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Secondary Malignancies After Hemopoietic Stem Cell Transplantation*

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Abstract: Hemopoietic stem cell transplantation is being carried out for rapidly increasing numbers of patients. Survival probabilities have increased progressively, and most patients return to productive lives. However, delayed complications do occur. Here, we review the incidence and spectrum of post-transplant malignancies, discuss risk factors and mechanisms, and assess the efficacy of therapeutic interventions.

Key Words: Hemopoietic stem cell transplantation, post-transplant malignancies

Introduction

Many patients who have undergone hemopoietic stem cell transplantation (HSCT) have now been followed for two or three decades post-transplant. While most of them are presumably cured, some have developed long-term complications, including new malignancies. This may not be unexpected (1). There are large numbers of factors associated with HSCT that may predispose to the induction of new malignancies (Table 1) (2). For example, studies in the 1970s and 1980s showed a significant increase in the incidence of malignancies relative to controls in rhesus monkeys and dogs irradiated with lethal doses of total body irradiation (TBI) and infused with autologous or allogeneic marrow cells (radiation chimeras). Patients undergoing transplantation, who by definition are cancer susceptible, may have genetic defects associated with their primary disease predisposing them to new malignancies. Immunodeficient patients are susceptible to viral infections, and these viruses, e.g., Epstein-Barr virus (EBV), and human papilloma virus (HPV), can transform cells in vivo (3,4). A summary of the factors associated with the development of new malignancies in HSCT recipients is presented in Table 2.

Malignancies of the lymphoid system

Post-transplant lymphoproliferative disorders (PTLDs) occur mostly in allogeneic, and not in autologous, transplant recipients. They are usually of B-cell lineage (3,5), although some T-cell PTLDs have been reported, as have Hodgkin disease and non-Hodgkin lymphoma.

B-cell PTLD

An analysis in 18,014 allogeneic transplant recipients followed for up to 25 years revealed 78 patients with post-transplant lymphoid malignancies, 82% of which were diagnosed within 1 year [peak occurrence (120 cases/10,000 patients/year) at 2–5 months, and a decline to <5 cases/10,000/year among 1-year survivors] (3). The incidence at 4–10 years was 1–2%. Higher figures have been reported in patients transplanted for immunodeficiency disorders (6). These PTLDs are almost always of donor origin. They are clinically and morphologically heterogeneous and usually associated with EBV infection (7,8). At least half show aggressive features of immunoblastic lymphoma (5,9). Most PTLDs after HSCT are oligoclonal or monoclonal, as determined by analysis of immunoglobulin gene rearrangement

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Table 1. Components contributing to post-transplant malignancies.

Milieu
– pre-existing
– genetic pre-disposition
– chromosomal instability
– mutation
–pre-transplant therapy
– transplant related
– chemotherapy
– irradiation
– antibodies
Source of HSC
– syngeneic
– allogeneic
– chronic stimulation
– autologous
– pre-exposed to therapy
Immunoincompetence
– slow immune reconstitution
– GvHD
– prophylaxis
– therapy
Infections
– viral
– EBV
– HPV
– other?
– bacterial
Chronic Disease
– chronic GvHD
– inflammation
– immunosuppressive therapy
– defective repair
– hormonal imbalance
– nutritional deficiencies
Social habits
– smoking
– other?

HSC = hemopoietic stem cells; GvHD = graft-vs.-host disease; EBV = Epstein Barr virus; HPV = human papillomo virus.

(5,6,10,11). There is no strong correlation between clonality and morphology (9). Exceptional cases show the characteristic t(8;14) translocation of Burkitt's lymphoma (12).

Risk factors for PTLD include use (7,13,14) of antithymocyte globulin (ATG) or anti-CD3 monoclonal antibody (MAB) for GvHD prophylaxis, or in the preparative regimen, use of TBI, T-cell depletion of donor marrow (15), unrelated donor or HLA non-identical related donor, primary immune deficiency disease, occurrence of acute GvHD, and treatment of acute GvHD with ATG or anti-T cell MAB (Table 3) (5). In patients transplanted with marrow depleted of T-cells with specific anti-CD3 MAB, the incidence of EBV + PTLD was 11% to 25% but less than 1% with techniques removing both T and B lymphocytes (e.g., soybean agglutinin or Campath-1) (5,16). There is a direct correlation between

Table 2. New malignancies after hemopoietic stem cell transplantation.

1. Malignancies of the lymphoid system
   a) B-cell PTLD
   b) T-cell lymphomas
   c) Hodgkin disease and other late lymphomas

2. Hematologic malignancies
   a) Leukemia recurrence in donor cells
   b) New leukemias in host cells
   c) Myelodysplastic syndrome/AML

3. Solid tumors
   a) Carcinomas
   b) Sarcomas
   c) CNS tumors*

*CNS = central nervous system; AML = acute myelogenous leukemia; PTLD = post-transplant lymphoproliferative disorder.

viral (EBV) load in peripheral blood and the development of PTLD (17,18). The role of HLA-mismatching in the pathogenesis of B-cell PTLD may consist in chronic antigenic stimulation, or delayed immune reconstitution. The impact of risk factors is additive (or synergistic). In one large study the incidence of PTLD was 8% ± 2.9% with one or two risk factors, and 22% ± 17.9% with three or more risk factors present.

EBV is a herpes virus latently present (in B lymphocytes and certain epithelial cells) in 95% of individuals by adulthood. In most cases of PTLD after solid organ transplantation EBV type A is isolated (19). Several strains have been identified. Whether the same applies to HSCT recipients remains to be determined. The molecular biology of cellular transformation by EBV has been described in detail elsewhere (4,20).

Investigators at Memorial Sloan-Kettering Cancer Center (11) used unirradiated donor leukocytes (1.0 x 10^6 CD3+ T cells/kg) to treat PTLD. Fourteen of 15 patients responded, and 6 of 12 evaluable patients developed GvHD. Gene-marked EBV-specific cytotoxic T-lymphocytes persisted in vivo and restored cellular immunity against EBV.

The St. Jude's team used rising titers of EBV DNA in patient plasma as a criterion to institute pre-emptive therapy with EBV-specific T-cell clones in 25 high-risk patients, and none developed PTLD (21). Bonini et al. showed that HSV-TK gene-modified donor lymphocytes can be used effectively and can be inactivated by ganciclovir if GvHD develops (22). Rooney (23) and Heslop (21) confirmed the efficacy of gene-marked EBV-specific T lymphocytes and showed long-term restoration of anti-EBV immunity.

Table 3. Risk factors.

Allogeneic HSCT	Type of Secondary Malignancy	Risk Factor
	PTLD	EBV+ donor EBV– patient HLA non-identity T-cell depletion ATG Irradiation GvHD – acute – chronic Primary disease
	Hematologic disorders	(undetermined)
	Solid Tumors	Irradiation Chronic GvHD Male gender Younger patient age T-cell depletion
	Solid tumors	Irradiation Virus
	Hematologic disorders	Intensity/duration of pre-transplant therapy Alkylator exposure Conditioning regimen Source of stem cells Older patient age

HSCT = hemopoietic stem cell transplantation; PTLD = post-transplant lymphoproliferative disorder; ATG = anti-thymocyte globulin; GvHD = graft-vs.-host disease.

Anti-CD21 and anti-CD24 antibodies were tested in a multicenter trial (24). Among 19 marrow transplant recipients, 10 achieved complete remissions, and 6, all with oligoclonal disease, survived at a median follow-up of 20 months (25). However, studies in SCID mice (26) indicate that residual EBV + B cells persist and can provoke a second tumor in the absence of efficient cytotoxic T cells.

The best current strategy for treatment of PTLD is close monitoring of plasma EBV DNA and institution of pre-emptive therapy in patients with rising EBV DNA titers (5).

T-cell Lymphoproliferative Disorders

Rare T-cell proliferative disorders with or without EBV association occur usually more than 1 or 2 years after transplantation. After HSCT only few such cases have been reported (27), none associated with HTLV1, HIV or HHV6 infection.

Hodgkin Disease and Other Late-Onset Lymphomas

Some late occurring lymphomas have been reported (28), occasionally linked to EBV (just as early onset PTLD). Others have been associated with T-cell depletion of the graft. Clinical presentation was as in non-transplanted patients, with lymph node enlargement with or without generalized symptoms.

A recent collaborative study found 8 cases of Hodgkin disease, at 2.9 to 9.1 years after HSCT (observed/ expected ratio 6.2) (29). Five cases (67%) showed mixed cellularity subtype, and 5 of 6 cases studied contained the EBV genome. Patients with Hodgkin disease were more likely to have acute GvHD and require therapy for chronic GvHD. These data add support to the hypothesis that links overstimulation of cellular immunity and exposure to EBV to various subtypes of Hodgkin disease (30).

Hematologic Malignancies

After Allogeneic HSCT

Acute lymphoblastic leukemia (ALL) in donor cells was first recognized 30 years ago (31-32). These events appear to be infrequent (33). However, cases of leukemia or MDS transplanted from the donor into the patient have been reported (34-35). In addition, new leukemias in patient cells, i.e leukemias of a different morphology or

lineage than the patient's original disease have also been described (reviewed in 36).

Recent work suggests that "replicative stress" after transplantation may result in accelerated telomere shortening of donor HSC (37-38). This, in turn, might lead to chromosomal instability and increased probability of MDS or leukemia. While telomere shortening occurs in HSCT recipients, the concept has remained controversial (39-40). Nevertheless, several cases of MDS/AML in donor cells presenting 5 or 10 years or even later after HSCT have been observed (unpublished). There is no known prophylaxis, and no therapeutic standards have been established. Some patients have recently been treated with second transplants using myeloablative or non-myeloablative protocols.

After Autologous HSCT

"Secondary" MDS and AML occur after conventional chemotherapy and, to a lesser extent, after radiotherapy for Hodgkin disease and non-Hodgkin lymphoma, as well as some solid tumors (1,41-44); they also are a major complication after autologous HSCT (reviewed in 28, 45-48).

In studies involving more than 1200 patients the incidence of MDS at 3–6 years after transplantation was 4–18% (49-52). A case control study revealed 12 cases of MDS/AML in 511 patients after autologous transplants for Hodgkin disease or non-Hodgkin lymphoma for a cumulative incidence of 4% at 5 years. Another report showed clonal chromosomal abnormalities in 10 of 275 patients 1.8 to 6.5 years after chemotherapy, and 0.5 to 3.1 years after autologous transplant for Hodgkin disease or non-Hodgkin lymphoma (52). The cumulative probability of developing clonal chromosomal abnormalities reached 9% ± 4.7% at 3 years after transplantation. However, only 5 patients had morphological evidence of MDS or AML.

Prolonged pre-transplant interval and use of radiotherapy were significant pre-transplant risk factors. The risk appears to be higher with peripheral blood cell transplants (53), in patients more than 35 (40) years of age at transplantation, and with the use of TBI (49).

A case control study by Metayer et al. analyzed data on 56 patients who developed MDS/Leukemia, and 168 controls within a cohort of 2739 patients with Hodgkin disease or NHL transplanted at 12 institutions (54). Intensity of pre-transplant chemotherapy, specifically with mechlorethamine and chlorambucil, was a significant factor ($P = 0.0009$) . Higher doses of TBI (>1200 cGy) also increased the risk.

Whether MDS/AML arises from infused HSC or from residual cells in the patient is controversial. If the former were true, then the type of conditioning therapy given for transplant should not be a risk factor—unless we postulate that conditioning (TBI) modifies the microenvironment and enhances the risk of leukemogenesis. If MDS/AML is related to transplantation, then the culprit may be the procedure itself or the status of immunoincompetence after transplantation. In some patients, autologous cells contain cytogenetic abnormalities pre-transplant.

More than one mutagenic/leukemogenic event is thought to be required for MDS or AML to develop. Gene fusion products recognized as leukemogenic (e.g. BCR/ABL, TEL/AML 1) are present even in normal individuals with the use of sensitive PCR technology. Thus, such clones may exist in patients pre-transplant, and a 'second hit' might occur during or after transplantation. It has also been argued that the picture with which some of these patients present is related to "disordered engraftment" rather than the development of MDS (47). Thus, reducing pre-transplant exposure to alkylating agents, topoisomerase inhibitors and irradiation, and shortening the duration of therapy should reduce the risk of MDS (55). If cytogenetics are abnormal at the time of stem cell harvest, an allogeneic transplant should be considered. In addition to standard cytogenetics, interphase FISH, determination of loss of heterozygosity or point mutations, and X-inactivation-based clonality assays may be useful. Once MDS/AML has evolved, the options are limited. Chemotherapy is often not well tolerated, and remissions are of short duration. Allogeneic HSCT with standard or reduced intensity conditioning is a realistic option for some patients (56).

Carcinomas and Sarcomas

After Allogeneic HSCT

Several single-institution studies have reported a higher than expected incidence of solid tumors in transplanted patients (14,15,57). A collaborative study analyzed results in 19,220 patients (97.2% allogeneic, 2.8% syngeneic recipients) transplanted between 1964 and 1992 (58) and observed 80 solid tumors [observed/expected (O/E) ratio of 2.7 ($P < 0.001$)]. In

10-year survivors, the risk was increased 8-fold. The tumor incidence was 6.7% at 15 years. The risk was increased significantly for melanoma, cancers of the oral cavity, liver, CNS, thyroid, bone, and connective tissue. The risk was highest for the youngest patients and declined with age.

This study, comprising now 28,874 patients (<1–72 years of age, 74% with leukemia, 76% transplanted from an HLA-identical sibling, 59% given TBI was part of the conditioning regimen) transplanted from 1964 to 1996, was recently updated. There were 161 solid tumors among 5-year survivors for an O/E ratio of 2.2. The highest ratios were observed for bone, buccal cavity, connective tissue, liver, brain, thyroid, and melanoma (in that order). Among 10-year survivors, the O/E ratios were 26 for buccal cavity, 32 for liver, 18 for thyroid, 6 for melanoma, and 3 for breast. Table 4 illustrates the spectrum of malignancies observed in patients transplanted at FHCRC.

Risk factors for solid tumors are summarized in Table 3. In the above collaborative study, the rates of excess cancers /10,000/year were highest in patients <17 years, and lowest for patients >40 years of age. Results in a study of 700 patients with aplastic anemia suggested that irradiation, treatment of chronic GvHD with azathioprine, and older age increased the risk of a post-transplant malignancy (59). The incidence was highest in patients transplanted for Fanconi anemia (Kaplan-Meier estimate at 15 years 40%). Irradiation, especially limited field irradiation, also was a significant risk factor for the development of solid tumors (59). In addition, donor age, chronic GvHD, and treatment of GvHD with cyclosporine or azathioprine, and the number of agents used for therapy were found to be significant risk factors. There was a strong link between chronic GvHD (and male gender) and squamous cell carcinoma. Preliminary data from an ongoing nested case control study in a cohort of 29,737 patients suggest that duration of chronic GvHD

Table 4. Malignancies after hemopoietic stem cell transplantation.*

Malignancy	Donor				
	Allogeneic		Syngeneic	Autologous	Total
	Related	Unrelated			
Basal cell CA	47	6	4	6	63
Squamous cell CA	37	10		2	49
Adeno CA	25	5	4	8	42
PTLD	22	3		25	
Hodgkin	2			2	
Malignant melanoma	5	2		1	8
Papillary CAs†	5	2	1	3	11
Mucoepidermoid CA	1	1		2	
Renal cell CA	1	1		1	3
Gliobastoma/astrocytoma	6	2	1	1	10
Fibrous histiocytoma (liver)	1		1		
Sarcoma	3	2		2	7
MDS	3	1		1	2
AML	4		2	6	
ALL	6		1	7	
Neuro. misc.	6			6	
Other	7		2	9	
Total	180	36	11	31	258
No. pts. transplanted	5093	520	250	2166	9029

*Observed among 9,029 patients transplanted at the Fred Hutchinson Cancer Research Center as of 12/31/00.
†Thyroid and other locations.
CA = carcinoma; MDS = myelodysplastic syndrome; AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; Neuro. misc. = miscellaneous tumors of the nervous system; PTLD = post-transplant lymphoproliferative syndrome.

>2 years and prolonged therapy are risk factors, in particular, for the development of squamous cell carcinoma.

After Autologous HSCT

A French study in 4,322 patients with Hodgkin disease found 18 new malignancies in the 467 patients who had received autologous HSCT (8.9% at 5 years; P = 0.039 in comparison with non-transplanted patients).[53] Another study found seven solid tumors in 750 autotransplant recipients for an incidence of 5.6% at 13 years (15). In a third analysis among 625 autologous transplant recipients who survived at least 3 years after HSCT, 14 developed second neoplasms at 4–116 months; 10 of these had been given TBI (unpublished). The types of tumors observed were similar to those seen with allogeneic transplants. As with MDS/AML, the incidence was particularly increased in patients more than 35 years of age and in recipients of peripheral blood (rather than marrow) HSC.

Pathogenesis of Solid Tumors Post-Transplant

Interactions of various factors (Table 1) contribute to the development of secondary solid tumors. Socié et al (60). identified human papilloma viruses (HPV) 13, 15 or 16 in three of eight squamous cell carcinomas; HHV8 was present in one. The pattern of p53 expression suggested mutations of this gene in all eight tumors studied. Mutations might be induced by cytotoxic therapy, and suppressed immunity would interfere with normal surveillance. Chronic inflammation and impaired DNA repair are other factors. Observations in autologous patients will be of great interest because etiologic factors, such as chronic alloantigenic stimulation and GvHD, are absent, thus allowing one to focus on cytotoxic therapy and genetic pre-disposition (xenobiotic polymorphism). Clearly, more work is needed for a better understanding of those questions.

Prophylaxis and Therapy

Omission of (high-dose) irradiation from the conditioning regimen should be beneficial, in particular for the prevention of melanomas, thyroid carcinomas, carcinomas of the buccal cavity, and breast cancer. Prevention (or different therapy) of chronic GvHD should have an effect on the development of buccal carcinomas.

Surgical resection, whenever possible, is the front-line therapy for solid tumors. Selective immunostimulation and measures aimed at scavenging free radicals have yielded some promising results in experimental studies.

Conclusions

Currently more than 100,000 survivors of HSCT are living in the United States alone, and many more around the globe. Most patients who do not relapse within a year or two of transplantation do well, and lead productive lives. However, some develop complications, including new malignancies. While the overall incidence is low, longer observation is required before the full extent of the risk of second cancers and new solid tumors in particular can be assessed. The underlying diagnosis of immunodeficiency or other genetic defects, high-dose irradiation for conditioning, T-cell depletion of the marrow, HLA nonidentity of the donor, and chronic GvHD have been identified as primary risk factors. The role of environmental factors, e.g., smoking before or after HSCT, needs to be examined further. An understanding of the mechanism involved in PTLD has emerged, but insights into the development of hemopoietic disorders and solid tumors are more limited.

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