

Malignant Neoplasms Following Bone Marrow Transplantation

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We undertook an analysis of 2,150 recipients of bone marrow transplant (BMT) at the University of Minnesota to determine the incidence of post-BMT malignant neoplasms (MNs). Fifty-one patients developed 53 MNs, compared with 4.3 expected from general population rates (standardized incidence ratio [SIR], 11.6, 95% confidence interval [CI], 8.2-14.5). These included 22 occurrences of B-cell lymphoproliferative disorder (BLPD), 17 solid nonhematopoietic tumors, 10 myelodysplastic syndromes (MDS), 1 acute myelogenous leukemia (AML), 2 non-Hodgkin's lymphoma (NHL), and 1 Hodgkin's disease (HD). The estimated actuarial incidence of any post-BMT malignancy was $9.9\% \pm 2.3\%$ at 13 years posttransplant. The cumulative probability of BLPD plateaued at $1.6\% \pm 0.3\%$ by 4 years from transplant and factors independently associated with increased risk included in vitro T-cell depletion of marrow (relative risk (RR) = 11.9, P

$< .001$), HLA mismatch (RR = 8.9, $P < .001$), use of antithymocyte globulin (ATG) for graft versus host disease (GVHD) prophylaxis (RR = 5.9, $P < .001$) or in the preparative regimen (RR = 3.1, $P = .03$) and primary immunodeficiency (RR = 2.5, $P = .06$). The cumulative probability of developing solid malignancy was $5.6\% \pm 2.2\%$ at 13 years from BMT. Malignant melanomas were the most common (SIR, 10.3, 95% CI 1.9 to 25.4). The actuarial incidence of MDS/AML plateaued at $2.1\% \pm 0.8\%$ at 9 years and was seen most often in older patients receiving autologous peripheral blood stem cells for HD or NHL. These data document that BMT recipients are at an increased risk of later malignancy, which may add significant morbidity and mortality to the transplant process. Methods for screening and identification of individuals at increased risk need to be addressed in future studies.

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BONE MARROW transplantation (BMT) is now a widely accepted and frequently used therapeutic modality for hematologic malignancies, solid tumors, and certain nonmalignant disorders.¹⁻³ However, with the improvement in survival, post-BMT neoplasms are emerging as a serious complication in this group of survivors. Second neoplasms are a known complication of chemotherapy and irradiation used to treat Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL).^{4,5} In addition, malignancies have been associated with immunosuppression after solid organ transplants.⁶ A higher incidence of cancer has also been reported in dogs administered DLA-identical marrow after total body irradiation, as compared with control dogs or those who received only myelosuppressive chemotherapy.⁷ Previous studies have shown a low but significant risk of post-BMT neoplasm among recipients of BMT for leukemias and aplastic anemia.⁸⁻¹³

We undertook this analysis, to investigate the incidence of malignant neoplasms and to determine the specific host or treatment factors associated with this risk, in a large cohort of patients undergoing BMT for a variety of underlying disorders.

MATERIALS AND METHODS

Between January 1, 1974 and January 1, 1995, 2,150 patients underwent BMT at the University of Minnesota. Allogeneic BMTs using HLA-matched or partially matched family-member donors were performed in 1,063 patients, 337 patients received unrelated donor grafts matched for HLA-phenotype, and 750 patients received autologous marrow.

Conditioning regimens used in this patient population are listed in Table 1. Briefly, of 1,345 patients who received transplants for leukemia (451 patients with acute lymphocytic leukemia [ALL], 403 with acute myelogenous leukemia [AML], 419 with chronic myelogenous leukemia [CML] and 72 with myelodysplastic syndromes [MDS]), 1,021 (76%) received cyclophosphamide at 120 to 180 mg/kg body weight and 7.5 to 13.2 Gy total body irradiation (TBI) delivered in single or multiple fractions. The remaining 24% received TBI either in combination with cytarabine or cyclophosphamide and etoposide, or some other combination of chemotherapy, with or without TBI. Of the 150 patients with aplastic anemia, 103 (68.7%) received total lymphoid irradiation (TLI) in combination with cyclophosphamide, while 27 (18%) received TBI (13.2 Gy) in addition to cyclophosphamide. The remaining 20 patients received

cyclophosphamide alone (8%) or in combination with other chemotherapy agents (5.3%). Patients with lymphoma received either cyclophosphamide and TBI (NHL) or combinations of cyclophosphamide with etoposide and carmustine (NHL and HD). Conditioning regimens for neuroblastoma contained cyclophosphamide, TBI, and melphalan in various combinations. Patients with breast cancer received cyclophosphamide, etoposide, and carmustine.

Patients and donors were typed for HLA A and B using serologic techniques identifying all World Health Organization (WHO)-recognized specificities current at the time of transplant. Typing for DR was performed either by DNA techniques or serologically. Eleven hundred and thirty-six patients (81.1%) received marrow serologically matched at HLA A and B, and were DR subtype-identical. Two hundred and sixty-four patients (18.9%) received marrow that was mismatched (single DR subtype mismatch, single minor serologic HLA mismatch or major serologic mismatch).

Clinical data were abstracted from the patients' hospital charts and from the BMT Database. These data included recipient and donor sex, date of birth, date of diagnosis of the primary disease, date of transplant, type of transplant, presence or absence of HLA-mismatch, whether the marrow had been purged with monoclonal antibodies before infusion, conditioning regimen used, date of last visit, status of patient at time of last visit, nature of graft versus host disease prophylaxis including T-cell depletion, presence or absence of acute and/or chronic graft versus host disease (GVHD) and severity, and presence or absence of post-BMT malignancy. In addition, an active updating of patients who had not been seen within 18

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Table 1. Primary Diagnosis and Conditioning Regimens Used

Primary Diagnosis*	Conditioning Regimens								
	Cy/TBI	Cy/TLI	Cy	Bu/Cy	Bu/Cy/VP16	Cy/TBI/VP16	AraC/TBI	Cy/VP16/BCNU	Other
AA (n = 150)	27	103	12	—	—	—	—	—	8
Immunodeficiency (n = 92)	22	1	1	37	13	6	—	—	12
Metabolic disorders (n = 91)	13	—	—	—	72	—	—	—	6
ALL (n = 451)	307	—	—	—	—	48	77	—	19
AML (n = 403)	283	—	—	83	1	25	4	—	7
CML (n = 419)	378	—	—	3	—	11	3	—	24
MDS (n = 72)	53	—	—	3	—	9	7	—	—
NHL (n = 201)	152	—	—	—	—	2	—	9	38†
HD (n = 86)	—	—	—	—	—	2	—	84	—
NBL (n = 75)	—	—	—	—	—	2	—	8	65‡
Breast (n = 30)	—	—	17	—	—	—	—	2	11§
Σ = 2070	1235	104	30	126	86	105	91	103	190

VP16 denotes etoposide, NBL denotes neuroblastoma, Cy denotes cyclophosphamide, Bu denotes busulphan, AraC denotes cytarabine, BCNU denotes carmustine, and Melph denotes melphalan.

*Numbers do not add up to 2,150 as table does not include "miscellaneous diagnoses" (n = 80).

†BCNU containing regimens.

‡(Cy/TBI/Melph = 13; TBI/Melph/VM26 = 13; TBI/VP16/Melph = 25; TBI/VP16 = 7; Cy/VP16 = 5; VP16/Melph = 2).

§(Cy/BCNU = 8; Cy/VP16 = 3).

months was conducted in mid-1994 to determine current status and the presence or absence of any post-BMT malignancy. For patients who developed a post-BMT malignancy, the date of diagnosis, histology, and site of tumor were recorded. If the patient had died, date and cause of death were also recorded. Reports of pathologic findings of the post-BMT malignancies were reviewed.

To estimate the risk of post-BMT neoplasms, age- and sex-specific person-years of observation were compiled for the cohort. Cancer incidence rates (obtained from the SEER Registry)¹⁴ were used to calculate the expected number of cancer cases. Standardized incidence ratios were calculated by obtaining a ratio of the observed and the expected cases. The 95 percent confidence limits were estimated by a method described by Vandenbroucke.¹⁵ The absolute risk, defined as the excess number of cases of cancer per 10,000 patients per year, was also calculated. The time at risk for second neoplasms was computed from the date of BMT to the date of post-BMT malignancy, the date of last contact, date of death or January 1, 1995, whichever came first. Cumulative probabilities of developing post-BMT malignancy over time were calculated using actuarial methods.¹⁶ Cox regression techniques were used for calculating relative risk estimates. Variables included in the regression model included primary diagnosis, gender, age at transplant, an HLA mismatch between donor and recipient, conditioning regimens with and without TBI, individual chemotherapeutic agents used for conditioning, prophylaxis for acute GVHD with antithymocyte globulin (ATG), methotrexate, and/or cyclosporine, T-cell depletion of donor marrow, presence of acute and/or chronic GVHD. Age at transplant was taken both as a categorical variable (≤ 18 vs > 18) and as a continuous variable. GVHD was dichotomized combining grades I and II versus grades III and IV.

RESULTS

As of January 1995, 40% of the cohort of 2,150 patients who had undergone a BMT at the University of Minnesota were alive as of the time of last contact and had a median follow-up of 3.1 years (range 0.6 to 18.8 years). The median age at transplant for the entire cohort was 20 years (range 0.2 to 67 years) and the cohort had accrued 5,025 person-years of follow-up from BMT (Table 2).

A total of 51 patients developed 53 post-BMT malignan-

cies, including 22 EBV-related BLPD, 17 solid nonhematopoietic tumors, 11 MDS/AML, 2 NHL, and 1 HD.

Observed and expected post-BMT malignancies are shown in Table 3. There were significantly elevated relative risks for all cancers combined and for NHL (including 22 cases of BLPD and 2 cases of NHL), MDS/AML, malignant melanoma, and brain tumors. The absolute risk for all cancers was 87 cases/10,000 patients/yr.

The actuarial risks for all post-BMT malignancies are shown in Fig 1. The mean (\pm SE) cumulative incidence of any malignancy was $9.9\% \pm 2.3\%$ at 13 years. The actuarial risks for BLPD, MDS/AML, and solid tumors are shown in Fig 2. Solid tumors accounted for a large portion of this risk, with a sharp increase after 8 years, increasing to $5.6\% \pm 2.2\%$ at 13 years. In contrast, the risk of MDS/AML plateaued at $2.1\% \pm 0.8\%$ at 9 years post-BMT and BLPD plateaued at $1.6\% \pm 0.3\%$ at 4 years.

BLPD-Epstein-Barr Virus (EBV)-Related Lymphoma

Twenty-two patients developed BLPD (eight of these patients have been reported previously).¹¹ Histologic appearance was similar to EBV-induced polymorphic B-cell proliferation described following solid organ transplantation, or which occurs de novo in primary immunodeficiency. Clonality was determined by immunophenotyping and/or immunoglobulin gene rearrangement, and the presence of EBV was determined by in situ hybridization and/or Southern blot analysis. Primary diagnosis for these patients included CML (n = 9), primary immunodeficiency (n = 8), AML (n = 2), aplastic anemia (AA) (n = 1), metabolic disorders (n = 1), and HD (n = 1). No cases of BLPD developed in the group receiving autologous marrow transplants. The cumulative risk of BLPD was significantly higher ($P = .001$) in the group receiving unrelated donor transplants ($3.0\% \pm 1.3\%$ at 1 year), than in the group receiving allogeneic transplants from sibling donors ($1.8\% \pm 0.5\%$).

Univariate analysis revealed that patients transplanted for

Table 2. Characteristics of the Patient Population

	Total Cohort	Malignant Neoplasms (MNs)				
		MDS/AML	BLPD	Solid Tumors*	HD	NHL
No. of patients	2,150	11	22	15	1	2
Primary diagnosis						
Aplastic anemia	150 (7%)	0	1 (4%)	0	0	0
Leukemias	1,366 (64%)	1 (9%)	11 (50%)	12 (80%)	1 (100%)	1 (50%)
Lymphomas	287 (13%)	10 (91%)	1 (4%)	3 (20%)	0	1 (50%)
Immunodeficiency	92 (4%)	0	8 (36%)	0	0	0
Metabolic	91 (4%)	0	1 (4%)	0	0	0
Other	164 (8%)	0	0	0	0	0
Type of BMT						
Allogeneic	1,400 (65%)	1 (9%)	22 (100%)	8 (53%)	1 (100%)	1 (50%)
Related	75%	100%	73%	100%	100%	100%
Unrelated	25%	0	27%	0	0	0
Autologous	750 (35%)	10 (91%)	0	7 (47%)	0	1 (50%)
Gender						
Males	1,260 (59%)	7 (64%)	13 (59%)	11 (73%)	0	1 (50%)
Females	890 (41%)	4 (36%)	9 (41%)	4 (27%)	1 (100%)	1 (50%)
Age at BMT (yr)						
Range (median)	1-67 (20)	28-59 (36)	1-51 (9)	1-49 (18)	7	9-2 (21)
Years to MNs				‡		
Range (median)	—	0.3-9 (3)	0.1-3 (0.2)	0.2-13 (4)	4	6-8 (7)
Status						
Died	1,290 (60%)	8 (73%)	20 (91%)	6 (40%)	1 (100%)	1 (50%)

*The solid tumors do not include the two carcinoma in situ (cervix and vulva that developed as third neoplasms).

Table 3. Observed and Expected Rates of Second Malignancies in Entire Cohort, According to Site

Site	Observed Cases	Expected Cases	SIR* (95% CI)	Absolute Risk (per 10 ⁴ /yr)†
All cancers‡	48	4.3	11.6 (8.2-14.5)	87.2
MDS/AML	11	0.04	285.5 (136.5-461.5)	21.8
NHL	24	0.2	105.6 (76.8-172.8)	47.4
HD	1	0.1	7.2 (0.003-28)	1.7
Solid tumors§	12	3.7	3.2 (1.7-5.3)	16.6
Melanoma	3	0.3	10.3 (1.9-25.4)	5.4
Brain	2	0.2	11.8 (1.1-33.7)	3.7

* SIR denotes standardized incidence ratios (calculated by obtaining a ratio of the observed and the expected cases).

† Absolute risk was calculated by taking the difference between observed and expected number of cases, divided by person-years of observation and multiplied by 10,000.

‡ Excludes nonmelanoma skin cancers (n = 3), and carcinoma in situ (n = 2).

§ Excludes lymphatic and hematopoietic tumors. The solid tumors listed do not add up to the total number of solid tumors because only tumor types associated with significantly elevated risks are included.

a primary immune deficiency were significantly more likely to develop BLPD, when compared with those with a primary diagnosis other than immunodeficiency (relative risk [RR] = 15.5, *P* < .001). In addition, risk of BLPD was associated with receiving an HLA-mismatched transplant (RR = 13.7, *P* < .001), receiving T-cell depleted marrow (RR = 11.6, *P* < .001), ATG as preparative regimen (RR = 9.4, *P* < .001) or as GVHD prophylaxis (RR = 2.9, *P* = .009), and busulphan as preparative regimen (RR = 2.9, *P* = .02). The cumulative risk of developing BLPD in patients with primary immune deficiency, who underwent a T-cell depleted, HLA-mismatched transplant, was 64.8% ± 17.7% at 4 years, com-

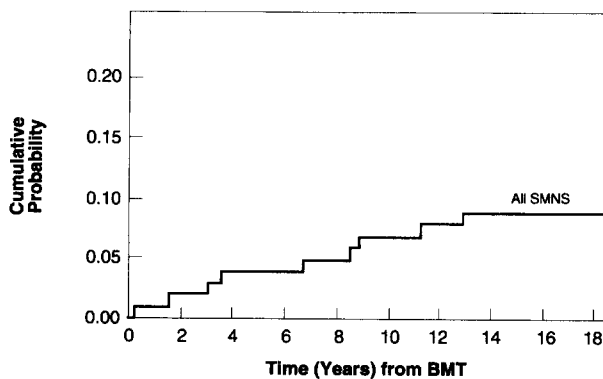


Fig 1. Cumulative probability of second malignant neoplasms in 2,150 patients undergoing bone marrow transplantation.

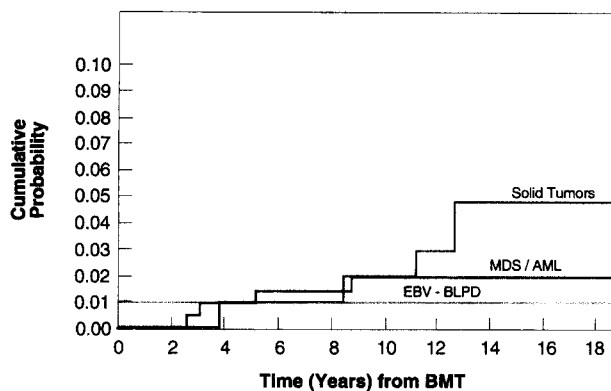


Fig 2. Cumulative probability of EBV-induced B-cell lymphoproliferative disease (BLPD), MDS, and solid tumors in 2,150 patients undergoing bone marrow transplantation.

pared with patients with primary diagnoses other than immune deficiency, who had an HLA-matched transplant, with no in vitro manipulation of the marrow ($0.9\% \pm 0.2\%$, $P < .001$). An increasing risk of BLPD was also observed with increasing severity of acute GVHD, with the relative risk rising from 1 for patients with no GVHD (reference group) to 9.4 for patients with grade IV GVHD ($P < .001$). Standardized incidence ratios obtained for these risk factors revealed significantly increased risk as compared with the general population (Table 4).

Multivariate analysis revealed in vitro T-cell depletion of the marrow before transplant ($RR = 11.9$, $P < .001$), HLA-mismatched transplants ($RR = 8.9$, $P < .001$), ATG used as GVHD prophylaxis ($RR = 5.9$, $P < .001$) or in the preparative regimen ($RR = 3.1$, $P = .03$) and immune deficiency as primary diagnosis ($RR = 2.5$, $P = .06$) to be independently associated with an increased risk of developing BLPD.

Of these 22 patients, 20 have died. Nineteen died because of BLPD and one died because of aspergillosis. The diagnosis of BLPD was made postmortem in 11 patients. In the 9 patients diagnosed pre-mortem, the median actuarial survival was 7 days, range 0 to 2.6 years. The two surviving patients were alive with no BLPD at 1 and 7 years from the diagnosis of BLPD.

Myelodysplastic Syndromes/Acute Myeloid Leukemia

Ten patients developed MDS and one patient was diagnosed with AML. Nine of these 11 patients have been the subject of a previous report.¹⁷ Primary diagnosis for this group of patients included NHL ($n = 6$), HD ($n = 4$), and AML ($n = 1$). Ten of the 11 patients had received an autologous BMT and one patient received a matched sibling allogeneic transplant.

Allogeneic transplants for lymphoma were performed before the initiation of autologous BMT for lymphoma in 1982. Of the 201 patients with NHL who underwent BMT, 25 (12.4%) had received an allogeneic transplant. Similarly, of the 86 patients with HD, only 4 (4.7%) had received an allogeneic transplant. Restricting the analysis to patients who received an autologous transplant for either HD or NHL ($n = 258$), the estimated cumulative probability of developing

MDS/AML was $13.5\% \pm 4.8\%$ at 6 years. Within this subgroup, cumulative probability of developing MDS/AML was significantly higher ($P = .004$) among patients who had received autologous peripheral-blood-stem-cell (PBSC) transplant ($35.8\% \pm 16.3\%$ at 4 years), as compared with patients who received autologous marrow ($4.1\% \pm 2.6\%$) after cytoreductive therapy. Use of PBSC for autologous transplant ($RR = 5.8$, $P = .01$) and age >35 years at transplant ($RR = 3.5$, $P = .07$) were independently associated with an increased risk of developing MDS/AML.

Of the 11 patients, eight have died from progressive MDS and complications of pancytopenia, with the median actuarial survival being 7 months from the diagnosis of MDS/AML (range 3 to 51 months). The remaining three patients are surviving a median of 6 months from diagnosis.

Solid Malignancies

Seventeen solid tumors developed in this cohort. These included malignant melanoma ($n = 3$), brain tumors ($n = 2$), basal cell carcinoma ($n = 3$), one each of squamous cell carcinoma of the skin, osteosarcoma, papillary carcinoma of the thyroid, malignant fibrous histiocytoma, breast cancer, prostate cancer, carcinoma in situ of the cervix and vulva, and an adenocarcinoma with an unknown primary. A risk factor analysis was conducted both including and excluding basal cell carcinomas. There was no difference between the two analyses, and hence the inclusive analysis is being reported, though for computing standardized incidence ratios, basal cell carcinomas and carcinomas in situ were excluded from the analysis since they are not included in the SEER incidence data. The original primary diagnoses included ALL ($n = 4$), AML ($n = 4$), CML ($n = 4$), NHL ($n = 2$),

Table 4. Observed and Expected Rates of EBV-Related B-Cell Lymphoproliferative Disease, According to Risk Factors

Risk Factors	Observed Cases	SIR (95% CI)	Cumulative Probability (\pm SE) at 10 yr
Primary diagnosis			
Immunodeficiency	8	5,801.3 (2477.7-10517.9)	17.8 \pm 6.6%
Preparative regimen			
ATG	6	2,987.2 (1079.7-5880.7)	11.3 \pm 2.1%
GVHD prophylaxis			
T-cell depletion	12	598.9 (308.5-987.5)	11.4 \pm 6.7%
Type of BMT			
Allogeneic			
Unrelated	6	449.8 (166.1-904.7)	2.3 \pm 1.2%
Related	16	124.4 (70.9-192.8)	2.3 \pm 0.8%
Mismatched marrow	7	67.8 (13.1-106.4)	14.2 \pm 4.3%

Abbreviations: SIR, standardized incidence ratios (calculated by obtaining a ratio of the observed and the expected cases); CI, confidence interval; GVHD, graft-versus-host disease; ATG, antithymocyte globulin.

and HD ($n = 1$). Eight of the 15 patients had undergone an allogeneic transplant and 7 had received an autologous transplant. The cumulative probability of developing a solid tumor was higher ($P = .06$) among patients who had received TBI ($8.3\% \pm 3.5\%$ at 13 years) as compared with those who had not received TBI ($0.4\% \pm 0.4\%$). Three patients with skin cancer (two with basal cell carcinoma and one with squamous cell carcinoma) also had chronic GVHD. Univariate analysis, however, failed to reveal a statistically significant association between chronic GVHD and skin cancer ($RR = 1.5$, $P = .9$).

In multivariate analysis, TBI was associated with an increased risk of developing a solid tumor, which approached statistical significance ($RR = 6.0$, $P = .08$). The solid tumors that developed among the recipients of TBI included basal cell carcinoma ($n = 2$), and one each of papillary carcinoma of the thyroid, osteosarcoma, malignant melanoma, glioblastoma, squamous cell carcinoma, prostate carcinoma, primitive neuroectodermal tumor of the central nervous system, and an adenocarcinoma of an unknown primary.

Six of the 15 patients have died, with the median actuarial survival being 1.5 months (range 0 to 12 months). The remaining 9 patients are surviving a median of 13 months from diagnosis.

DISCUSSION

Second neoplasms are well known late complications after conventional treatment for NHL,⁴ HD,⁵ and ALL¹⁸ and many other malignancies. The risks reported in the literature range from as low as 1.3-fold¹⁹ to 20-fold²⁰ in comparison with the general population. Previous studies have shown that BMT recipients have a slight but significant risk of cancer, particularly NHL, epithelial tumors, MDS, and a variety of solid nonhematopoietic tumors, with the reported incidence being four- to seven-fold that of the general population.^{8-13,21-23} The etiology of second malignancy is multifactorial and may include immune deficiency resulting in EBV associated B-cell lymphoproliferative disease, irradiation, and possibly chemotherapy resulting in leukemias and solid nonhematopoietic tumors, and finally an interaction of any of these factors with genetic predisposition resulting in a variety of malignancies. Among 2,150 patients who underwent BMT between 1974 and 1994 at the University of Minnesota for a variety of disorders, the 53 post-BMT malignancies represent an 11-fold increased risk over that of a comparable normal population.

EBV-associated BLPD was the most common malignancy seen in this group of patients, with the EBV genome detectable in the tumor DNA in most of the patients. Our cohort was at a 105-fold increased risk of developing a lymphoma over that of the general population. Moreover, the cumulative probability of developing BLPD approached 65% among patients who received a T-depleted marrow from a mismatched donor in a setting of primary immune deficiency.

BLPD is a well-known complication of immune deficiency, both inherited and acquired, and in most cases is associated with EBV.^{24,25} In our study, factors found to be predictive of BLPD such as ex vivo T-cell depletion, HLA-mismatched marrow transplant, and use of ATG for pretrans-

plant conditioning as well as GVHD prophylaxis all tend to compromise host immunity, thus allowing the development of BLPD. Mismatched marrow transplants and ex vivo T-cell depletion of the marrow have been shown previously to be associated with an increased risk of developing BLPD.¹¹ In organ transplant recipients, the incidence of BLPD is related to the degree of immunosuppression, and several reports suggest that reduction or cessation of immunosuppressive drugs in this population may lead to a regression of tumor in some patients.^{26,27}

As has been previously reported,^{17,28-32} the risk of MDS/AML was considerably increased over that of the general population. In our population of patients there was a relatively short latent period (4 months) and the cumulative incidence of MDS rose sharply, plateauing at 8 years post-transplant, which is consistent with data from other studies.³³ Among patients with a primary diagnosis of lymphoma (NHL or HD), those who received PBSC for transplant were at an increased risk of developing MDS as compared with those who received marrow reinfusion. Patients received PBSC rather than marrow reinfusion for lymphomas for several reasons: as part of a randomized study ($n = 30$, 41.5%), residual disease in the marrow ($n = 22$, 31%), hypocellular marrow ($n = 5$, 7%), difficulty in aspirating marrow as a result of radiation to the pelvic region or myelofibrosis ($n = 4$, 5.5%), or because of other miscellaneous reasons ($n = 11$, 15%). Any of these reasons for choosing PBSC over marrow (except for the randomized study) could be surrogates for other factors that may be associated with the development of MDS. However, patients receiving peripheral stem cells as part of a randomized study were as likely to develop MDS (cumulative probability \pm SE at 2 years, $4.4\% \pm 4.3\%$) as the patients who received PBSCs outside the randomization process ($6.6\% \pm 4.5\%$). Furthermore, there was no difference in the preparative regimens used for patients who received autologous peripheral stem cells versus those who underwent an autologous BMT. Peripheral stem cells were collected in the steady state until November of 1993. Since then cytokine priming has been used for collecting stem cells. So far, only 13 patients with lymphoma have undergone a PBSC transplant using cytokine primed stem cell collection, making it difficult to evaluate whether methodology of collecting stem cells could potentially influence the development of MDS. In addition, MDS tended to develop in older patients. This could be a reflection of accumulation of mutagenic exposures with increasing age. It is also difficult to separate the relative roles of the transplant preparative regimen and prior therapy in inducing neoplastic transformation in this situation, since the majority of patients had received alkylating agents and radiation before their conditioning for transplantation. Prior therapy received by these patients and cytogenetic analysis have been reported previously.¹⁷

Overall, our cohort of transplant recipients was at a three-fold increased risk of developing solid malignancies, when compared with the general population. TBI was the only independent risk factor associated with an increased risk of developing a solid malignancy. As the length of follow-up increases, an increasing number of radiation-associated solid tumors may emerge as has been reported among the long-

term survivors of HD treated with conventional therapy.^{34,35} Similar reports are available for the long-term complications of irradiation in marrow transplant recipients. Socie et al described carcinomas in 4 of 147 patients with aplastic anemia given HLA-identical marrow transplants with the estimated actuarial incidence being 22% at 8 years of follow-up.³⁶ Among the solid tumors in our cohort, malignant melanomas were the most common, with our cohort demonstrating a 10-fold increased risk. Chronic GVHD, with its chronic skin inflammation, has been long suspected to be a potential risk factor for the development of skin cancers. Lishner et al showed a modest association between chronic GVHD and the development of skin cancers.³⁷ In our cohort, there were three patients with skin cancers who also had chronic GVHD. Univariate analysis in this subset of patients failed to reveal any association; however, the small number of cases limits our ability to statistically assess risk-related features.

Prior reports have shown an increased incidence of malignant neoplasms following BMT for aplastic anemia.^{12,38,39} This increase in risk has been attributed to differences in the conditioning regimens, with patients receiving cyclophosphamide and radiation³⁶ having a higher actuarial risk of developing a malignancy, as compared with patients who received only cyclophosphamide.¹² Of the 150 patients with aplastic anemia transplanted at the University of Minnesota, only one developed a malignancy (BLPD). The conditioning regimens used in this group of patients included cyclophosphamide and TLI (68.7%), cyclophosphamide and TBI (18%), and cyclophosphamide alone or in combination with other agents in the remaining 13.3%. Eighty percent of the patients were alive at the last follow-up, with the median length of follow-up being 9.6 years (range 0.9 to 18.1 years). Differences in the extent of radiation and radiation practices might have accounted for the low incidence of malignancies in this cohort of patients.

We conclude that patients undergoing BMT are at a substantial risk of developing malignancies from treatment experienced both before and during their transplant. The contribution of each of these factors remains unclear, and the critical question of the actual additive contribution of the transplant procedure above the already increased risk of MN these patients enter the BMT process with, remains unresolved. Although the risk of leukemia and lymphoma may not extend beyond the first decade after transplant, the risk of radiation-associated solid tumors will likely increase with longer follow-up. This underscores the importance of continued monitoring of the patients with careful evaluation of medical symptoms. Changes in BMT practices, with increasing use of HLA-mismatched marrow donors, in vitro manipulation of marrow, and in vivo T-cell depletion to prevent GVHD, may alter the incidence of post-BMT neoplasms, particularly EBV-associated BLPD. On the other hand, identification of BMT candidates earlier in the disease course, before years of mutagenic chemotherapy or radiation therapy, might result in reduction of risk of post-BMT malignancy.

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