Old and New Cancers after Hematopoietic-Cell Transplantation

Navneet S. Majhail [1,2]

[1]*Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, MN*
[2]*Center for International Blood and Marrow Transplant Research, Minneapolis, MN*

Relapse of primary disease and occurrence of new cancers can cause significant morbidity and mortality in recipients of autologous and allogeneic hematopoietic-cell transplantation (HCT). Treatment options for relapse are generally limited and can include disease-specific chemotherapy or targeted therapy. Additional relapse-directed therapies that are available for allogeneic HCT recipients include withdrawal of immunosuppression and donor lymphocyte infusion. Selected patients can be offered a second transplant procedure. Newer strategies to eliminate minimal residual disease and, in allogeneic HCT recipients, to augment the graft-versus-tumor effect are needed for patients who are at high risk for relapse after HCT. Second cancers after HCT include post-transplant lymphoproliferative disorder, hematologic malignancies and new solid cancers. The incidence of second solid cancers continues to rise without a plateau with increasing follow up of HCT survivors. Secondary myelodysplastic syndrome and acute leukemia are almost exclusively seen in autologous HCT recipients while post-transplant lymphoproliferative disorders complicate recipients of allogeneic HCT. Appropriate screening evaluations should be performed in HCT survivors to facilitate early detection and treatment of second cancers.

Hematopoietic-cell transplantation (HCT) can be potentially curative for a variety of malignant and non-malignant hematological disorders. HCT is typically reserved for diseases that are associated with high risk for relapse following conventional chemotherapy. Transplantation is pursued as a means to decrease this hazard, but some degree of risk for relapse persists. Due to a variety of treatment exposures and other risk factors, HCT recipients can also be at risk for the development of second cancers. In general, the risk of recurrent malignancy continues to decrease while that of second cancers continues to rise with increasing survival after transplantation (**Figure 1**). This review discusses the problems of recurrent malignancy and occurrence of new cancers after HCT.

Relapse of Primary Disease

HCT is usually reserved for patients with diseases that are associated with a high risk of relapse where the benefits of transplantation outweigh the risk of treatment-related mortality (TRM). Also, it is not unusual for patients with some diseases to be offered HCT after they have failed multiple lines of therapy or to have residual or refractory disease at the time of transplantation. In these high-risk patients, the expectation is that conditioning regimen chemotherapy and/or radiation therapy and, in allogeneic HCT recipients, the alloreactive graft-versus-tumor (GVT) effect will overcome this adversity and will lead to long-term remissions and a potential cure. However, a subset of patients does not benefit from this aggressive treatment approach and can relapse after HCT. Among deaths occurring 2 or more years after HCT, relapse is the primary cause of death in 30% to 50% allogeneic and 60% autologous HCT recipients.[1-3]

Relapse after allogeneic HCT

Risk factors

Disease and disease stage are among the strongest predictors for relapse following allogeneic HCT (**Figure 2**). The

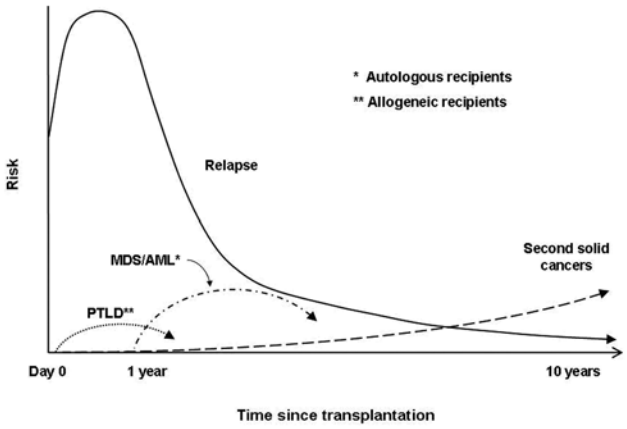

Figure 1. Risk of relapse and second cancers after hematopoietic-cell transplantation. The schema for relapse may not apply to diseases such as multiple myeloma where autologous transplantation primarily prolongs remission duration and does not lead to long-term cure.

Abbreviations: PTLD, post-transplant lymphoproliferative disorder; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.

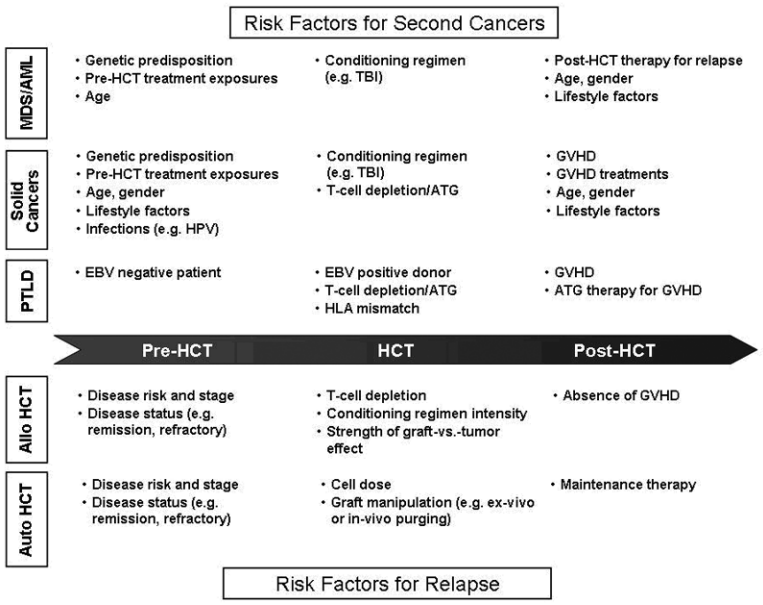

Figure 2. Risk factors for relapse and second cancers after hematopoietic-cell transplantation.

Abbreviations: HCT, hematopoietic-cell transplantation; PTLD, post-transplant lymphoproliferative disorder; TBI, total body irradiation; ATG, anti-thymocyte globulin, GVHD, graft-versus-host disease; EBV, Epstein Barr virus; HPV, human papilloma virus.

GVT response has been observed to be most potent in patients with chronic myeloid leukemia (CML) and, although present, is not as robust in patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL).[4] Additionally, this effect is also dependent upon disease stage and bulk at transplantation. Patients with early-stage disease (e.g., CML chronic phase versus accelerated or blast phase) and minimal disease (e.g., AML in complete remission instead of relapsed or refractory disease) have a lower probability of relapse. Disease-specific prognostic factors, which often are the basis for considering transplantation as a therapeutic option in the first place, are also associated with an increased risk of relapse after HCT. For example, patients with Philadelphia chromosome–positive ALL or AML with poor cytogenetic abnormalities have very high rates of disease recurrence with chemotherapy alone and are typically offered allogeneic HCT in first complete remission.[5,6] Compared to patients undergoing HCT for similar disease stage but standard- or good-risk disease, the patients with poor cytogenetic abnormalities have higher rates of relapse.[7-9]

Transplant-related factors can also affect the risk of disease relapse after transplantation. GVHD and GVT effect are largely mediated by the same graft effector cells, and the two phenomena have been shown to be closely associated.[4] Factors that increase the risk of GVHD may decrease the risk of relapse; however, GVHD by itself can lead to significant morbidity and mortality and in clinical practice donors and grafts that are associated with the lowest risk of GVHD (i.e., sibling donors) are preferred. In comparison to unmanipulated grafts, ex-vivo or in-vivo T-cell depletion decreases the risk of GVHD but increases the risk of relapse.[4] Although still controversial, published reports suggest lower rates of relapse with the use of partial HLA matched grafts and with peripheral blood instead of bone marrow–derived hematopoietic stem cells.[10]

Prevention

Various strategies may decrease the risk of relapse after HCT, including transplantation earlier in the disease course and in complete remission, augmenting the graft versus tumor effect through tumor specific vaccines or other strategies, use of myeloablative conditioning when possible, maintenance therapies after HCT, close monitoring and early intervention for recurrent/residual disease. An important first step in decreasing the risk of post-transplant relapse is the process of patient referral and selection. Patients with diseases that are associated with high risk for relapse after conventional chemotherapy (e.g., Philadelphia chromosome–positive ALL) should be referred for a transplant evaluation early in the course of their disease. Early referral can also facilitate the logistics of proceeding towards an HCT as soon as a patient achieves remission since the donor selection process can be initiated and any comorbid conditions that might impact the risk of post-transplant complications can be identified and treated. For diseases such as acute leukemia, where the presence of a minimal residual disease status is an important determinant of post-transplant outcomes, additional therapy should be considered for patients whose disease is not in complete clinical remission prior to proceeding with transplantation. Additional strategies for the prevention of relapse after allogeneic HCT include reinforcement of the GVT effect (**Table 1**).[11-13] Techniques to potentiate the GVT effect have the potential to increase the risk and severity of GVHD. The use of tumor-specific vaccines to augment the GVT effect without exacerbating GVHD is currently being investigated.[14] If age, performance status and comorbidities permit, patients undergoing allogeneic transplantation are usually offered myeloablative conditioning regimens to get the additional benefit of intensive preparative regimen chemotherapy and/or radiation therapy in eradicating minimal residual disease. Emerging data indicate that for some diseases the immunosuppressive effect of non-myeloablative or reduced-intensity conditioning regimens is suf-

Table 1. Strategies for preventing relapse after hematopoietic-cell transplantation (HCT).

Allogeneic HCT	Autologous HCT
Pre-transplantation	
Therapy to achieve maximal remission pre-HCT	Therapy to achieve maximal remission pre-HCT
Consider HCT early in disease course for high risk diseases (e.g., poor cytogenetics, presence of minimal residual disease)	Consider HCT early in disease course for high risk diseases (e.g., early relapse, presence of minimal residual disease)
At transplantation	
Use novel therapies to maximize eradication of minimal residual disease (e.g., radioimmunotherapy, monoclonal antibodies)	Use novel therapies to maximize eradication of minimal residual disease (e.g., radioimmunotherapy, monoclonal antibodies)
Graft selection (e.g., HLA or KIR mismatched donors)	Graft selection (e.g., maximize $CD34^+$ cell collection)
Graft manipulation (e.g., selective T-cell depletion)	Graft manipulation (e.g., ex-vivo or in-vivo purging)
Avoid T-cell deplete grafts	
Use full ablative conditioning regimens	
Post-transplantation	
Immune modulation (e.g., tumor vaccines, interleukin-2)	Immune modulation (e.g., tumor vaccines, interleukin-2)
Maintenance therapy after HCT (e.g., tyrosine kinase inhibitors in CML)	Maintenance therapy after HCT (e.g., rituximab in low-grade lymphomas or IMiDs in myeloma)
Accelerated taper of immune suppression	
Prophylactic DLI (e.g., following T-depleted grafts in diseases at high-risk for relapse)	

Abbreviations: HLA indicates human leukocyte antigen; KIR, killer immunoglobulin-like receptor; GVHD, graft-versus-host disease; DLI, donor leukocyte infusions; CML, chronic myeloid leukemia; IMiD, immunomodulatory drug

ficient to allow for engraftment and the subsequent GVT effect and that myeloablation may not be necessary.[15] Patients who remain at high risk for relapse following allogeneic HCT might benefit from maintenance therapy (**Table 2**). Although the rationale of using drug therapy to maintain a minimal residual disease status in order to give an advantage to the GVT effect is attractive, this approach needs to be explored in clinical trials. Agents that warrant investigation as prophylactic therapy include tyrosine kinase inhibitors (e.g., imatinib, dasatinib and nilotinib) for CML and Philadelphia chromosome–positive ALL,[16] FLT-3 inhibitors (e.g., lestaurtinib) for FLT3 internal tandem duplication mutation–positive AML and immunomodulatory drugs (e.g., lenalidomide) for high-risk multiple myeloma. Carpenter et al have recently demonstrated the safety and tolerability of administering imatinib prophylaxis in the early post-engraftment period after allogeneic HCT for high-risk Philadelphia chromosome–positive leukemias.[16] The role and optimal techniques for monitoring of minimal residual disease in patients with diseases other than CML also needs to be studied; earlier detection might allow for disease control with less intense therapy before florid relapse has occurred. Risk-adapted transplant strategies such as tailoring the conditioning regimen along with graft selection to maximize the GVT effect and/or post-transplant maintenance therapy need to be explored for high-risk patients.

Table 2. Representative examples of agents that can be considered for further investigation as maintenance therapy after hematopoietic-cell transplantation.

Disease	Agent
ALL (Ph^+)	Imatinib, dasatinib, nilotinib
AML ($FLT3^+$)	Lestaurtinib
CLL	Rituximab, alemtuzumab
CML	Imatinib, dasatinib, nilotinib
MDS	Decitabine, 5-azacytidine, lenalidomide
Mutliple myeloma	Thalidomide, lenalidomide, bortezomib
Myelofibrosis	JAK2 inhibitors
NHL	Rituximab, alemtuzumab

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leumkeima; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma

Treatment

Treatment of relapse depends on a variety of factors such as underlying diagnosis, patient performance status, disease bulk at relapse, time since HCT and patient preference. Response rates are most favorable for patients with chronic-phase CML and long-term survival rates of 60% to 90% have been reported after donor lymphocyte infusions (DLI).[17-19] Treatment options are generally limited and not very effec-

tive for patients who relapse after allogeneic HCT for diseases other than chronic-phase CML, and survival is universally dismal.[20-22] In an analysis conducted by Mielcarek et al, among 307 patients with recurrent high-risk hematologic malignancies (acute leukemia, CML in blast phase and advanced MDS) who received at least one relapse-directed intervention, the 2-year overall survival rates for patients with early (within 100 days), intermediate (between 100 and 200 days) and late recurrences (after 200 days) were only 3%, 9% and 19%, respectively.[20] Selected patients with moderate to good performance status and late recurrences can be considered for additional therapies enumerated below.

Withdrawal of immunosuppression: For patients who relapse in the early post-transplant period and are still on immunosuppressive therapy for prophylaxis or treatment of GVHD, a rapid taper of immunosuppression to optimize the GVT effect is usually the first step for treatment. However, this is not feasible in patients with active GVHD. Although it has not been systematically investigated, its overall efficacy is very low and anecdotal experience suggests that only an occasional patient may achieve durable remission with this approach.[20,22]

Chemotherapy and targeted therapies: Imatinib has been used successfully to achieve long-term remissions in patients with CML who relapse after allogeneic HCT. The European Group for Blood and Marrow Transplantation (EBMT) reported 128 patients with CML who received imatinib for post-transplant relapse; among patients with chronic, accelerated and blast phase disease, a complete cytogenetic response was seen in 58%, 48% and 22% patients, respectively, while a complete molecular response was detected in 37%, 33% and 11% patients, respectively.[23] The 2-year overall survival rate for the three disease stages was 100%, 86% and 12%, respectively. However, response and survival after single or multi-agent salvage chemotherapy for diseases other than CML is generally poor.[20] Selected patients with good performance status can be offered disease-specific chemotherapy with the intent of achieving significant disease debulking and possibly another remission prior to proceeding with DLI or a second transplant; however, this strategy needs to be explored further in clinical trials since its impact on improving overall outcomes and survival is not well known.

Donor lymphocyte infusion: DLI involves administration of donor lymphocytes, specifically T cells, to potentiate the GVT reaction. It is not feasible in patients with active GVHD where donor T-cell infusion can cause exacerbation of GVHD, which at times can itself be severe and fatal. **Table 3** summarizes contemporary, relatively large studies of DLI and highlights the heterogeneity and limitations of reported case series; however, several important generalizations can be made from the available literature. (1) DLI is most effective for relapsed chronic-phase CML where long-term survival rates of 60% to 90% can be expected. It is less effective for recurrent advanced phase CML and non-CML hematologic malignancies. (2) Development of GVHD after DLI predicts for a GVT effect and a subsequent response. (3) Response rates are higher in patients with longer duration of remission after HCT and in those with minimal disease bulk prior to DLI. Hence, selected patients might benefit from disease specific chemotherapy before proceeding with DLI. (4) A sufficient number of donor T cells (~1×10^7 or 10^8 $CD3^+$ cells/kg) are required to produce a meaningful GVT response. Lower doses (<1×10^7 $CD3^+$ cells/kg) may be efficacious in patients with CML with low disease burden (e.g., molecular relapse only). Higher doses, especially if preceded by lymphodepleting chemotherapy, may increase the risk of severe GVHD.[29]

With the low response rates and survival with DLI for diseases other than CML, there is a need for substantial progress to fruitfully harness the GVT effect. More studies are needed to address a number of unanswered questions, such as the role of dose-escalating DLI and the need for chemotherapy before DLI, and to further define its role in recipients of non-myeloablative and reduced-intensity HCT and in diseases where effective therapies (e.g., imatinib) are available for the treatment of relapse.

Second transplant: Second allogeneic transplants can be offered to selected patients with good performance status. They are especially applicable in recipients of unrelated umbilical cord blood grafts where DLI is not an option. Reduced-intensity preparative regimens have contributed to the increasing use of second transplants. In a study conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR), the 5-year rate of overall and leukemia-free survival in 279 patients with relapsed acute and chronic leukemia undergoing a second transplant following an HLA-identical sibling HCT was 28%.[30] The risks of relapse were lower in patients who relapsed more than 6 months after first HCT and in those who were in complete remission at the time of second HCT. In another large analysis conducted by the Société Française de Greffe de Moelle (SFGM) among 150 recipients of a second allogeneic HCT, the 5-year overall and disease-free survival rates were 32% and 30%, respectively.[31] Factors associated with improved outcomes included younger age at second transplant (<16 years), more than12 months between first HCT and relapse, female donor, absence of acute GVHD and occurrence of chronic GVHD. The TRM rate was 30% in the CIBMTR study and 45% in the SFGM study. More clinical studies are still needed to determine which subset of patients will benefit the most from this approach without a prohibitive increase in the risk of TRM or early and late morbidity.

Relapse after autologous HCT

For some diseases (e.g., mantle-cell lymphoma and multiple myeloma), autologous HCT is offered with the intent

Table 3. Selected large studies of donor lymphocyte infusion after allogeneic hematopoietic-cell transplantation (HCT).

Reference	N	Diagnoses	Cell dose; Type	Outcome	Comments
Kolb et al (1995)[19]	135	various	Median 3.0×10^8/kg; mononuclear cells	2 yr OS 68% for CML vs. <20% for AML & ALL	Higher response rates in CML patients who developed GVHD after DLI
Collins et al (1997)[24]	140	various	Mean 4.7×10^8/kg; mononuclear cells	2 yr OS 60% for CML vs. <20% for AML & ALL	Higher response rates in CML patients with early stage disease & post-HCT chronic GVHD; development of GVHD after DLI correlated with response
Dazzi et al (2000)[17]	66	CML	Median 1.5×10^8/kg; lymphocytes	3 yr OS 95% in responders vs. 53% in non-responders	Higher response rates in early phase disease and longer remission duration after HCT
Porter et al (2000)[25]	58	various	Median 1.0×10^8/kg; mononuclear cells	2 yr DFS 65% for CML vs. ~25% for AML & ALL	DLI from matched unrelated donors; higher response rates in longer remission duration after HCT
Guglielmi et al (2002)[18]	344	CML	Median 1.0×10^8/kg; mononuclear cells	2 yr OS ~70%	Low-dose DLI (0.2×10^8 mononuclear cells/kg) leads to similar response but lower GVHD than high-dose DLI
Levine et al (2002)[26]	65	various (no CML CP)	1.0×10^8/kg; $CD3^+$ cells	2 yr OS 19%	Patients received cytarabine-based chemotherapy; higher response rates in longer remission duration after HCT; GVHD not required for durable remission
Mielcarek et al (2007)[20]	65	various (no CML CP)	1.0×10^8/kg (related), 1.0×10^7/kg (unrelated); $CD3^+$ cells	Survival/response not described	Subset of patients in a cohort of 307 patients with post-HCT relapse; DLI not associated with response or survival
Miller et al (2007)[27,29]	78	various	1.0×10^8/kg; $CD3^+$ cells	2 yr OS 75% for CML vs. 17% for non-CML	15 pts received Cy-Flu chemotherapy; lymphodepleting chemotherapy increased risk of severe acute GVHD
Schmid et al (2007)[28]	171	AML	Median 2.8×10^8/kg; mononuclear cells	2 yr OS 21%	Higher response rates if low disease bulk at relapse, favorable cytogenetics and in CR at DLI; development of chronic GVHD after DLI correlated with response

Abbreviations: CML, chronic myeloid leukemia; CP, chronic phase; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; GVHD, graft-versus-host disease; DLI, donor lymphocyte infusion; OS, overall survival; DFS, disease-free survival; Cy, cyclophosphamide; Flu, fludarabine; CR, complete remission

PTLD

PTLD comprises of a heterogeneous group of lymphoid proliferations, primarily involving B-lymphocytes, which arise as a result of Epstein-Barr virus (EBV) infection. PTLD was initially recognized in solid organ transplant recipients where its incidence can range from 1% to 6%.[33] Among patients undergoing HCT, PTLD occurs almost exclusively in recipients of allogeneic grafts with an overall incidence rate of 1% to 2% and typically manifests early post-transplantation with more than 80% cases diagnosed within the first year.[32,34] Although reported, PTLD is extremely rare in patients undergoing autologous HCT. PTLD after solid organ transplantation is of recipient origin whereas in HCT recipients it arises in donor cells.[33] The World Health Organization (WHO) classification is commonly used to classify PTLD and recognizes early benign PTLD, polymorphic PTLD, monomorphic PTLD and Hodgkin's lymphoma–like PTLD; the WHO and other classification schemes have been reviewed elsewhere.[32,33]

Table 4. Cumulative incidence of second cancers after hematopoietic-cell transplantation (HCT).

Second cancer	Cumulative incidence
Solid cancers	1.2-1.6% at 5 years 2.2-6.1% at 10 years 3.8-14.9% at >15 years
PTLD	0.6-1.4% (~75% occur within 1 year) after allogeneic HCT Rare after autologous HCT
MDS/leukemia	5-15% at 5 years after autologous HCT Rare after allogeneic HCT

Abbreviations: PTLD, post-transplant lymphoproliferative disorder; MDS, myelodysplastic syndrome

Besides EBV, T-cell depletion of the graft in any form, including use of anti-thymocyte globulin (ATG) or anti-CD3 monoclonal antibody, is among the strongest risk factors for PTLD (**Figure 2**).[32,34] Other important risk factors include acute GVHD and use of grafts from unrelated or mismatched related donors. Extensive chronic GVHD increases the risk of late onset (>1 year post-HCT) PTLD.[34]

Since monomorphic PTLD is associated with high mortality rates, active surveillance for EBV reactivation in high-risk settings (e.g., T-cell depletion, use of ATG) is being increasingly advocated with initiation of preemptive therapy with rituximab once EBV levels rise above a certain threshold (e.g., >1000 copies/mL on quantitative DNA PCR). Treatment of established PTLD is usually challenging, especially because the disease usually involves multiple organs at presentation, causing considerable morbidity and decline in performance status, and can be associ-

ated with fungal and cytomegalovirus infections. Antiviral therapy with acyclovir or ganciclovir is of limited benefit. Withdrawal of immunosuppression should be attempted, but this can be difficult in patients with active GVHD. Although studies in HCT patients are lacking, response rates of 50% to 80% have been reported with single agent rituximab in solid organ transplant recipients.[33] Involvement of multiple extranodal sites and late-onset PTLD are predictors of poor response to rituximab alone, and these patients can be considered for cytotoxic chemotherapy in addition to rituximab (e.g., CHOP-R regimen). Infusion of EBV-specific cytotoxic lymphocytes is a novel approach towards prevention and treatment of PTLD that is being currently investigated.[35]

Hematologic malignancies

Secondary myelodysplastic syndrome (MDS) and AML can be seen in 5% to 15% of autologous HCT recipients and occurs with a latency period of 2 to 5 years.[36] Bone marrow evaluation can show characteristic cytogenetic abnormalities (e.g., balanced translocations to 11q23, monosomy of 5q and 7q) and multiple chromosomal aberrations are frequent. Risk factors for secondary MDS/AML include older age at HCT, the type and intensity of pre-HCT chemotherapy (especially alkylating agents) and use of total-body irradiation (TBI) in conditioning.[36,37] Initial therapy is similar to de novo AML and an allogeneic HCT, if feasible, should be performed in first remission. Outcomes are still poor and long-term survival rates of less than 20% have been reported.

Therapy-related myelodysplastic syndrome and acute leukemias are extremely rare following allogeneic HCT. Albeit rare (<1% incidence), leukemia can arise in donor cells. Putative pathogenetic mechanisms for development of donor cell leukemia include oncogenic alteration or premature senescence of transplanted donor cells in an immunosuppressed host and disruption of normal homeostasis within the marrow microenvironment after HCT.[38]

Solid cancers

There is a latency period of 3 to 5 years before second solid malignancies are seen after HCT. Subsequently, their incidence continues to rise with time (**Table 3**). In one of the largest studies conducted to date among 19,229 recipients of allogeneic and syngeneic HCT (collaborative study between the CIBMTR and Fred Hutchinson Cancer Research Center [FHCRC]), the cumulative incidence of second cancers at 5, 10 and 15 years after transplantation was 0.7%, 2.2% and 6.7%, respectively, compared to the general population rates of 0.3%, 0.6% and 0.8%.[37]

Several exposures in the peri- and post-transplant period can impact the risk of second cancers (**Figure 2**). However, determining the impact of pre-transplant cancer therapy versus specific transplant-related factors on the risk of second cancers in allogeneic HCT recipients has not been possible since reported studies have only used general population controls and have not included survivors of hematologic malignancies who did not receive HCT. Younger age at transplantation, use of TBI in conditioning regimen and chronic GVHD have been implicated as risk factors in some studies while a strong association between these factors and second cancers has not been observed in others.[32] In the CIBMTR-FHCRC study, younger age at transplantation and higher doses of TBI significantly increased the risk of new solid cancers in general while chronic GVHD was specifically associated with squamous cell cancers of the buccal cavity and skin.[39] In a subsequent study, severity of chronic GVHD and duration of immunosuppressive therapy (>24 months) were found to be major risk-factors for invasive squamous cancers.[40] TBI has been reported to increase the risk of breast cancer; in a cohort of 3337 female 5-year survivors, the 25-year cumulative incidence of breast cancer was 17% in recipients of TBI compared to 3% in those who did not receive TBI as a part of their conditioning.[41] Experience with atomic bomb survivors and with Hodgkin's lymphoma patients treated with radiation therapy suggests that second solid cancers can take decades to develop, and even longer follow-up than what is currently available might be needed before the true magnitude of risk becomes apparent.[32]

A variety of cancer types and sites have been reported. In the CIBMTR-FHCRC study, risks for cancers of the buccal cavity, liver, brain and central nervous system, thyroid, bone and connective tissue and for melanoma were significantly elevated compared to the general population.[39] Other studies have reported similar patterns of second solid cancers after allogeneic HCT.[33]

Guidelines for screening and prevention of second malignancies have been published by the Children's Oncology Group and by the EBMT, CIBMTR and American Society of Blood and Marrow Transplantation (**Table 5**).[42,43]

Conclusions

In the absence of evidence based guidelines and good treatment options, treatment of relapse after HCT, especially for high-risk hematologic malignancies, remains challenging. Given the heterogeneous clinical scenarios that are encountered in this setting, questions about relapse-directed therapies can be best answered by collaborative multicenter clinical trials. Depending on patient performance status, underlying diagnosis, disease status and time since transplantation, therapies for relapse can include chemotherapy or targeted therapies, DLI or second HCT. Obviously the best approach is preventing relapse in the first place. Timely HCT in high-risk patients can decrease the risk of relapse, and consultation with a transplant center should be considered early in the disease course for patients in whom

Table 5. Guidelines for screening for common cancers after hematopoietic-cell transplantation (HCT).*

Site	Screening recommendations
Breast	Mammogram annually starting at age 40†; begin at age 25 or 8 years after radiation, which ever occurs later, in women who have received ≥ 20 Gy to the chest region
Cervix	PAP smear every year (for regular PAP test) or every 2 years (for liquid-based PAP test); after age 30, if patient has had 3 consecutive normal tests, may screen every 2-3 years†
Colorectal	Beginning at age 50, fecal occult blood annually and/or flexible sigmoidoscopy every 5 years, or double contrast barium enema every 5 years, or colonoscopy every 10 years; certain high-risk groups (e.g., patients with inflammatory bowel disease) may need earlier initiation and more frequent screening†
Lung	Yearly pulmonary exam with imaging as appropriate
Oral	Yearly oral cavity exam
Thyroid	Yearly thyroid exam
Skin	Skin exam as a part of periodic health exam†

*Adapted from Children's Oncology Group[25] and EBMT/CIBMTR/ASBMT guidelines[42]

† Similar to American Cancer Society recommendations for general population cancer screening

transplantation might be a part of the treatment regimen.

Second cancers are relatively rare complications of allogeneic HCT but their risk continues to increase over time. Longer follow up of survivors is still needed to realize the complete risk and impact of second solid cancers. Studies are beginning to explore risk factors for specific cancers and the contribution of transplant related events to such risks. Appropriate screening recommendations should be followed to detect and treat these cancers at an early stage.

Acknowledgments

I gratefully acknowledge Dr Linda J Burns and Dr Daniel J Weisdorf, University of Minnesota, Minneapolis, and Dr Stephanie J Lee, Fred Hutchinson Cancer Research Center, Seattle, for their thoughtful review of this manuscript.

Disclosures

Conflict-of-interest disclosure: The author declares no competing financial interests.

Off-label drug use: None disclosed.

Correspondence

Navneet S. Majhail, Division of Hematology, Oncology and Transplantation, University of Minnesota, 420 Delaware St SE, MMC 480, Minneapolis, MN 55455; Phone: 612-624-6982; Fax: 612-625-6919; e-mail: majha001@umn.edu

References

1. Bhatia S, Francisco L, Carter A, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. Blood. 2007;110:3784-3792.
2. Socie G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med. 1999;341:14-21.
3. Bhatia S, Robison LL, Francisco L, et al. Late mortality in survivors of autologous hematopoietic-cell transplantation: report from the Bone Marrow Transplant Survivor Study. Blood. 2005;105:4215-4222.
4. Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. Blood. 1990;75:555-562.
5. Byrd JC, Mrozek K, Dodge RK, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood. 2002;100:4325-4336.
6. Dombret H, Gabert J, Boiron JM, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia—results of the prospective multicenter LALA-94 trial. Blood. 2002;100:2357-2366.
7. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008;111:1827-1833.
8. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood. 2000;96:4075-4083.
9. Ferrant A, Labopin M, Frassoni F, et al. Karyotype in acute myeloblastic leukemia: prognostic significance for bone marrow transplantation in first remission: a European Group for Blood and Marrow Transplantation study. Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Blood. 1997;90:2931-2938.
10. Stem Cell Trialist's Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. J Clin Oncol. 2005;23:5074-5087.
11. Lutz C, Massenkeil G, Nagy M, et al. A pilot study of prophylactic donor lymphocyte infusions to prevent relapse in adult acute lymphoblastic leukemias after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2008;41:805-812.
12. Hsu KC, Keever-Taylor CA, Wilton A, et al. Improved outcome in HLA-identical sibling hematopoietic stem-cell transplantation for acute myelogenous leukemia predicted by KIR and HLA genotypes. Blood. 2005;105:4878-4884.
13. Miller JS, Cooley S, Parham P, et al. Missing KIR ligands are associated with less relapse and increased graft-versus-host disease (GVHD) following unrelated donor allogeneic HCT. Blood. 2007;109:5058-5061.

14. Mullen CA. Influence of tumor vaccines on graft versus tumor activity and graft versus host disease in allogeneic bone marrow transplantation. Leuk Lymphoma. 2002;43:503-510.
15. Sorror ML, Storer BE, Maloney DG, Sandmaier BM, Martin PJ, Storb R. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative conditioning regimens for treatment of lymphoma and chronic lymphocytic leukemia. Blood. 2008;111:446-452.
16. Carpenter PA, Snyder DS, Flowers ME, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. Blood. 2007;109:2791-2793.
17. Dazzi F, Szydlo RM, Cross NC, et al. Durability of responses following donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. Blood. 2000;96:2712-2716.
18. Guglielmi C, Arcese W, Dazzi F, et al. Donor lymphocyte infusion for relapsed chronic myelogenous leukemia: prognostic relevance of the initial cell dose. Blood. 2002;100:397-405.
19. Kolb HJ, Schattenberg A, Goldman JM, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. Blood. 1995;86:2041-2050.
20. Mielcarek M, Storer BE, Flowers ME, Storb R, Sandmaier BM, Martin PJ. Outcomes among patients with recurrent high-risk hematologic malignancies after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2007;13:1160-1168.
21. Arellano ML, Langston A, Winton E, Flowers CR, Waller EK. Treatment of relapsed acute leukemia after allogeneic transplantation: a single center experience. Biol Blood Marrow Transplant. 2007;13:116-123.
22. Oran B, Giralt S, Couriel D, et al. Treatment of AML and MDS relapsing after reduced-intensity conditioning and allogeneic hematopoietic stem cell transplantation. Leukemia. 2007;21:2540-2544.
23. Olavarria E, Ottmann OG, Deininger M, et al. Response to imatinib in patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. Leukemia. 2003;17:1707-1712.
24. Collins RH, Jr., Shpilberg O, Drobyski WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J Clin Oncol. 1997;15:433-444.
25. Porter DL, Collins RH, Jr., Hardy C, et al. Treatment of relapsed leukemia after unrelated donor marrow transplantation with unrelated donor leukocyte infusions. Blood. 2000;95:1214-1221.
26. Levine JE, Braun T, Penza SL, et al. Prospective trial of chemotherapy and donor leukocyte infusions for relapse of advanced myeloid malignancies after allogeneic stem-cell transplantation. J Clin Oncol. 2002;20:405-412.
27. Chiorean EG, DeFor TE, Weisdorf DJ, et al. Donor chimerism does not predict response to donor lymphocyte infusion for relapsed chronic myelogenous leukemia after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2004;10:171-177.
28. Schmid C, Labopin M, Nagler A, et al. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. J Clin Oncol. 2007;25:4938-4945.
29. Miller JS, Weisdorf DJ, Burns LJ, et al. Lymphodepletion followed by donor lymphocyte infusion (DLI) causes significantly more acute graft-versus-host disease than DLI alone. Blood. 2007;110:2761-2763.
30. Eapen M, Giralt SA, Horowitz MM, et al. Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. Bone Marrow Transplant. 2004;34:721-727.
31. Michallet M, Tanguy ML, Socie G, et al. Second allogeneic haematopoietic stem cell transplantation in relapsed acute and chronic leukaemias for patients who underwent a first allogeneic bone marrow transplantation: a survey of the Societe Francaise de Greffe de moelle (SFGM). Br J Haematol. 2000;108:400-407.
32. Lowe T, Bhatia S, Somlo G. Second malignancies after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2007;13:1121-1134.
33. Loren AW, Tsai DE. Post-transplant lymphoproliferative disorder. Clin Chest Med. 2005;26:631-645, vii.
34. Curtis RE, Travis LB, Rowlings PA, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood. 1999;94:2208-2216.
35. O'Reilly RJ, Doubrovina E, Trivedi D, Hasan A, Kollen W, Koehne G. Adoptive transfer of antigen-specific T-cells of donor type for immunotherapy of viral infections following allogeneic hematopoietic cell transplants. Immunol Res. 2007;38:237-250.
36. Pedersen-Bjergaard J, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. Blood. 2000;95:3273-3279.
37. Metayer C, Curtis RE, Vose J, et al. Myelodysplastic syndrome and acute myeloid leukemia after autotransplantation for lymphoma: a multicenter case-control study. Blood. 2003;101:2015-2023.
38. Flynn CM, Kaufman DS. Donor cell leukemia: insight into cancer stem cells and the stem cell niche. Blood. 2007;109:2688-2692.
39. Curtis RE, Rowlings PA, Deeg HJ, et al. Solid cancers after bone marrow transplantation. N Engl J Med. 1997;336:897-904.
40. Curtis RE, Metayer C, Rizzo JD, et al. Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study. Blood. 2005;105:3802-3811.
41. Friedman DL, Rovo A, Leisenring W, et al. Increased risk of breast cancer among survivors of allogeneic hematopoietic cell transplantation: a report from the FHCRC and the EBMT-Late Effect Working Party. Blood. 2008;111:939-944.
42. Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2006;12:138-151.
43. Children's Oncology Group. Long term followup guidelines for survivors of childhood, adolescent and young adult cancers (version 2.0 - March 2006). http://www.survivorshipguidelines.org/pdf/LTFUGuidelines.pdf, accessed 9/8/08.