9.6 NANDA model spiritual distress (Herdman and Kamitsuru 2017)

Spiritual distress = disruption of the life principles that pervades a person's entire being and integrates one's biological and psychosocial nature	
Related factors	Defining characteristics
Separation from religion	Expresses concern with meaning of life
Loss of cultural ties	Describes inner conflicts about beliefs
Challenged belief system	Questions meaning of existence
Challenged value system	Questions meaning of suffering
	Describes nightmares
	Unable to accept self
	Describes illness as punishment
	Expresses anger toward their god
	Engages in self-blame
	Seeks spiritual assistance

9.5 Spirituality and Hematopoietic Cell Transplantation

Hematopoietic cell transplantation is a life-saving treatment for patients with life-threatening blood cancers including lymphoma, leukemia, and multiple myeloma. The transplant carries a significant risk of morbidity and mortality. The morbidity of transplant is both physical and psychological and the impact to sense of spirituality may be significant (Wong et al. 2010). Recovery from the fatigue, depression, anxiety, and diminished functioning as a result of transplant may take months to years (Andrykowski et al. 2005). A study of survivors of hematopoietic cell transplant found recipients 9 years posttransplant reported growth in their spirituality after transplant (Tallman et al. 2010). Similarly, a study of patients pretransplant and at set timepoints posttransplant found that spiritual well-being increased after transplant and remained stable for the 3 years of study follow-up (Wong et al. 2010). A study of 220 patients immediately after transplant found their sense of meaning and peace actually decreased in the first month after transplant then returned to baseline at 6 months following the same pattern as their physical recovery (Leeson et al. 2015).

Spiritual growth during a cancer diagnosis and treatment is not unique to hematopoietic cell transplant patients. Participants in the Midlife in the United States (MIDUS) survey diagnosed with cancer during the survey periods reported increased spirituality following the diagnosis (Costanzo et al. 2009). These findings have been reported in patients with breast cancer and survivors of childhood cancer (Cotton et al. 1999; Langeveld et al. 2002; Manos et al. 2009) Spiritual well-being has been found to improve functioning and resilience, improve psychological adjustments, and help patients find inner meaning and peace during and after cancer treatments (Cotton et al. 1999; Visser et al. 2010; Andrykowski et al. 1996; Krupski et al. 2006; Zavala et al. 2009; O'Connor et al. 2007). Patients suffering chronic graft-versus-host disease, a devastating late and long-term complication of hematopoietic cell transplant, with low spiritual well-being had worse physical, functional, and emotional outcomes (Harris et al. 2010). In fact, intact spirituality is associated with decreased depression, improved coping, and possibly improved survival after transplant (Grulke et al. 2008; Gall and Grant 2005; Pereira et al. 2010).

Spirituality is a core factor in the assessment of quality of life and failure to assess spirituality in cancer patients is failure to assess the true burden of their diagnosis (Whitford et al. 2008). In patients with advanced cancer, their spirituality significantly predicted their quality of life more strongly than physical, emotional, and social well-being (Bai et al. 2014). Spirituality helps patients find meaning and hope; provides comfort, courage, fulfillment, and interconnectedness; attain inner peace and harmony; and impart a sense of security and stability (Krupski et al. 2006). Survivors of colorectal cancer reported their sense of meaning and peace, more so than faith, were associated with their healthcare quality of life (Salsman et al. 2011). A longitudinal study of women with breast cancer also associated the sense of meaning and peace with improved quality of life. This study also found that patients reporting increased faith, but poor sense of meaning and peace had poorer quality of life and increased depression (Yanez et al. 2009). Like an advanced cancer diagnosis, spinal cord injury is a catastrophic event with impacts on patient's

Table 9.7 End-of-life spiritual struggles (Ellison and Lee 2010)

Category	Examples
Divine	Feelings of abandonment Questioning divine power
Religious	Chronic religious doubting Question core belief system
Interpersonal	Support does not align with needs Community provides poor assistance

physical functioning and psychological status, leading to significant caregiver responsibility and burden. Spirituality and resilience are well studied in this population and are positively associated with coping and adaptation after injury. Patients with spinal cord injury with strong spiritual well-being were associated with increased resilience that translated clinically to decreased levels of depression and improved satisfaction with life. This increased spirituality led to positive psychological outcomes for both patients and their family members (Jones et al. 2019).

While spiritual well-being is important for coping and recovery from cancer, it is also important when cancer becomes terminal. Spiritual struggles at the end of life are consequential and place patients in greater risk for a spiritual crisis. Existential plight refers to heightened concern about life and death when people are diagnosed with terminal illness such as cancer (Bai et al. 2014). Three types of spiritual struggles at the end of life should be considered and assessed for the dying patient, see Table 9.7 (Ellison and Lee 2010). Successful spiritual assessment and treatment for the dying patient has measurable outcomes. These outcomes include helping patients achieve the sense their life has meaning and positive impact on their community, receive or give forgiveness and reconciliation as needed, and express emotions and say farewells. Employing spiritual care and end of life discussions by medical teams reduces aggressive care at the end of life allowing for peaceful death (Balboni et al. 2013b).

9.6 Expert Recommendations

Spirituality is a vital, multidimensional aspect of the human experience that is difficult to fully understand or measure. The 2018 American Society of Clinical Oncology (ASCO) guidelines for palliative care include spiritual care as an essential component of care of patients with cancer (Bickel et al. 2016; Osman et al. 2018). Physicians and nurses caring for hematopoietic cell transplant patients need additional training in spirituality recognition and assessment. Transplant services should incorporate spiritual care and specialists into their multidisciplinary rounds. Transplant teams must increase their recognition of patients who need specialty referral to chaplain services or Palliative Medicine.

Professional societies need to develop stronger guidelines of spiritual assessment, provide training tools for their specialties, and follow-up their recommendations.

In the context of research on spiritual support, it would be valuable to know how spiritual assistance is provided to hematopoietic cell transplant patients and what types of support are most or least helpful. There are long-term posttransplant studies that demonstrate the positive association of spiritual well-being and improved physical, functional, emotional, and social outcomes. Studies of the immediate posttransplant period are lacking. This is an intense period of social isolation for patients and their caregivers. This is also a period of closest contact to inpatient chaplain services that is understudied. Research on the spiritual assessment and spiritual treatment of these patients would be impactful to both transplant physicians and spiritual care providers.

One way to improve the overall strength of this research is to standardize tools of measurement and language/terminology used to describe outcomes. One tool used in the study of spirituality is the validated Functional Assessment of Chronic Illness Therapy—Spiritual Well Being (FACIT-Sp) measuring sense of meaning and peace and the role of faith in illness (Canada et al. 2008). This three-factor model has also been found superior to other models as it discriminates between factors that have a greater association with quality of life and coping styles (Peterman et al. 2002; Whitford and Olver 2012). Development of new tools to assess and measure spirituality should be a research consideration. In addition, many studies of spirituality in cancer and transplant patients are designed and executed by traditional healthcare providers. Future studies of spirituality should involve multidisciplinary transplant teams, with social services, chaplain services, and Palliative Medicine influencing study questions and design.

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Supportive Care Aspects in Pediatric Population

10

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10.1 Education and Preparation for Hematopoietic Cell Transplantation: Are All Potential Recipients Equal Candidates?

A toddler is referred to a hematopoietic cell transplant (HCT) program approximately 6 h from his home. His family has multiple stressors, including lack of transportation, a home environment with health concerns (water contamination concern in the community, no air conditioning, wood burning stove for heat), and limited parental literacy. Additionally, the proposed HCT was to occur during "flu restriction season," thus, limiting visitors to the parents alone, thus, placing additional emotional stress on the patient and family to be separated. To mitigate this, the transplant social worker performed a home visit, which is not routine but given the many stressors, deemed an appropriate intervention by the transplant team to ensure optimal education and preparation prior to HCT was provided. The visit allowed the social worker to build relationships with the patient and his family prior to transplant to optimize compliance posttransplant. The social worker also

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*provided the family with the video "Super Sam and the Marrow Monsters." (*National Marrow Donor Program 2012*) Accompanying the video are tools to use art and other modalities to foster conversation about transplant. Such interventions allowed the social worker to build relationships prior to transplant to optimize compliance posttransplant.*

10.1.1 Pretransplant Assessment

There are several important nonmedical issues that warrant consideration for transplant readiness. Some of these include assessment of the family unit and determination of caregiver roles inside and outside of the hospital, financial issues, and potential child care issues for siblings. It is important to assess family cohesiveness and expression early on to help promote collaborative decision making between caregivers, as well as the patient. Assessing caregiver mental health and coping strategies is important as it can be predictive of the child's adjustment to transplant (Jobe-Shields et al. 2009). While many transplant patients may be well known to the transplant center's team, patients may also come to tertiary care centers from outside hospitals and require psychosocial assessment as less is known about how they have adjusted to their treatments thus far.

10.1.2 The Standards for Psychosocial Care for Children with Cancer and Their Families

Studies suggest that assessment should include family beliefs, structure, coping strategies, social support network, additional stressors, barriers to care, preexisting mental and physical health concerns, and financial status (Kazak et al. 2015). With regard to financial burden specifically, families need to receive information about foundations and groups that might be able to provide instrumental support and advocacy (Pelletier 2015). In order to make an informed decision about whether or not to proceed with transplant, the patient's caregivers, and other key stakeholders should receive developmentally appropriate information regarding anticipated procedures, side effects, and long-term late effects (e.g., infertility) designed to meet the needs of the specific family (Thompson and Young-Saleme 2015).

10.1.3 Special Consideration for HLA-Matched Sibling Donors

Siblings who serve in a donor capacity require additional considerations with regard to assessment. The American Academy of Pediatrics released recommendations in 2010 that a donor advocate who is separate and independent from medical and mental health providers working with the HCT patient and family work with the sibling to provide developmentally appropriate understanding of the procedure and

anticipated risks and side effects and ensure informed and uncoerced assent (American Academy of Pediatrics. Committee on Bioethics 2010; Williamson and Vercler 2016). Potential ethical dilemmas may also arise in the special case of the "savior sibling" where biological parents undergo in vitro fertilization with preimplantation genetic diagnostic testing to ensure a tissue match that would make their umbilical cord usable for a cord blood transplant (Strong et al. 2014).

10.1.4 Role of Palliative Care

Pediatric palliative care is the medical subspecialty that combines medical, psychosocial, and spiritual care to enable children and young adults with life threatening conditions to have medical decisions made based on their goals and values to maximize their quality of life. It is distinct from hospice as it is applicable to patients pursuing life prolonging and curative therapies. For over 15 years, the American Academy of Pediatrics has sought to have palliative care introduced early for children with life threatening conditions such as high-risk cancers and to have a continued presence in their lives regardless if the outcome results in cure or death (American Academy of Pediatrics 2000). Thus, to optimally treat patients undergoing a HCT, the patient and their caregivers need ready access to palliative care and ideally this relationship is initiated prior to transplant.

However, pediatric palliative care is often not an early referral in pediatric oncology as there is concern that involving palliative care can erode parental confidence in the health care team or can diminish a patient and/or family's hope for survival (Wentlandt et al. 2014; Dalberg et al. 2013). Pediatric oncology teams also may possess concern that pediatric palliative care is redundant to the skills of their group and thus do not consult for concern of poor role allocation (Wentlandt et al. 2014; Dalberg et al. 2013). However, like the American Academy of Pediatrics, oncology groups such as the American Society of Clinical Oncology now encourage integration of palliative care into routine comprehensive cancer care in the United States to optimize the health care of oncologic patients.

To accomplish this, multiple models for pediatric palliative care integration have been proposed (Kaye et al. 2016; Baker et al. 2008). Integration can vary from a consult only model to an integrated model that differentiates elementary level pediatric palliative care in that all pediatric practitioners working with patients with life threatening conditions should possess up to a tertiary level patient that requires active involvement by a multidisciplinary pediatric palliative care team (Kaye et al. 2016). Underlying all of these models is a collaborative spirit with the family, the patient, and the oncology team to identify an individualized care plan that is best defined prior to HCT (Baker et al. 2008). Partnership with the medical team is critical from the beginning to ensure that appropriate psychosocial and palliative care team referrals are made early on and that there is a "warm hand off" in terms of endorsement and rationale for these services from the transplant team to patients and families (Olshefski et al. 2016; Weaver et al. 2015).

10.2 The Transplant Period: Hopes, Fears, Burdens, and the Pursuit of Relief

A 10-year-old patient with relapsed acute myeloid leukemia is admitted for a sibling matched HCT. The patient voices frustration that he will miss the school harvest party and is frustrated that he cannot eat his beloved fast food while hospitalized. The patient has had mucositis related pain with prior chemotherapy regimens and voices great anxiety for pending pain secondary to the preparative regimen. As the patient is 10 years old and thus a concrete thinker, he refuses to be admitted assuming this will remove any threat of hospitalization. The parents seek assistance in reassuring the patient through discussion of a comprehensive pain and anxiety plan. The parents are hesitant to rely solely on opioids for the pain management plan and seek additional support.

10.2.1 Pain and Symptom Burden

Along with the importance of providing anticipatory guidance, psychosocial health care team members can provide strategies to decrease pain from procedures, ongoing treatment, side effects, and distress, including empirically supported treatments of distraction, hypnosis, deep breathing, biofeedback, cognitive reframing, and other Cognitive Behavioral Therapy techniques (Flowers and Birnie 2015). Parent-based interventions can also be used to decrease pain attending behaviors that may contribute to a child's pain experience (Caes et al. 2014). Patients may also benefit from massage therapy to improve symptom burden and promote relaxation (Ackerman et al. 2012) and physical therapy to help decrease physical deconditioning and fatigue (Rossi et al. 2016).

10.2.2 Family Support

Mental health support for parents during HCT is critical. Typically, this includes normalization of their experience, problem-solving skills training, coping with illness uncertainty, and focusing on resiliency and growth (Kearney et al. 2015). Few psychosocial interventions have been developed for the HCT patient and caregiver populations, specifically, but evidence-based interventions such as the Surviving Cancer Competently Intervention Program (Kazak et al. 2005) and the Problem-Solving Skills Training program (Sahler et al. 2002) are very applicable for use with this population. A newer intervention Parent-Social Cognitive Intervention Program is specific to HCT transplant families and seems especially promising for caregivers who enter transplant with a higher level of anxiety or depressive symptoms or whose children are dealing with graft-versus-host disease (Manne et al. 2016). While most transplant units restrict room access from young siblings during transplant, these brothers and sisters nonetheless would benefit from support before, during, and after the transplant process to address typical concerns that arise with worry about

their sibling and difficulty dealing with changes to the family routine and more limited access to custodial caregivers (Gerhardt et al. 2015) along with the anxiety and isolation reported by matched sibling donors (Hutt et al. 2015).

10.2.3 Patient Support

In addition to general cognitive behavioral therapy strategies to encourage emotional expression, promote adaptive behavioral functioning, and coping strategies, cancer and/or HCT-specific resources may be useful. Bibliotherapy and videos are used to normalize the patient's experience, and games such as Shop Talk (Wiener et al. 2011) and Re-Mission (Kato et al. 2008) that can help patients open up about their feelings and improve disease-related self-efficacy and adherence. Opportunities for developmentally appropriate positive distraction and emotional expression through art therapy (Lawson et al. 2012) and music therapy may help to promote positive coping and access to religious/spiritual support to help provide existential meaning for interested parties (Ragsdale et al. 2014). HCT patients can expect to be out of school for a minimum of 6 months following their transplant and so another important component of normalization and daily functioning is the promotion of academic continuity via hospital-based school services, video conferencing, computer-based services, or homebound services. It is also recommended that psychosocial personnel collaborate with the patient's school and family to ensure a smooth school reentry process (Thompson et al. 2015). Fortunately, most transplant patients end up coping well and demonstrate remarkable resilience in the face of this intensive medical process (Phipps et al. 2012); however, a portion of patients will continue to experience ongoing depression and anxiety and it is important to have both intensive psychological and, if appropriate, psychotropic medication options available for these youths. Teenagers and those transplant patients who receive opiate analgesic medications are more likely to receive antidepressant medications than the general pediatric cancer population (Portteus et al. 2006).

10.2.4 Palliative Care During Transplant

As noted above, the burden of symptoms and psychosocial and spiritual suffering of patients with high-risk cancer are significant. Palliative care teams can utilize their expert symptom management skills to mitigate the physical discomfort associated with HCT. Additionally, their unique comfort in discussing the risk of death and anticipatory grief allows them to augment the work being done by the transplant psychosocial team during this difficult period. In fact, the threat of death resides with most parents' thoughts, regardless of their child's prognosis (Ullrich et al. 2016a) and whether or not they are openly discussing it with the health care team. In fact, many parents do not discuss death as families feel pressure to be positive, thus, setting a universal HCT social tone that optimism is preferred to pessimism or realism (McGrath et al. 2006; Grulke and Bailer 2010). Similarly, parent reports are

discordant from the patient's as they consistently under-identify the level of psychosocial and physical suffering reported by patients (Chang et al. 2012). It is in this juxtaposition that pediatric palliative care teams have an integral role alongside the HCT psychosocial team members. Pediatric palliative care teams can act as a broker between oncology teams and their patients and families to ensure optimal identification of values, stressors, and needs to facilitate the best care plan and communication to the betterment of all involved.

10.3 Breathing Relief While Reckoning the Impact: Living as a Hematopoietic Cell Transplant Survivor

A 16-year-old patient with acute myeloid leukemia who is now 10 months post-HCT transplant is in the outpatient transplant clinic for routine follow-up care. He is seen by the psychologist for issues of medication nonadherence, and it is elicited that the patient is experiencing significant anxiety regarding the potential for leukemia relapse. This anxiety was significantly compounded by a recent breakup with his long-term girlfriend who he identified as a significant source of support during his transplant.

10.3.1 The First Year of Survival

In the first year, following initial hospitalization for HCT, patients will be returning to clinic on a frequent and regular basis with a high possibility of repeat hospitalization for transplant or graft versus host disease related morbidity. Collaborative medical and psychosocial team care is warranted to help assess and manage concerns that are more likely to arise in this time frame. The assessment tool Pediatric Quality of Life Inventory Stem Cell Transplant (PedsQL SCT) module can help to structure these assessments in the areas of pain, sleep/fatigue, nausea/vomiting, nutrition, anxiety, neurocognitive concerns, communication with the medical team, and other somatic complaints (Lawitschka et al. 2014). It is also critical to routinely assess adherence to medication and HCT restrictions (Pai and McGrady 2015). Research suggests that adolescents miss approximately 27% of their medications following transplant (McGrady et al. 2014). Increasing structure around medications, including caregivers in monitoring, identifying problem-solving barriers, and when necessary teaching pill swallowing techniques and instituting a behavior chart/reward system can all be helpful in decreasing these medication adherence challenges. Nausea and changes in taste are a very common concern and often contributes to barriers to eating a balanced diet and maintaining adequate nutrition in the weeks to months following transplant. Psychosocial team members can help to normalize the patient's experience, decrease anxious and nonproductive behaviors on the part of the caregivers, and help to develop individualized cognitive behavioral strategies to gradually increase tolerance to food (Rodgers et al. 2013). When not in the clinic, adolescents and families can utilize online and mobile device applications ("apps")

to help track their progress on symptoms and behaviors and facilitate communication with the transplant team. Some pertinent apps include Eating After Transplant (EAT!) (Stinson et al. 2013) and Pain Squad (Majhail et al. 2012).

Long-Term Survivorship: International guidelines recommend the inclusion of mental health monitoring yearly posttransplant, including assessment of psychological adjustment and functioning in family members as part of a comprehensive annual follow-up (Majhail et al. 2012). Annual screening of cognitive development and referral when indicated for more comprehensive neuropsychological evaluation is also recommended, particularly when a child, 3 years of age or younger, has received total body irradiation as part of conditioning treatment (Annett et al. 2015; Smedler and Winiiarski 2008). Specifically, it is recommended that psychosocial team members assess for not only mental health concerns, but also risky health behaviors, challenges with academic or vocational progress, social functioning, and to provide guidance and readiness assessment for transition to adult medical providers for our young adult survivors (Lown et al. 2015). Fertility and sexual functioning are also important areas to provide counseling (Nahata et al. 2016). Fatigue does tend to be a persistent concern, significantly affecting more than a quarter of survivors long term (Graef et al. 2016). Nonetheless, research supports that HCT survivors and their family members do very well emotionally and functionally several years posttreatment (Uderzo et al. 2012).

10.4 When Fear Becomes Reality: Facing End-of-Life Care for the Hematopoietic Cell Patient

A 20-year-old patient with high-risk acute lymphoblastic leukemia who failed induction therapy and after several more rounds of chemotherapy plus transfers to the intensive care unit proceeds to HCT. He relapses on day 22 posttransplant. The team had historically approached him regarding advanced directives and health care power of attorney allocation. However, despite the patient voicing a desire to complete advance care planning, he had not completed the paperwork prior to relapse due to tensions with family who actively voiced a belief that he need not worry about such paperwork as he would not face end-of-life care. The patient is approached to complete his advance directives and health care power of attorney at time of relapse. He becomes agitated and voices resentment that he must complete the paperwork as it is an upsetting "reminder that he is going to die." The patient suddenly worsens with death imminent and a harried do-not-resuscitate order (DNR) is acquired. The patient dies 30 h later in the hospital with no completed legacy work and minimal family present.

Despite the many medical advances in oncology and supportive care, over 2000 of the 12,000 patients with cancer die per year (Jemal et al. 2010). There are many urgent aspects of care to address during this period at the end of life. Symptoms of dying have historically been and continue to be underdiagnosed and undertreated in the pediatric cancer patient population (Wolfe et al. 2000, 2015). This has direct impact on the child's quality of life during the dying period and parents who

perceive low quality of life in their dying child are more likely to have grief complicated by anxiety (Rosenberg et al. 2012). Palliative care and hospice teams' focus on symptoms can be of great benefit to the patient and the bereaved families. Similarly, discussing death with the patient and providing anticipatory guidance about the death to the family is often deficient but improved when a palliative care or hospice program has been involved (Kassam et al. 2015).

Finally, advanced care planning, including desired location of death and code status, are important aspects of optimal end-of-life care but such discussions remain insufficient as HCT pediatric patients continue to die more frequently in a medicalized setting than other pediatric end-of-life patients (Ullrich et al. 2016b). While having these discussions can be difficult for the patient, family members, and even providers, research suggests that parents do not regret having these discussions if their child dies but do regret not talking about it (Kreicbergs et al. 2004). Some wonderful semistructured instruments exist for children (My Wishes) and adolescents (Voicing My Choices) to help team members or family members review options for comfort (Wiener et al. 2012). Cultural as well as religious considerations should be discussed with the family ahead of time to help the team navigate this challenging period in a sensitive and more connected way with the family (Wiener et al. 2013). It is strongly recommended that there be some contact from the medical team after the patient's death in order to assess coping and provide resources (Lichtenthal et al. 2015).

10.5 Expert Point of View

The needs of a pediatric HCT patient and their family preparing, enduring, and either thriving posttransplant or sadly facing end-of-life care are many, see Table 10.1 for pediatric transplant issues and resources. It is the strong recommendation of this authorship that a medical plan alone is insufficient to optimize the overall health of the HCT patient. Rather, thoughtful consideration of the developmental needs of the patient, their mental health considerations, and the needs of the family who desire to support the patient all require meticulous attention. This is best attained through the HCT team having a skilled set of psychosocial team members focused on the needs of the transplant and joint collaboration with pediatric palliative care programs. While difficult conversations such as death anxiety, decision-making, and hope can be in themselves anxiety provoking for health care team members, to not address is to provide inadequate health delivery. By providing, you optimize a patient's health and hope, despite outcome.

10.6 Future Directions

As HCT programs look to the future, it is the consensus of this authorship that hospitals should be working toward optimal adherence to the Psychosocial Standards of Care for Children with Cancer and their Families. In addition, it is strongly

Table 10.1 Key pediatric hematopoietic cell transplant issues and resources

Pretransplant support	
Pretransplant education	Super Sam and the marrow monsters
Hematopoietic Cell transplant support	
Symptom support	Consult pediatric palliative care
Family support	Surviving Cancer competently intervention Program
Family support	Problem-solving skills training program
Family support	Parent-social cognitive intervention Program
Patient support	Shop talk game
Patient support	RE-Mission game
Posttransplant assessment and support	
Medication adherence support	
Assessing coping post-HCT	Pediatric quality of life inventory stem cell transplant
Symptom support	Eating after transplant
Symptom support	Pain squad
End-of-life support	
Symptom support	Consult pediatric palliative care
Identify and ensure desired location of death	Hospice referral
Family-centered advanced care planning	My wishes
Young adult advanced care planning	Voicing my choices

encouraged that incorporation of palliative care, as put forth by the American Society of Clinical Oncology, is accomplished by HCT programs. Through these additions, patients and their families will receive optimal supportive care that is developmentally appropriate and meets the many hopes and fears that these patients and families face before, during, and after transplant.

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11 Considerations for Improving Care and Outcomes of Adolescents and Young Adults Undergoing Hematopoietic Cell Transplantation

Stefanie M. Thomas, Andrew Dietz, and David R. Freyer

11.1 Introduction

Adolescents and young adults (AYA) with cancer, defined by the United States (US) National Cancer Institute (NCI) as being 15–39 years of age, are a population characterized by health disparities. As summarized in the landmark 2006 report of the US NCI AYA Oncology Progress Review Group, "Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer," historically AYA patients with cancer have differed from their younger and older counterparts by their constellation and distinctive biology of malignancies, under-representation in cancer research, delayed access to appropriate care, daunting psychosocial challenges related to life stage, low level of participation in clinical trials, and significantly inferior survival gains (US Department of Health and Human Services,

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National Institute of Health, National Cancer Institute and LiveStrong™ Young Adult Alliance 2006). In the decade since, there has been an enormous increase in research focused on these issues, and greater attention placed on meeting the clinical needs of AYAs. Although progress has been made, much remains to be done, particularly in improving survival for high-risk disease, mitigating excess short- and long-term toxicity, enhancing health care access and services, navigating care transitions, and improving palliative care (Barr et al. 2016). In few other arenas do such challenges converge with comparable urgency as for AYAs undergoing hematopoietic cell transplantation (HCT). The purpose of this chapter is to highlight several distinctive aspects of AYAs relevant to HCT in hopes of improving care and outcomes for AYAs undergoing this potentially life-saving therapy.

11.2 Epidemiology of Hematopoietic Cell Transplant Relative to AYAs

With expanding indications, and with improvement in both supportive care and human leukocyte antigen (HLA) matching, increasing numbers of patients undergo HCT each year (D'Souza and Zhu 2016). This increase in the number of transplants is true for all age categories, from pediatric to AYA to older adults, including geriatric patients. Additionally, with the above factors and improved transplant strategies by disease, there are more patients surviving long term (D'Souza and Zhu 2016; Majhail et al. 2013). By 2030, it is estimated there will be 64,000 survivors transplanted under age 18, 276,000 transplanted between the ages of 18 and 59, and 113,000 transplanted age 60 and older (D'Souza and Zhu 2016). Unlike younger children where many transplants are autologous CD34+ cell rescue from myeloablative chemotherapy for high-risk solid tumors like neuroblastoma and medulloblastoma, AYAs tend to be transplanted for high-risk leukemias and therefore require allogeneic grafts, with their greater attendant risks.

In general, taking into account multiple factors including disease and transplant strategies, survival is consistently better with younger age at time of HCT (D'Souza and Zhu 2016; Woods et al. 2014). AYAs are at a survival disadvantage compared to pediatric patients, but have a survival advantage compared to older adults (Woods et al. 2014; Burke et al. 2013; Majhail et al. 2012a).

11.3 Sources of Hematopoietic Cell Transplant-Related Pain Among AYAs

Pain and perception of pain are complex issues that carry significant impact on health-related quality of life throughout the HCT process (Reinfjell et al. 2017; Pulewka et al. 2017). Development of pain is often multifactorial and can arise from transplant complications such as mucositis, avascular necrosis of the bone or osteonecrosis, graft-versus-host disease (GVHD), peripheral neuropathy, and other conditions (Reinfjell et al. 2017; Kashiwazaki et al. 2012; Sakellari et al. 2015; Bardellini et al. 2013; Li et al. 2014). In HCT, AYA patients appear to fall between

pediatric and older adult patients in reporting overall pain and its impact on quality of life (Pulewka et al. 2017). Among other variables, age influences pain and symptom-reporting across transplant-related complications.

Mucositis is a painful result of chemotherapy, radiation, and neutropenia. The pain can be significant enough to require intravenous nutritional supplementation and narcotics (Kashiwazaki et al. 2012; Sakellari et al. 2015; Bardellini et al. 2013). In adult studies, younger age is typically seen as a risk factor (Kashiwazaki et al. 2012; Sakellari et al. 2015). Interestingly, in pediatric studies infants under 9 months of age appear to have less risk than older children (Bardellini et al. 2013). These risks appear to be related to underlying proliferation capacity of basal cells in the oral mucosa, which is lower in infants and older age (Kashiwazaki et al. 2012; Sakellari et al. 2015; Bardellini et al. 2013). Intensity of conditioning and duration of neutropenia also influence mucositis during transplantation. Another source of pain for AYAs is osteonecrosis (Li et al. 2014). A known complication of steroid exposure often seen among AYAs treated for acute lymphoblastic leukemia, osteonecrosis can also be triggered by steroids used to treat GVHD, where AYAs are at greater risk than children (Li et al. 2014). Bone health naturally deteriorates over the lifespan, so when osteonecrosis occurs in older adults it may be difficult to distinguish the effects of aging. GVHD itself may produce painful symptoms, with age being a risk factor for developing GVHD, as discussed below. Chemotherapy-induced peripheral neuropathy, a more common problem among AYAs than younger children being treated for cancer, may occur post-HCT and be related to GVHD, as well (Ruzhansky and Brannagan 2015). Management of distress in AYAs, which affects quality of life, is also discussed further below.

11.4 Variations in Hematopoietic Cell Transplant Toxicity for AYAs

Numerous serious toxicities after HCT contribute to treatment-related morbidity and mortality, including GVHD, infection, veno-occlusive disease, thrombotic microangiopathy, and others (Sahin et al. 2016a, b). In general, the AYA population appears to have a higher risk for complications and treatment-related morbidity and mortality when included in pediatric studies (Burke et al. 2013; Majhail et al. 2012a; Tomizawa et al. 2017), but a lower risk when included in studies of older adults (Majhail et al. 2012a). Fortunately, overall treatment-related morbidity and mortality has been declining in all age groups (Majhail et al. 2012a).

Age is related to development of infections in post-HCT, one of the most important causes of transplant-related morbidity and mortality. Older age is a risk for overall infectious complications and more specifically for invasive fungal infections, varicella zoster, cytomegalovirus, and polyomavirus associated hemorrhagic cystitis (Sahin et al. 2016a). As suggested earlier, age may also contribute to developing infections by causing predisposing toxicity, such as mucositis. Veno-occlusive disease, a manifestation of endothelial damage in the liver, exhibits a bimodal association with age, where the highest risk patients are the youngest, especially under age 2 (Cheuk et al. 2007; Cesaro et al. 2005), and those with advancing age (Sahin

et al. 2016b). This is thought be explained by a smaller caliber of hepatic venules more prone to obstruction early in life (Cheuk et al. 2007), and more prevalent pre-existing liver dysfunction with advancing age (Sahin et al. 2016b). Thrombotic microangiopathy, like infections and veno-occlusive disease/sinusoidal obstruction syndrome, also has a long list of causative factors. Advancing age is not only an independent risk factor for the development of this generalized endothelial injury but is also an independent risk factor for prognosis in those who develop thrombotic microangiopathy (Sahin et al. 2016b).

11.5 How Graft-Versus-Host Disease Differs Among AYAs

Graft-versus-host disease is one of the most important and unique complications of allogeneic-HCT, including a more acute version prior to day 100 post-transplant consisting of fevers, rashes, and diarrhea, as well as a more chronic version after day 100 affecting potentially any organ, though most notably the skin, gastrointestinal system, and lungs. In both pediatric and adult studies, data indicate that risk for both acute and chronic GVHD rises with increasing age (Watkins et al. 2017; Vignon et al. 2017). This positions the AYA population more favorably in adult studies, but worse in pediatric studies. Interestingly, age of the donor also appears to affect incidence of GVHD in the recipient (Watkins et al. 2017).

In one study of GVHD, AYAs appeared to be at higher risk than both younger and older patients (Vignon et al. 2017). A variety of age-related factors could influence this risk, including lower adherence to medications aimed to prevent GVHD (McGrady et al. 2014), physiologic changes related to puberty that affect drug metabolism, and a different gut microbiome (Vignon et al. 2017). Barriers affecting adherence may be related to the developmental stage of AYAs, including conflict with caregivers and psychological disorders (McGrady et al. 2014).

11.6 Comorbidities Among AYAs: Hidden or Apparent

One of the major determinants of transplant-related morbidity and mortality and long-term survival in older adults is the presence of comorbid conditions, such as cardiovascular, renal, pulmonary, and metabolic disease (Saber and Horowitz 2016; Artz 2016). These comorbidities are more common with advancing age and are included in HCT prognostication scales for older adults, but rarely in pediatrics because younger children rarely have these comorbidities. AYAs represent a unique population of patients in physiological transition between children without comorbidities and their older adults with multiple comorbidities. In young adulthood, these conditions may be present in early stages but clinically unrecognized. Obesity, an increasingly common comorbidity affecting AYAs, was significantly associated with more GVHD and lower survival after HCT in a recent meta-analysis (Nakao et al. 2014).

11.7 Distress, Mental Health, and Psychosocial Function: Hallmark Issues for AYAs

AYAs undergoing HCT present several difficulties in the recognition and management of mental health disorders. This stage in life is tumultuous even for patients without medical conditions. HCT adds additional stressors by requiring an increased dependence on parents during an age of natural emerging autonomy, separation from peers and activities, lack of career and educational growth, and overall feelings of loss of control (Cooke et al. 2011). Additionally, many psychological conditions have their onset during this age, including panic, generalized anxiety, post-traumatic stress, mood, and psychotic disorders (Kessler et al. 2007). Substance abuse disorders typically begin during late adolescence and sharply rise during young adulthood (McGorry et al. 2011). These disorders can be triggered or exacerbated during illness and other times of acute stress.

Although these disorders are not well described in the context of HCT, studies of AYA patients with cancer can be extrapolated to this group. Substance use is reported as lower for AYA cancer survivors (Milam et al. 2016), while the incidences of distress, anxiety, and depression are reported higher for AYAs with cancer than the general population and healthy peers (Jörngården et al. 2007; Hedström et al. 2005; Enskär and von Essen 2007; Larsson et al. 2010). Additionally, because medical practitioners often do not accurately identify psychosocial distress in AYAs, relying on providers to assess psychosocial well-being is problematic (Hedström et al. 2006). Despite this, screening is not standardized and many AYAs report their psychosocial supports are not met (Zebrack et al. 2013). AYAs have reported need for more information, practical support, and emotional support. Limited access to counseling by mental health professionals is a risk factor for ongoing distress (Zebrack et al. 2014). Despite these issues, AYAs undergoing HCT report optimism regarding treatment (Pulewka et al. 2017). Strategies for addressing these mental health issues include prioritizing peer-to-peer connection, developing dedicated young adult and parental/caregiver support groups, utilizing social networking technology, and standardizing psychological assessment and counseling (Cooke et al. 2011). Based on a model of resilience in illness, a therapeutic music video intervention was shown in a randomized clinical trial to improve coping and other psychosocial outcomes among AYAs undergoing HCT (Robb et al. 2014).

11.8 The Importance of Spirituality for AYAs

Adolescence and young adulthood are typically a time of spiritual questioning and meaning-making. When adolescents face a life-threatening situation, they may seem reluctant to pursue spiritual support, and health care providers may be uncomfortable discussing spirituality. In the adult population, clinicians often expect the illness will have a negative effect on the patient's well-being, but often this is not the case (Sinclair et al. 2015). Though little data exist regarding spiritual well-being in AYAs

undergoing HCT, what has been reported is similar to older adults. A recent longitudinal, qualitative study reported results from patient interviews of AYAs undergoing HCT conducted within 100 days and 1 year following transplant (Ragsdale et al. 2014). Results indicated that initially, AYAs ask fundamental questions ("Why me?" and "What will happen to me?") and rely on faith practices, spiritual support persons, and belief that God has a reason. Later, AYAs report finding purpose through their experience, having strengthened faith, believing God chose them, and receiving spiritual encouragement (Ragsdale et al. 2014). This positive meaning-making experience is similar to what is reported in the older adult literature and in the AYA cancer literature (Bellizzi et al. 2012). Thus, resources supporting spirituality, including chaplains or their own faith representatives, should be offered to AYAs undergoing HCT.

11.9 Caregivers for AYAs: Who They Are

Caring for a patient undergoing HCT is associated with significant psychological morbidity (Armoogum et al. 2013). Complicating this already difficult time, AYAs undergoing HCT encompass a spectrum of life stages. Because of this, caregivers for younger AYAs are typically parents, and those for older AYAs are more often spouses and significant others. Differences in these relationships create difficulties in developing standard supportive strategies for AYA caregivers.

Caregivers of AYA patients have higher reported unmet needs than caregivers of older patients (Armoogum et al. 2013). This is likely multifactorial and changes with the life phase of the patient. Adolescence and young adulthood are a time of emerging independence. When AYAs are diagnosed with a life-threatening condition needing HCT, they become more highly dependent on others than do healthy peers. Especially for younger AYAs needing increased reliance on parents, the reversion from emerging independence to dependence causes conflict (Cooke et al. 2011). Caregivers of older AYAs have very different sources of distress. These patients are starting families and may have young children. Not only does the partner become the patient's primary caregiver, but also responsible for child care. Additionally, as discussed further below, AYA cancer patients experience more financial distress than older patients because they are still building careers and have limited reserves.

11.10 Differences in Palliative Care/End-of-Life for AYAs

Given the intensity of typical HCT conditioning regimens, the severity and complexity of complications, and the high risk for cancer recurrence, the capacity to provide skilled palliative, and end-of-life care is essential. For AYAs as well as others, experts recommend viewing palliative care as the overarching paradigm that encompasses end of life and should be instituted early to maximize comfort in all phases of cancer treatment (Coccia et al. 2012). The question here is what aspects of AYAs require a different approach to palliative and end-of-life care than in younger and older patients?

As in many other aspects of hematology/oncology care, developmental considerations of adolescence and young adulthood influence how palliative and end-of-life care is approached in this age group (Clark and Fasciano 2015). Among older teens, cognition is characterized by an emerging ability to make complex decisions involving future consequences and impact on other persons. Among young adults, these abilities are enhanced and may be conditioned by their roles as partners, parents, employees, and children of aging parents. These considerations influence how decisions concerning end-of-life care are approached.

AYAs with cancer have a prominent symptom burden (Wein et al. 2010; Cohen-Gogo et al. 2011), which clinical experience and some research suggest is greater than in children (Pöder et al. 2010). This is particularly true at end of life, where physical symptoms accumulate and accelerate against a backdrop of declining likelihood of survival. While the pharmacological approach to pain control generally involves the same medications and initial doses as used for all adults, for AYAs the provider should be prepared to respond quickly to the need for rapid and dramatic increases in dose, addition of more medications, treatment of coexisting anxiety, and addressing of multiple sources of distress through counseling and spiritual support (Cohen-Gogo et al. 2011).

With attainment of independence being normative for adolescence and young adulthood, it is important to involve even younger AYAs in as many aspects of medical decision-making as possible, including palliative/end-of-life care. Most HCT patients have received extensive prior cancer treatment that, along with their transplant therapy, makes adolescents more medically experienced and knowledgeable than expected for their age. Therefore, they are capable of understanding relatively complex scenarios, especially if explained honestly and understandably. In the care of adolescents who are minors, these patients do not have conventional legal authority to make binding medical decisions for themselves, but research and clinical experience favors allowing them to do so on the basis of their functional competence (Hinds et al. 2005; Freyer 2004). For optimal communication at the end of life, engagement of AYAs should begin early at initial diagnosis and treatment, utilize a consistent approach, engage the entire family, and tap the expertise of the multidisciplinary team (Wiener et al. 2013).

There are two major situations where HCT patients may be confronted with decisions relating to end-of-life care. The first is following an extended course of medical problems including post-transplant relapse(s) and/or progressive complications, such as severe GVHD and infections. The second situation occurs when the overall prognosis may be good, but an acute, life-threatening complication develops from which recovery is doubtful, such as sepsis that evolves into systemic inflammatory response syndrome and refractory cardiopulmonary decompensation. In the first setting, there is often substantial lead-time prior to facing a decision about forgoing additional disease-directed treatment with curative intent. This tempo allows the provider many opportunities to help patients/families clarify their values related to balancing quality of life and continued pursuit of survival. Even younger AYAs should be invited to participate actively in those discussions and decisions (Freyer 2004). In the second setting, a cascade of unexpected medical events may overtake

the AYA's ability to make decisions about life-sustaining treatment. In these cases, having an advanced care directive is indispensable for ensuring that a patient's instructions for care at end of life are followed despite being incapacitated.

Although advance care directives are routinely used for adults, their status among younger AYAs with cancer is evolving because minors lack the legal authority to execute traditional advance care directives. This has led to development of advance care planning tools adapted for minors. In two randomized clinical trials, the Family-centered Advance Care Planning for Teens with Cancer (FACE-TC) intervention was found to be feasible, acceptable, and associated with successful limiting of treatment (Lyon et al. 2014; Lyon et al. 2013). Inspired by the popular Five Wishes™ program for adults, Voicing My CHOiCES™ was developed to assist AYAs with planning end-of-life care through expressing their values and preferences concerning comfort, support, medical decisions, and treatment (Zadeh et al. 2015). More work is needed to achieve routine clinical implementation of such interventions, as one recent study documented advance care planning in only 23% of AYAs undergoing HCT (Needle and Smith 2016).

Following the death of an AYA after HCT, it is important to ensure that bereavement services are offered to significant others and friends, as peers in this age group are often deeply affected by this loss (Herberman Mash et al. 2013).

11.11 Survivorship for AYAs: The Growing Need for Longitudinal Care

In caring for the AYA survivor following HCT, both medical and psychosocial issues must be addressed. Drawing on the general model of comprehensive survivorship care widely used in pediatric oncology, these issues fall into four major categories: (1) persistent or late-onset health problems related to cancer treatment (also called "late effects"); (2) psychosocial functioning; (3) health education; and (4) financial challenges (Friedman et al. 2006).

Compared with long-term survivors of childhood/adolescent cancer, much less is known about the prevalence of late effects and risk factors for their development among survivors of AYA cancer. Indirect insights are afforded by descriptive studies among adult survivors of childhood/adolescent cancer, which indicate that by 30 years post-treatment 73.4% have at least one clinically significant late effect and 42.4% have at least one that is severe or life-threatening (Oeffinger et al. 2006). Among survivors of AYA cancer, some late effects are well-documented, such as cardiovascular disease, lymphedema, ototoxicity, second malignancies, erectile dysfunction, and fatigue (Chao et al. 2016; Chow et al. 2016a; Bokemeyer et al. 1998; Lee et al. 2016; Wettergren et al. 2016). Compared with younger patients, AYAs treated for cancer are at significantly greater risk for developing steroid-induced osteonecrosis (Mattano Jr et al. 2012), alkylator-induced gonadal failure (Sklar et al. 2006), and vincristine-induced peripheral neuropathy (Langholz et al. 2011). Although AYA survivors of HCT appear to be at lower risk for ovarian failure than older adults, fertility preservation measures should be considered prior to

transplant, if not already taken prior to cancer therapy (Joshi et al. 2014). In a recent study comparing young adult long-term survivors of childhood cancer treated with either HCT or conventional chemotherapy, the risk for developing late effects was significantly higher for HCT across virtually every organ system (Armenian et al. 2011). Thus, survivors of AYA cancer treated with transplant are at substantial risk for having late effects that include gonadal failure and other endocrine problems, musculoskeletal abnormalities, neurosensory impairment, cardiovascular disease, and second malignancies. Because they are relatively young, it should be stressed that, like children, AYAs face a long survival trajectory over which late effects may emerge and have negative effects upon physical function and quality of life during their lifetimes. However, unlike children, the evidence base for late effects after HCT and other cancer therapies remains relatively scant in this emerging survivorship discipline.

For this reason, systematic, longitudinal monitoring for late effects is recommended for HCT survivors of all ages, including AYAs, to support both their clinical care and needed research. To facilitate this effort, surveillance guidelines have been developed, which are modeled along the lines of the widely used, risk-adapted Children's Oncology Group Long-term Follow-up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers (Children's Oncology Group 2013). Recommendations for survivors of childhood/adolescent HCT derived from these Children's Oncology Group guidelines are available (Chow et al. 2016b). Specific to survivors of transplant received as adults, international consensus recommendations for late effects screening and preventive practices were recently published (Majhail et al. 2012b). To support survivors of AYA cancer, these transplant-focused screening guidelines may be complemented by the survivorship component of AYA oncology practice guidelines published by the National Comprehensive Cancer Network (Coccia et al. 2012). Anecdotally, some cancer survivorship programs have developed their own clinical screening practices for survivors of AYA cancer by amalgamating portions of the National Comprehensive Cancer Network, adult stem cell transplant, and extrapolated Children's Oncology Group guidelines.

In any discussion of survivorship after AYA cancer, it is important to mention the daunting health behavior, psychosocial and financial difficulties reflecting the life stage of these patients. Survivorship care must address concerns involving intimate relationships, sexuality, fertility, education, vocation/career, and desire for health information. AYAs report decreased confidence in their ability to form new romantic relationships after cancer (Warner et al. 2016), as well as greater social strains and isolation (Warner et al. 2016; Evan and Zeltzer 2006). Sexuality, as opposed to infertility, is a topic important to AYAs after cancer, but is often overlooked or actively avoided by health care teams uncomfortable with discussing it. HCT and other cancer treatments among AYAs cause excess financial burden, limit financial independence, have a negative impact on education, and threaten long-term career opportunities and success (Bellizzi et al. 2012; Warner et al. 2016). After transplant, AYAs who return to work report feeling rushed, left behind by their peers, and overwhelmed trying to meet the physical and cognitive demands of jobs they once held

(Brauer et al. 2017). Although the US Affordable Care Act moved millions of previously uninsured AYAs onto health insurance plans (The Commonwealth Fund 2017), in the US health insurance remains a shifting, complex patchwork of private and public plans that remains a barrier to obtaining appropriate care (Parsons et al. 2014). Further, for AYAs the excess direct and indirect costs associated with obtaining cancer treatment continue long into survivorship due to the need for post-treatment medical care, monitoring, and expensive interventions for problems, such as infertility, a common late effect after HCT (Guy et al. 2013; Kirchhoff et al. 2012). Finally, a majority of survivors after AYA cancer report substantial unmet informational needs, which compromise care and are associated with lower health-related quality of life (DeRouen et al. 2015).

In pediatric/adolescent oncology where cancer survivorship has evolved into a recognized discipline of care and research, the plethora of medical and psychosocial needs described above is frequently addressed in the context of dedicated long-term follow-up clinics for cancer survivors (Eshelman-Kent et al. 2011). This approach has been recommended for optimal care of transplant survivors, including AYAs (Hashmi et al. 2015; Cupit et al. 2016). For younger AYAs treated in a pediatric center, lifelong survivorship care requires successful transition of that care to adult-focused providers in an appropriate setting, which is a challenging process and is inextricably linked to concurrent, complex life transitions characteristic of this age group (Freyer 2010). Although a variety of successful long-term follow-up clinic models exist, an essential ingredient for all is a multidisciplinary team involving clinicians from medicine, nursing, social work, physical and occupational therapy, nutrition and mental health, available during clinic or on a consultative basis. A major issue limiting the impact of long-term follow-up clinics is nonadherence to recommended follow-up by AYAs. Studies of young adult survivors of childhood/adolescent cancer have documented that only a minority of at-risk individuals receive survivorship-focused care and recommended screening for specific medical conditions such as cardiomyopathy and secondary breast cancer (Nathan et al. 2008). Focus group research indicates that barriers to AYAs utilizing specialized follow-up care are plentiful, including unreimbursed cost, competing responsibilities, low motivation, fears, and lack of perceived need, some of which may be addressable through practical interventions, such as flexible appointment times and on-site child care services (Smits-Seemann et al. 2017). However, use of telemedicine, mobile health technology, and social media platforms to improve virtual access to survivorship care is being explored and could have particular relevance for this "tech savvy" demographic (Prochaska et al. 2017; Cox et al. 2017).

11.12 Expert Point of View

Faced with an AYA undergoing HCT, the most important question to be asked by the provider is, "How might this patient be different from what I am used to seeing in the younger or older patient?" AYAs are in a life stage where both physiology and psychosocial development may be different in ways that alter their responses

to disease and treatment, see Table 11.1. These differences underlie the numerous health disparities that define AYAs with cancer. Currently, many of these differences are only partially understood, underappreciated, or as yet unknown, requiring vigilance on the part of the provider. For AYAs, the multiple life domains impacted at diagnosis and during treatment, coupled with their long survival trajectory, make this age group uniquely challenging and necessitates a long-term

Table 11.1 Key challenges and recommendations for adolescents and young adults undergoing hematopoietic cell transplantation

Topic	Key challenges	Recommendations
Pain and quality of life	• Unique developmental perspective	• Age and maturity-appropriate assessment and treatment
Toxicities	• Variable age-dependent risks, intermediate level for many	• AYA-specific studies so as to better understand risk in this group
Graft-versus-host disease	• Intermediate risk level	• AYA-specific studies so as to better understand risk in this group
	• Suboptimal adherence to prophylaxis and therapy	• Proactive counseling, monitoring, and partnering with family members
Comorbidities	• Under-recognized adverse health conditions	• Screening for comorbidities even if no clinical signs or symptoms
Mental health	• Acute stress may lead to anxiety and depression, possibly exacerbate other disorders	• Early psychology screening • Involvement of psychiatry as needed • Use of resilience-based interventions
	• Loss of age-appropriate autonomy and peer support	• Peer support groups and online communities
Spirituality	• Meaning-making during a stressful time	• Spiritual resources and support
	• Discomfort of health care providers discussing spirituality	• Utilization of chaplains as part of the medical team
Caregiver needs	• Wide spectrum of AYA caregivers depending on age	• Clarifying of decision-making and sharing of medical information
	• Family stresses outside of hospital	• Social work assessment and referral to appropriate resources
Palliative care/ end of life	• Excess symptom burden	• Early involvement of palliative care team • Aggressive, multimodal support
	• Complex decision-making and need for age-appropriate support	• Use of advance care planning tools (e.g., Five Wishes™ for adults; Voicing my CHOiCES™ for adolescents)
Survivorship	• High risk for multiple late complications of therapy	• Systematic monitoring in long-term follow-up clinic
	• Suboptimal adherence to follow-up	• Targeted outreach to survivors • Addressing of practical barriers • Collaboration with primary care providers • Telemedicine care, provision of online survivorship resources

perspective and care commitment. Utilization of multidisciplinary teams is essential, and caring for them in the context of an institutional AYA program offers additional benefits (Ferrari et al. 2010). HCT providers should leverage the growing number of AYA-specific informational resources to assist them in their task (Bleyer et al. 2017).

11.13 Future Directions

More research specific to the AYA population is needed to improve our understanding of their medical issues and risks, to identify biopsychosocial support that may be helpful, and to design specific interventions that will improve outcomes for AYA patients and their caregivers. In the meantime, encouragement of interested clinicians and researchers to develop expertise in the AYA population will improve care and advance this discipline.

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Caregiver Support Strategies: Why Should We Care?

12

Alejandra del Toro and Laura Finn

12.1 Introduction

Patient caregivers are an under-acknowledged yet essential resource in the care of hematopoietic cell transplant (HCT) patients throughout the continuum of their health care. As the number of patients receiving transplants steadily increases each year, the burden on our caregiver resources is also increasing. The health care trajectory for transplant patients can be prolonged and unpredictable with variable caregiver obligations dependent on their own personal relationships, underlying health, preparedness, and patient outcome and survivorship. There is a growing need to address the long-term well-being of caregivers and provide them with support to enhance their ability to care for themselves and their loved ones, see Fig. 12.1. The diagnosis of cancer becomes a crisis on many levels for patients and their support systems including family, friends, co-workers, and more. It disrupts emotions, social and family functioning, communication, and the confrontation with mortality becomes the focus of the support system. The quality of a patient's support system is a forefront determinant of their healthcare outcome, highlighting the caregiver as a vital member of the patient's multidisciplinary care team.

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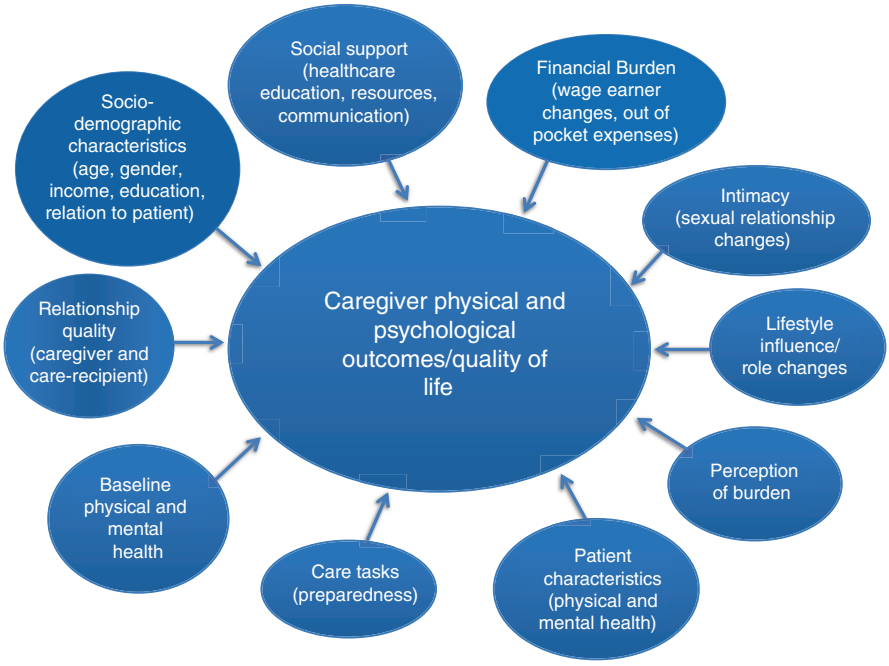

Fig. 12.1 Caregiver support needs

12.2 Caregiver: Definition and Responsibilities

Recipients of HCT often become significantly debilitated and frequently experience treatment related complications. During and after transplant, caregivers assist with activities of daily living, prepare meals, provide transportation, administer medications, manage finances, provide emotional support, and advocate for the health care of the patient. Caregivers often spend more than 40 h a week providing these services (Bevans and Sternberg 2012). This investment requires significant lifestyle modifications including time lost from occupations, restrictions in leisure activity, and decreased exposure to friends and family. These are great demands to place on an individual but without a caregiver, transplant may not be a treatment option compromising a patient's survival. The Family Caregiver Alliance defines two groups of caregivers. Informal caregivers are an unpaid population of caregivers involved in helping patients with activities of daily living and their medical needs including medication administration and use of personal and home medical equipment. Formal caregivers in comparison are paid care providers who assist in the care setting whether it is the hospital, clinic, or patient's home (Family Caregiver Alliance 1996–2016). In this chapter, discussion of caregivers will only refer to informal caregivers.

Selecting an individual to provide this level of care, one who is willing to accept the limitations of this role will pose on their lives, is a difficult task. A potential

caregiver may or may not be prepared for this undertaking as they will tread an uncertain path riddled by physically and emotionally taxing experiences. However, a patient's life depends on the acceptance of this challenge. Patients cannot go through a transplant without a caregiver, therefore, physicians must form a care partnership with caregivers (Rabow et al. 2004). The toxicity and the complexity of transplant simply cannot be managed alone and availability of professional care in the outpatient setting is finite.

Given the high costs of inpatient autologous stem cell transplant, many programs have sought to perform outpatient transplants. This requires that at least one caregiver be constantly available to provide the care the outpatient nurse or the outpatient facility would not provide. A prospective study comparing the societal costs and quality of life associated with inpatient versus outpatient autologous transplant revealed that almost half of the screened patients were not eligible for the study because they lacked a caregiver (Frey et al. 2002). Common reasons for absence of caregivers are that patients are widowed or single, the only available caregiver is needed to care for children, or they are already supporting another sick family member. Caregivers may be obligated to their employment to maintain household finances and insurance coverage or they may have their own underlying medical or psychosocial issues. Many insurance plans do not provide financial coverage for caregivers or personnel for the assistance needed after transplant either short- or long–term, therefore, this care aide and financial need must be supplemented by the caregiver.

12.3 Caregiver Burden and Stress

Caregiver burden and stress is a vital transplant-related factor to address professionally as higher caregiver burden is associated with decreased patient survival (Dionne-Odom et al. 2016). The impact of stress related to the transplant process typically begins with the diagnosis of cancer. The stress experienced during the cancer diagnosis, treatment, and transplant includes social isolation, exhaustion, and financial trauma and may be categorized as either objective or subjective burden (Beattie and Lebel 2011). Objective burdens are defined by concrete events and situations including financial strain, personal activity limitations, household disruptions, and friction within the social support system or family. Subjective burdens include feelings, attitudes, and emotions about caregiving such as usefulness, fear, anxiety, or guilt (Foxall and Gaston-Johansson 1996). Both patients and caregivers experience the emotional impact of a cancer diagnosis and the resultant psychological and social adjustments are a continuous process from diagnosis through transplant into survival and the post-transplant period. The level of distress felt by both patients and caregivers is higher prior to transplant and measured higher for caregivers during this time period as noted in a study following the psychosocial adjustment of patients and caregivers prior to transplant (Siston et al. 2001). The emotional distress experienced by caregivers of transplant patients can equal that of psychiatric inpatients (Fife et al. 2009). This may be related to new and increased strains on family relationships and responsibilities and poor insight into expectations about

the patient's illness and treatment. It has also been noted that caregivers report more anger and intrusive reactions than patients in relation to the transplant process (Siston et al. 2001).

Caregivers may be unfamiliar with health care language and processes and feel uninformed regarding physical effects a patient may experience with treatment. Even in long-term follow-up, caregivers compared to patients and controls demonstrated poorer outcomes in quality of life, spiritual well-being and growth (Bishop et al. 2007). Long-term issues include financial strain and social isolation that may last for years. Caregivers need ongoing support and education to help deal with rebuilding and redefining family relationships and social roles. Even though caregivers report poor quality of life, over the long-term they are also less likely to be offered or seek medical assistance, such as mental health aide. Both patients and caregivers require sustained support long after transplant, avoiding presumptions of outward appearances that they may be managing well on their own (Boyle et al. 2000).

12.3.1 Fatigue

A great deal of time and energy are expended on caring for a patient with advanced illness. This coupled with lack of sleep and fears of the uncertain may bring heavy fatigue and exhaustion to the caregiver and may be compounded by the perception of overall distress. Caregivers tend to place the patient's needs above their own and this may lead to a deviation from healthy behaviors (Bishop et al. 2007). They may focus less on nutrition and interpersonal relationships. They may ignore their own health concerns and perform less physical activity (Ross et al. 2016). These behavioral changes may affect stress management and may ultimately have an effect on sleep quality and enhance the perception of fatigue (Deniz and Inci 2015). In a study by Langer et al., it appeared that compared to patients, caregivers report elevated levels of dysphoria. Fatigue may be associated with mental stress, which can manifest as mood disturbances including depression and anxiety (Langer et al. 2003; Krug et al. 2016).

12.3.2 Relationships

Marital dissatisfaction by caregivers is a readily reported phenomenon (Langer et al. 2003). In a study by Langer et al., female spouses reported more relationship maladjustment and decreased marital satisfaction 6 months to 5 years after transplant (Langer et al. 2010). Increased marital discord was also reported by men in a study by Bishop et al. (2007) Relationship conflicts may be due to established societal norms of gender roles that place greater household and caregiving responsibilities on women or role reversals for men. Caregiving roles may be regarded as expected among spouses rather than rewarded leading to a negative impact of the caregiving demand. Regardless of gender, relationship coping in the form of protective buffering where individuals deny worry and concern, hide discouraging

information, and prevent thinking about the cancer can increase distress of both patient and the caregiver. While there may be relationship discordance throughout the trajectory of transplant, in general patient and caregivers report overall marital satisfaction and rates of divorce are low (Langer et al. 2010).

Concerns among partners may also arise about sexual intimacy which is disrupted during a cancer diagnosis and transplant. For caregiver/patient couples, the transplant process can affect sexual intimacy and become an important factor in both patient and caregiver quality of life. Throughout the treatment process, a patient may experience bodily changes in hair quality, skin tone, muscle mass, and fluid retention that can affect the patient's body image in a negative way. This can lead to decreased sense of sexual attraction that alters a patient's desire to be intimate with their partner/caregiver. In turn their partner/caregiver may negatively sense the impact of these bodily changes and lose their sexual attraction to their loved one (Otis-Green and Juarez 2012). Physiological changes such as decreased strength and increased fatigue may limit the physical capacity for sexual activity (Norskov et al. 2015). Graft-versus-host disease (GVHD) is one of the major determinants of sexual dysfunction as it can directly and indirectly affect genitalia with chronic GVHD being particularly debilitating (Noerskov et al. 2016). Caregivers need a forum to discuss sensitive intimacy issues with their partners and/or the health care team and further research in this area is warranted (Norskov et al. 2015).

12.4 Physical Health of the Caregiver

The physical health of caregiver may be significantly compromised as the emotional and physical demands of caring for transplant patient create negative psychological responses that may manifest as depression and/or anxiety. Sociodemographic attributes of the caregiver (age, gender, income, relationship to care recipient) have been linked to caregiver outcomes. In general, younger age, female gender, low income, and spouses are at greater risk of negative psychological and behavioral responses (Schumacher et al. 2008). Additional studies have reported poorer outcomes in male caregivers measuring increased burden and decreased quality of life (Deniz and Inci 2015). Caregivers may perform less physical exercise and experience fluctuations in sleep patterns as discussed earlier. They may seek fewer preventative health visits and increase tobacco and alcohol use (Sherwood et al. 2008). With a higher degree of patient cognitive and physical disability, there is an increase in the duration, amount of care, and vigilance required from the caregiver. The activities of daily living are defined as eating, bathing, dressing, toileting, transferring including walking, and continence (Katz et al. 1963). About 50% of caregivers who have to assist with all 6 activities report difficulty helping with these tasks (AARP 2015). Personal care activities such as feeding, bathing, and toileting which involve greater degrees of physical burden are reported as most difficult compared to tasks, such as paying bills or running errands (Deniz and Inci 2015). This may lead to increased distress which may manifest as a detriment in physical wellbeing (Bevans and Sternberg 2012; Nijboer et al. 1998, 2001; Kurtz et al. 2001).

Psychological responses to stressors may be influenced by the amount of allostatic load experienced by the caregiver. Allostatic load is defined as the total burden of multiple stressors (Juster et al. 2010). Caregiver physical health research has included applications of mind body models that evaluate biological and behavioral markers of distress. The concept of these models suggest that psychological, behavioral, and biological responses are interrelated and are part of the body's stress response (Sherwood et al. 2008). The biological response to stress includes the activation of the hypothalamic pituitary adrenal and the sympathetic adrenal medullary axes which leads to increased glucocorticoid and catecholamine production. This may be a beneficial response to a short-term stressor but when the stressor is prolonged by factors such as disease progression or prolonged treatment, resultant hypertension, and altered cytokine production may manifest as cardiovascular disease, diabetes, and immune dysfunction (Gouin et al. 2008; Lee et al. 2003; Roepke et al. 2011). Caregivers have been found to suffer immune impairments as long as 3 years after the caregiver role has ended (Golant and Haskins 2008). Higher levels of caregiver strain correlate with a higher risk of caregiver mortality (Schulz and Beach 1999; Lucini et al. 2008).

Over recent years, there has been an increase in the number of elderly patients undergoing transplants as reduced intensity conditioning (RIC) regimens became available and improvements in supportive care have been made. Elderly caregivers are a unique caregiver population at increased risk for adverse effects of caregiving as they may have a higher prevalence of physical disabilities and health concerns that may be intensified by the strain of caring for a seriously ill spouse or partner (Schulz and Beach 1999). One must be cognizant of the elderly caregivers own health care course throughout the transplant process, as the function of the caregiver is essential for patient outcomes.

12.5 Mental Health of Caregiver

Strained caregivers compared with controls matched for age and gender have significantly higher levels of anxiety and depression. Certain time periods throughout the transplant are associated with greater levels of distress. During the transplant hospitalization caregivers experience a great decline in social and emotional function (El-Jawahri et al. 2015). Peaks of distress have also been shown to occur before and immediately after transplant (Fife et al. 2009). Levels of strain may decrease after the 100 days post-transplant milestone is achieved as transplant recovery is noted (Eldredge et al. 2006). Caregiver perception of how much the patient is suffering can greatly influence their personal mental health. Caregivers of patients experiencing emotional suffering are more prone to depression (Krug et al. 2016; Schulz and Sherwood 2008). Personality type, relationship satisfaction, social networks, and availability of backup caregivers may influence this perception of distress (Sherwood et al. 2008). About 50% of caregivers report they get help from another informal caregiver (AARP 2015). Social isolation definitely affects caregivers and as the needs and dependency of the patient persist, the caregiver's ability to

dedicate attention to other relationships decreases creating a negative effect on overall quality of life (Deniz and Inci 2015). Caregiver work-life issues and income can be significantly affected by their new role and the economic burden of caregiving can further contribute to anxiety and depression (Zabora et al. 1992). Depression and cognitive dysfunction are long-term consequences of caregiving, reported years after the caregiving role has ended. Caregivers also report worse spiritual well-being and post-traumatic growth and recovery (Bishop et al. 2007).

Research has sought to identify variables that may have stress buffering effects such as the perception of mutuality in the caregiver/patient relationship and higher degree of preparedness which may be provided by the way of social support and caregiver education (Schumacher et al. 2007). A combination of these resources needs to be readily available at high degrees to see a protective effect of stress buffering. Research has also shown that caregivers who believe they are highly capable of managing the demands of their situation and thus have a high level of mastery tend to be less susceptible to depressive symptoms (Jo et al. 2007). It appears that lower levels of emotional distress are perceived when caregivers report a sense of personal control and spirituality (Fife et al. 2009).

12.6 Financial "Unseen" Challenges: Impact on Patient and Caregiver

There are immense financial challenges for the patient and caregiver involved with the transplant process that are not well delineated by hospital and transplant center costs. Temporary lodging, meals, and transportation expenses are often not covered by health insurance. Transplants are only offered at selected cancer treatment centers that may be great distances from caregiver/patient homes acquiring the expense of long-term relocations. Prescription and clinic visit copayments will be ongoing after transplant. In addition, an unanticipated lengthy recovery period may prolong the need to be away from home, delay return to work, and lead to loss of work-related benefits, such as paid leave (Denzen et al. 2016). Up to 56% of caregivers report acquiring a work-related strain including changing their work hours or taking leave from work both paid and unpaid (Rainville et al. 2016). The substantial out of pocket expense and potential loss of income caused by transplant can be debilitating and must be considered carefully for caregivers and patients living with fixed incomes. Caregivers managing substantial care needs report spending 10–20% or more of their household income on health insurance and selling assets, taking out loans, or getting extra jobs to pay for health care costs (Rainville et al. 2016; Emanuel et al. 2000). In a pilot study to determine the financial impact of allogeneic stem cell transplant on patient and caregivers, 80% of patients and caregivers reported that household income was reduced prior to transplant and only 32% felt confident in their abilities meet their financial obligation. Financial coping capacity was associated with availability of financial resources such as savings, paid time off, donations, disability income, and existing household income (Denzen et al. 2016). Only 33% of patients who were primary or secondary household wage earners were

able to resume this role 2 years after transplant, further evidence of the long-term financial burdens placed on caregivers and family members (Majhail et al. 2013; Syrjala et al. 2004). Additional research of the financial burden of HCT may elucidate strategies to prepare for the expense management of sociodemographically unique households. Social services and financial counselors are available in some transplant centers to provide finance education and resources in the peri-transplant period. Preparations and education to meet these financial demands could help alleviate finance related stress.

12.7 Important Aspects and Resources for Caregiver Support

Caregiving is not usually a role one envisions and interaction with the health care community is often limited before the cancer diagnosis. The greatest need of caregivers has been identified as the need for reassurance and hope as information can be overwhelming and constitutes a whole new language for caregivers. Reassurance and hope may be expressed by tracking laboratory data to see progress, receiving compassion from the care team, and meeting survivors of similar type of transplantations. Uncertainty and waiting can impact the caregiver's ability to plan and maintain a sense of control. Relationships between the patient and caregiver or caregiver and their social network can alter creating another sense of waiting for a return to normalcy (Sabo et al. 2013; Keogh et al. 1998). Many strategies are used by caregivers to manage uncertainty. Caregivers and patients may create rituals. Examples include planning daily activities such as a walk, scheduling visitors, and tracking daily labs to mark the progress of transplant. Caregivers may envision a good life after the transplant to maintain a positive attitude. Setting realistic upfront expectations will help caregivers and patients cope as adverse or unexpected transplant side effects occur (Wilson et al. 2009).

12.7.1 Interventions

There are multiple opportunities to provide caregiver interventions and support. First, the caregiver situation must be clarified including caregiver quality of life, the caregiver's perspective of their role, available resources, and active stressors and buffers. Interventions may include personalized education to improve caregiver preparedness, psychosocial counseling to improve coping skills and relationships, and promotion of self-care to maintain physical health and mental well-being (Gemmill et al. 2011). Caregivers may need a reduction in the amount of care they provide through the opportunity for respite and skill training. Additional caregivers (family members and/or friends) willing to help with care tasks or provide caregiver relief should be identified early to avoid a caregiver distress crisis or burnout. Online resources are available to help create care coordination calendars (see Table 12.1) and a social caring network may need to be discussed at patient visits.

Table 12.1 Caregiver resources

Resource	Website	Comments
American Association for Retired Persons	www.aarp.org/home-family/caregiving	Senior oriented but universal advice Multilanguage guides for first time caregivers Financial advice Advice for sensitive populations—Lesbian, gay, bisexual, or transgender Phone and online support groups
Cancer Support Community	www.cancersupportcommunity.org	Caregiver advice, resources, and education Focuses on caring for patients with cancer Video and online resources
Caregiving 101	www.caregiving101.com	Online resources Caregiver testimonials Online store for caregiving literature
Caregiver Action Network	www.caregiveraction.org	Caregiver tips and resources Online community and support groups
Caring.com	www.caring.com	Online caregiver wellness advice and education Online support groups and blogs
Family Caregiver Alliance	www.caregiver.org	Caregiver education and resources Caregiver policy and advocacy Caregiver support groups and resources
Lotsa Helping Hands	www.lotsahelpinghands.com	Care coordination service that provides a private, group task calendar caregivers post when help is needed and family/friends sign up
National Caregiver Alliance	www.caregiving.org	Caregiver research and advocacy
National Transitions of Care Coalition	www.NTOC.org	Collection of resources to help caregivers with health care transitions
Next Step in Care	www.nextstepincare.org	Easy to use guides to help caregivers plan transitions (hospital to home, etc.)
Women's Institute for A Secure Retirement	www.wiserwomen.org	Identifies financial concerns faced by caregivers to help plan for financial security

Psychoeducation may be provided to improve caregiver well-being and coping skills. Psychoeducation includes education about the patient's disease and disease related problems though lectures, group discussions, and written material (Sorensen et al. 2002; Mittelman 2005). Caregiving learning needs may include setting expectations for the hospital stay, transplant side effects, potential outcomes, and expectations of caregiver responsibilities after hospital discharge (Stetz et al. 1996). Both patients and caregivers describe the time of hospital discharge as a time of increased vulnerability with increased anxiety, depression, and stress. See Table 12.1 for resources to help prepare caregivers for these transitions in care. Providing education, counseling, and support groups may assist in this transition (Grant et al. 2005).

Within 6 months after transplant, families and caregivers report emotional and physical exhaustion. They report expectations that the patient would be ready to resume their pretransplant roles by this time resulting in unfulfilled hopes and further increased stress. Expectations at 1 year include an improved outlook by caregivers with a sense of safety but doubts that pretransplant normality will return with concerns about cancer relapse (Zabora et al. 1992). Counseling and improving problem solving skills are a method to improve caregiver coping abilities. This may include social problem-solving therapy which is a form of cognitive behavioral therapy that helps participants learn to understand the problem and work to change the nature of the situation, reactions to the situation, or both. Problem solving education increases self-efficacy and decreases stress levels even with just a few hours of intervention (Bevans et al. 2014). Another model of problem solving training includes the COPE model. This model teaches creativity to help caregivers view the conflict or situation from various perspectives to work through the problem. Optimism is applied to maintain a positive but realistic attitude. Planning is taught to help set realistic goals and outline steps to achieve them. Finally, caregivers are taught to seek expert opinions or to recognize when they need to ask for help (McMillan et al. 2006). Caregivers may need to work through hypothetical situations to improve their coping and problem solving skills and need time for counseling (Bucher et al. 2001). Outcomes of problem solving training include improved caregiver quality of life, decreased patient symptom burden, and decreased caregiver task burden (McMillan et al. 2006).

Supportive and palliative care services are a vital resource to providing caregiver support. The ENABLE (Educate, Nurture, Advise Before Life Ends) studies evaluated the efficacy of early incorporation of palliative medicine into oncology practices through face to face and telephone counseling. Caregivers were randomized to early versus delayed palliative medicine counseling in the ENABLE III study. Caregivers receiving early intervention had decreased depression and improved quality of life (Dionne-Odom et al. 2015). Another benefit to early supportive and palliative medicine intervention is the completion of advanced directives. Early and clear advanced care decision making by patients provides significant burden relief to caregivers. Early identification of the health care proxy or execution of a living will can help avoid family conflict during difficult health care decisions (Rabow et al. 2004). Early consultations with supportive and palliative medicine can also provide improved communication among the patient–caregiver dyad and among the patient/caregiver and healthcare team, further decreasing caregiver burden.

12.8 Expert Opinion

Informal caregivers are vital members of a patient's health care team and successful HCT would not be possible without this fundamental resource. As health care professionals, we need to be conscious of the burden and stress the process of transplant place on caregivers who are often underprepared and overwhelmed by the

tasks expected from them. Caregiver physical and mental well-being need to be monitored closely. Distressed caregivers need access to respite and resources to improve coping and problem-solving skills. Sensitive issues such as personal finances and relationship intimacy should have a forum for open discussion and counseling. Early inclusion of supportive and palliative medicine can be critical in improving caregiver burden and quality of life.

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Advance Care Planning: A Forgotten Art

13

C. Christopher Hook and Cory Ingram

13.1 Realities and the Need

B.T. is a 35-year-old male with acute myeloid leukemia (AML) in remission after induction with 7+3 chemotherapy, followed by CLAG-M re-induction chemotherapy, when his first-day 14 marrow reveals 35% residual blasts. He is undergoing an allogeneic hematopoietic cell transplant (allo-HCT) from his HLA-matched sister given the high risk of leukemia recurrence. Prior to the transplant, it was determined that he wanted to maintain full resuscitation status, but he did not have a formal advance directive, not even an appointed medical surrogate. It was presumed that his wife would be the decision maker, if required. On day 14 posttransplant he developed a fatal mucormycosis infection involving his right maxillary sinus, retrolaryngeal space, right upper and left lower pulmonary lobes, and numerous skin lesions, despite antifungal prophylaxis. His blood cell counts have shown no sign of engraftment. The transaminases are now five times the upper limit of normal, his creatinine is 3.7 mg/dL and rising, and he is bordering on requiring intubation because of respiratory distress. He has seizures due to what is subsequently identified as intracranial lesions most consistent with the fungal infection. The seizure precipitates full respiratory failure and intubation, and he requires vasopressors for vascular support and complete sedation.

The patient's nuclear family consists of his wife and two children aged 12 and 10 years, and his extended family includes his widowed mother (her husband died of complications of treatment for secondary acute myeloid leukemia arising from myelodysplastic syndrome after spending close to 2 months in the hospital) and four siblings, including his donor. Because of his clinical deterioration, his extended family members have joined his wife at the hospital. The intensive care unit (ICU)

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and the transplant teams meet with B.T.'s family and share the bad news that the prognosis is very grim. Even with granulocyte transfusions to try to contain the disseminated fungal infection until engraftment, the multisystem organ failure will likely continue to worsen and lead to tragic demise. The physicians broach the possibility of maximizing comfort but recommend making the patient DNR (do not resuscitate), and consider withdrawal of intensive life support. It is at this moment when a close, mutually supportive family quickly breaks down into intense disagreement. The patient's wife wants all care to continue; his mother disagrees and feels that all that is being accomplished is torturing him during his last moments. His four siblings are split, two siding with the wife's conclusion and two with the patient's mother. The only advance care directive they all have to work with is the patient's stated desire to be "full-code" when he started the process. To make matters worse, this tragic case is transpiring in one of the few states in which the law provides no guidance regarding who speaks for a patient lacking decision-making capacity, in the absence of a formal designation in an advance directive. The clinical care team is stuck, with no clear direction on how to proceed.

Unfortunately, this terrible situation happens more than any of us may believe likely. This situation could have been prevented if prior to induction chemotherapy and transplant, his primary hematologist and transplant team had engaged in a deliberate goals of care and advance care planning discussion(s) with the patient preparing an advance directive. This preparation could formally appoint a health care surrogate and articulate his values and express his wishes should the clinical course not proceed as desired.

Allo-HCT is a highly specialized process that is done with curative intend; however, it is associated with high risk of morbidity and mortality. Despite advances in infectious disease management, leading to a reduction in treatment-related mortality (TRM) at 5 years (36–26%), death from graft-versus host-disease (GVHD), disease relapse, and "other causes," mortality has not improved much in the past four decades. Mean time to death from all causes remains early in the course of the transplant (3 months, range 2–10 months for the majority) (Gratwohl et al. 2005). If patients survive the first 2 years after allo-HCT, and remain free of their underlying disease, they have a 70–92% likelihood of long-term survival. (Henig and Zuckerman 2014; Bhatia et al. 2007) Long-term complications, such as cardiomyopathy, valvular heart disease, dysrhythmias, pulmonary disease (including pulmonary fibrosis and interstitial pneumonitis), chronic renal failure, and secondary malignancies (such as therapy-related myelodysplastic syndromes and secondary leukemia) may also shorten the patient's life and/or significantly impair quality of life (Bhatia 2011). The implications of these data are that death or debilitating illness is not uncommon after allo-HCT especially during the early phase of transplant.

13.2 No Adult Is Too Young to Have an Advance Directive

Advance directives started to become commonplace in American culture and Medicine in the mid-1970s with the sensational case of Karen Ann Quinlan. Ms. Quinlan was only 21 years old at the time of her cardiopulmonary arrest due to a

combination of alcohol, benzodiazepines, and likely other substance(s) ingested at a friend's party. Resuscitated and maintained on a ventilator and with a feeding tube, she never regained consciousness. After a year in this condition, her parents requested the ventilator be discontinued claiming that their very independent daughter would not want to live in her current condition. Ultimately the New Jersey Supreme Court ruled the ventilator could be discontinued. Although her medical course would go on for over a decade beyond the ventilator's ultimate removal, many individuals stated that they would not want to be kept alive by machines in an unconscious or debilitated state like Karen Quinlan (Gostin 1997). A little known or used document at that time, produced by the Hemlock Society, called the Living Will became popular.

In 1983, another young woman, 25-year-old Nancy Cruzan, was involved in a motor vehicle accident. Resuscitated at the scene, she also never regained consciousness and was diagnosed as being in a persistent vegetative state. She did not require a ventilator, but her life was maintained with the use of a feeding tube. Five years into the persistent vegetative state, her parents sought removal of the feeding tube. The courts concluded that in the absence of a Living Will, or another document that had come into frequent use, the Durable Power of Attorney for Health Care, or other clear and convincing evidence Nancy would want life-sustaining treatment to be discontinued, the tube feedings must continue. The decision was appealed to the US Supreme Court, which ruled patients may refuse any and all forms of treatment, including life-sustaining treatment such as artificial nutrition and hydration, and if lacking decision-making capacity, could articulate their wishes via a designated surrogate and/or advance directive. The court also concluded states such as Missouri, where the Cruzans resided, could establish their own requirements as to the degree of certainty of the patient's wishes, such as Missouri's clear and convincing evidentiary standard, before acting upon them (Greco et al. 1991; Court USS 1990). This ruling led to the passage of the Patient Self Determination Act, which requires medical institutions to inform patients of their right to have an advance directive.

The third highly influential case demonstrating the importance of having an advance directive or advance care planning discussions with one's health care professionals and loved ones, particularly one's desired or designated medical surrogate, involved a 27-year-old female, Theresa (Terri) Marie Schiavo, at the time of her cardiac arrest in 1990. Terri also never regained consciousness, was declared to be in a persistent vegetative state, and was sustained by a feeding tube. Because of disagreements between her court-appointed surrogate, her husband, Michael Schiavo, and her parents, the Schindler's, regarding her treatment course, particularly whether or not to continue the artificial nutrition and hydration, the basic question, "what would Terri want?" became a national spectacle, with millions spent in attorneys' and court fees during a 12-year battle. The battle to resolve one question, "what would Terri want?" led to the appointment of three guardians ad litem, ten decisions by the second District Court of Appeals of Florida, four reviews by the Florida Supreme Court, four requests, all denied, for review by the US Supreme Court, and unprecedented involvement by the executive and legislative branches of the State of Florida and the United States. Ultimately, the tube feedings were discontinued, and she passed away in May of 2005 (Hook and Mueller 2005).

Advance care planning should begin in early adulthood for all individuals. The three cases, which have established law in the United States concerning the right to, and illustrating the need for, advance care planning, occurred in young adults, aged 21, 25, and 27 years at the time of their sudden change of health status. Each event occurred suddenly and without advance warning. Consequently, no adult is too young to engage in advance care planning. Advance care planning is much more important when an individual has a serious illness and is embarking on a treatment course known to have a high degree of morbidity and mortality such as allo-HCT. We need to consider the future with advance directives, explained, discussed and signed by the patient. These decisions need to be clear in the medical record and easily accessible to health care providers.

13.3 Impediments to Advance Care Planning

Barriers to advance care planning typically fall into one of three categories: (1) the practice, (2) the patient and their family, and (3) the health care system (De Vleminck et al. 2014). Barriers often coexist in all three categories simultaneously. This likely contributes to the low rates of advance care planning (Tung and North 2010). In successful community-wide advance care planning interventions, such as, La Crosse, Wisconsin, these barriers were addressed by trained advance care planning facilitators, educational materials for patients, and advance care planning documentation in the electronic health record (Schickedanz et al. 2009). These efforts resulted in a greater prevalence (90%) of advance care planning in the community and a greater availability (90%) of advance care planning documents at the time of death (Schickedanz et al. 2009).

13.3.1 Barriers in Medical Practice

There are many reasons why clinicians are not having advance care planning conversations with their patients. These clinician- and practice-related barriers often arise around issues of skill, role, and time. Communication and prognostication skills are the two most readily identifiable barriers standing between clinicians and these conversations (Greutmann et al. 2013; Hagen et al. 2015). Surrogates also use information to form opinions about prognosis that the clinicians may not be aware of, for instance, individual attributes of the patient, such as their strength of character and life history (Boyd et al. 2010). In addition, clinicians have reported emotional discomfort initiating conversations, (Hagen et al. 2015) yet, the role of the clinician is an important factor in advance care planning. Some clinicians have attitudes and beliefs about the importance of advance care planning or who should initiate advance care planning that prohibit them from having the conversations and raises the question: Whose role is it? (De Vleminck et al. 2013) Eighty-two percent of Veterans Affairs general medical physicians surveyed believe that the role of advance care planning rests with the physician (Markson et al. 1997). Attending

physicians are more likely to engage a patient in advance care planning than resident physicians (Tung and North 2010). The same attending physicians are also more likely to engage in advance care planning if the patient starts the conversation or has a change in health status. This emphasizes that clinicians should be sensitive to clues from the patient, and be willing to follow the patient's lead in advance care planning. Still, over a quarter (27.7%) of attending physicians rarely discuss advance care planning with their patients, which is a number we must strive to reduce (Tung and North 2010). Last, there are many demands on a clinician's time (Lund et al. 2015). Advance care planning conversations can be time consuming and may negatively impact the productivity or financial performance of a clinician.

13.3.2 The Patient and Family

The patient and family often have barriers related to one or more of the following: lack of knowledge, misconceptions, mistrust, health literacy, paperwork practicalities, and culture (Schickedanz et al. 2009; Hagen et al. 2015; Davis 2009; West and Reeves 2012). To meet the needs of patients with health literacy challenges, educational videos on advance care planning may be helpful (Volandes et al. 2008). Historically, there is evidence that advance directives in the medical record did not inform medical decision making beyond naming a health care proxy or documenting general preferences in a standard living will format (Teno et al. 1997).

For patients living with a serious illness, one recommended approach to the advance care planning process includes (Gratwohl et al. 2005) assessing readiness for participation, (Henig and Zuckerman 2014) personalizing relevance to the individual, (Bhatia et al. 2007) routinely offering scheduled family meetings for exploring personal goals and sharing information, (Bhatia 2011) training clinicians to have advance care planning discussions and leading family conferences, and (Gostin 1997) adequate, helpful documentation of advance care planning in the electronic health record (Simon et al. 2015). In certain disease-specific situations such as dementia, videos have been found more helpful than verbal descriptions to educate patients and families on the relevance of advance care planning for that particular disease (Volandes et al. 2009). In addition, disease-specific advance care planning in close proximity to a high-risk procedure has demonstrated benefits. For example, advance care planning before cardiac surgery increased patient-surrogate decision-making congruence and reduced decisional conflict (Song et al. 2005). Patients and caregivers identify four main issues and expectations for conversations with clinicians near the end of life: awareness of impending death, management/coping with daily living, relationship fluctuations, and personal experiences associated with facing the end of life (Farber et al. 2003). When needing to make decisions, most surrogates strive to respect the patient's input and use past knowledge about the patient's wishes. However, it should be remembered that surrogates often reflect on their own wishes, religious beliefs, self-interests, and family consensus when making decisions on behalf of the patient (Fritsch et al. 2013). These data emphasize the importance of advance care planning prior to emergence of medical urgency to

allow the surrogate to process their own feelings and beliefs in light of the patient's wishes.

Black and Hispanic older Americans are less likely than white counterparts to possess an advance directive. African American race is an independent predictor for advance directive possession after adjustment for other demographic variables, religious characteristics, and personal health values (Huang et al. 2016a; Yancu et al. 2010). In addition, African Americans and Hispanic patients are less likely to consider themselves terminally ill and more likely to want intensive treatment. These factors alone do not explain all of the observed disparities in advance care planning (Smith et al. 2008). Efforts to increase advance care planning in African Americans have been helpful in narrowing the gap between whites and African Americans in advance care planning (Huang et al. 2016b; Koss and Baker 2017).

13.3.3 Problems with the System

Health systems around the world struggle with conflicting initiatives and priorities, lack of infrastructure, and ineffective public awareness regarding advance care planning (Hagen et al. 2015). Advance care planning often does not align with common medical services, including financial and organizational models (De Vleminck et al. 2013).

13.3.4 Solutions

In order to remove barriers to advance care planning in medicine, leadership must first communicate the importance of advance care planning for the care of patients and families. Second, health care providers must have training and develop comfort with advance care planning. Third, integrating advance care planning into the electronic health record is necessary. Last, and likely foundationally, there must be widespread, available, accessible public awareness and education on advance care planning (Hagen et al. 2015).

The thought that advance care planning takes time that will not be reimbursed has fortunately been resolved. Since 2016, clinicians may bill for advance care planning services. This is a tremendous benefit to promote advance care planning. Billing codes 99,497 and 99,498 allow a clinician to bill for the time spent explaining and discussing advance care planning. A clinician must spend a minimum of 16 of 30 min of face-to-face time with the beneficiary, family member(s), and/or surrogate to bill a 99,497. Code 99,498 may be used for each additional 30 min of time spent face to face. Clinicians may also bill for other clinical services performed at the time advance care planning conversations take place. There are no limits on the number of times these codes may be used in a given time period. There are also no limits on the place of service to use these codes. The clinician documents the conversation in the medical record and should include the voluntary nature of the encounter, the explanations given, the participants involved, and the time spent. No specific diagnosis is required to use advance care planning codes (Donath et al. 2009).

13.4 Problems with Advance Directives

An advance directive is only useful if (Gratwohl et al. 2005) it exists and (Henig and Zuckerman 2014) its contents are accessible and known to the patient's caregivers and surrogate.

Another problem with advance directive preparation involves the comprehensibility of the forms preprinted by state governments for use by their citizens. Mueller et al. studied the advance directives for all 50 states and the District of Columbia, revealing that the average readability for the documents was the 11.9th grade. The reading level recommended by the National Work Group on Literacy and Health is the fifth grade. None of the 62 advance directive forms obtained were at a fifth grade reading level, and only 5 had a readability score at the eighth grade level or lower, which is the US average reading level for adults (Mueller et al. 2010). Having personally read many of these documents and been involved in ethics consultations in which key medical concepts mentioned in the forms are not understood by patients, the authors can attest that limited health literacy is a substantial impediment to the preparation of meaningful, representative advance directives.

13.4.1 Problems with Surrogate Decision-Making

Without efforts to encourage patients to discuss their health care goals, desires, and instructions with their appointed surrogates, it has been demonstrated that surrogates' accuracy of predicting the patients' wishes is often little better than chance, the flip of a coin (Uhlmann et al. 1988; Seckler et al. 1991; Sulmasy et al. 1998).

13.5 The Current Status of Advance Care Planning

13.5.1 Types of Advance Care Planning Documents

Advance directives come in a variety of forms. The oldest is the Living Will. The living will basically articulate what the patient does or does not want in terms of treatment should he or she lose decision-making capacity. Often, the Living Will has a second triggering criterion: the patient also be terminal, that is, a prognosis of ≤6 months to live. The Living Will does not appoint a health care surrogate, and therefore is limited in its utility to address situations when the patient is profoundly ill, but not necessarily terminal, or when interventions not explicitly covered by the contents of the document needed to be considered.

The next development in advance care planning documents, the Durable Power of Attorney for Health Care, aims to address the weaknesses of the Living Will. This document formally appoints a health care surrogate when the patient loses decision-making capacity. It may also include specific directions from the patient regarding certain kinds of treatment, personal values and beliefs. By providing a surrogate who can incorporate the patient's expressed wishes, values, and so on, and interact with the health care team in all situations, the Durable Power of Attorney for Health

Care is a more dynamic and broader source of guidance. Some states have called their advance care planning document by another name, for example, Minnesota's Health Care Directive. The Minnesota Health Care Directive not only serves as a Durable Power of Attorney for Health Care but also prompts the patient to consider other issues, such as desire for aggressive mental health treatment such as electroconvulsive therapy, how women wish to proceed with maintaining a pregnancy, or not, if they should become decisionally incapable while pregnant, and views concerning organ donation, which are not usually pertinent to hematopoietic cell transplant recipients. However, the Minnesota Health Care Directive specifically prompts patients to address the issue of artificial nutrition and hydration, which has become an increasingly contentious issue, in the aftermath of the Schiavo case (Minnesota Health Care Directive 2017).

The newest story on the advance care planning document block is the Physician Orders for Life-Sustaining Treatment (POLST). Physician Orders for Life-Sustaining Treatment documents may be called by other names, including Medical Orders for Life-Sustaining Treatment (MOLST), Medical Orders on the Scope of Treatment (MOST), Physician's Orders on the Scope of Treatment (POST), and Transportable Physician Orders for Patient Preferences (TROPP). Physician Orders for Life-Sustaining Therapy was created in Oregon in 1991, and is now legally recognized, or being developed, in the majority of states. An organization called the National POLST Paradigm hosts a website of the same name (www.polst.org) and has up-to-date information about the status of Physician Orders for Life-Sustaining Therapy in each state.

In contrast to a patient-prepared advance directive, the Physician Orders for Life-Sustaining Therapy is an actual legal prescriber (physician, PA, NP, etc.)-signed medical order that governs the implementation of life-sustaining interventions such as a do-not-resuscitate (DNR) order that applies in all locations, not just in the hospital or nursing home. It provides coverage of situations not otherwise governed by a physician's orders, such as during transportation between facilities or in the home setting. Physician Orders for Life Sustaining Therapy, however, has come under significant opposition from some critics. First among the concerns regard patient autonomy: in many jurisdictions where recognized, the Physician Orders for Life-Sustaining Therapy document only requires a physician's signature and not the patient's as well. The order can be signed and activated without sufficient discussion with the patient. Because many long-term institutions, such as nursing homes, are now pressuring physicians to issue Physician Orders for Life-Sustaining Therapy for their patients, several concerns arise. The patient may not be near the end of life. Physicians who do not know the patients well may prepare Physician Orders for Life-Sustaining Therapy documents without sufficient advance care planning discussions with the patient in question, in clear violation of the intent and procedural requirements for the documents (Brugger 2011; Brugger et al. 2013).

Though not a formal legal advance directive in the sense of being notarized, and so on, the Advance Care Planning Note is a recent innovations in advance care planning for the age of electronic medical records. An advance care planning note is a

communication tool in the electronic health record to convey a patient's important advance care planning data elements: their surrogate decision maker, and their values, preferences, and priorities for health care. The advance care planning note makes this information easy to find in the medical record. The advance care planning note removes the necessity for clinicians to review multiple clinic notes to find if there has been an advance care planning conversation. It also allows for iterative updating of advance care planning information. Often many clinicians are caring for a single patient and the advance care planning note allows each clinician to easily find and know when and where the last advance care planning conversation with the patient left off. This is particularly helpful for emergency room and ICU clinicians who may be encountering a transplant patient for the first time. The advance care planning note may convey important information from a conversation with their hematologist or primary care clinician. The emergency room clinician can also note the essence of their conversation with the patient concerning advance care planning issues so the hematologist can easily pick up the conversation back in the hematology clinic or hospital. There are no widely accepted standards for advance care planning notes. We have shared a template of the note we created for use at Mayo Clinic (Fig. 13.1).

13.5.2 What Happens When a Surrogate Is Not Formally Appointed?

A particular challenge can arise when a patient does not have decision-making capacity, and has not appointed a health care surrogate. Who then speaks for the patient? In the United States, most, but not all, states have statutory designations for who should serve as the legal health care surrogate. The majority of states designate the spouse, followed by secondary, tertiary, and so on, designees, in the absence of more primary individuals. For example, the ranking may proceed as (Gratwohl et al. 2005) spouse, (Henig and Zuckerman 2014) adult child or majority of adult children, (Bhatia et al. 2007) parent(s), (Bhatia 2011) adult sibling or majority of adult siblings, (Gostin 1997) close relative, and (Greco et al. 1991) in the absence of any kin, a close personal friend with excellent knowledge of the patient and the patient's values, wishes, and so on. Colorado declares that a consensus of interested persons will serve as the surrogate. Michigan and Indiana place the spouse and a parent on equal status. Minnesota and a few other states do not provide specification on who has decision-making authority, creating the critical need for every adult patient to prepare at least a Durable Power of Attorney for Health Care or Minnesota Health Care Directive appointing a health care surrogate. Finally, Texas and Connecticut allow the patient's physician to serve as the surrogate in the absence of an advance directive, which, while codified in state law, is ethically imprudent, if not inappropriate. The variability among state statutes necessitates physicians know the specific rules in the state(s) where they practice to help patients in advance care planning.

Advance Care Planning Note

Service GroupXX Patient Location:Outpatient/Inpatient Hospital Day: XX

Reason for Conversation
This patient is a XX year old male/female that presents for XX
1. Patient has understanding of condition: YES/NO
2. Patient understands treatment options: YES/NO
3. Patient understands potential benefits and risks of proposed treatments/interventions: YES/NO
Alternative Decision Maker:

The patient, XX, expresses the following preference:

Free Text

Optional Expression of Values/Preferences for Specific Life-Prolonging Treatments:

Free Text

The patient, XX, if indicated below, Innovation expresses preferences for specific life-prolonging treatments to be used or withheld /withdrawn at a future time of incapacity. Please choose one of the following:

- o Allow Natural Death*, No CPR or Mechanical Ventilation will be performed
- o Attempt CPR, this requires full medical treatment including mechanical ventilation
- o Mechanical Ventilation ONLY without attempts of CPR
- o Patient undecided at this time
- o Not discussed at this time

Free Text

*if the patient indicates desire to Allow Natural Death at the present time, a Do Not Resuscitate/ Do Not Intubate order should be written AND a corresponding code status should be completed

Others Present:

The following person/people were also present during the discussion: Name/Relationship to patient

Other Comments:

Free Text

Fig. 13.1 The advance planning note

13.6 The Literature on Advance Care Planning in Transplant Recipients: Limited Data

To date, there have been few publications looking specifically at advance care planning in the HCT population. Following is a brief summary of the available findings.

Joffe et al. surveyed 335 pretransplant patients, and reviewed patient records to determine if advance care planning discussions were documented, and/or the presence of written advance directives. Forty-six percent (46%) of the patients (155) returned the survey forms, and 137 (88%) provided permission to examine their medical record. Sixty-nine percent (69%) had designated a health care surrogate, 46% prepared a living will, but only 39% had written advance directives in their

chart, and 63% had had a discussion with their family and friends about their wishes for life-sustaining therapy. Disappointingly, discussions between the patient and their physicians occurred only 16% of the time, with documentation of advance care planning rarely occurring (Joffe et al. 2007).

Loggers et al. interviewed surviving HCT patients and bereaved caregivers via retrospective, taped telephone surveys. Among the 18 survivors, 50% had living wills and 72% had a formal proxy. Only 12 (67%) reported pretransplant discussions with their physicians concerning mortality risk. Yet of those, 92% reported that their perception of the treating team's truthfulness, as well as their own hopefulness for the procedure and their future, was improved or unchanged by the discussions. Eighty-two percent (82%) of the bereaved caregivers reported discussing mortality risk with the treating team, and 78% stated that their hope was improved or unchanged. Importantly, 67% stated that advance care planning discussions reduced their burden (Loggers et al. 2014).

One of the reasons cited for not having advance care planning discussions with HCT patients and surrogates is that such conversations will produce or increase distress. Duckworth et al., however, have demonstrated that while emotional stress in both groups is quite high, advance care planning did not worsen that stress in 40 HCT patients, and 39 surrogates, during the pretransplant process (Duckworth et al. 2014).

One of the most intriguing articles dealing specifically with advance care planning in HCT revealed that patients who did not undergo advance care planning prior to HCT (i.e., by the definition of the study, had a Living Will, Durable Power of Attorney of Health Care, or some other form of life-sustaining treatment instruction) had worse clinical outcomes. The study examined 343 patients, 172 without advance care planning and 171 with advance care planning. Those patients without advance care planning had a significantly greater risk of death (HR 2.11) compared with those who had performed advance care planning. The cause of this disparity is unknown, requires replication in other studies, and if confirmed to be a repeatable observation, should be the subject of future investigation to understand why and identify explanatory factors (Ganti et al. 2007).

13.7 Useful Documents

Following is a list of significant documents regarding advance care planning that contain substantially more useful information than can be summarized sufficiently within the limits of this chapter, and are worth the reader's attention:

- Bernacki, RE, Block, SD, for the American College of Physicians High Value Care Task Force. "Communication About Serious Illness Care Goals: A Review and Synthesis of Best Practices." *JAMA Internal Medicine* (2014) 174(2): 1994–2003.
- Butler, M, Ratner, E, McCreedy, E. Shippee, N, Kane, RL. "Decision Aids for Advance Care Planning: An Overview of the State of the Science." *Annals of Internal Medicine* (2014) 161: 408–418.

- Committee on Approaching Death: Addressing Key End of Life Issues; Institute of Medicine. *Dying in America: Improving Quality and Respecting Preferences Near the End of Life.* Washington, DC: The National Academies Press. 2015. A PDF of the book is available at http://nap.edu/18748.

13.8 Expert Point of View

There are several key takeaway points from this chapter:

- No adult is too young to prepare an advance directive and appoint a health care surrogate.
- Every patient who uses a life-sustaining treatment (such as a pacemaker, dialysis), or a medical intervention with significant potential morbidity and mortality, such as HCT, should undergo formal advance care planning with their caregivers and family members with thorough documentation of the discussions, and the preparation of a legal advance directive that should include at a minimum the appointment of a Durable Power of Attorney for Health Care or surrogate.
- Deliberate efforts must be made to ensure that when patients have prepared written advance directives, the documents must be obtained and placed in the formal medical record in a way that is easily accessible.
- It is the duty of physicians to review advance directives with the patient on a regular basis (the authors recommend every 5 years, or sooner if there is a major change in the patient's status), and encourage patients to discuss the documents and their wishes with their appointed surrogates. The purpose of these reviews is to make sure that patients have not changed their wishes for their health care and their lives. This review should include consideration of new technologies that may have a bearing on their medical course.
- Billing codes 99,497 and 99,498 allow a clinician to bill for the time spent explaining and discussing advance care planning.
- Physicians should practice and routinely incorporate advance care planning conversations in the care of their patients. As mentioned earlier, advance care planning discussions do not cause patients to lose hope, but rather tend to build confidence and trust in their health-care professionals.

13.9 Future Directions in Advance Care Planning Methodology

The next wave in advance care planning will utilize the proliferation of cellular devices with video capability and patient portal applications for those devices. At the time of the writing of this chapter, there are already commercial applications that allow patients to prepare advance directives, including videos of the patient expressing his or her wishes and other messages the patient wishes to share with his or her loved ones or care team. It is likely that medical offices will be equipped with

video cameras on the terminal for the electronic medical record, enabling a recording of a care provider-directed interview of the patient regarding the patient's health care values and goals. These videos will enable patients to go into greater detail about their desires and concerns than would typically be included in a written document. Perhaps these videos will induce greater adherence to the articulated choices, because when properly structured and clarified by follow-up questions, it may be harder for physicians and/or surrogates to dispute the contents of the record. Challenges in using video advance care planning documents include (Gratwohl et al. 2005) how the videos will be shared across operating systems, electronic medical record platforms, and health systems, and (Henig and Zuckerman 2014) the fact that commercial entities producing some of the products charge an annual fee to maintain the record and access to it, when it is our opinion that patients should not have to pay to have an advance directive.

It is the authors' hope that health care institutions and individual programs, such as HCT programs, will pursue dedicated efforts to ensure all of their patients will be engaged and assisted in advance care planning conversation and documentation. In medicine, we must never forget, and always prepare for, the future.

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End-of-Life, Grief, and Bereavement: Strategies to Provide Comfort?

14

Sonia Malhotra

14.1 Introduction

Patients facing life-threatening illnesses often have questions about what their last days and hours will look like. There is an equal concern from patients about effective symptom control at the end of life and the fear of becoming a burden on loved ones. Communication during the dying phase is incredibly important. This chapter will identify methods used in patient–doctor communication that can assist clinicians when discussing end-of-life issues. In addition, clinicians will have a greater understanding of common signs and symptoms at the end of life, so they can effectively manage them. Key issues in the transition to hospice and advance care planning are discussed. Clinicians will also learn to identify grief and understand what causes it to be prolonged or complicated in nature.

14.2 Communication at the End-of-Life

Five domains of effective end-of-life care have been identified for clinicians to remember when caring for the dying (Fig. 14.1) (Prendergast and Luce 1997). Dignity and respect should be of utmost importance during this process with reassurance that symptoms will be effectively managed, and communication will occur honestly and empathetically.

One of the major challenges of supportive care in hematopoietic cell transplant (HCT) recipients is the discussion of end-of-life care. For patients and families who

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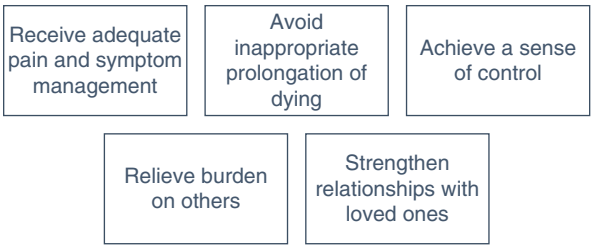

Fig. 14.1 Five domains of effective end-of-life care

often must be positive when dealing with setbacks, this topic can be difficult to absorb. Clinicians often have difficulty disclosing such bad news. In a study of 602 cancer patients, physicians only discussed imminent death with 31% of patients (Wright et al. 2008). Other studies have demonstrated that medical oncologists have difficulty discussing prognosis in patients receiving palliative chemotherapy (Koedoot et al. 2004) and often death is not discussed with hospitalized patients who are reasonably expected to die (Sullivan et al. 2007).

Another complicating factor to end-of-life discussions is that HCT patients tend to have greater optimism about their outcomes when compared to the physicians treating them (Lee et al. 2001). In this prospective study, the sickest patients who had an actual mortality rate of >30% were less likely to perceive their high mortality rate and poor prognosis. Those patients with more of an optimistic outlook who overestimated their odds of survival did not survive longer than those who were realistic or pessimistic (Lee et al. 2003). The SUPPORT trial showed that patients who overestimated their survival did not live longer than those who were realistic or pessimistic and optimistic patients were more likely to die in the hospital or ICU setting and to suffer from side effects of their treatments (Weeks et al. 1998). Another issue that complicates end-of-life discussions is that patients are often willing to undergo treatments such as Phase I clinical trials and risk a high percentage of death from an experimental drug without proven track record (Agrawal et al. 2006) even when well informed but with a different perspective from their physician (Matsuyama et al. 2006). However, the data are clear that patients want honest and truthful information especially when the prognosis is noted as being "extremely" or "very upsetting" (Mack et al. 2006).

Clinicians caring for HCT patients have important communication tasks including conveying serious news and discussing goals of care. A single family meeting is one part of a series of conversations that patients need to absorb serious news. Several models of patient–doctor communication exist to provide a map for leading these conversations (Figs. 14.2 and 14.3) (Ulep and Malhotra 2017). These conversations are best held with the individuals of a family that patients would like to present as well as other clinicians whose presence will assist with the content of the conversation. Information should be given in small amounts while avoiding medical jargon. Clinicians should expect to respond to emotion through verbal empathetic statements (Fig. 14.4) or nonverbal methods such as touch, nodding, silence, or eye contact.

S Setting	Prepare yourself with the medical facts
P Perception	Find out the patient's perception of the medical situation
I Invitation	Find out how much information the patient wants to hear
K Knowledge	Give information in clear, simple, direct language
E Empathize	Respond to patient emotions
S Summarize	Summarize the clinical information and make a plan for the next steps

Fig. 14.2 SPIKES model for giving bad news

Ask	Ask the patient what their current understanding of their medical course is
Tell	Tell patients information that needs to be communicated (such as bad news or treatment options) in clear, direct, simple language
Ask	Ask the patient for their understanding of the information you gave them

Fig. 14.3 Ask-Tell-Ask model for giving bad news news (adapted from VitalTalk)

N: Name	Decreases the emotional intensity of the conversation "It sounds like you are frustrated"
U: Understand	Acknowledges the intensity of what the patient and/or family is going through "I can't even begin to imagine what you all are going through"
R: Respect	Praises the patient and/or family's efforts "You have done an amazing job with everything"
S: Support	Aligns the clinician with the patient and/or family "I will do everything I can to help"
E: Explore	Allows more information to be obtained "Would you be able to explain what you meant by that?"

Fig. 14.4 NURSE mnemonic for statements of verbal empathy (adapted from VitalTalk)

14.3 Signs of End-of-Life

At different points of the course of a serious illness, patients may show signs and symptoms similar to those that are present at the end of life. However, when observed simultaneously, this generally indicates that a patient is entering the last phase of life. During the last weeks to days of a patient's life, the "transitional phase" of dying occurs (Doyle-Brown 2000). This phase consists of symptoms and signs that occur simultaneously (Fig. 14.5). It is important to educate family members on these symptoms and signs, so an understanding of the dying process can start. This will help family members understand that the patient does not have control over this natural course. It may also help lessen frustrations that may occur and allow families to plan for what is to come next.

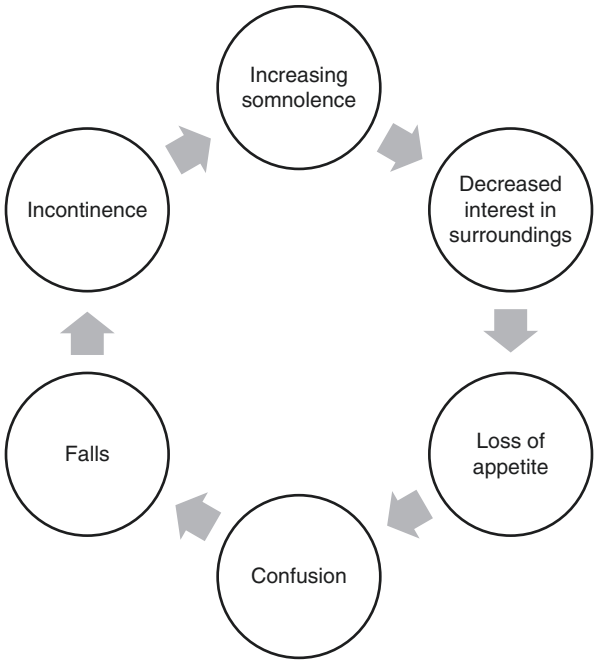

Fig. 14.5 The "Transitional Phase" of the dying process

Fig. 14.6 Opioid equianalgesia table

Medication	Parenteral (mg)	Oral (mg)
Morphine	10	30
Oxycodone	-	20
Hydromorphone	1.5	7.5
Oxymorphone	1	10
Fentanyl	0.1	-

14.4 Symptoms at the End-of-Life

14.4.1 Pain

Pain is a common symptom experienced in patients with serious illness that changes as the terminal phase of life is entered. Reports of new pain can be the result of disease progression or a new problem related to the dying process. Cancer-related pain is generally due to the activation of pain receptors, known as nociceptors that are present in the skin, soft tissue, skeletal muscle, bone, and certain viscera. Opioids are a mainstay of treatment and clinicians should be well versed in equianalgesia conversions (Fig. 14.6). Opioid conversions are discussed in chapters separate from this one.

Assessing pain in the last days to hours of life can be challenging as patients are generally unable to report this verbally. Clinicians should watch for nonverbal signs of pain such as grimacing, moaning, withdrawing from stimuli, as well as changes in vital signs. Almost half of dying patients will need an increase in their opioid dose during the last days to hours of life (Twycross and Lack 1983). Routes of pain

Table 14.1 Sample calculation of continuous opioid infusion and bolus doses

Patient A:	Morphine 2 mg intravenous every 1 h as needed	
	– Used 10 doses in 24 h	OME = 60
To start continuous infusion:		
– 2/3 of total OME in long acting form	60 × 2/3 = 40 40 divided by 24 h	CI = 1.6 mg/h
– Bolus dose 5–15% of total OME	60 × 0.05	Bolus dose = 3 mg IV q15 min PRN

OME oral morphine equivalent

medications will need to be reevaluated as swallowing becomes more difficult. Approximately 60% of patients are able to retain their ability to swallow until death (Twycross and Lack 1983). Patients unable to take pills can receive opioid pain medications via the buccal, sublingual, rectal, or transdermal routes. When higher doses are required, subcutaneous or intravenous infusions might be required. It is important to note that continuous infusions of opioid medications should not be started on opioid naive patients who are dying (Portenoy 1986). In these patients, bolus doses or as-needed pain medications should be used to determine an oral morphine equivalent (OME). Bolus doses are more effective for immediate symptom relief and if enough bolus doses are used, this will guide what dose of continuous infusion should be initiated (Table 14.1). When a continuous infusion is started, boluses should still be continued for immediate symptom relief. Continuous infusions can take anywhere from 4 to 8 half life cycles to reach steady state, so boluses will assist with keeping patients comfortable. Opioid infusion titrations should only occur two to three times daily at most. Opioids correctly titrated for symptom relief will not cause respiratory depression. When pain becomes difficult to manage, consultation with a palliative medicine team or pain specialist should occur.

14.4.2 Dyspnea

The prevalence of dyspnea in cancer patients ranges from 20 to 60% (End of Life Online Curriculum Project 2012). Dyspnea can be described as the subjective sensation of breathlessness. It is often distressing to patients and their families. Generally, at the end of life, dyspnea is caused by a combination of factors that have already received maximal treatment (Fig. 14.7). Nonpharmacologic treatments for dyspnea include repositioning, oxygen, and fans providing cool air. Pharmacologic treatments consist of opioids and benzodiazepines.

14.4.3 Anorexia and Decreased Oral Intake

It is common in the year after HCT for patients to have long-term issues with appetite, taste, and weight maintenance (Iestra et al. 2002). As patients near the

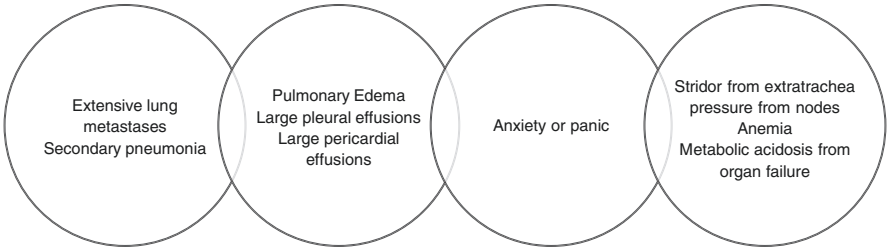

Fig. 14.7 Common causes of dyspnea

end of life, they often have a lack of interest in eating and drinking due to the body's inability to metabolize food. This can have significant cultural, familial, and personal implications. Families may worry about contributing to their loved one's suffering and even death. Clinicians need to educate patients and caregivers about the loss of appetite that occurs in the terminal phase of life and how little benefit nutrition provides. Families should be encouraged to provide sips of fluid and moisten the lips with the fluid and/or pureed food of their loved one's choice that has been shown to provide comfort and negate the need for intravenous hydration (McCann et al. 1994).

14.4.4 Terminal Delirium and Agitation

Terminal delirium and agitation are the fluctuating levels of consciousness that vary from hour to hour in terminal illness. They are due to a combination of factors, including the underlying illness(es), untreated pain, constipation, urinary retention, prolonged hospitalization, and other factors. In terminal cancer patients, it is a common symptom that occurs in 85–90% of patients during the final 24–48 h of life (Macleod 2006; Bruera et al. 2009). Patients may have insomnia, nightmares, restlessness, combative behavior, and/or sensory distortions that can be distressing to patients and families (Morita et al. 2004). These behaviors may have long-lasting impressions on family members and loved ones and have been associated with long-term anxiety (Buss et al. 2007).

Nonpharmacologic interventions for delirium include frequently orienting the patient, having familiar family members and loved ones visit, reminding the patient about daytime versus nighttime and minimizing caretaker interruption (Inouye et al. 1999). Patients should be in well-lit rooms (Moyer 2011) and have their glasses and hearing aids with them to avoid sensory deprivation. The use of restraints, including mittens, should be minimized if used at all.

The mainstay for pharmacologic treatment of terminal delirium consists of typical or atypical antipsychotics (Longergan et al. 2007; Dvelin et al. 2010). The difference in terminal delirium is that there is no expectation of it improving as the dying process progresses. For this reason, benzodiazepines may be needed in

conjunction with antipsychotics (Cook 2004). If a patient is still on immunosuppressant and/or antirejection medications, consultation with an HCT pharmacologist should occur to avoid medication interactions.

14.4.5 Terminal Secretions

Also known as the "death rattle," dying patients may often make gurgling noises from their inability to swallow or clear secretions at the back of their throats (Hugel et al. 2006). This occurs in 31–92% of dying patients and often causes clinicians and family members greater distress than patients. Nonpharmacologic interventions such as positioning in a lateral recumbent position and light suctioning may help. Anticholinergic agents such as glycopyrrolate or scopolamine patches assist in drying secretions. Other agents such as hyoscyamine and atropine drops are not as efficacious but can be used as adjuncts to anticholinergics. Often, terminal secretions are refractory to treatment and educating families to ease their fears and concerns is of utmost importance (Wee and Hillier 2008).

14.4.6 Transfusion Dependence

Occasional transfusions may improve the quality of life for patients who fail myeloablative therapy and HCT. This should be a conversation held between clinician, patient, and family prior to a patient entering the imminently dying phase. Studies have shown that transfusions in the hospice setting are more cost-effective (Cartoni et al. 2007) and may improve survival benefit at the end of life when compared to transfusions required in an inpatient setting (Brown and Bennett 2007). Subjective improvement of symptoms in greater than 50% of terminally ill patients was demonstrated by one study, irrespective of pre- and posttreatment hemoglobin levels (Monti et al. 1996).

14.5 Existential Distress

Spiritual distress, also known as existential distress, can be a source of challenge at the end of life. Spiritual well-being is one of the six domains of quality supportive care of the dying according to the Institute of Medicine. Spiritual distress can manifest as physical, psychological, religious, or social symptoms (Fig. 14.8). There is a lack of consensus on how to treat the spiritual aspects of dying and the best intervention may lie in clinicians acknowledging it. A simple mnemonic named FICA (Fig. 14.9) (Puchalski and Romer 2000) can help clinicians screen for spirituality and possibly identify any issues of existential distress.

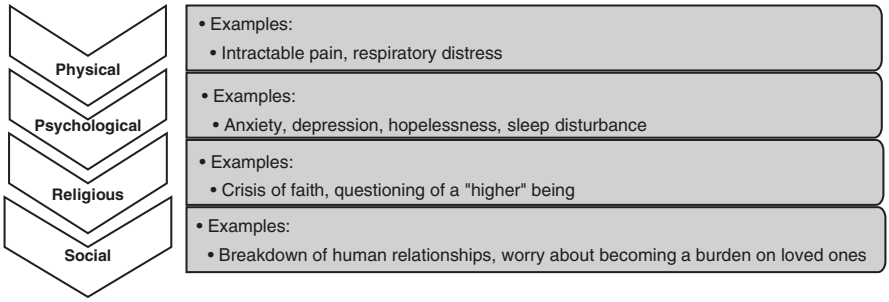

Fig. 14.8 Symptoms that existential distress may manifest as

Fig. 14.9 FICA screening tool for spiritual inquiry

14.6 Transition to Hospice and the Final Hours

Clinicians must be able to have open and honest conversations regarding futile medical management and the risks of continued treatment outweighing the benefits. When medical management has reached its maximal efforts and the primary goal of medical care is comfort, rather than longevity, clinicians need to have these conversations as empathetically as possible with patients and families.

Hospice is a model for quality compassionate care that focuses on caring, not curing. It is both a philosophy of care and a regulated insurance benefit through the Medicare Hospice Benefit (MHB). If patients want to die at home and avoid the back and forth of admissions to the hospital, home hospice would be an appropriate recommendation. Challenges with home and inpatient hospice care include the consequence of shortened life span when discontinuing certain antibiotics for infection, transfusions, and antirejection medications that may assist with quality of life and

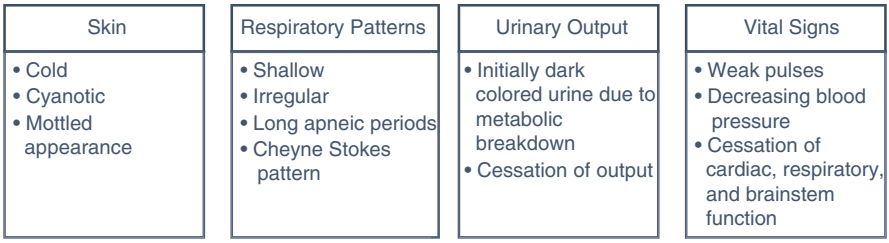

Fig. 14.10 Syndrome of impending death

pain control. Hospices are only allotted a certain amount of dollars to care for patients on a daily basis and many of these medications are cost prohibitive to patients going home with hospice or to an inpatient hospice unit. Each hospice agency is unique and may be able to cover a wider variety of services, medications, and interventions depending on their philanthropy funding. Clinicians need to weigh out whether there truly is benefit to medications and interventions before proposing hospice care. A careful review of medications is important to avoid those that are unnecessary, to avoid pill burden and avoid adverse effects.

The "syndrome of imminent death" is a group of symptoms that patients exhibit in the last hours of life (Fig. 14.10). It is important for clinicians to understand these symptoms, so they can educate family members on what to expect when impending death is imminent. Studies have shown that when impending death is expected, this is not well communicated to fellow colleagues, patients, or families (Ray et al. 2006). One of the first changes to occur is skin changes in temperature and appearance from the periphery to inwards, becoming more cold, cyanotic, and mottled. Breathing patterns may become more shallow, slow, and irregular with long apneic pauses. Urinary output will decrease and eventually cease altogether. Pulses will weaken and blood pressure will decrease. Patients become more mentally altered as the dying process occurs.

14.7 Advance Care Planning

Physicians should engage patients and families in advance care planning discussions early in the disease process (refer to Chap. 13). This process should not focus around creating a document. Rather, conversations should center on patient's goals of care and how to best approach treatments in the setting of serious illness. The first step is for patients to identify a surrogate decision maker who knows the patient's wishes well enough to represent their decisions should the patient be unable to. Conversations should encourage patients to spend time thinking about what is important to them and what types of interventions and situations they would like to avoid. Clinicians can then make recommendations based on what is likely to achieve these goals. This creates a plan that can be summarized in a formal document and presented at any hospitalization or clinic visit. Documents such as the 5 Wishes can be used to help address certain topics of relevance in serious illness.

As patients near the end of life, a Physician Orders for Life-Sustaining Treatment (POLST) form can reflect patient's wishes regarding resuscitation, intubation, and other advanced medical interventions. It is a mobile form that can be transported between various settings (refer to Chap. 13).

14.8 Grief and Bereavement

Grief is a normal response to loss that occurs when a serious illness is diagnosed. It continues through treatment, remission, recurrence, exacerbation, and re-hospitalization and intensifies through the dying process. It is important for clinicians to recognize the loss that occurs through all stages of illness and treatment and address these with the patient and family.

Difficult or complicated grief is defined as the intensification of grief to a level where a person is overwhelmed, cannot perform their activities of daily living, and remains in a progressive state of mourning (Prigerson et al. 1995). There are seven symptoms that characterize complicated grief (Fig. 14.11). Prolonged grief has now been included in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) (Fig. 14.12) and has been recognized as a distinct mental disorder that can cause clinically significant distress and disability.

Fig. 14.11 Seven symptoms classifying complicated grief

Category:	Definition:
A: Event	Death of a close other
B: Distress	Since the death, at least one of the following on most days for at least 12 months following the death: 1. Persistent yearning for the deceased 2. Intense sorrow and emotional pain 3. Pre-occupation with the deceased
C: Behavior	At least six of the following on most days for at least 12 months after the death 1. Marked difficulty accepting the death 2. Disbelief or emotional numbness over the death 3. Difficulty with positive reminiscing about the deceased 4. Bitterness or anger related to the loss 5. Maladaptive appraisals about oneself in relation to the deceased or death 6. Excessive avoidance of reminders of the loss 7. A desire to die to be with the deceased 8. Difficulty trusting others since the death 9. Feeling alone or detached from other people 10. Feeling that life is meaningless without the deceased or belief that one cannot function without them 11. Confusion about one's role in life or diminished sense of identity 12. Difficulty or reluctance to pursue interests or to plan for the future
D: Functioning	The disturbance causes significant distress or impairment in social, occupational, or other areas of functioning
E: Impairment	The bereavement reaction must be out of proportion or inconsistent with cultural or religious norms

Fig. 14.12 Persistent complex bereavement-related disorder in *DSM-V.* Adapted from Prigerson et al. (2009) and Duffy and Wild (2017)

14.9 Conclusion

End-of-life care can be one of the most difficult stages of serious illness care and yet one of the most rewarding tasks. Clinicians need to be well versed in the medical and emotional aspects of managing end-of-life care. Various pharmacologic and nonpharmacologic treatments are used to treat symptoms in the dying phase of illness. Communication should be clear and done as empathetically as possible. Spirituality, grief, and advance care planning are issues that should be addressed early in the course of illness.

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Survivorship Issues: Practices, Guidelines and Controversies

15

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15.1 Introduction

Significant advancements in hematopoietic cell transplant (HCT) have greatly improved early transplant-related mortality (TRM) and broadened the applicability of this potentially curative treatment modality. And due to this success, there is increasing awareness within the transplant community (but not by the general medical community) of unique survivorship issues, which can culminate in significant morbidity and mortality in HCT survivors. Many "late complications" which are also known as "late effects", or "transplant complications" in the literature occur with a wide spectrum in terms of intensity, latency, and mortality. For simplicity, we would use the term *late effects* for all transplant- (and those related to pre-transplant chemotherapy, radiation, or transfusions) related morbidities. For practicing clinicians whether they would be in the field of hematology, oncology, hospital medicine, pediatrics, or primary care, there is an essential need to understand the pathology, management, and preventative strategies in order to deliver optimum care to the HCT survivors. Herein, we mention the current advances and certain key controversies relevant to survivorship issues, and then portray the future directions of survivorship care.

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15.2 What Is HCT Survivorship and Why Is It Essential?

Experts have defined cancer survivorship as the life beyond active treatments for the cancer; however, it starts at cancer diagnosis. Recently the National Institutes of Health (NIH) Late Effects Initiative have dealt with issues revolving around HCT survivorship and have defined it in the broad context of preventative strategies as well as psychosocial and physical issues complications starting after 1 year of HCT (Battiwalla et al. 2017). Practically, survivorship issues can start at any time after the first few months of HCT, especially in cases of autologous HCT (auto-HCT) since the confounding factor of survivorship issues with the graft-versus-host-disease is absent in the cases of auto-HCT. The issue of relapse of the original indication for HCT is the main barrier to successful survivorship; however, this mainly applies to malignant conditions. This field of HCT survivorship is currently in its infancy; however, just over the past decade, a tremendous momentum has been observed in this field's activity as indicated by increasing publications, grants and presentations/sessions at the national HCT-related meetings.

More than 65,000 HCTs are occurring annually globally with half of them being allogeneic HCT (Gratwohl et al. 2015). At the inception of HCTs in 1950s, majority of the patients transplanted did not survive beyond 6 months. Fast forward half a century, most of the transplant survivors are living beyond the first couple of years of HCT. Since HCT centers are scarce, many transplant recipients travel to a tertiary care center. This trend is not unique to the United States and other developed countries, but a similar pattern is observed in developing countries too. Thus, the long-term care of the HCT survivors is divided between transplant and non-transplant physicians.

Studies show that HCT survivors have increased frailty compared to their siblings even several years after HCT (Arora et al. 2016). Risks of subsequent neoplasm is greatly increased in HCT survivors compared to the general population due to chemotherapy and/or radiation exposure as well as immune dysregulation (Gea-Banacloche et al. 2017; Morton et al. 2017). Late infectious complications are common. Endocrinopathies are extremely common in HCT survivors particularly, hypogonadism, hypothyroidism, metabolic syndrome, and diabetes. Growth retardation and neurocognitive deficits may complicate pediatric survival. Additionally, cardiovascular conditions are more prevalent in HCT survivors compared to the general population as a result of significant pre- and peri-HCT cardiotoxic exposures (Armenian et al. 2017). Taken together, all these complications can exert a devastating effect on the quality of life (QOL) of the HCT survivors (Bevans et al. 2017).

Cure from the original underlying condition whether it be cancer, or a genetic disease is not the only goal of HCT. The emphasis on QOL after completing active treatments is increasing both in cancer and HCT arenas. Thus, currently, the focus of post-HCT care should include optimizing preventive strategies to promote healthy lifestyle and to avoid comorbidities. Thus, we believe that provision of survivorship care is essential for HCT survivors.

15.3 Do We Know Enough about Survivorship Biology to Devise Targeted Interventions? How Do We Best Address the Paucity of Information about Late Effects?

In the field of cancer survivorship, over 30 million long-term survivors of cancer globally are alive (Ferlay et al. 2014). By 2025, an estimated 19 million new cancer cases will be diagnosed each year, the majority of which will produce long-term survivors (Cupit-Link et al. 2017). Significant resources from various governmental (National Institutes of Health, US) and non-governmental (American Cancer Society, American Society of Clinical Oncology, European Society of Medical Oncology, and others) institutes have made cancer survivorship one of their priority areas of research. Although long-term studies in HCT survivors have been published over the past two decades, this field is in infancy with respect of HCT survivors currently compared to cancer survivorship. A wealth of observational data is available in HCT literature on late complications, yet the biologic determinants of causality are lacking in current literature. The NIH Late Effects Initiative has been the largest effort addressing the most critical HCT survivorship issues in an organized framework, and has recently provided the research priorities for HCT survivorship which include the platforms for specimen collection for (a) germline DNA, (b) total leukocyte or cell-specific RNA, (c) Plasma/serum for outcomes associated with therapeutic exposures to potentially evaluate genome-wide association studies, whole exome studies, whole genome sequencing, methylome assays, gene expression analysis, and lastly metabolomics and proteomics (Shaw et al. 2017). This framework, once initiated, would elucidate the pathobiology of late effects, many of which truly mimic the clinical phenotype of accelerated aging. Development of coronary artery disease, new cancer development, osteoporosis, frailty, and neurocognitive decline are both classic late effects of HCT treatment paradigm and of geriatric syndromes. There is a growing collaboration between HCT scientific community and bio-gerontology which will hopefully lead to exciting discoveries in the biology of premature aging in HCT survivors. But to answer the above question whether we know enough about the biology of late effects to intervene with therapeutics in 2017—we would say not enough. But we remain hopeful to overcome the paucity of information about late effects in HCT survivorship.

15.4 Responsibility Designation for HCT Survivorship: Who Is Ultimately Responsible? How to Improve Accountability? How Can We Incentivize Appropriate Healthcare Delivery?

The indications of HCT are numerous, and include bone marrow failure syndromes, hemoglobinopathies, genetic diseases, cancers, and autoimmune diseases. The list of approved indications keeps on increasing and many clinicians are involved in the care of a typical HCT patient from diagnosis until post-HCT. Who is ultimately

responsible for pre- and post-HCT longitudinal care, is still a matter of controversy since clear guidelines on this matter from any society do not exist.

For illustration of this common issue, let's consider a clinical scenario—Tom is a cheerful five-year-old boy living in Eliot, Maine (United States [US]), has two sisters, is interested in going to Mars or Space, and has been doing fairly well in kindergarten until recently. He is taken to his pediatrician Dr. Jekyll since he is complaining of bone pains and has been missing school days due to fatigue. Since the history is not specific for any pathology, Dr. Jekyll orders blood work and since blasts are found in peripheral blood, the lab informs the pediatrician of the suspicious cells. The pediatrician asks referral to the only oncologist nearby in Dover, Maine (nearest urban development)—Dr. Hyde—who performs a bone marrow biopsy (BMB) and conducts in-depth conversation about the diagnosis of a new cancer with both Victoria and David (Tom's parents). Dr. Hyde recommends treatment with induction chemotherapy for this leukemia at a large tertiary care hospital in Boston, Massachusetts, and the parents take Tom for treatment at the recommended hospital where they first confirm the diagnosis by repeating the BMB (t(v;11q23) mutated pre-B ALL) and then start multi-drug regimen. Post-induction, he is consolidated with an allogeneic HCT with preparation from cyclophosphamide and total body irradiation (CY/TBI) from his sister's stem cells. After staying 100 days in Boston, the family returns to Eliot, with regular follow-ups every 3 months at the original transplant center. Approximately 2 years post-HCT, he is recommended to follow annually at the transplant center for regular check-ups post-HCT. The parents religiously bring him to the transplant center and have developed an excellent relationship over years with the transplant physician Dr. Seuss. But over years, the visits to the original transplant center have become less frequent and after 7 years Tom only follows up with Dr. Jekyll as strongly recommended by his parents.

Fast forward 13 years from transplant, Tom is preparing to move to the West Coast since his dream is to join Caltech's department of Aerospace (GALCIT) for further studies; however, he is slowly developing signs of heart failure and is undergoing regular echocardiograms (and is on low doses of both ACE inhibitors and beta blockers) at Dover. A few months later, in California, his condition deteriorates further, and he is unable to carry out preparations for exams and he returns to New England for full-time cardiac care.

Fortunately, late cardiac dysfunction after HCT is not extremely common; however, approximately 1–5% of the HCT survivors may develop symptomatic heart failure over the course of their life time (Armenian et al. 2017). This range is wide since a number of factors play a possible etiologic role in its pathogenesis, which include the type of transplant (auto vs. allo), pre-HCT number of chemotherapy cycles, radiation use, the type of chemotherapies (e.g., anthracycline), conditioning regimen, GVHD, lifestyle factors (e.g., smoking, diet, exercise pattern), and the age at transplant (besides other factors). Tom is unlucky in a "statistical sense", since he took good care of his health and never smoked. Thus, chemotherapies and radiation are to mainly blame for his heart condition. Unfortunately, Tom did not (or could not!) follow up with transplant experts in Boston after many years of HCT due to

multiple reasons—so the obvious questions that arise include (a) is specialized or focused longitudinal care necessary to prevent morbidity and mortality due to late effects of HCT? (b) Could the heart failure have been prevented? (c) If yes, then whose ultimate responsibility was it to maximize the preventative and surveillance strategies against the late effects? A year after the first echocardiogram showing an EF of 25%, Tom succumbed to heart failure at the age of 19 years.

Lifelong care for HCT survivors is recommended by transplant experts, professional transplant societies and groups, and currently many transplant accreditation societies are looking into this important issue of long-term follow-up for the survivors to possibly suggest this as a standard of care. In Tom's case, was Dr. Jekyll unaware of the cardiac complications of HCT, and on the same lines, how much expertise did Dr. Hyde have in preventing late effects of HCT? The answer to the questions is probably that both were not aware, educated, or trained in evaluating the late effects of this highly specialized procedure (HCT is one of the many specialized procedures in Medicine). Moreover, did Dr. Suess (renowned transplant physician nationwide and has published more than 400 papers on HCT) actually directly communicate the risks of exposures of HCT to either Drs. Jekyll or Hyde? What measures did the transplant center take for follow-up care of all the patients who come from long distances to Boston for specialized procedures and return to their native towns for future care? Were electronic check systems in place for screening?

A devil's advocate would bring into the societal bioethics discussion of responsibility, and indicate that David or Victoria should have been responsible (partly if not fully) enough to assure that annual follow-ups at the original transplant center take place religiously. Although we acknowledge that all team players (Tom, Victoria, David, nurses, coordinators, Drs. Jekyll, Hyde, and Seuss, and the healthcare system itself), should play a vital role for the care of each individual (as Shakespeare stated "All the world's a stage, and all the men and women merely players: they have their exits and their entrances; and one man in his time plays many parts, his acts being seven ages"), we believe that the patients and their families should not be blamed for a preventable condition. In fact, no one should be blamed for Tom's lamentable demise and system-wide changes and a culture change is necessary for the *next generation of survivorship care*. Healthcare is not a competitive market (definition—a free market where buyers and sellers are equally informed). Thus, patients can never have the power or the knowledge to make all decisions by themselves, although they should be fully informed for an educated joint decision-making.

We believe that transplant centers must take a pivotal role in longitudinal management of survivorship care, but as a whole, the healthcare system has to improve at institutional, payer/third-party and federal policy level to implement systems in place for healthcare delivery for improvement of mortality and morbidity of transplant survivors. One of the most powerful tools for behavioral change in the field of medicine is by incentivizing. Fortunately, the current US healthcare system is moving away from the traditional fee-for-service (FFS) payment system and focusing on outcome-driven healthcare, which we believe will help in providing quality care for HCT survivors.

15.5 Which Preventative Care Guidelines Should Be Followed, and Do They Help in Preventing Adverse Outcomes?

On the top floor of a Manhattan skyscraper (a popular hospital) on a chilly January morning, Edward ("Ed") is having a prolonged, yet intellectual discussion with Dr. Doyle (his transplant physician) regarding cancer screening. Ed is a 68-year-old New Yorker, an influential physician/businessman, heading a Fortune 500 nanotechnology company, who underwent allograft from a fully matched unrelated donor after receiving a reduced intensity conditioning with fludarabine and melphalan a year ago for monosomy 7, myelodysplastic syndrome (MDS). The canvass of the current issue is what should be ideal regimen for screening for cancers, now that there is no evidence of MDS in his blood or bone marrow (yet continues to be at a risk of relapse given his cytogenetics). Ed has medication controlled GVHD of the skin and the liver which at times culminates into fatigue but is still trying to work 17 h a day.

Dr. Doyle had indicated to him at an earlier visit that the "national guidelines" for HCT survivors for cancer screening should be followed given an increased risk of new cancers in these survivors. Ed has already read the preventative practices and preventative screening paper published in 2012 jointly by the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Group for Blood and Marrow Transplantation (EBMT), American Society of Blood and Marrow Transplantation (ASBMT), Asia Pacific Blood and Marrow Transplantation 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) to have an educated discussion with Dr. Doyle (Majhail et al. 2012). The official recommendations are presented in Table 15.1.

Dr. Doyle has referred Ed to a dermatologist for annual screening of skin cancers. The official guidelines from the aforementioned paper indicate that all patients should at least receive country-specific general population recommendations for screening for cancers (Majhail et al. 2012). In the US, most common preventative recommendations which the insurance agencies and the Centers of Medicare and Medicaid Services (CMS) utilize for coverage are produced by an expert panel appointed by the U.S. Department of Health and Human Services' Agency for Healthcare Research and Quality (AHRQ). It is called United States Preventive Services Task Force (USPSTF) and constitutes an independent panel of the scientific community from primary care and preventive medicine that systematically reviews the evidence of effectiveness and develops recommendations for preventive services. The current guidelines from the USPSTF for skin cancer screening for asymptomatic individuals concludes that the current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults thus giving a grade "I" recommendation (Force USPST 2016). The USPSTF encourages to offer or provide the service if it is a grade "A" or "B" recommendation. Yet, the transplant community is well aware of the increased risk of the skin cancers particularly squamous cell carcinomas in HCT

Table 15.1 Summary recommendations for screening and prevention of late complications in long-term HCT survivors (Majhail et al. 2012)

Tissues/or gans	Late complications	General risk factors	Monitoring tests	Monitoring tests and preventive measures on all HCT recipients	Monitoring tests and preventive measures in special populations
Immune system	– Infections	– Donor source – HLA disparity – T cell depletion – GVHD – Prolonged immunosuppression – Venous access devices	– CMV antigen or PCR in patients at high risk for CMV reactivation	– PCP prophylaxis for initial 6 months after HCT – Immunizations post-transplantation according to published guidelines – Administration of antibiotics for endocarditis prophylaxis according to American Heart Association guidelines	– Patients with cGVHD: antimicrobial prophylaxis targeting encapsulated organisms and PCP for the duration of immunosuppressive therapy – Patients with cGVHD: screening for CMV reactivation should be based on risk factors, including intensity of immunosuppression
Ocular	– Cataracts – Sicca syndrome – Microvascular retinopathy	– TBI/radiation exposure to head and neck – Corticosteroids – GVHD	– Ophthalmologic exam	– Routine clinical evaluation at 6 months and 1 year after HCT and at least yearly thereafter – Ophthalmologic examination with measurement of visual acuity and fundus examination at 1 year after HCT, subsequent evaluation based on findings and risk factors – Prompt ophthalmologic examination in patients with visual symptoms	– Patients with cGVHD: routine clinical evaluation, and if indicated, ophthalmologic examination more frequently
Oral	– Sicca syndrome – Caries	– GVHD – TBI/radiation exposure to head and neck	– Dental assessment	– Education about preventive oral health practices – Clinical oral assessment at 6 months and 1 year after HCT and at least yearly thereafter with particular attention to intraoral malignancy evaluation – Dental assessment at 1 year after HCT and then at least yearly thereafter	– Pediatric recipients: yearly assessment of teeth development – Patients with cGVHD: consider more frequent oral and dental assessments with particular attention to intraoral malignancy evaluation

(continued)

Table 15.1 (continued)

Tissues/or gans	Late complications	General risk factors	Monitoring tests	Monitoring tests and preventive measures on all HCT recipients	Monitoring tests and preventive measures in special populations
Respiratory	– Idiopathic pneumonia syndrome – Bronchiolitis obliterans syndrome – Cryptogenic organizing pneumonia – Sinopulmonary infections	– TBI/radiation exposure to chest – GVHD – Infectious agents – Allogeneic HCT – Busulfan exposure	– PFTs – Radiologic studies (e.g., chest X-ray, CT scan)	– Routine clinical evaluation at 6 months and 1 year after HCT and at least yearly thereafter – Assessment of tobacco use and counselling against smoking – PFTs and focused radiologic assessment for allogeneic HCT recipients with symptoms or signs of lung compromise	– Patients with cGVHD: some experts recommend earlier and more frequent clinical evaluation and PFTs
Cardiac and vascular	– Cardiomyopathy – Congestive heart failure – Arrhythmias – Valvular anomaly – Coronary artery disease – Cerebrovascular disease – Peripheral arterial disease	– Anthracycline exposure – TBI/radiation exposure to neck or chest – Older age at HCT – Allogeneic HCT – Cardiovascular risk factors before/after HCT – Chronic kidney disease – Metabolic syndrome	– Cumulative dose of anthracyclines – Echocardiogram with ventricular function, ECG in patients at risk and in symptomatic patients – Fasting lipid profile (including HDL-C, LDL-C and triglycerides) – Fasting blood sugar	– Routine clinical assessment of cardiovascular risk factors as per general health maintenance at 1 year and at least yearly thereafter – Education and counseling on "heart-healthy" lifestyle (regular exercise, healthy weight, no smoking, dietary counseling) – Early treatment of cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia – Administration of antibiotics for endocarditis prophylaxis according to American Heart Association guidelines	

Liver	– GVHD – Hepatitis B – Hepatitis C – Iron overload	– Cumulative transfusion exposure – Risk factors for viral hepatitis transmission	– LFTs – Liver biopsy – Serum ferritin – Imaging for iron overload (MRI or SQUID)	– LFTs every 3–6 months in the first year, then individualized, but at least yearly thereafter – Monitor viral load by PCR for patients with known hepatitis B or C, with liver and infectious disease specialist consultation – Consider liver biopsy at 8–10 years after HCT to assess cirrhosis in patients with chronic HCV infection – Serum ferritin at 1 year after HCT in patients who have received RBC transfusions; consider liver biopsy or imaging study for abnormal results based on magnitude of elevation and clinical context; subsequent monitoring is suggested for patients with elevated LFTs, continued RBC transfusions, or presence of HCV infection	
Renal and genitourinary	– Chronic kidney disease – Bladder dysfunction – Urinary tract infections	– TBI – Drug exposure (e.g., calcineurin inhibitors, amphotericin, aminoglycosides) – CMV – Hemorrhagic cystitis	– Urine protein – Serum creatinine – BUN	– Blood pressure assessment at every clinic visit, with aggressive hypertension management – Assess renal function with BUN, creatinine, and urine protein at 6 months, 1 year and at least yearly thereafter – Consider further workup (kidney biopsy or renal ultrasound) for further workup of renal dysfunction as clinically indicated	

(continued)

Table 15.1 (continued)

Tissues/or gans	Late complications	General risk factors	Monitoring tests	Monitoring tests and preventive measures on all HCT recipients	Monitoring tests and preventive measures in special populations
Muscle and connective tissue	– Myopathy – Fasciitis/scleroderma – Polymyositis	– Corticosteroids – GVHD	– Evaluate ability to stand from a sitting position – Clinical evaluation of joint range of motion	– Follow general population guidelines for physical activity – Frequent clinical evaluation for myopathy in patients on corticosteroids	– Patients with cGVHD: physical therapy consultation in patients with prolonged corticosteroid exposure, fasciitis, or scleroderma – Patients with cGVHD: frequent clinical evaluation by manual muscle tests or by assessing ability to go from sitting to standing position for patients on prolonged corticosteroids
Skeletal	– Osteopenia/ osteoporosis – Avascular necrosis	– Inactivity – TBI – Corticosteroids – GVHD – Hypogonadism – Allogeneic HCT	– Dual photon densitometry – MRI to evaluate patients with joint symptoms	– Dual photon densitometry at 1 year for adult women, all allogeneic HCT recipients and patients who are at high risk for bone loss; subsequent testing determined by defects or to assess response to therapy – Physical activity, vitamin D, and calcium supplementation to prevent loss of bone density	– Patients with cGVHD: consider dual photon densitometry at an earlier date in patients with prolonged corticosteroid or calcineurin inhibitor exposure
Nervous system	– Leukoencephalopathy – Late infections – Neuropsychological and cognitive deficits – Calcineurin neurotoxicity – Peripheral neuropathy	– TBI/radiation exposure to head – GVHD – Exposure to fludarabine – Intrathecal chemotherapy	–	– Clinical evaluation for symptoms and signs of neurologic dysfunction at 1 year and yearly thereafter – Diagnostic testing (e.g., radiographs, nerve conduction studies) for those with symptoms or signs	– Pediatric recipients: annual assessment for cognitive development milestones

Endocrine	– Hypothyroidism – Hypoadrenalism – Hypogonadism – Growth retardation	– TBI/radiation exposure (e.g., head and neck, CNS) – Corticosteroids – Young age at HCT – Chemotherapy exposure	– Thyroid function tests – FSH, LH, testosterone – Growth velocity in children	– Thyroid function testing yearly post-HCT, or if relevant symptoms develop – Clinical and endocrinologic gonadal assessment for post-pubertal women at 1 year, subsequent follow-up based on menopausal status – Gonadal function in men, including FSH, LH, and testosterone, should be assessed as warranted by symptoms	– Pediatric recipients: clinical and endocrinologic gonadal assessment for pre-pubertal boys and girls within 1 year of transplantation, with further follow-up as determined in consultation with a pediatric endocrinologist – Pediatric recipients: monitor growth velocity in children annually; assessment of thyroid and growth hormone function if clinically indicated – Patients with cGVHD: slow terminal tapering of corticosteroids for those with prolonged exposure – Patients with cGVHD: consider stress doses of corticosteroids during acute illness for patients who have received chronic corticosteroids
Mucocutaneous	– Cutaneous sclerosis – Genital GVHD	– GVHD – TBI/radiation exposure to pelvis	– Pelvic exam	– Counsel patients to perform routine self-exam of skin and avoid excessive exposure to sunlight without adequate protection – Annual gynecologic exam in women to detect early involvement of vaginal mucosa by GVHD	– Patients with cGVHD and TBI recipients: consider more frequent gynecologic evaluation based on clinical symptoms

(continued)

Table 15.1 (continued)

Tissues/or gans	Late complications	General risk factors	Monitoring tests	Monitoring tests and preventive measures on all HCT recipients	Monitoring tests and preventive measures in special populations
Second cancers	– Solid tumors – Hematologic malignancies – PTLD	– GVHD – TBI/radiation exposure – T cell depletion – Exposure to alkylating agents or etoposide	– Mammogram – Screening for colon cancer (e.g., colonoscopy, sigmoidoscopy, fecal occult blood testing) – Pap smear	– Counsel patients about risks of secondary malignancies annually and encourage them to perform self-exam (e.g., skin, testicles/genitalia) – Counsel patients to avoid high-risk behaviors (e.g., smoking) – Follow general population recommendations for cancer screening	– Patients with cGVHD: clinical and dental evaluation with particular attention toward oral and pharyngeal cancer – TBI and chest irradiation recipients: screening mammography in women starting at age 25 or 8 years after radiation exposure, whichever occurs later but no later than age 40
Psychosocial and sexual	– Depression – Anxiety – Fatigue – Sexual dysfunction	– Prior psychiatric morbidity – Hypogonadism	– Psychological evaluation	– Clinical assessment throughout recovery period, at 6 months, 1 year, and annually thereafter, with mental health professional counseling recommended for those with recognized deficits – Encouragement of robust support networks – Regularly assess level of spousal/caregiver psychological adjustment and family functioning – Query adults about sexual function at 6 months, 1 year, and at least annually thereafter	
Fertility	– Infertility	– TBI/radiation exposure – Chemotherapy exposure	– FSH, LH levels	– Consider referral to appropriate specialists for patients who are contemplating a pregnancy or are having difficulty conceiving – Counsel sexually active patients in the reproductive age group about birth control post-HCT	
General health				– Recommended screening as per general population (see text)	

survivors especially when the literature clearly indicates a significantly heightened risk of the skin cancers compared to the general population in patients with GVHD.

Similarly, when it comes to prostate cancer screening, Ed is respectfully reminding Dr. Doyle of his earlier discussions with his primary care that even in a primary care setting, occasionally, there can be confusion regarding implementation of guidelines, since within the US, the USPSTF and American Urologic Association guidelines differ with respect to PSA screening. In fact, there are no uniform "global" preventive guidelines since the risks of the cancers differ according to the region. Most notable guidelines for cancer screening come from the American Cancer Society (ACS), National Comprehensive Cancer Network (NCCN), U.S. Preventive Services Task Force (USPSTF), and European Society for Medical Oncology (ESMO), and then from each individual specialty (e.g., skin cancer screening guidelines from American Academy of Dermatology [AAD]). When so many guidelines exist on the same issue (and differ from each other), the actual implementation of guidelines nationwide becomes difficult, and hence systematic research on length and lead time bias as well as outcomes becomes impossible due to non-standardization of follow-up for screening and surveillance.

Cancer screening guidelines are not the only controversial area in HCT survivorship, the vaccination timing and which immunizations to include is a matter of continuous debate among the experts. In 2009, the ASBMT guidelines were assimilated to guide the general community about the immunization schedule. A comprehensive expert review of the level of evidence of the immunization in HCT by the Infectious Disease Society of America (IDSA) in 2013 yielded that administration of not a single vaccine in HCT recipients was based on high-quality evidence unfortunately (Table 15.3) (Rubin et al. 2013). Thus, it is imperative that HCT experts collaborate with vaccinologists to produce high quality evidence defining the exact role of immunizations in HCT recipients.

In Ed's case, the authors of this chapter would agree with Dr. Doyle for exaggerated screening based on the observational data, yet do realize the literature and research gaps, and strongly recommend that it is of utmost importance to perform longitudinal studies in HCT survivors to truly evaluate the number needed to harm (NNH), number needed to treat (NNT), and the number needed to prevent (NNP) the late effects of HCT. Until such studies occur, it is impossible to formulate grade "A" recommendations as suggested by the GRADE working group.

Ed eventually submitted to the suggestions of Dr. Doyle and an early melanoma was resected when the dermatologist found a tiny spot on the intergluteal cleft on full body exam (a body area that transplant clinicians don't routinely examine!).

15.6 Patient-Reported Outcomes Are Important, But Which Ones Are Most Meaningful and How Do We Best Address the Needs?

Patient-reported outcomes (PRO) are traditionally defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." The PROs can be

related to any symptoms that a patient exhibits, but additionally to functional status, tolerability, and spirituality. The general concepts included in PRO scales should be elicited from target populations; thus, patient involvement in designing a new PRO questionnaire design is essential for content validity.

Current research focusing on transplant survivor's symptoms and quality of life has utilized a variety of instruments. Shaw et al. has recently reviewed the literature on PROs and found that conclusions regarding PROs in HCT patients were significantly limited by methodological issues, including the use of multiple different and non-comparable assessment tools (Table 15.2) (Shaw et al. 2016). The most frequently used scales in HCT literature were FACT-BMT, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ30), and the SF-36, but at least 25 more scales had been used in various studies. Thus, the recommendation was to agree upon a set of measures to address the core domains important to patients, to reduce heterogeneity and to allow comparisons across studies and between different populations. This would require the transplant-associated organizations to take the lead on assimilating standard PRO scales.

Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children (Cella et al. 2007). Since it can be used in individuals living with chronic conditions, we can consider the assimilation of scales based on the concepts of PROMIS for HCT survivors. In 2017, we did not know that which scale is most optimal, but the initiative taken by the CTN and CIBMTR (Shaw et al.) to have a unified scale for HCT survivorship for clinical trials, is a first hopeful movement to better address the needs and QOL parameters of HCT survivors (Shaw et al. 2016).

15.7 Future Directions

The field of HCT survivorship has taken an upward trajectory in implementing systematic approaches towards both research and clinical endeavors. The 2016 NIH Late Effects initiative has united scientists, clinicians, patient advocacy groups, and the policy makers to brainstorm and come up with research priorities for organized research in this arena. Similarly, the professional transplant-related societies, for example, EBMT and ASBMT (now called ASTCT [American Society of Transplantation and Cellular Therapy]) have indicated their special interest in collaborating with investigators and the policy makers for longitudinal research in HCT survivors. We hope that all patients who have undergone HCT will receive individualized, risk-adapted, and multidisciplinary follow-up longitudinal care preferably in a dedicated LTFU clinic, so that the late effects can be diagnosed and appropriately treated. Prospective clinical trials investigating the long-term sequelae are essential to alleviate the controversies mentioned above.

Table 15.2 Measures used in health-related quality of life studies in hematopoietic cell transplant (adapted from Shaw et al.; Bone Marrow Transplantation (2016) 51, 1173–1179)

Tool	No. of studies	Subscale(s)	Time to complete (min)	Target population	Question type
*Tools: *Free (F) or Require Registration (R)*					
FACT-BMT (TOI) *F, R	28	Multidimension	<10	HCT	47 (ordinal scale)
HADS (Hospital Anxiety And Depression Scale) *F	7	Limited Domain	<10	Patient	14 (ordinal scale)
Chronic GvHD Symptom Scale *F	4	Multidimension	<10	GvHD	30 (ordinal scale)
COH (City of Hope) -QOL (BMT) F	4	Multidimension	>10	HCT/cancer	41/84 (interview)
SIP (Sickness Impact Profile) *F	6	Multidimension	>10	Patient	136 (ordinal scale)
FACT-G *F	4	Multidimension	<10	Cancer	28 (ordinal scale)
SLDS-C (BMT) —Satisfaction with Life Domains Scale for Cancer *F	4	Limited Domain	<10	HCT	18 (faces)
Center for Epidemiological Studies (CES)-D (Depression) *F	4	Limited Domain	<10	Healthy	20 (ordinal)
FACIT (−Spiritual) *F,R	3	Limited Domain	<10	Cancer/ chronic illness	12 (ordinal scale)
RSCL (Rotterdam Symptom Checklist) *F	3	Multidimension	<10	Cancer	39 (ordinal scale)
NHP (Nottingham Health Profile) *F	2	Multidimension	>10	Healthy/ patient	38 yes/no
HRQoL index *F	2	Multidimension	<10	Healthy/ patient	66 (ordinal scale)
HAP (Human Activity Profile) *F (academic)	2	Limited Domain	<10	COPD	94
(Revised) Piper Fatigue Scale *F	2	Limited Domain	<10	Cancer	27 (1–10, 4 open ended)
**Tools: Payment (P) or Require License (L)*					
EORTC QLQ-C30 *L (F in academic)	26	Multidimension	<10	Cancer	30 yes/no or ordinal scale
Symptom Checklist-90 (revised) *P	3	Multidimension	>10	Healthy > age 13	90 (ordinal scale)

(continued)

Table 15.2 (continued)

Tool	No. of studies	Subscale(s)	Time to complete (min)	Target population	Question type
SF-36 *L (F in academic)	26	Multidimension	<10	Healthy/ patient	36 yes/no or ordinal scale
POMS (SF) (profile of mood state) *P	4	Limited domain	<10	Psychiatry/ psychology	65 (30) (ordinal scale)
SF-12 *L (F in academic)	4	Multidimension	<10	Healthy/ patient	12 yes/no or ordinal scale
BDI (Beck's Depression Inventory) *P	3	Limited Domain	<10	Psychiatry/ psychology	21 (ordinal scale)
Spielberger State Anxiety Scale (subscale) *P	3	Limited Domain	<10	Patient	40/20 (ordinal scale)
EQ-5D (VAS) *R,P	2	Limited Domain	<10	Healthy/ Patient	5 (Visual analog)
SDS (Symptom Distress Scale) *R	2	Limited Domain	<10	Cancer	13 (ordinal scale)
EORTC QLQ-HDC29 *L, F in academic	2	Multidimension	<10	Cancer	29 (ordinal scale)
Coping Responses Inventory *P	2	Limited Domain	>10	Healthy	48 (ordinal scale)
Interpersonal Support Evaluation List–Short Form (ISEL-SF) *L, F in academic	2	Limited Domain	>10	Healthy	12/40/48 (ordinal scale)

Table 15.3 2013 IDSA clinical practice guideline for vaccination of HCT recipients (Rubin et al. 2013)

	Pre-HCT		Post-HCT	
Vaccine	Recommendation	Strength, evidence quality	Recommendation; earliest time post-transplant; number of doses	Strength, evidence, quality
Haemophilus influenzae b conjugate	U	Strong, moderate	R; 3 months; 3 doses	Strong, moderate
Hepatitis A	U	Strong, very low	R; 6 months; 2 doses	Weak, low
Hepatitis B	U	Strong, low	R; 6 months; 3 doses	Strong, moderate
DTaP, DT, Td, Tdap	U	Strong, low	R; age <7 years: DTaP; 6 months; 3 doses R; age ≥7 years: DTaP; 6 months; 3 doses OR 1 dose Tdap, then 2 doses DT or Td; 6 months	Strong, low Weak, very low DTaP: weak, moderate DT, Td: weak, low
Human papillomavirus	U: 11–26 years	Strong, very low	U; 6 months; 3 doses	Weak, very low
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, low	R; 4 months	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–live	U	Strong, very low	X	Strong, low
Measles, mumps, and rubella–varicella–live	U	Weak, very low	X	Strong, very low
Meningococcal conjugate	U	Strong, very low	R; age 11–18 years; 6 months; 2 doses	Strong, low
Pneumococcal conjugate (PCV13)	R	Strong, low	R; 3 months; 3 doses	Strong, low
Pneumococcal polysaccharide (PPSV23)	R	Strong, very low	R; ≥12 months post if no GVHD	Strong, low

(continued)

Table 15.3 (continued)

	Pre-HCT		Post-HCT	
Vaccine	Recommendation	Strength, evidence quality	Recommendation; earliest time post-transplant; number of doses	Strength, evidence, quality
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong, very low	R; 3 months; 3 doses	Strong, moderate
Rotavirus–live	X	Weak, very low	X	Weak, very low
Varicella–live	U	Strong, low	X	Strong, low
Zoster–live	R: Age 50–59 years U: Age ≥60 years	Weak, very low Strong, low	X X	Strong, low Strong, low

Acknowledgements *Disclaimer*: Herein we present expert opinion and views on transplant survivorship that do not represent official societal or organizational views. We have utilized case scenarios to discuss certain controversial areas; all patient and doctor names used in this chapter are fictional.

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The Importance of Self-Care for Physicians and Providers

16

Molly Sonenklar and Sonia Malhotra

16.1 Introduction

To heal a person, one must first be a person.—Abraham Joshua Heschel (1964)

One of the greatest shortcomings faced in the field of medicine is its dehumanization. Rather than learning all the aspects of Medicine as an art, it has been taught only as a science that focuses and treats the disease, rather than the person. In profound ways, this has affected the care provided to individual patients and their perceptions of the medical profession. In this chapter, we will define and identify differences between health-care provider burnout, compassion fatigue, and compassion satisfaction. Additionally, we will discuss different methods such as mindfulness and self-care rounds that can help clinicians focus on their own self-care as well as those of their trainees. Also, we will identify how clinicians can impact and assist with the self-care of family caregivers.

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16.2 Burnout and Compassion Fatigue: Costly at Many Fronts

The dehumanization of Medicine's art has led to suffering in health-care providers. As Thomas Cole points out, "the patient is not the only 'whole person' in the consulting room" (Cole and Carlin 2009). The other individual, the clinician, the one who is meant to care for and heal patients, is actually among the population that suffers most from anxiety, depression, even in severe cases, suicide. This is particularly true when it comes to caring for critically ill patients, such as those faced with cancer. A number of studies suggest that physicians involved in serious illness care face high rates of burnout. Burnout can be defined as "a prolonged response to chronic emotional and interpersonal stressors on the job" (Maslach et al. 2001). It most frequently occurs among those whose professions require intense (regularly and prolong) involvement with sick people and their caregiver(s)/family members. Emotional exhaustion, cynicism, depersonalization, and low personal sense of accomplishment all contribute to the phenomena of burnout (Maslach et al. 2001; Asai et al. 2007). In surveys of American and British Oncologists in the 1990s, one-third to one-half of respondents reported burnout and psychiatric morbidity (Asai et al. 2007). In the years 2018 and 2019 surveys of physicians across specialties 42 and 44%, respectively, reported burnout, alarmingly 14% reported thoughts of suicide (Yates 2020). The result of physician burnout can be poorer quality of patient care, patient dissatisfaction, and frequent medical errors (Vachon 2010). Burnout and the resultant decrease in productivity are expected to contribute to a shortfall of up to 90,000 physicians in the United States by 2025 (Yates 2020). Approximately $4.6 billion in costs related to physician turnover and reduced clinical hours is attributable to physician burnout each year in the United States (Han et al. 2019).

Compassion fatigue can be understood as a specific type of burnout experienced by those caring for the traumatized. It has been described as a "secondary traumatic stress, defined as the cost of caring for others in emotional pain" (Sanso et al. 2015). This, in turn, may also lead to an inability of the professional to continue providing compassionate care to the suffering patient.

16.3 Provider Satisfaction and Self-Care-Overlooked and Underreported

Palliative care physicians, though at high-risk of burnout and fatigue due to the nature of their work, report high levels of satisfaction and experience a deep, enriching purpose to their work unlike their Oncology colleagues. This satisfaction can be characterized as *compassion satisfaction*, defined as "the ability to receive gratification from care giving" (Sanso et al. 2015). Similarly, a questionnaire-based study in Japan by Asai and colleagues in 2006 demonstrated that palliative medicine physicians had lower levels of psychiatric morbidity when compared to oncologists (12% versus 21% with $p = 0.05$). Of note, a total of 697 physicians returned the questionnaires (response rate, 49.6%). A majority of oncologists (65%) experienced low

levels of accomplishment versus 53% of palliative medicine specialists ($p = 0.05$). It is suggested that environmental and training factors could contribute to this difference such as time to communicate and build rapport with patients, skills in assessing the mental state of patients, adequate support and resources for patients, and environmental stress levels (Asai et al. 2007). Noteworthy, confidence in having sufficient time to communicate with patients was significantly associated with all the burnout subscales.

One of the most fundamental components of palliative care medicine training is the incorporation of *self-care*. Self-care is multi-faceted, involving physical, emotional, psychological, spiritual, interpersonal, and environmental components.

Kearney and colleagues propose an awareness-based model of self-care which demonstrates a positive relationship to compassion satisfaction and negative relationship with burnout and compassion fatigue (Kearney et al. 2009). It is an integrative model that focuses on how self-care, awareness, community support, and specific training all impact physicians' ability to cope with death. Sanso and colleagues took another step by proposing that this model could improve professionals' quality of life and work satisfaction. Using the areas of self-care, qualitative data was collected among a cross-section of Spanish palliative care professionals (Spanish Society of Palliative Care), using the measures indicated in Table 16.1. The survey results indicate that inner and social self-care as well as awareness were positively associated with the ability to cope with death (Sanso et al. 2015). Furthermore, it demonstrated with greater levels of self-awareness, a physician's inner life is enhanced and quality of life is improved and thus leads to lower levels of compassion fatigue and burnout. Physician well-being is a shared responsibility, and guidelines to safeguard this responsibility were outlined in a charter for physician well-being in 2018 (Thomas et al. 2018). It is important that institutions identify specific ways physicians can engage in self-care and what can be provided to help physicians enhance their role as healers.

Table 16.1 Areas of self-care

Physical self-care
• Physical activity/exercise
• Relaxation techniques
• Nature/outdoors
• Nutrition/healthy eating
• Sleep management
Inner self-care
• Mindfulness/awareness of day-to-day experiences
• Practicing self-empathy
• Counseling/therapy
• Reflective writing
Social self-care
• Social activities
• Relationships outside of work
• Communication in work environment

16.4 Mindfulness and Self-Care

Mindfulness is defined as "a person's tendency to remain purposefully and non-judgmentally attentive to their own experiences, thoughts and feelings" (Epstein 1999). Mindfulness is increasingly used for the treatment of patients with pain, autoimmune diseases, and psychiatric illness (Ludwig and Kabat-Zinn 2008). Recent studies show that mindfulness can improve physician well-being while reducing burnout, increasing empathy, and compassion satisfaction among providers (Krasner et al. 2009). Randomized control trials of mindfulness training among Internists and Residents demonstrated reduced stress and burnout while improving sense of compassion and accomplishment (Ireland et al. 2017; Verweij et al. 2018). This type of awareness building can help make physicians better healers and improve quality of patient care (Epstein 1999). A cross-sectional study of data from the Enhancing Communication and HIV Outcomes (ECHO) Study looked at the association between clinical self-reported mindfulness, audio-recorded clinician–patient communication, and patient evaluations of care (Beach et al. 2013). The results of the survey demonstrated that higher levels of mindfulness among healthcare professionals were associated with increased patient-centered communication, more attentive listening, as well as a sense of empowerment among patients that their voice should be heard (Fig. 16.1) (Beach et al. 2013). Ultimately, mindful clinicians tend to pay closer attention to the complexity of their own, as well as their patients' lives and fully engage with the patient, rather than distancing themselves from distressing or emotional situations. By providing this type of training to physicians caring for the seriously ill, quality of life for clinicians and patients can be improved.

Mindfulness training involves building the skills to lower reactivity and enhance responsiveness to stressful situations. Meditation is the primary way to cultivate mindfulness. This can include transcendental or object-focused meditation, in which thoughts are observed and accepted without expectations and without the need to change or manipulate those thoughts (Irving et al. 2009). Mindfulness-based stress reduction (MBSR) is one specific psycho-educational practice developed at the University of Massachusetts's Medical Center by Kabat-Zinn and colleagues. It is an 8-week program where participants are taught different types of meditation to apply to their daily lives (Fig. 16.2). Controlled studies give evidence

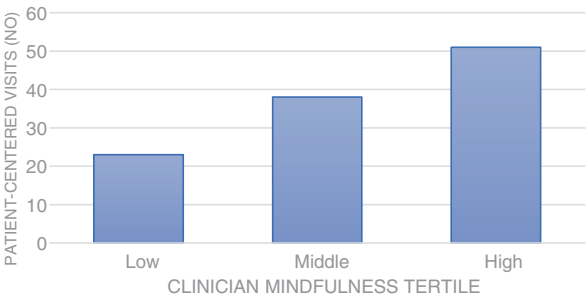

Fig. 16.1 Number of patient-centered clinical encounters based on clinician-reported mindfulness. Adapted from data in Beach et al. (2013)

Week 1: What is mind-body medicine and how to apply it to day-to-day life through eating, breathing, body-scanning and being present.

Week 2: Examining one's perceptions and how one reacts to stressful situations using the body-scan method.

Week 3: Learning meditation and mindful yoga practices

Week 4: Expanding awareness and mindful strategies for responding to stressful situations.

Week 5: Applying mindfulness when experience intense emotions and how one's reactivity affects health and illness.

Week 6: Bouncing back after stressful situations and learning styles of effective communication.

Nature Retreat

Week 7: How to adapt mindfulness into one's life as it changes over time.

Week 8: Review and reflections. What are resources, support systems available.

[http://www.umassmed.edu/cfm/mindfulness-based-programs/mbsr-courses/mbsr/mbsr-course-outline/]

Fig. 16.2 MBSR Course Outline (summarized)—University of Massachusetts Center for Mindfulness

to MBSR effectiveness among patient populations and for trainees and clinicians. Practitioners involved in MBSR showed greater attention to patient's non-verbal signals, better client evaluations, reduced stress levels, and higher rates of self-compassion (Grepmair et al. 2006; Shapiro et al. 2005).

16.5 Spirituality and Self-Care

Spirituality has been explored as a means to improve physician's quality of life and the patient–clinician experience. Spirituality may be associated with physician's engagement in religious practices or communities. Physicians may draw from their own spiritual resources and well-being to build resilience during the care of seriously and terminally ill patients (VanderWeele et al. 2017; Balboni et al. 2013). More often, spirituality relates to the recognition of a professional calling (Yoon et al. 2017). A Consensus Conference on Inter-professional Spiritual Care within Palliative Care in 2009 concluded that professional development must include spiritual development specifically "as it relates to the healthcare professional's sense of calling to their profession" (Puchalski and Guenther 2012). When health

professionals are able to relate their sense of calling, this helps stimulate their development of self-care, stress management, self-examination, and reflection. It also helps them relate to their patients on a level independent of the medical illness being cared for.

16.6 Trainee Education in Self-Care

Formal education in the areas of humanism, professionalism, communication, and collaboration is not often well integrated into Medical Education despite these being competencies expected of medical trainees. Awareness of this important aspect of Medicine lacks at administrative level as well. Medical students, residents, and fellows may complete their studies feeling poorly equipped to engage in the healing process and address the complex needs of their patients (Dossett et al. 2013). Trainees may also sacrifice their self-care during training. A survey of nearly 300 residents across multiple specialties found one-third did not practice self-care and 75% had seen a mental health professional (Rangel et al. 2019). There is evidence that skills related to humanism and self-care can be taught. Studies of medical students and residents assigned to mindfulness training and self-reflection resulted in reduced psychological distress, fewer medical errors in patients' care, and increased empathy (Ludwig and Kabat-Zinn 2008). Organizations such as the Accreditation Council on Graduate Medical Education (ACGME), American Board of Internal Medicine (ABIM), American Association of Medical Colleges (AAMC), and Institute of Medicine (IOM) have established guidelines to include topics relating to stress reduction in trainee education; however, there is significant room for further improvement. When looking at competencies specifically for Hematology and Oncology Fellows, there is attention given to professional boundaries and coping skills and yet there is no mention of self-care (Sanchez-Reilly et al. 2013). For a physician population at highest risk for burnout and depression, self-care and awareness training should be given higher importance for best outcomes of both the patient and the provider. The Training Committee of the American Society of Pediatric Hematology and Oncology (ASPHO) conducted a needs assessment survey of pediatric Hematology and Oncology Fellows which found nearly half of the programs did not include a humanism and professional curriculum. The ASPHO then went on to develop a curriculum in humanism and professionalism involving four modules focused on competing demands of fellowship, challenging relationships with patients, depression, and burnout, and difficult choices with patients who are dying. This curriculum was piloted in 10 Fellowship programs and 90% of Fellows and faculty that participated reported that the modules allowed them to reflectively communicate and addressed valuable issues relevant to their training (Kesselheim et al. 2015)—an important finding.

Another specific initiative used to address the gap in self-care education is the Humanism Elective in alternative medicine, Activism, and Reflective Transformation

(HEART) sponsored by the American Medical Students Association (AMSA). In this fourth-year medical school elective, physicians lead students through didactic and experiential encounters all focused on relationship-centered medicine, spirituality, social justice, community building, communication, reflection, and self-care. A retrospective cross-sectional survey of the 2002–2009 participants found most participants felt that the program addressed the ACGME core competencies of patient care (81%), professionalism (89%), and communication (92%) (Dossett et al. 2013). Overall, participants described how HEART contributed to the development of their relationships to self, to others, and to the medical profession. The HEART curriculum is an example of how physicians can be taught to incorporate self-care and awareness into their professional lives to become healthier providers and improve patient care.

At the University of Texas Health Science Center, a program for physicians involving self-care rounds has been developed. These occur bi-monthly and provide physicians a forum to share how their work is affecting their personal lives. Using cases stories, they discuss how caring for specific patients impacts them. They go into challenges of time management in patient's decision-making. At the conclusion of the year, a self-care retreat is held to delve deeper into self-care strategies (Sanchez-Reilly and Horn 2015).

16.7 The Impact of Serious Illness on Caregiver(s)

Studies have demonstrated a majority of deaths worldwide occur due to serious, chronic illnesses such as cancer, heart, and lung disease and for every ten deaths in the United States, seven occur at the end of one of these illnesses (Waldrop and Kutner 2012a, b). When an individual is diagnosed with a serious illness, family member(s) are often called upon to be caregivers. These "*informal*" caregiver(s) are generally family or friends who are unpaid and assist patients with one or more activities of daily living (ADLs). "*Formal*" caregivers are paid professionals providing similar care. Informal caregivers for family members with serious illness may find themselves transitioning into a "caregiving career" which is associated with stressors related to that family member's care as well as other life roles. These stressors can often lead to physical, emotional, or psychological problems, resulting in caregivers being referred to as "hidden patients." Simultaneously patient and caregiver need support and skills in self-care to optimize their quality of life and that of their loved ones. Waldrop and Kutner identify six areas in which caregiver's lives are affected: Physical and mental health, family communication, social impact, work and finances, social identity, and positive impacts. Physicians and providers can play an important role in enhancing the quality of life of their patients and of their patients' caregivers (Table 16.2) (Waldrop and Kutner 2012a, b). Additional discussion regarding caregivers is also found in Chap. 12. When physicians and providers manage their own self-care, they are better able to assist caregivers with these areas.

Table 16.2 Areas caregiver's lives affected and how providers can help

Caregiver's affected area	How providers can help
Physical and mental health: Stress of caregiver role and other life roles → higher risk for cardiovascular disease, stroke, depression	• Provider communication on prognoses • Individual and family counseling • Education in caregiving skills • Partner-guided pain management (Keefe Ahles et al. 2005)
Family communication: Caregiver emotions, sense of self-efficacy, length of time in caregiver role, family response styles	• Provider communication on prognoses • Family counseling • The CARE Project (Cravens et al. 2005)
Social impact: Serious illness and home caregiving in context of community, culture, religion	• Bereavement care • Culturally sensitive end of life care • Support groups
Work and finances: Financial burden of balancing work and caregiving	• Resources for financial assistance • Social worker
Social identity: Spouses, parents, children as caregivers → changes to the preexisting relationship, burden of decision-making	• Support groups • Home-Based Palliative Care Program (Fernandes et al. 2010)
Positive impacts: Providing comfort, care, and decisions for their loved ones	• Memory-making activities • Building security and trust in health-care providers

16.8 Conclusion

Burnout and compassion fatigue are important topics for clinicians and the care they provide for seriously ill patients. Physician burnout leads to poorer quality of care, patient dissatisfaction, and frequent medical errors. Clinicians in specialties with high stress need to have methods to provide self-care and must make it a priority to teach this to their trainees, so a greater level of compassion satisfaction can ensue. This will result in an overall culture of improved health care for physicians, providers, patients, and family caregivers.

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Owing to an inadvertent error, the name of the co-author of chapter 9 was misspelt as Rev. Estrelle Valino. The name has now been updated rightly to Rev. Estrella Valino.

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