Autologous and Allogeneic Hematopoieitic Cell Transplantation: Risk of Second Malignancies

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Abstract

With improved measures for supportive care and an increasing number of hematopoietic cell transplants being performed for both malignant and non-malignant disorders, many patients are surviving for longer periods of time following transplantation. Unfortunately, second malignancies in survivors are well-described complications that often carry a very poor prognosis and thus are devastating for patients and their families. The magnitude of risk ranges from 4- to 11-fold that of the general population. The types of second malignancies, current understanding of their pathogenesis, prognosis and available therapies are detailed here.

Introduction

The field of hematopoietic cell transplantation (HCT) continues to evolve, offering potentially curative therapy for individuals with fatal hematologic conditions. Through advances in treatment regimens and supportive care, the number of long-term HCT survivors, as well as the median duration of survival, can be expected to grow over the coming years. For individuals who survive transplant-related and disease-related mortality early on, increasingly recognized late complications await. Of these late complications, second malignancies following HCT unfortunately portend poor prognoses and treatment options carry significant risk-benefit ratios for the patient.

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M.A. Hayat (ed.), *Stem Cells and Cancer Stem Cells, Volume 11*,
DOI 10.1007/978-94-007-7329-5_19, © Springer Science+Business Media Dordrecht 2014

Second malignancies following HCT fall into three categories: (1) post-transplant lymphoproliferative disease (PTLD), (2) therapy-associated myelodysplastic syndrome/acute myeloid leukemia (t-MDS/AML) and (3) solid cancers. Each subset demonstrates unique latency periods in relation to time since transplant. To this point, the vast majority cases of PTLD occur within the first year after transplant (Landgren et al. 2009) while t-MDS/AML predictably follow a 2–5 year latency period (Pedersen-Bjergaard et al. 2009). Unfortunately, the most recent long-term follow-up of HCT patients demonstrates an ever-growing incidence of solid malignancies occurring with time since transplant when compared to the general population (Rizzo et al. 2009).

Post-Transplant Lymphoproliferative Disease (PTLD)

PTLD represents a spectrum of lymphoid malignancies, largely Epstein-Barr virus (EBV) driven, occurring as a result of chronic immunosuppression in allogeneic-HCT patients. Following primary infection, EBV infects host B-lymphocytes using altered viral antigen production to evade cytotoxic T-cell mediated recognition and destruction (Cohen 2000); the end-result is latent infection similar to other members of the herpes virus family. In the post-HCT setting, a number of factors impair cytotoxic T-cell surveillance, ultimately allowing for viral reactivation. By definition, the very purpose of allogeneic HCT is to destroy and replace the recipient's immune system; any acquired immunity to control latent viral infections is sacrificed during the transplant process. For this reason, PTLD is seen exclusively in the allogeneic population of transplant recipients. Full donor immune reconstitution can take upwards of a year post-transplant. Additionally, to prevent both donor graft rejection and prevent/treat graft versus host disease (GVHD), varying degrees of immunosuppression are necessary, further impairing cytotoxic T-cell function.

During this time of impaired T-lymphocyte function, viral proteins encoded by EBV act as oncogenes within B-cells, leading to unchecked cellular proliferation and ultimately lymphomatous transformation (Cohen 2000). Based upon this line of reasoning, the great majority of observed PTLD cases are expectantly B-cell lymphomas and EBV-mediated; however, a much smaller fraction of T-cell/NK-cell-based lymphomas and EBV negative cases do occur (Curtis et al. 1999).

The World Health Organization (WHO) officially recognizes four forms of histologically-defined PTLD: (1) early lesions characterized by reactive B-cell proliferation, (2) polymorphic PTLD demonstrating nodal architecture effacement, (3) monomorphic PTLD marked by nodal destruction through monoclonal cellular proliferation and (4) Hodgkin lymphoma-type PTLD (Swerdlow et al. 2008). All PTLD forms may be EBV-associated; diffuse large B-cell lymphoma (DLBCL) represents the single most common form of monomorphic PTLD malignancy (Swerdlow et al. 2008).

With a growing understanding of PTLD's pathogenesis, epidemiologic studies focused on incidence and risk factors have been ongoing for the last several decades. Landgren et al. recently published an update on the largest, ongoing retrospective analysis of PTLD following HCT (Landgren et al. 2009). Reviewing 26,901 patients from the Center for International Bone Marrow Transplant Research (CIBMTR) and Fred Hutchinson Cancer Research Center (FHCRC) registries, the overall incidence of PTLD was noted to peak approximately 2–3 months after transplant with a sharp decline seen after 12 months (see Fig. 19.1). Polymorphic PTLD comprised the majority of cases within the first year while cases of monomorphic disease occurred years, even upwards of a decade, later. Reasons for the sharp decline observed after 12 months are hypothesized to correlate with return of cytotoxic T-cell immune reconstitution (Lucas et al. 1998). Late-occurring (greater than 12 months post-HCT) PTLD remains poorly understood, possibly due to a separate pathogenesis and set of risk factors, as many cases are EBV-negative.

Regarding risk factors for the development of PTLD, Landgren et al.'s updated review analyzed

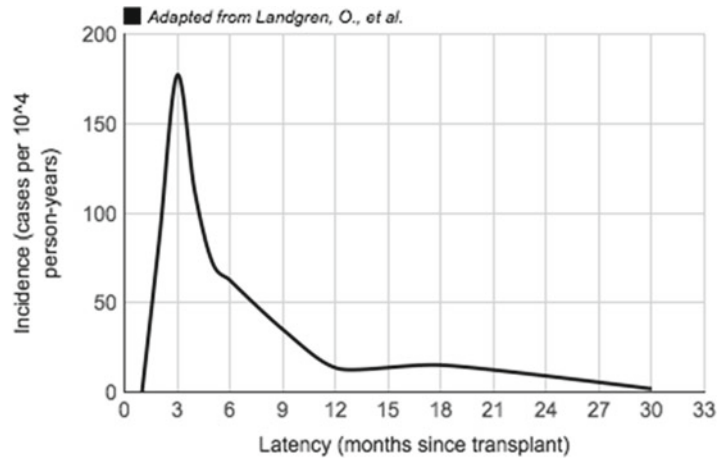

Fig. 19.1 Latency and post-transplant lymphoproliferative disease incidence

previously identified risk factors and identified several new risks as well. Previously identified risk factors included the use of unrelated or human leukocyte antigen (HLA) mismatched graft, T-cell depletion of donor marrow, use of antithymocyte globulin (ATG) or anti-CD3 antibody for prevention or treatment of GVHD as well as acute GVHD grades II through IV (Curtis et al. 1999). Newly identified risk factors included age greater than 50 years and second transplantation (Landgren et al. 2009). The use of ATG and T-cell depleted grafts has consistently represented the strongest risk factors for the development of PTLD (Landgren et al. 2009; Curtis et al. 1999). Pooling these risk factors, individuals with three or more risk factors experienced a 110 relative risk increase for the development of PTLD compared to those patients with no risk factors; the cumulative incidence with three or more risk factors was 8.1% compared to 0.2% for those with no identified risk factors. The use of total body irradiation (TBI) has not been identified as a risk factor.

Taking these identified risk factors into account, many transplant centers perform EBV surveillance using polymerase chain reaction (PCR) testing on high-risk individuals. Van Esser et al. retrospectively analyzed the incidence of EBV reactivation and PTLD development in 85 EBV-seropositive patients undergoing T-cell depleted allogeneic HCT and 65 EBV-seropositive patients receiving an unmanipulated allogeneic HCT (van Esser et al. 2001). The incidence of EBV reactivation, defined as >50 copies EBV genome/mL, occurred in 65% of patients receiving a T-cell depleted graft compared with 31% receiving an un-manipulated HCT. While the overall positive predictive value of detectable EBV reactivation was low at 39%, increasing levels of EBV copy correlated with increasing positive predictive values. Yet despite surveillance, EBV viremia does not confirm the diagnosis of PTLD and several cautions must be addressed. First and maybe most importantly, EBV reactivations occur without ensuing PTLD. Additionally, EBV quantification suffers a large degree of inter-laboratory variability making standardization difficult; therefore, Gulley and Tang (2010) recommend monitoring EBV kinetics measured as doubling time to further best identify patients with imminent EBV-driven PTLD.

Guided by risk factors and EBV surveillance, providers additionally need to be able to gauge the level of clinical suspicion based on presentation. Several features of PTLD separate it from other forms of non-Hodgkin lymphoma (NHL) seen in the general population. PTLD presents in an aggressive fashion, often with advanced stage and extra-nodal manifestations at the time of diagnosis. Presentations vary from asymptomatic to constitutional complaints to lymphadenopathy and organ involvement/dysfunction. Similar to NHL and other malignancies, the role of positron emission tomography/computed tomography (PET/CT) is evolving, but small case series point out its ability to better detect

organ involvement for staging as well as response to therapy (Bianchi et al. 2008).

Treatment options ultimately concentrate on restoring balance between latently infected B-lymphocytes and impaired cytotoxic T-cell function. Attempts to provide return of cytotoxic T-cell function focus on four broad areas: (1) reduction of immunosuppression, (2) antiviral therapy, (3) donor lymphocyte infusions and (4) EBV-specific cytotoxic T-cell infusions. Unlike recipients of solid organ transplantation, HCT patients do not appear to benefit from reductions in immunosuppression. Post-HCT, patients already suffer from impaired immune function and reductions in immune suppression come with the risk of graft rejection and/or GVHD. Additionally, antiviral therapies have not proven largely beneficial as the targets are oncogenic B-lymphocytes. In a small case series of five patients, donor lymphocyte infusions (DLI) ultimately resulted in fatal, immune-mediated respiratory failure in two patients and GVHD within the remaining survivors (Papadopoulos et al. 1994). In an attempt to reduce the risk of GVHD from non-specific donor lymphocytes, Heslop (2009) engineered EBV-specific cytotoxic T-cells for short-term restoration of immune surveillance. Used in both high-risk preventative as well as treatment settings, 80% remission rates with treatment have been reported.

With limited, risky options aimed at returning cytotoxic T-cell function, other treatments options focus on reducing the burden of disease within B-lymphocytes. Using EBV PCR as PTLD surveillance, Van Esser compared the use of single agent rituximab in a prospective cohort series involving 17 patients (van Esser et al. 2002). Using an EBV viral load of 1,000 copies as indication of developing PTLD and an indication to treat, when compared with a historical cohort series, the use of rituximab demonstrated a reduction in PTLD incidence from 49 ± 11% to 18 ± 9% with no mortality seen in the treated group compared with 26 ± 10% in the historical group. For patients who fail to respond to single-agent rituximab, infusional cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy remains the standard of care. A paucity of comparative data regarding response rates and outcomes exists regarding HCT-related PTLD. When used as salvage therapy following immunosuppression reduction and rituximab, CHOP salvage chemotherapy induced a complete remission (CR) in 5 and a partial remission in 2 of 11 treated patients within a small case series (Trappe et al. 2007). Four of five complete responders remained in CR at a median duration follow-up of 44.2 months while non-responders (stable and progressive disease) died at the time of study close from PTLD-related complications.

Poor prognostic factors for PTLD include advanced stage at the time of diagnosis, central nervous system involvement, late-occurring PTLD and EBV-negative PTLD. Diminished drug delivery beyond the blood brain barrier has hampered efforts to improve central nervous system (CNS)-PTLD. Whole brain radiation as well as intrathecal agents such as rituximab and methotrexate represent potential treatment options. With regards to late-occurring PTLD and EBV-negative PTLD, an entirely separate pathogenesis may be at play; current therapies may be ineffective due to tumor biology or underlying reasons as yet to be determined.

Therapy-Associated Myelodysplastic Syndrome/Acute Myeloid Leukemia (t-MDS/AML)

Following the initial reports of t-MDS/AML post autologous HCT in 1994, subsequent studies reported actuarial or cumulative incidences ranging from 1% to 24% with a wide range of follow-up (Pedersen-Bjergaard et al. 2009). Furthermore, there is concern that the incidence may rise due to the increasing age that patients undergo transplantation with the advent of nonmyeloablative and reduced-intensity conditioning regimen. t-MDS/AML represents a major cause of nonrelapse mortality post-autologous HCT, particularly for patients with lymphoma as compared with other diseases including multiple myeloma or germ cell tumors (Hake et al. 2007; Barlogie et al. 2008; Kollmannsberger et al. 1999).

Physicians must not assume that MDS/AML diagnosed post allogeneic transplantation is secondary to relapse of the patient's pre-transplant disease. Although more commonly seen following autologous HCT, t-MDS/AML has also been reported following related-donor and unrelated donor HCT. Baker and colleagues reported that 2 of 1,407 patients developed t-MDS/AML after related-donor and 2 of 772 patients after unrelated donor HCT in recipient cells (Baker et al. 2003). These newly developed diseases had morphologically and cytogenetically distinct abnormalities compared with the patients' underlying AML or chronic myeloid leukemia, inconsistent with disease relapse. Furthermore, leukemia may also arise following allogeneic transplantation in donor cells, so-called "donor cell leukemia (DCL)." First recognized in 1971, DCL was initially felt to be rare but additional reports suggest the incidence may be as high as 5% of all post-transplant "relapses" (Wiseman 2011).

Patients with t-MDS/AML post-transplant typically present with peripheral blood cytopenias and multilineage dysplasia on bone marrow examination. Criteria for diagnosing t-MDS/AML include: (1) significant marrow dysplasia in at least two cell lines, (2) peripheral cytopenias without alternative explanations, and (3) blasts in the marrow (Gilliland and Gribben 2002). Historically, two classes of chemotherapy agents have been associated with t-MDS/AML, topoisomerase II inhibitors and alkylators. Topoisomerase II inhibitor-associated t-MDS/AML typically has a short latency period of 2–3 years with chromosome gene rearrangements involving the *MLL* gene at 11q23. In contrast, alkylating agent-associated t-MDS/AML has a longer latency of 5–8 years and is associated with abnormalities of chromosomes 5 and/or 7 (del 5q, del 7q).

There has long been discussion among physicians caring for patients as to whether post-HCT t-MDS/AML is secondary to therapy received prior to transplant or if the transplant itself is to blame. Most likely, it is a combination of factors; thus, numerous studies have attempted to identify specific risk factors. A number have been reported, including increased age, therapy with increasing cumulative doses of alkylators and topoisomerase II inhibitors, TBI-based conditioning regimens, peripheral blood stem cells as the graft source, stem cell mobilization with etoposide, four or more chemotherapy regimens prior to transplant, difficult mobilization of adequate numbers of stem cells, and delayed platelet and neutrophil engraftment (Kalaycio et al. 2006). More recently, fludarabine, particularly at a cumulative dose of >150 mg/m^2, has been associated with t-MDS/AML (Carney et al. 2010; Waterman et al. 2012). It is unclear which factors are most important as the patient population, heterogeneous underlying diseases and conditioning regimens, as well as the strength of each factor's association varies among studies.

In addition to evidence that pre-transplant and transplant therapies (including priming chemotherapy and the conditioning regimen) contribute to post-transplant t-MDS/AML, there is evidence that the engraftment process itself may also contribute. It has been hypothesized that the proliferative stress of engraftment may lead to the expansion of pre-leukemic clones from stem cells with genotoxic damage secondary to exposure from prior therapies. Along these lines, shortened telomere length, a measure of proliferative stress, has been reported in patients who developed t-AML/MDS (Chakraborty et al. 2009).

Finally, in both de novo and therapy-associated AML, a variety of inherited polymorphisms and acquired mutations have been identified that may play a role in t-MDS/AML susceptibility (Rund et al. 2005). These include cell signaling genes and transcription factors in the "leukemia pathway" as well as genes involved in drug metabolism and DNA repair. Whether any or all of these genes contribute to t-MDS/AML arising in the post-transplant is under investigation.

The prognosis of t-MDS/AML following transplantation is very poor with a median survival of 6–12 months. In a report from the Dana Farber Cancer Institute, 13 of 41 patients who developed MDS following autologous HCT for non-Hodgkin lymphoma underwent allogeneic HCT and all died of transplant-related complications (11 patients) or relapse (2 patients) with a median survival of only 1.8 months (Friedberg et al. 1999). Clearly,

strategies to decrease the risk of t-MDS/AML post transplant need to be implemented. Interventions should include avoiding leukemogenic agents, including radiation, whenever possible during therapy, performing transplants earlier in the disease course when warranted to avoid excess therapy and consideration of alternative approaches other than autologous HCT for those patients with difficulty mobilizing stem cells. As genetic polymorphisms that confer a risk of t-MDS/AML are identified and confirmed in the future, an individualized approach to patients at high risk may be possible.

Solid Tumors

In comparison to PTLD and t-MDS/AML, secondary solid cancers demonstrate a latency period of approximately 3–5 years followed, more importantly, by a steadily increasing risk associated with time since transplant (see Table 19.1). Because the post-HCT cohort is so heterogeneous with respect to age, most investigators have utilized standardized incidence ratios (SIR) focusing on observed to expected ratios when compared to the general population. Expected cases for the general population can be approximated using the Surveillance Epidemiology and End Results (SEER) database for age-appropriate incidences of cancer.

Risk factors for the development of a second solid malignancy across the majority of studies focus on age at transplantation and use of radiation for conditioning. Children are at particularly high risk from radiation-induced damage for reasons not entirely clear, but multiple long-term duties involving Hodgkin lymphoma and other hematologic malignancies confirm this association (Dores et al. 2002). Rizzo et al. (2009) published results from the largest, retrospective patient cohort from the combined CIBMTR-FHCRC database. Within this cohort of 28,874 patients, young patients (less than 10 years of age) and the use of TBI were associated with an excess absolute risk (EAR) of 43.2 and 76.40 after 1 and 5 years post-transplant time, respectively. A trend in decreasing EAR with increasing age at time of transplantation was noted in association with the use of TBI. Specific cancers associated with the use of TBI included breast, thyroid, brain and CNS, bone and melanoma. The presence of chronic GVHD was associated with the development of squamous cell carcinomas (SCC). Across multiple studies, younger age at the time of transplantation as well as the use of TBI has been associated with the development of second malignancies (Curtis et al. 1997; Baker et al. 2003; Bhatia et al. 2001). Regarding timing and onset, comparable cumulative incidences of 2.5%, 5.8% and 8.8% have been observed at 10, 15 and 20 years following HCT, respectively (Rizzo et al. 2009).

Reviewing specific examples of post-HCT solid malignancies, the European Group for Blood and Marrow Transplantation (EBMT) Late Effects Working Group retrospectively reviewed 68,936 patients who had undergone allogeneic and autologous transplantation (Cohen et al. 2007). Thirty-two cases of thyroid cancer (23 papillary and 9 follicular) were identified. In comparison with the European population, the SIR for transplant patients was 3.26 (95% CI 2.23–4.60) for the development of thyroid cancer. Similar to other second malignancies, age at time of transplant (0–10 years) was identified as the strongest risk factor in multivariate analysis when compared to older patients (>20 years). So strong was younger age as a risk factor that the relative risk, 24.61 (95% CI 4.45–136.25), was greater than the sum of other identified risk factors: use of conditioning irradiation (RR 3.44, 95% CI 1.41–8.37), female sex (2.79, 95% CI 1.34–5.79) and chronic GVHD (RR 2.94, 95% CI 1.21–7.15). Considered a cancer of older patients in the general population, thyroid cancers in the HCT population occurred at a median age of 23.5 years and a median latent period of 8.5 years following transplant.

Female HCT survivors not only are at increased risk of thyroid cancer compared to the general population, but they are also at increased risk of breast cancer. Friedman et al. (2008) analyzed a combined cohort comprised of FHCRC and EBMT patients who had undergone allogeneic transplantation and observed 52 cases of breast cancer among 3,337 patients surviving

Table 19.1 Second solid tumors and demographics, incidences and risk factors

Cancer	Median age	Median time from transplant	5-year incidence	10-year incidence	15-year incidence	20-year incidence	25-year incidence	Risk factors	Reference
All	NS	NS	NS	2.5% (95% CI: 2.0–3.0)	5.8% (95% CI: 4.3–7.0)	8.8% (95% CI: 6.2–12.3)	NS	Younger age at transplant, TBI	Rizzo, J.D., et al.
Thyroid	23.5 years (range: 8.8–52.2)	8.5 years range: 0.6–18.5)	NS	NS	NS	NS	NS	Younger age at transplant, TBI, female sex, chronic GVHD	Cohen, A., et al.
Breast	47.5 years (range: 25.5–65.8)	12.5 years (range: 5.7–24.8)	NS	0.8% (95% CI: 0.5–1.2)	NS	4.6% (95% CI: 3.1–6.7)	10.8% (95% CI: 6.8–15.8)	Time from transplant, younger age at transplant, TBI	Friedman, D.L., et al.
BCC	47.9 years (range: 12.6–72.3)	7.9 years (range: 0.5–30.2)	1.4% (95% CI: 1.0–1.7)	2.5% (95% CI: 2.0–3.0)	4.0% (95% CI: 3.3–4.8)	6.5% (95% CI: 5.3–7.7)	8.4% (95% CI: 6.8–10.2)	Time from transplant, younger age at transplant, TBI, white race, chronic GVHD	Leisenring, W., et al.
SCC skin and mucosa	48.9 years (range: 17.4–72.1)	6.3 years (range: 0.3–24.8)	1.0% (95% CI: 0.7–1.3)	1.4% (95% CI: 1.1–1.9)	2.2% (95% CI: 1.7–2.8)	3.4% (95% CI: 2.6–4.3)	5.5% (95% CI: 4.1–7.3)	Time from transplant, younger age at transplant, acute GVHD, chronic GVHD	Leisenring, W., et al.

BCC basal cell carcinoma, *GVHD* graft versus host disease, *NS* not stated, *SCC* squamous cell carcinoma, *TBI* total body irradiation

greater than 5 years. Compared to the general population, the SIR of observed to expected malignancies was 2.2 (95% CI 1.7–2.9) for female HCT survivors. Breast cancers occurred at an earlier age, with a median age of 47.5 years. Multivariate Cox regression analysis determined that time from transplantation, TBI-containing conditioning regimens and age at time of transplantation were all independent risk factors for the development of breast cancer. Adjusted hazard ratios rose with time since transplantation when compared to the 5–9.9 year follow-up period: 10–14.99 years (HR 2.7, 95% CI 1.2–6.4), 15–19.99 years (HR 5.1, 95% CI 1.9–13.6) and >20 years (HR 10.8, 3.2–36.1). Accordingly, the cumulative incidence of breast cancer in patients surviving greater than 25 years was 11.0% (95% CI 7–16%), rising to 17% (95% CI 9–26%) for patients who had received TBI. But similar to other solid cancer risks, age at time of transplantation was also a highly significant risk factor with an adjusted hazard ratio of 9.5 (95% CI 1.8–51.1) and SIR of 25.0 (95% CI 12.5–50.1) for female patients younger than 18 years at the time of transplantation.

Focusing on skin and mucosal cancers, Leisenring et al. (2006) analyzed risk factors for the development of these post-HCT malignancies from a retrospective cohort study of 4,810 patients in the FHCRC database. One hundred fifty-eight patients developed basal cell carcinomas (BCC) while 95 patients developed SCCs (tongue, tonsil, vocal cord, esophagus, genitourinary tract and skin); 58 patients had one more than one occurrence. Significant risk factors for the development of BCCs were age at transplantation, TBI-containing regimen, white race and chronic GVHD; age at time of transplant and both acute and chronic GVHD were significant risk factors for the development of SCCs.

Prognosis of second solid malignancies has not been well studied with respect to the general population. Factors such as low overall incidence and a heterogeneous population make such comparisons difficult. Reviewing solid malignancies in a cohort of patients from the University of Minnesota, Baker et al. (2003) determined that 42% of patients who developed a solid cancer died from that malignancy, but ultimately mortality from a given cancer likely relates more to the nature of the cancer.

Treatment at the present time does not appear to differ for respective cancers when compared to those developing within the general population. However, as with any effort behind successful screening campaigns, long-term follow-up clinics focusing on the continuing health of HCT survivors have concentrated their attention on early detection. An international collection of hematopoietic transplant experts has recently updated and published the most recent recommendations for screening and preventative practices for HCT-survivors (Majhail et al. 2012). Specifically regarding screening for breast cancer, the panel recommends initiation of mammography at 25 years of age or 8 years after receiving radiation. Protecting the skin against ultraviolet light and frequent oral health examinations, in addition to heightened surveillance for second cancers, rounds out updated screening efforts in addition to a healthy lifestyle.

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