Second Malignancies after Allogeneic Hematopoietic Cell Transplantation

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ABSTRACT

Allogeneic hematopoietic cell transplantation (allo-HCT) may prolong life and cure patients suffering from otherwise fatal diseases. However, the growing population of long-term survivors has led to the realization of multiple long-term complications, including the risk of second malignancies. Compared to the autologous setting, allo-HCT carries a much higher risk of posttransplant lymphoproliferative disorder (PTLD), which usually occurs within the first year after allo-HCT and is strongly associated with the Epstein-Barr virus (EBV). Treatment-related myelodysplastic syndromes (tMDS) and second leukemias are extremely rare. Both autologous and allo-HCT carry increased risks for second solid malignancies (SSM). The cumulative incidence of SSM continues to increase in each of the largest studies with as much as 20 years of follow-up, likely related to the long latency of radiation-related SSM. Systematic, prospective monitoring, vigilant screening processes, and well-maintained survivorship clinics and databases are absolute necessities, and should be included in the infrastructure of individual transplant centers and networks, with mandatory periodic reporting of second malignancy incidences. Primary care and transplant physicians alike must be aware of the risk of second malignancies after allo-HCT. Most importantly, guidelines should be developed in regard to screening and prevention of second malignancies, so that physicians can provide state-of-the-art counsel and care for the benefit of our patients.

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KEY WORDS

Allogeneic • Transplant • Second malignancy • PTLD

INTRODUCTION

There are almost 10 million cancer survivors in the United States, representing 3.5% of the population. This number has tripled since 1971, and is growing at approximately 2% per year [1,2]. For many hematologic diseases the treatment with greatest potential for cure includes an allogeneic (matched sibling or unrelated donor-derived) hematopoietic cell transplant (allo-HCT). The National Marrow Donor Program (NMDP) has facilitated unrelated HCT in 25,000 patients since 1987, and currently averages more than 220 per month [3]. The improvement in cancer survival comes with the realization of many potential long-term effects and complications of treatment. One of the most devastating long-term complications is the development of a second malignancy. Second or higher order cancers accounted for 16% of cancer diagnoses in 2003, an incidence that has doubled over the last 20 years [4,5]. Second malignancies are well described after treatment and exposure to radiation [6-9], certain chemotherapy agents [10-12], and in a variety of disease settings including treatment for Hodgkin disease [13,14]. Children particularly may be at increased risk secondary to their long life expectancy and potentially increased sensitivity of proliferating tissue to carcinogens [13-21]. With the growing number of patients treated for hematologic diseases surviving long term and possibly being cured, the risk of developing second malignancies after allo-HCT has been increasingly recognized over the past 2 decades [22-44]. The largest studies of second malignancies after allo-HCT are listed in Table 1. There are multiple factors possibly involved in second malignancy in the allo-HCT setting, including cytotoxic che-
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>No. pts</th>
<th>Median Time to Malig (Years)</th>
<th>Median Age (Years) at Trans</th>
<th>Median f/u (Years)</th>
<th>Relative Risk</th>
<th>Cumulative Incidence of New Second Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallagher, 2007 (multi-institution, British Columbia)</td>
<td>Second solid malignancies after allogeneic transplant 1985-2003</td>
<td>926</td>
<td>6.8</td>
<td>39</td>
<td>1.8</td>
<td>1.85*</td>
<td>2.3% at 10 years*</td>
</tr>
<tr>
<td>Baker, 2003 (single institution, U Minnesota)</td>
<td>Second malignancies after autologous and allogeneic transplant 1974-2001</td>
<td>3372 (2179 allo)</td>
<td>NR</td>
<td>24</td>
<td>5</td>
<td>8.1* (auto and allo)</td>
<td>6.9% at 20 years*</td>
</tr>
<tr>
<td>Bhatia 2001 (single institution, City of Hope)</td>
<td>Second solid malignancies after autologous and allogeneic transplant 1976-1998</td>
<td>2129 (1370 allo)</td>
<td>NR</td>
<td>33.9</td>
<td>3.3 (3.6 &gt; 1 year survival)</td>
<td>2.1* (auto and allo)</td>
<td>6.4% at 10 years for allogeneic subset</td>
</tr>
<tr>
<td>Socie, 2000 (multi-institution, international bone marrow transplant registry/U Wash)</td>
<td>Second malignancies after allogeneic transplant for childhood acute leukemia (&lt; age 17) 1964-1992</td>
<td>3,182</td>
<td>6</td>
<td>8.2</td>
<td>0.9 (3.6 &gt; 1 year survival)</td>
<td>45.1*</td>
<td>11% at 15 years (solid tumors) 1% at 5 years (PTLD)</td>
</tr>
<tr>
<td>Kolb, 1999 (multi-institution, Late Effects Working Party-Europe)</td>
<td>Second malignancies in long-term survivors (&gt; 5 years) after allogeneic and autologous transplant before 1986</td>
<td>1036 (982 evaluable) (903 allo)</td>
<td>NR</td>
<td>21</td>
<td>10.7 years</td>
<td>3.8</td>
<td>12.8% at 15 years</td>
</tr>
<tr>
<td>Curtis, 1999 (multi-institution, international bone marrow transplant registry/U Wash)</td>
<td>PTLD after allogeneic bone marrow transplantation 1964-1992</td>
<td>18,014</td>
<td>NR</td>
<td>25</td>
<td>NR</td>
<td>51.5</td>
<td>1% at 10 years</td>
</tr>
<tr>
<td>Curtis, 1997 (multi-institution, international bone marrow transplant registry/U Wash)</td>
<td>Second solid malignancies after allogeneic and syngeneic transplant 1964-1992</td>
<td>19,229 (18,696 allo)</td>
<td>NR</td>
<td>25.5</td>
<td>3.5 years</td>
<td>2.7* 8.3 for &gt; 10 year survivors</td>
<td>6.7% at 15 years*</td>
</tr>
<tr>
<td>Witherspoon, 1989 (single institution, U Wash)</td>
<td>Second malignancies after allogeneic and autologous transplant for leukemia or aplastic anemia 1970-1987</td>
<td>2246 (1993 allo)</td>
<td>1.0</td>
<td>NR</td>
<td>NR</td>
<td>6.69* (auto and allo)</td>
<td>1.6% at 18 years*</td>
</tr>
</tbody>
</table>

ALLO indicates allogeneic; AUTO, autologous; PTLD, posttransplant lymphoproliferative disorder.

* Excluding nonmelanoma skin cancer as not recorded in SEER database.
motherapy, radiation, immunosuppressive therapy, immune stimulation, immune suppression from graft-versus-host disease (GVHD), antigenic stimulation, oncogenic virus activity, and genetic predisposition [30]. We will describe these second malignancies after allo-HCT by dividing them into posttransplant lymphoproliferative disorders (PTLD), hematologic malignancies, and second solid malignancies (SSM).

Posttransplant Lymphoproliferative Disorders

Posttransplant lymphoid neoplasms were first recognized in 1969 in the setting of solid organ transplantation [45,46]. PTLD is relatively common in organ transplantation with an incidence of 1%-20%, depending on the type of allograft [47]. Initially it was felt that PTLD was universally malignant, but it is now recognized that PTLD is a diverse group of disorders ranging from benign self-limited polyclonal hyperplasias to clonal malignancies [48-52]. Historically, PTLD has been attributed to uncontrolled proliferation of the Epstein-Barr virus (EBV) transformed B-lymphocytes; however, EBV negative PTLD has also been recognized [53]. PTLD also occurs after hematopoietic cell transplantation (HCT), although the entity is observed almost entirely following allo-HCT [25,27,29,42]. PTLD has been reported after umbilical cord [54-56] and nonmyeloablative allo-HCT [56,57].

Classification

Before PTLD was defined, posttransplant lymphoid neoplasms were classified as immunoblastic sarcomas. Frizzera et al. [58] in 1987 appreciated certain polymorphic morphologic changes in renal transplant patients and introduced a classification distinguishing nonspecific hyperplasia, polymorphic hyperplasia, and polymorphic lymphoma from immunoblastic sarcoma. In 1988, Nalesnik et al. [59] combined the previous descriptions under the heading of polymorphic PTLD [59]. Monomorphic PTLD was also introduced, and was felt to be indistinguishable from non-Hodgkin lymphomas (NHL). However, morphology alone does not provide reliable prognostic information. Knowles et al. [60] used morphology in combination with molecular genetic analysis in order to evaluate clonality. PTLD was then reclassified into polyclonal plasmacytic hyperplasia, monoclonal polymorphic B-cell hyperplasia or lymphoma, and monoclonal pleomorphic immunoblastic lymphoma or multiple myeloma.

In 1995, the City of Hope National Medical Center in Duarte, CA, hosted the Society for Hematopathology workshop on immunodeficiency-related lymphoproliferative disorders. Eighty-two cases from different settings; including posttransplant immunosuppression, other iatrogenic immunosuppression, congenital immunodeficiencies, and the acquired immune deficiency syndrome, were reviewed. This led to discussions that culminated in the 1997 Society for Hematopathology classification including (1) early lesions, (2) polymorphic PTLD, (3) PTLD-monomorphic, (4) plasmacytoma-like lesions, and (5) T cell-rich large B cell lymphoma/Hodgkin disease like lesions [61]. This was the first classification system that appreciated the clinical differences between early and late PTLD.

In 2001, the World Health Organization (WHO) published a revised PTLD classification, which is most commonly used today. This includes (1) early lesions such as reactive lymphoplasmacytic hyperplasia and infectious mononucleosis like lesions, (2) polymorphic PTLD, (3) monomorphic PTLD, and (4) Hodgkin lymphoma (HL) and Hodgkin lymphoma-like PTLD (Table 2) [62].

Epidemiology

The incidence of PTLD in allogeneic bone marrow transplantation has been reported as between 0.5% and 1.8%, with the majority occurring within the first year after transplantation [25,27,29,32,42,63]. PTLD may be asymptomatic, and diagnosed only at autopsy [25]. EBV is more prevalent in early PTLD, and is found in >90% of B cell PTLD within the first year after transplantation. The proportion of EBV negative disease increases in late (>1 year) PTLD and encompasses 21% to 32% of cases overall [64].
The largest retrospective review to date of PTLD after allo-HCT included 18,014 patients from 234 centers reporting to the International Bone Marrow Transplant Registry (IBMTR) and the Fred Hutchinson Cancer Research Center between 1964 and 1992 [29]. The cumulative incidence of PTLD was 1% at 10 years. Fifty-eight percent of PTLD occurred within 1-5 months, and 82% occurred before 1 year.

Etiology

Primary EBV infection after transplantation is the greatest risk factor in solid-organ PTLD, with a 10- to 76-fold increased risk of PTLD [47,64-67]. EBV, the etiologic agent of infectious mononucleosis, is a member of the human herpes virus family [64,68]. In immuno compromised hosts it is transmitted via body fluids such as saliva. More than 90% of the population has immunity to EBV by the age of 40, and it usually establishes life-long viral latency after primary infection. The immunocompromised host has several mechanisms to control EBV proliferation after primary infection including cytotoxic T cell response, and to a lesser extent humoral immune response, natural killer activity, and cytotoxic regulation [63,69-73]. The transmission of EBV in the transplant population occurs mainly from blood products, but the transmission rate is unknown. Although the pathophysiology is still unclear, B cell PTLD is thought to be related to factors that stimulate B cell proliferation and depress EBV-specific control mechanisms [74].

Risk Factors

In addition to EBV infection, a number of other risk factors have been identified (Table 3) [25,27,29,32,42]. Common risk factors include HLA disparity (relative risk [RR] 3.8-9.0), T cell depletion of the graft (RR 4.0-12.7), use of antithymocyte globulin (ATG) in the preparative regimen or GVHD prophylaxis (RR 3.1-6.4), and GVHD (RR 1.9-6.5). Use of anti-CD3 monoclonal antibody (mAb) was associated significantly with PTDL in 2 studies [29,42]. In regard to T cell depletion of the graft, Curtis et al. [29] found that the methods applied for T cell depletion were relevant: specifically, sheep red blood cell E-rosetting techniques (RR 15.6) and mAb-based depletion of T cells (RR 12.3) were associated with an increased risk of early onset PTLD. As for development of late onset PTLD (>1 year), Curtis et al. [29] only identified chronic GVHD (cGVHD) as a significant risk factor.

Prevention

Perhaps the best management of PTLD is prevention by addressing the known risk factors. Although GVHD may be better controlled with T cell depletion of donor grafts, ATG, and the use of anti-CD-3 antibodies, the increased risk of PTLD must also be recognized. The risk factor for PTLD well-described in the solid transplant literature is development of new EBV infection in seronegative patients, and is largely from blood transfusions [64-67]. Hence, testing for EBV immunity status should be considered in allo-HCT candidates. In one study, leukoreduction of packed red blood cells rendered 13 of 14 EBV-positive units negative by PCR [75]. There are no studies to date on whether this type of intervention translates to clinical benefit. CMV immunity is routinely tested as part of standard practice before allo-HCT, and CMV infection has also been implicated as a cofactor in solid organ PTLD.

Rituximab appears to be active in treatment of EBV reactivation after allo-HCT, and therefore, in the prevention of PTLD. A prospective study from The Netherlands in 2002 monitored 49 matched sibling or matched unrelated donor T cell-depleted allo-HCT patients [76]. EBV quantitative real-time PCR was measured weekly. Preemptive therapy with a single dose of rituximab was given in patients with more than 1000 copies/mL. Median time to preemptive therapy in 15 patients was 113 days (range: 41-202 days) after allo-HCT. Fourteen patients had a complete response by quantitative EBV PCR. One patient progressed to PTLD but obtained a complete response with 2 doses of therapeutic rituximab and donor lymphocyte infusion. Notably, Weinstock et al. [77] published a comprehensive review of the preemptive diagnosis and treatment of EBV-associated PTLD in 2006.

At the City of Hope, we monitor for EBV reactivation in “high risk” patients such as those treated with thymoglobulin. EBV quantitative PCR is evaluated weekly starting at 21 days after allo-HCT. A single dose of rituximab is given for EBV levels >1000 copies/mL. Response is measured by quantitative PCR for at least 6 weeks after the infusion. If the level remains >1000 copies/mL thereafter, 3 additional doses of rituximab are given for a total course of 4 doses. EBV titers >1000 copies/mL at 6 weeks are monitored weekly until the titer returns to baseline. T cell-depleted and mismatched donor grafts are not commonly used, but both have been identified as also high-risk factors for PTLD after allo-HCT (Table 3).

The use of anti-EBV agents, such as acyclovir or ganciclovir, is also of interest. Ganciclovir has the greatest activity against EBV in vitro, but increased myelosuppression may be of concern [78]. Several single institutional reports suggest some efficacy in prevention of PTLD [79-81]; however, contradictory reports exist [82,83]. A recent multicenter case-control study of ganciclovir or acyclovir in renal transplant patients demonstrated an 83% reduction in the risk of PTLD with the former showing better efficacy [84]. Finally, early studies of infusion of EBV-cytotoxic T cells have also shown efficacy in decreasing
Table 3. Studies of PTLD after Allogeneic HCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Number of Patients</th>
<th>Median Time to PTLD (Years)</th>
<th>Cumulative Incidence of New PTLD</th>
<th>Relative Risk</th>
<th>Significant Risk Factors (Excluding Primary Immunodeficiency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker, 2003 (single institution, U Minnesota)</td>
<td>Second malignancies after autologous and allogeneic transplant 1974-2001</td>
<td>3372 (2179 allo)</td>
<td>0.3 (auto and allo)</td>
<td>1.4% at 20 years (71% of pts &lt; 1 year) All but 1 in allo BMT</td>
<td>54.3</td>
<td>-Mismatched related donor (RR 9.0) -T cell depletion (RR 4.0) -Use of ATG for aGVHD (RR 3.7) -Grade 3-4 aGVHD (RR 2.4)</td>
</tr>
<tr>
<td>Socie, 2000 (multi-institution, international bone marrow transplant registry/U Wash)</td>
<td>Second malignancies after allogeneic transplant for childhood acute leukemia (&lt; age 17) 1964-1992</td>
<td>3182 allo</td>
<td>Unknown (1.5 years in text; however, 75% of pts &lt; 1 year in table)</td>
<td>0.6% at 15 years (75% of pts &lt; 1 year)</td>
<td>182</td>
<td>-Unrelated or mismatched related donor (RR 7.5) -Mod-severe GVHD (RR 6.5) -T cell depletion of graft (RR 4.8) -Use of ATG for aGVHD (RR 3.1)</td>
</tr>
<tr>
<td>Curtis, 1999 (multi-institution, international bone marrow transplant registry/U Wash)</td>
<td>PTLD after allogeneic bone marrow transplantation 1964-1992</td>
<td>18,014 allo</td>
<td>0.2-0.3</td>
<td>1% at 10 years (82% of pts &lt; 1 year)</td>
<td>51.5</td>
<td>Early Onset PTLD (&lt; 1 year) -Use of anti-CD3 mAb for aGVHD (RR 43.2) -T cell depletion of graft (RR 12.7) -Use of ATG for aGVHD (RR 6.4) -Unrelated or mismatched related donor (RR 4.1) -aGVHD grades II-IV (RR 1.9) -Late-onset PTLD (&gt; 1 year) -Extensive cGVHD (RR 4.8)</td>
</tr>
<tr>
<td>Witherspoon, 1989 (single institution, U Wash)</td>
<td>Second malignancies after allogeneic and autologous transplant for leukemia or aplastic anemia 1970-1987</td>
<td>2246 (1993 allo)</td>
<td>0.2</td>
<td>0.7% at 18 years (auto and allo) (75% of pts &lt; 1 year)</td>
<td>355</td>
<td>-Use of anti-CD3 mAb for aGVHD (RR 15.6) -T cell depletion of graft (RR 12.4) -Use of ATG for aGVHD (RR 4.9) -Mismatch donor (RR 3.8)</td>
</tr>
</tbody>
</table>

mAb, indicates monoclonal antibody; ALLO, allogeneic; ATG, antithymocyte globulin; AUTO, autologous; GVHD, graft-versus-host disease; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; HCT, hematopoietic cell transplantation; PTLD, posttransplant lymphoproliferative disorder; TBI, total-body irradiation; RR, relative risk; pts, patients.
viral loads, and may turn out to be useful in preventing and ameliorating EBV-related PTLD [85-87].

Treatment

There have been no randomized trials of treatment of PTLD. However, some recommendations may be made based on the WHO classification [62]. The clinical utility of the WHO classification system has been verified by at least 1 study [88]. Type I or early polyclonal lesions, which include reactive lymphoplasmacytic hyperplasia and infectious mononucleosis-like lesions, usually require no intervention and are self-limited, although reduction of immunosuppression may be considered. Type II polyclonal PTLD usually requires reduction of immunosuppression but has variable response. Type III monomorphic PTLD should be classified according to the WHO classification of lymphoma, and treatment includes reduction of immunosuppression and usually requires chemotherapy. Type IV HL and HL-like PTLD likewise require aggressive management, although there is some controversy in regard to classification of the latter. A recent retrospective report from Loma Linda University analyzed 5 cases of HL-like PTLD with respect to immunophenotype, EBV status, clonality, and clinical outcome [89]. Although HL-like PTLD was similar morphologically to classic HL PTLD, the immunophenotype, molecular genetics, and clinical course were more consistent with a monomorphic B-cell PTLD.

The anti-CD20 antibody rituximab has been shown to be effective in PTLD [90-95]. A multicenter phase II German study of 17 patients with solid-organ PTLD showed a 53% complete response rate using single agent rituximab with a mean duration of 17.8 months [93]. A retrospective study of solid-organ PTLD from the University of Pennsylvania found a 68% response rate in 22 patients treated with rituximab with a median duration not reached at 19 months [95]. In univariate analysis, EBV positivity predicted response. The authors concluded that PTLD patients requiring therapy beyond reduction of immunosuppression should be considered for rituximab, especially with EBV-positive disease, and chemotherapy should be reserved for those who fail rituximab, have EBV-negative tumors, or need a rapid response.

Infusion of EBV-cytotoxic T cells has also been studied in the treatment of PTLD [85,96,97]. In 1 study of patients with progressive PTLD unresponsive to conventional treatment, HLA-matched cytotoxic T cells were infused with a complete response in 3 of 8 patients, although responses were mainly in those with early, localized, and polyclonal disease [97]. Cytokine therapy has also been studied with a multicenter phase I-II trial of an anti-interleukin 6 monoclonal antibody showing a 41% response rate in early PTLD [98,99].

Treatment-Related Myelodysplastic Syndrome and Second Leukemia

There is significant controversy regarding risk factors for development of treatment-related myelodysplastic syndrome (tMDS) and second leukemias. tMDS and second leukemias in HCT occur almost entirely in the autologous setting where exposure to certain chemotherapeutics (alkylating agents, topoisomerase II inhibitors, and possibly anthracyclines) and total-body irradiation (TBI) appear to be the greatest risk factors [30,100-106].

tMDS and second leukemia are extremely rare after allo-HCT (Table 4) [25,27,28,42]. The low incidence supports the hypothesis that tMDS and second leukemia may be primarily related to pretransplant factors and not to HCT itself. The graft-versus-marrow effect of allo-HCT likely decreases the risk of recipient derived MDS/secondary leukemia [30]. Baker et al. [25] reported 4 cases of MDS/AML of 2179 allo-HCT patients during the period 1974 to 2001. The leukemic clones all originated in host cells but were morphologically and cytogenetically different from the initial malignancy. A large study from the Late Effects Working Party of Europe evaluating second malignancies in 903 allo-HCT patients observed more than 5 years from transplantation reported no incidence of second leukemia [28]. However, there was mention of 1 patient in the database who developed second leukemia before 5 years of follow-up, but details on cell origin were not provided. Witherspoon et al. [42], from the Fred Hutchinson Cancer Research Center, reported 6 second leukemias of 1993 allo-HCT for leukemia or aplastic anemia from 1970-1987, with 4 being of donor cell origin.

Given the rarity of second leukemia after allo-HCT, risk factors are likely to remain elusive. The reasons for developing leukemia from host derived cells may be similar to risk factors identified in autologous HCT where exposure to prior therapy may lead to chromosomal damage in progenitor cells that survive after transplantation. Many mechanisms have been proposed as possible causes of second leukemia in donor cells after allo-HCT. Antigenic stimulation through host tissue has shown to be able to transform donor cells in vivo [107-110]. An unknown factor in the marrow environment may lead to leukemic transformation (ie, an oncogenic virus) [107-112]. Preexisting genetic factors may certainly be important in related donor allo-HCT [113,114]. There is 1 case in the literature of allo-HCT donor-derived inadvertent transplantation of preexisting leukemia [115], and another case of liver transplant donor-derived acute myelocytic leukemia presumably from stem cells in the transplanted organ [116].
Second Solid Malignancies

Epidemiology. Unlike the short latency of PTLD, SSM have a long latency period of multiple years following allo-HCT. The largest studies report a 1.85- to 34-fold increased risk of SSM compared to the normal population with a median time from allo-HCT to diagnosis of 3.3 to 6.8 years (Table 5) [22,25-28,31,42]. Most of these studies exclude squamous and basal cell skin carcinomas, as they are not recorded in the SEER database. It is important to note that a plateau has not been reached in long-term follow-up, and the cumulative incidence continues to increase.

Curtis et al. [31] reported the largest study to date of SSM in 1997. A total of 19,229 patients underwent allogeneic (97.2%) and syngeneic (2.8%) HCT from 235 medical centers (IBMRT and Fred Hutchinson Cancer Research Center) between 1964 and 1992. The relative risk of SSM was 2.7, and increased to 8.3 for those who survived >10 years. The cumulative incidence of new solid malignancies also increased from 2.2% at 10 years to 6.7% at 15 years of follow-up. Significantly increased risks by tumor type were seen in bone (RR 13.4), oral cavity (RR 11.1), brain and central nervous system (RR 7.6), hepatocellular (RR 7.5), thyroid (RR 6.6), melanoma (RR 5.0), and connective tissue (RR 8.0) malignancies.

Risk factors. Several risk factors have been identified that may contribute to the development of SSM after allo-HCT. These include radiation and chemotherapy used in primary treatment and conditioning for allo-HCT, immunodeficiency from incomplete recovery after allo-HCT, and immune stimulation and suppression from GVHD [30]. Specific risk factors identified from the largest studies of second malignancies after allo-HCT are discussed later.

Radiation. Radiation may account for some if not most of the long latency seen in SSM after allo-HCT. These include radiation and chemotherapy used in primary treatment and conditioning for allo-HCT, immunodeficiency from incomplete recovery after allo-HCT, and immune stimulation and suppression from GVHD [30]. Specific risk factors identified from the largest studies of second malignancies after allo-HCT are discussed later.

Table 4. Studies of Second MDS/Leukemia after Allogeneic HCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Number of Patients</th>
<th>Incidence in Allogeneic HCT</th>
<th>Median Time to MDS/Leukemia (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker, 2003 (single institution, U Minnesota)</td>
<td>Second malignancies after autologous and allogeneic HCT at 1974-2001</td>
<td>3772 (2179 allo)</td>
<td>0 patients MDS/AML (all host)</td>
<td>2.1 (auto and allo)</td>
</tr>
<tr>
<td>Socie, 2000 (multi-institutional bone marrow transplant register/U Wash)</td>
<td>Second malignancies after allogeneic transplant in children &lt;5 years of age</td>
<td>3,312 allo</td>
<td>0 in database prior to 5-year follow-up (1,102 allo)</td>
<td>NA</td>
</tr>
<tr>
<td>Kolb, 1999 (multi-institutional Late Effects Working Party-Europe)</td>
<td>Second malignancies in long-term survivors after allogeneic transplant before 1986 (all host)</td>
<td>982 evaluable (903 allo)</td>
<td>0 (1 in database prior to 5-year follow-up but cell origin unknown)</td>
<td>0.6</td>
</tr>
<tr>
<td>Witherspoon, 1989 (single institution, U Wash)</td>
<td>Second malignancies after autologous transplant for acute myeloid leukemia</td>
<td>2246 (1993 allo)</td>
<td>6 leukemias (4 ALL, 1 ANLL, 1 granulocytic sarcoma, 1 donor/2 host)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

ALLO indicates allogeneic; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; ANLL, acute nonlymphocytic leukemia; AUTO, autologous; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome.

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Second Solid Malignancies after allo-HCT

Table 5. Studies of Second Malignancies after Allogeneic HCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
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Table 6. Studies of Second Malignancies after Allogeneic HCT

<table>
<thead>
<tr>
<th>Study</th>
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<th>Median Time to MDS/Leukemia (Years)</th>
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<tr>
<td>Baker, 2003 (single institution, U Minnesota)</td>
<td>Second malignancies after autologous and allogeneic HCT at 1974-2001</td>
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<td>Socie, 2000 (multi-institutional bone marrow transplant register/U Wash)</td>
<td>Second malignancies after allogeneic transplant in children &lt;5 years of age</td>
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<td>0 in database prior to 5-year follow-up (1,102 allo)</td>
<td>NA</td>
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<td>Second malignancies in long-term survivors after allogeneic transplant before 1986 (all host)</td>
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<td>Witherspoon, 1989 (single institution, U Wash)</td>
<td>Second malignancies after autologous transplant for acute myeloid leukemia</td>
<td>2246 (1993 allo)</td>
<td>6 leukemias (4 ALL, 1 ANLL, 1 granulocytic sarcoma, 1 donor/2 host)</td>
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ALLO indicates allogeneic; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; ANLL, acute nonlymphocytic leukemia; AUTO, autologous; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome.

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<th>Number of Patients</th>
<th>Median Time to Solid Malignancy (Years)</th>
<th>Cumulative Incidence of New Second Solid Malignancy</th>
<th>Relative Risk</th>
<th>Significant Risk Factors</th>
</tr>
</thead>
</table>
| Gallagher, 2007 (multi-institution, British Columbia) | Second solid malignancies after allogeneic transplant 1985-2003 | 926 | 6.8 | 2.3% at 10 years* | 1.85* | -Recipient age at BMT >40 (P = .005)  
-Woman donor (P = .0008)  
-age >20 years at time of BMT (RR 2.0); however, age <10 RR 33.3 |
| Baker, 2003 (single institution, U Minnesota) | Second malignancies after autologous and allogeneic transplant 1974-2001 | 3372 (2179 allo) | 4.2 (auto and allo) | 0.4% at 1 year*  
1.2 at 5 years*  
2.2 at 10 years*  
3.8% 20 years* (auto and allo) | 8.1* (auto and allo)  
Oral 10.2  
Brain 9.5  
Melanoma 8.3  
Lung 2.1  
Breast 1.5  
Colon 1.8  
Liver 1.0  
Oral cavity 1.0  
Cervical 1.0 | -Age < 34 years at time of BMT (RR 5.3) |
| Bhatia, 2001 (single institution, City of Hope) | Second solid malignancies after autologous and allogeneic transplant 1976-1998 | 2129 (1370 allo) | 3.3 Cervical  
7.6 Oral  
10.8 Liver (auto and allo) | 1.6% at 5 years*  
6.1% at 10 years*  
6.4% allo, 1.6% auto  
14.9% at 15 years* (auto and allo) | 2.1* (auto and allo)  
Liver 27.7  
Oral cavity 17.4  
Cervical 13.3 | |
| Socie, 2000 (multi-institution, international bone marrow transplant registry/U Wash) | Second malignancies after allogeneic transplant for childhood acute leukemia (<age 17) 1964-1992 | 3182 | 6 | 0.9% at 5 years*  
4.3% at 10 years*  
11% at 15 years* | 34*  
Tongue 27.65  
Sal. gland 519  
Thyroid 125  
Melanoma 65  
Brain/CNS 46  
Bone and Connective tissue 20 | -Recipient age <10 years at transplantation (RR 3.7)  
-High-dose TBI (RR 3.1)  
-(Chronic mod-severe GVHD lower risk RR 0.2) |
| Kolb, 1999 (multi-institution, Late Effects Working Party-Europe) | Second malignancies in long-term survivors (>5 years) after autologous and allogeneic transplant before 1986 | 982 evaluable (903 allo) | NR | 3.5% at 10 years  
11.5% at 15 years (auto and allo) | 3.8 (auto and allo)  
>10-fold for oral, esophagus, thyroid, skin ca(basal/sq cell),  
>5-fold for Hodgkin glioblastoma, uterus/cervix | -Older recipient age (RR 1.4)  
-Immunosuppressive therapy  
-Cyclosporine (RR 1.4)  
-Thalidomide (RR 3.4) |
| Curtis, 1997 (multi-institution, international bone marrow transplant registry/U Wash) | Second solid malignancies after allogeneic and syngeneic transplant 1964-1992 | 19,229 (18,696 allo) | NR | 2.2% at 10 years*  
6.7% at 15 years* | 2.7* (8.3 for survivors > 10 years)  
Bone 13.4  
Oral 11.1  
CNS 7.6  
Liver 7.5  
Thyroid 6.6  
Melanoma 5.0  
Connective tissue 8.0 | -High-dose TBI (RR 2.7-4.4)  
-Chronic GVHD (cGVHD) with oral and skin SCC (RR 6.0, 22.6)  
-Younger recipient age (age <10, RR 36.6) |
Second Malignancies after allo-HCT

Despite the well-described relationship between radiation and SSM, only 2 of the largest studies of SSM after allo-HCT, both from the IBMRT and Fred Hutchinson Cancer Research Center, describe a significant association [27,31]. Curtis et al. [31] found a highly significant dose related 2.7- to 4.4-fold higher risk with high-dose TBI. Socie et al. [27] reported a 3.1-fold risk with high-dose TBI. Notably, 6 of the 9 patients with second brain cancers and 3 of the 5 thyroid cancer patients had received cranial radiation for treatment or prophylaxis of acute leukemia before allo-HCT. Other studies of SSM have failed to show a significant association. Witherspoon et al. [42] reported a 3.9-fold increased risk of all second malignancies after TBI but this was not significant when assessing solid malignancies alone. A study from the University of Minnesota by Bhatia et al. [32] showed a 6-fold increased risk in patients treated with TBI which approached statistical significance \((P = .08)\); however, a more recent report with 6 more years of follow-up gave less conclusive results (RR 1.5, \(P = .27\)) [25]. There are multiple possible explanations for the negative findings. The large studies did report significantly increased risks of tumors previously attributed to radiation exposure such as head and neck, bone, brain, and thyroid cancers [22,25,26,28,32,42]. None of the studies quantify the amount of pretransplant exposure to radiation. Also, follow-up is still relatively short for most of these studies. Data from the atomic bomb survivor cohort and children treated for HD suggest that risk of second solid malignancy after radiation exposure remains elevated for multiple decades, and therefore many more radiogenic malignancies may emerge with longer follow-up [6,13,18-21].

**Age.** There is conflicting data regarding the relationship between age of the recipient at the time of allo-HCT and the risk of SSM. Some studies support that risk is increased in younger recipients [26,27,31]. The analysis from the City of Hope found a 5.3-fold increased risk in recipients less than age 34 at the time of allo-HCT [26]. Another analysis by Socie et al. [27] was limited only to children less than age 17, but reported the highest overall RR of SSM (RR 34). This included 3 tongue and 2 salivary gland cancers, which are extremely rare in children. Children ages 0-9 showed a 3.7-fold greater risk than those between the ages of 10 and 16. Curtis et al. [31] reported an RR of 36.6 for recipients less than age 10 at the time of allo-HCT.

The explanation for a possibly increased risk in young children, especially less than age 10, may be multifactorial. As discussed above, radiogenic tumors have a long latency, and therefore children may experience increased incidence of SSM simply because of

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**Table 5. (Continued)**

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<tr>
<th>Study</th>
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<th>Median Time to Solid Malignancy (Years)</th>
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<tr>
<td>Witherspoon, 1989 (single institution, U Wash) Second malignancies after autologous and allogeneic transplant for leukemia or aplastic anemia 1970-1987</td>
<td>NR</td>
<td>2246 (1993 allo) 4.7 (auto and allo)</td>
<td>4.7 (auto and allo)</td>
<td>NR</td>
<td>6.69*</td>
</tr>
<tr>
<td>GBM</td>
<td>Liver</td>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Excluding nonmelanoma skin cancer as not recorded in SEER database.

ALLO indicates allogeneic; ATG, antithymocyte globulin; AUTO, autologous; GBM, glioblastoma multiforme; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; SCC, squamous cell carcinoma; TBI, total-body irradiation; RR, relative risk.
longer life expectancy and follow-up. The literature on second breast malignancy after treatment for childhood HD also suggests that radiation may have increased carcinogenic potential on proliferating tissue in young patients [13,18-21].

Conversely, other studies suggest that older age at allo-HCT increases the risk of SSM [22,25,28]. Gallagher reported that age >40 was a significant risk factor; however, only 2% of the patients in the study cohort were <18 years old [22]. Baker et al. [23] found an increased risk in those more than age 20 years (RR 2.0), although subgroup analysis suggested the highest risk was actually among recipients <10 years old (RR 33). The second malignancies included rare pediatric tumors such as melanoma, renal cell, breast, and parotid cancer. Kolb et al. [28] observed a slightly increased risk with older age on a continuum at allo-HCT (RR 1.4). The authors concluded that the risk for GVHD increased with age, and may increase second tumor risk.

GVHD/Immunosuppressants. None of the large studies of SSM after allo-HCT report an overall association with GVHD. In fact, Socie et al. [27], in 2000, observed an unexpected decrease in risk with GVHD. Notably, most of these studies excluded nonmelanoma skin cancer in the multivariate analysis as these are not reported in the SEER database. The IBMTR and investigators from the Fred Hutchinson Cancer Research Center did find a 6-fold higher risk when evaluating separately for onset of oral and skin SCC [31]. The report by Bhatia et al. [26] from our institution found that all 6 patients with nonmelanoma skin cancer had developed GVHD. Many of the studies also found an association between use of immunosuppressants for GVHD and risk of second solid tumors. Witherspoon et al. [42] observed a 4.3-fold risk with the use of ATG in acute GVHD (aGVHD). The report from the Late Effects Working Party of Europe showed a 1.4-fold risk for cyclosporine [28]. Overall, it appears that immunosuppression rather than GVHD directly, except in nonmelanoma skin cancers as discussed below, increase the risk of SSM after allo-HCT.

Viruses. Viruses may play a small role in some SSM. Three of the large studies found a 7.5- to 125-fold increased risk of hepatocellular carcinoma (HCC) after allo-HCT, although this translates to only 6 patients of more than 22,000 allo-HCT recipients [26,31,42]. Both patients from our institution had a history of chronic hepatitis C, but viral status was not reported in the other studies. EBV has been implicated in a case report of an early second gastric carcinoma [117]. Human papillomavirus (HPV) may also play a role in SCC of the skin and mucous membranes [118]. Four patients in the cohort from City of Hope had cervical cancer attributed to HPV infection (RR 13.3) [26].

Nonmelanoma skin cancer. Many of the studies of second malignancies after allo-HCT exclude risk analysis for nonmelanoma SCC and basal cell carcinoma (BCC) skin cancer, as they are not reported in the SEER database. A recent report on second SCC and BCC of the skin and mucous membranes from the Fred Hutchinson Cancer Research Center and affili-ates contained follow-up on 4810 patients who underwent allo-HCT between 1969 and 2003 and survived at least 100 days [23]. Two hundred thirty-seven patients developed at least 1 cancer (158 BCC, median 7.9 years from allo-HCT; 95 SCC, median 6.3 years from allo-HCT). Twenty-year cumulative incidence was 6.5% for BSC for and 3.4% for SCC. The risk for BCC was significantly increased with TBI (P = .003), and was strongest for recipients <18 years old at allo-HCT (P = .02). The risk of SCC was significantly increased with aGVHD grades II-IV (P = .02) and cGVHD (P < .001), whereas the risk of BCC was increased with cGVHD (no mention of grade, P = .01).

CONCLUSIONS

HCT may prolong life and cure many patients suffering from otherwise fatal diseases. Most of the transplant literature concentrates on reporting short-term complications such as infection and GVHD. However, the growing population of long-term survivors has led to our realization of multiple long-term complications including the risk of second malignancies. There are multiple factors that may be involved in the development of second malignancies including cytotoxic chemotherapy, radiation, immunosuppressive therapy, immune stimulation and immune suppression from GVHD, antigenic stimulation, oncogenic virus activity, and genetic predisposition [30]. Compared to the autologous setting, allo-HCT carries a much higher risk of PTLD, but tMDS and second leukemias are extremely rare. Both autologous and allo-HCT carry increased risks for SSM.

PTLD after allo-HCT usually has a short latency period, with the majority of cases occurring within the first year, although EBV negative PTLD may increase in late-onset PTLD. PTLD encompasses a range of benign polyclonal hyperplasias to malignant monoclonal lymphomas, and standard treatment options include reduction of immunosuppression, cytotoxic chemotherapy, and use of rituximab. High-risk patients, such as those given thymoglobulin, should be monitored for EBV reactivation with EBV quantitative PCR. Rituximab appears to have efficacy in treating EBV reactivation and thereby preventing EBV-associated PTLD.

The latency period for solid malignancies is relatively long, usually being multiple years. Most notably, a plateau has not been reached in any of the
largest long-term studies. Data from the cohort of atomic bomb survivors suggests that such risk continues to be elevated >50 years from exposure [6]. As we obtain further follow-up, more solid tumors are likely to emerge. Hence, systematic, prospective follow-up, vigilant screening processes, and well-maintained survivorship clinics and databases are absolute necessities. Such entities should be included in the infrastructure of individual transplant centers and networks, with mandatory periodic reporting of second malignancy incidences. Primary care physicians may often have the most continuity years from allo-HCT, and must be aware of the continued risk of second malignancy. The highest risk cancers identified across the largest studies include cancers of the skin, oral cavity, thyroid, brain, and central nervous system, connective tissue, and bone. Hepatitis C patients and women affected with cervical HPV appear to be at particular risk for hepatocellular carcinoma and cervical carcinoma, respectively.

There are long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers based on type of cancers and exposures published by the Children’s Oncology Group [119]. The minimum follow-up guidelines for all allo-HCT recipients should include yearly history and comprehensive physicals. Special attention should be made to the organ systems at highest risk for second malignancy including the skin and oral cavity, thyroid, lymphatic, neurologic, musculoskeletal, and gynecologic. Breast and colon cancer risk may also be slightly increased and therefore current screening guidelines for the general population should be strictly followed. Further research is required to establish whether the screening age guidelines for colonoscopy and mammography after allo-HCT should be lowered.

Continued research is required to attempt to quantify risk based not only on transplant factors but pretransplant exposures as well. Primary care and transplant physicians alike must be aware of the risk of second malignancies after HCT. Guidelines for all HCT recipients in regard to screening and prevention of second malignancies based on available evidence and expert opinion should be developed, so physicians can provide state of the art counsel and care for the benefit of our patients.

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