

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

**Risk of Lymphoproliferative Disorders After Bone Marrow Transplantation:
A Multi-Institutional Study**

By Rochelle E. Curtis, Lois B. Travis, Philip A. Rowlings, Gérard Socié, Douglas W. Kingma, Peter M. Banks, Elaine S. Jaffe, George E. Sale, Mary M. Horowitz, Robert P. Witherspoon, Donna A. Shriner, Daniel J. Weisdorf, Hans-Jochem Kolb, Keith M. Sullivan, Kathleen A. Sobocinski, Robert Peter Gale, Robert N. Hoover, Joseph F. Fraumeni, Jr, and H. Joachim Deeg

We evaluated 18,014 patients who underwent allogeneic bone marrow transplantation (BMT) at 235 centers worldwide to examine the incidence of and risk factors for post-transplant lymphoproliferative disorders (PTLD). PTLD developed in 78 recipients, with 64 cases occurring less than 1 year after transplantation. The cumulative incidence of PTLD was 1.0% ± 0.3% at 10 years. Incidence was highest 1 to 5 months posttransplant (120 cases/10,000 patients/yr) followed by a steep decline to less than 5/10,000/yr among ≥1-year survivors. In multivariate analyses, risk of early-onset PTLD (<1 year) was strongly associated ($P < .0001$) with unrelated or human leukocyte antigen (HLA) mismatched related donor (relative risk [RR] = 4.1), T-cell depletion of donor marrow (RR = 12.7), and use of antithymocyte globulin (RR = 6.4) or anti-CD3 monoclonal antibody (RR = 43.2) for prophylaxis or treatment of acute graft-versus-

host disease (GVHD). There was a weaker association with the occurrence of acute GVHD grades II to IV (RR = 1.9, $P = .02$) and with conditioning regimens that included radiation (RR = 2.9, $P = .02$). Methods of T-cell depletion that selectively targeted T cells or T plus natural killer (NK) cells were associated with markedly higher risks of PTLD than methods that removed both T and B cells, such as the CAMPATH-1 monoclonal antibody or elutriation ($P = .009$). The only risk factor identified for late-onset PTLD was extensive chronic GVHD (RR = 4.0, $P = .01$). Rates of PTLD among patients with 2 or ≥3 major risk factors were 8.0% ± 2.9% and 22% ± 17.9%, respectively. We conclude that factors associated with altered immunity and T-cell regulatory mechanisms are predictors of both early- and late-onset PTLD. *This is a US government work. There are no restrictions on its use.*

ALLOGENEIC BONE MARROW transplantation (BMT), an effective treatment for leukemia and other disorders, produces profound immune deficiency in the early period after transplantation. Posttransplant lymphoproliferative disorders (PTLD) are an uncommon, but frequently fatal, complication of this defective immune function.¹⁻³ PTLD typically develop in the first 6 months posttransplant as clinically aggressive lymphomas of donor origin; most are related to Epstein-Barr virus (EBV).^{1,4,5} Previous studies indicate that patients at highest risk of PTLD are those receiving unrelated donor or human leukocyte antigen (HLA) mismatched related donor transplants, T-cell depletion, or antithymocyte globulin. However, prior studies of PTLD generally included small numbers of cases treated in a single institution, and did not separately analyze lymphoproliferative disorders that occurred beyond the first

posttransplant year. We evaluated the long-term incidence, risk factors, and outcome of lymphoproliferative disorders in a cohort of more than 18,000 allogeneic BMT recipients.

MATERIALS AND METHODS

Patients. The study included 18,014 patients receiving allogeneic BMT at 234 transplant centers reporting to the International Bone Marrow Transplant Registry (IBMTR), Milwaukee, between 1964 and 1990, and at the Fred Hutchinson Cancer Research Center, Seattle, between 1969 and 1992. Because of the potential difficulty in distinguishing PTLD from recurrent non-Hodgkin's lymphoma (NHL), we did not consider 729 patients transplanted for NHL. Also excluded were 577 patients transplanted for Fanconi anemia or a primary immunodeficiency disease who are known to have an increased susceptibility to cancer.^{6,7} Complete follow-up data through the study end date (December 31, 1991 and December 31, 1992 for the IBMTR and Seattle patients, respectively) were obtained for 91% of transplant recipients.

Table 1 lists subject- and transplant-related characteristics. Eighty-nine percent of patients received a transplant for leukemia or severe aplastic anemia; 81% of donors were HLA-identical siblings. Median age at transplant was 25 years (range, <1 to 72). Common conditioning regimens consisted of total body irradiation (TBI) combined with cyclophosphamide (64%) or other cytotoxic drugs (8%). Patients not given radiation typically received cyclophosphamide and busulfan (15%). In 14% of transplants, the graft was depleted of T cells, with the most frequent methods using monoclonal antibodies targeting T cells or T plus natural killer (NK) cells, CAMPATH-1 monoclonal antibodies, or elutriation. Most patients received posttransplant immune suppression to prevent graft-versus-host disease (GVHD), usually with cyclosporine, methotrexate, and/or corticosteroids. Acute GVHD was typically treated with corticosteroids, cyclosporine (usually continued from prophylaxis), antithymocyte (or antilymphocyte) globulin, or combinations of these drugs. Twenty-one patients from Seattle received an anti-CD3 monoclonal antibody (64.1) to treat acute GVHD.⁸ Data on drugs used to treat chronic GVHD were incomplete, and thus not further analyzed.

We identified 78 PTLD using well-established criteria⁹; some of these cases were described previously.^{2-3,10-15} Fifty-three cases (68%) were confirmed by centralized histopathologic examination of archived

From the Division of Cancer Epidemiology and Genetics, and the Division of Cancer Biology and Diagnosis, Laboratory of Pathology, National Cancer Institute, Bethesda, MD; International Bone Marrow Transplant Registry, Medical College of Wisconsin, Milwaukee, WI; Fred Hutchinson Cancer Research Center, Seattle, WA; Hôpital Saint Louis, Hématologie-Greffe de Moelle, Paris, France; Carolinas Medical Center, Charlotte, NC; University of Minnesota Medical School, Minneapolis, MN; Universität München, Munich, Germany; and Salick Health Care, Inc, Los Angeles, CA.

Submitted February 10, 1999; accepted May 26, 1999.

See Appendix for grant support information.

Address reprint requests to Rochelle E. Curtis, MA, Executive Plaza South, Room 7042, National Cancer Institute, Bethesda, MD 20892; e-mail: curtisr@epndce.nci.nih.gov.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

This is a US government work. There are no restrictions on its use. 0006-4971/99/9407-0130\$0.00/0

Table 1. Characteristics of 18,014 Patients Undergoing Allogeneic BMT

Characteristic	No. of Patients	Percent*
Cohort		
IBMTR, 1964-1990	14,041	77.9
FHCRC, 1969-1992	3,973	22.1
Female sex	7,404	41.1
Age at transplant (yr)		
<10	2,623	14.6
10-19	3,929	21.8
20-29	4,654	25.8
30-39	4,191	23.3
40+	2,617	14.5
Calendar year of transplant		
1964-1979	1,190	6.6
1980-1984	4,166	23.1
1985-1989	9,662	53.7
1990-1992	2,996	16.6
Primary disease†		
Acute nonlymphocytic leukemia	5,065	28.1
Chronic granulocytic leukemia	4,770	26.5
Acute lymphoblastic leukemia	4,139	23.0
Severe aplastic anemia	2,114	11.7
Other	1,926	10.7
Donor-recipient relationship and histocompatibility		
HLA-identical sibling	14,624	81.2
1 HLA-antigen mismatched sibling, relative	1,356	7.5
≥2 HLA-antigen mismatched sibling, relative	835	4.6
Unrelated donor	1,068	5.9
Other, uncertain	131	0.7
Transplant conditioning regimen		
TBI + Cy ± other drugs	11,544	64.1
TBI ± other drugs (no Cy)	1,481	8.2
LFI ± Cy ± other drugs	655	3.6
Busulfan + Cy ± other drugs	2,775	15.4
Cy ± other drugs	1,391	7.7
Other	168	0.9
T-cell depletion of marrow		
No T-cell depletion	15,518	86.1
Anti-T or anti-T + NK MoAb	1,255	7.0
Sheep red blood cell rosetting	166	0.1
Lectins	133	0.1
CAMPATH-1 MoAb	608	3.3
Elutriation/density gradient centrifugation	250	1.0
Unclassified/other	84	0.1
Drugs given for GVHD prophylaxis		
CsA + MTX (no ATG)	6,659	37.0
CsA (no MTX, no ATG)	5,628	31.2
MTX (no CsA, no ATG)	3,871	21.5
Any ATG	525	2.9
Other, none	1,331	7.4
Occurrence of acute GVHD II-IV	7,063	39.2
Treatment for acute GVHD II-IV		
Steroids (No CsA, no ATG)	3,285	18.2
CsA + steroids (no ATG)	1,776	9.9
Any ATG	1,101	6.1
Other, none	901	5.0
Occurrence of extensive chronic GVHD‡	3,872	30.0

Abbreviations: IBMTR, International Bone Marrow Transplant Registry; FHCRC, Fred Hutchinson Cancer Research Center; TBI, total-body irradiation; Cy, cyclophosphamide; LFI, limited-field irradiation; CsA, cyclosporine; MTX, methotrexate; GVHD, graft-versus-host disease; NK, natural killer cells; MoAb, monoclonal antibody; ATG, antithymocyte globulin.

*Percents do not always add to 100% because of rounding.

†Primary diseases excluded were non-Hodgkin's lymphomas (n = 729), Fanconi's anemia (n = 201), and immune deficiency diseases (n = 376). Other primary diseases included Hodgkin's disease (n = 163), other malignancies (n = 347), myelodysplastic syndromes or myeloproliferative disorders (n = 632), and other smaller groups of primarily nonmalignant diseases (n = 784), including inherited disorders of metabolism (n = 158), and hemoglobinopathies (n = 315).

‡Occurrence of extensive chronic GVHD among 13,107 patients who survived ≥90 days posttransplant.

tissue or slides (D.K., E.J.), 18% by review of clinical and pathology reports (P.B.), 9% by review of published case details,^{11,12,14} and 5% (4 cases) were evaluated using the transplant team report only. Sufficient tissue was available for 36 PTLD to perform in situ hybridization to detect expression of EBV-encoded RNA (EBER1) (methods described in Kingma et al¹⁶). Clonality and immunoglobulin gene rearrangement studies were not performed.

Statistical analyses. For each transplant recipient, person-years at risk were compiled from the date of transplant until one of the following events: death, last known follow-up, diagnosis of new malignancy (including PTLD), or end of study, whichever occurred first. The change in PTLD risk over posttransplant intervals was initially evaluated by estimating crude incidence rates, defined as the number of PTLD events divided by the person-years at risk accrued in that interval. To allow comparisons with previously published estimates, the observed (O) number of PTLD was compared with the expected (E) number of NHL in the general population by applying age-, gender-, calendar year-, and region-specific population-based incidence rates to the appropriate person-years at risk.¹⁷ However, it should be recognized that lymphoproliferative disorders after BMT are a unique set of polyclonal and monoclonal tumors, and thus not directly comparable to NHL in the general population. Kaplan-Meier methods were used to calculate the cumulative probability of developing a PTLD.¹⁸

Poisson regression methods for grouped survival data¹⁹ and Cox proportional hazards regression techniques²⁰ were used to compute estimates of relative risk (RR) of PTLD associated with various patient-, treatment-, and transplant-related variables. These 2 approaches gave nearly identical results and only Poisson analyses are presented. A forward step-wise selection procedure was used for variable selection. Poisson models included stratification on time since transplantation in 14 intervals to account for the sharp decline in the patients at risk during the first year post-transplant. Monthly cut-points were used during the first 9 months following transplantation, and at 1, 2.5, 5, 7.5, and 10 years thereafter. Models were also stratified by the underlying disease for which the transplant was performed using 5 categories: acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), severe aplastic anemia, and other diseases. Patient-related variables evaluated in multivariate models included cohort (IBMTR v Seattle), geographic region, gender, age and calendar year of transplant, and primary disease. Transplant-related risk factors included degree of HLA match and donor relationship, conditioning regimen, use of antithymocyte globulin for conditioning, occurrence and method of T-cell depletion, prophylaxis, or treatment for acute GVHD with antithymocyte globulin or anti-CD3 monoclonal antibody 64.1 (Seattle only), all of which have been identified as risk factors for PTLD in 1 or more prior studies.¹⁻³ The occurrence and treatment of acute GVHD (grades II to IV) and the occurrence of extensive chronic GVHD were entered into the model as time-dependent covariates. We also considered drugs commonly used to prevent or treat acute GVHD. Tests of statistical significance were 2-sided and 95% likelihood-based confidence intervals (CIs) were calculated.

To account for the nonconstant relative hazard for several risk factors over time since transplantation, we constructed a series of Poisson regression models, each of which included risk factors plus interaction terms. These interaction terms consisted of indicator variables (values 0, 1) that allowed for a step in the hazard function for a particular risk factor at prespecified follow-up times (ie, 4, 5, 6, 7, 8, 9 months, and 1 year posttransplant). Because the 1-year cut-point minimized the model deviance, these results will be presented in Table 3.

RESULTS

We identified 78 patients who developed PTLD, compared with 1.5 cases of NHL expected in the general population (O/E = 51.5; 95% CI, 40.7% to 64.3%). Sixty-four lymphoproliferative disorders occurred within the first year posttransplant

Table 2. Incidence Rate of PTLD by Time Since Transplantation

Time Since Transplantation	No. of Patients	Person-Years at Risk	No. of PTLD	Incidence Rate*
0-<1 mo	18,014	1,339	0	0.0
1-<2 mo	16,634	1,330	12	90.2
2-<3 mo	14,732	1,138	24	210.9
3-<4 mo	13,120	1,103	10	90.7
4-<5 mo	12,148	998	9	90.2
5-<6 mo	11,417	943	2	21.2
6-<12 mo	10,826	4,845	7	14.4
1-<2.5 yr	8,919	10,716	8	7.5
2.5-<10 yr	5,771	18,456	6	3.3
10+ yr	625	1,481	0	0.0
Total years	18,014	42,349	78	18.4

*Incidence rate is the observed number of PTLD cases divided by person-years at risk ($\times 10^4$).

while 14 arose 1 or more years after transplant (late-onset: range, 1 to 8.6 years posttransplant). Incidence was highest 1 to 5 months after transplant (120 cases/10,000 patients/yr) (Table 2). The peak incidence (210 cases/10,000/yr) occurred during the third month posttransplant; thereafter, a gradual but steep decline in the PTLD rate was observed, with the lowest incidence occurring among ≥ 1 -year survivors (<5 PTLD cases/10,000/yr). The risk of late-onset PTLD remained significantly higher than would be expected for de novo NHL in the general population (O = 14, O/E = 12.8; 95% CI, 7.0% to 21.4%). The overall cumulative incidence of PTLD was low, $1.0\% \pm 0.3\%$ at 10 years. Although no PTLD cases occurred among the 625 patients who survived more than 10 years post-BMT (Fig 1), only a small percentage of these long-term survivors were recipients of family mismatched, unrelated, or T-cell depleted bone marrow. The cumulative incidence of PTLD exceeded the rate for invasive solid tumors in this multiinstitutional cohort for nearly 5 years posttransplant (data for solid cancers from Curtis et al²¹).

Most of the 64 recipients with early-onset PTLD had a primary disease of leukemia, similar to the distribution in the entire cohort (16 ALL, 15 AML, 19 CML, 5 severe aplastic anemia, 5 myelodysplastic syndrome, 2 lysosomal storage

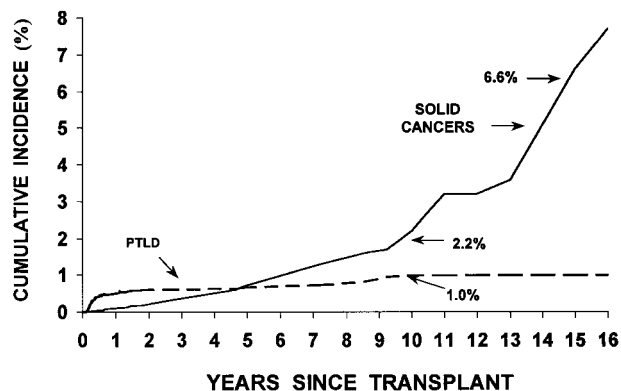


Fig 1. Cumulative incidence (%) of PTLD (78 cases) and invasive solid cancers (80 cases) following an allogeneic BMT; multi-institutional cohort of 235 transplant centers. (Data for solid tumors taken from Curtis et al.²¹)

disease, 1 Hodgkin’s disease, and 1 hemoglobinopathy). EBV-related sequences were detected by in situ hybridization in all 36 evaluable cases. Fifty-five (86%) patients with PTLD died during the survey period; in 51 cases, the PTLD was the primary (n = 39) or contributing (n = 12) cause of death. The diagnosis of PTLD was made pre-mortem in 39 cases and after death in 16. Disease progression was rapid among the 39 patients diagnosed before death (median survival, 0.6 months; range, 0.03 to 15 months). Nine patients with early-onset PTLD are alive at a median follow-up duration of 88 months after PTLD diagnosis (range, 3 to 131 months).

Among 14 patients with late-onset PTLD, 13 had a diagnosis of leukemia (5 ALL, 4 AML, 4 CML) and 1 had severe aplastic anemia. None of the late-onset cases was evaluable for EBV status in the current study; however, published case details indicate that 2 B-cell PTLD were EBV-related,^{11,15} while 3 cases (1 B-cell and 2 T-cell lymphomas) had no evidence of EBV-related sequences.^{12,13} Patients who developed late-onset PTLD had significantly longer survival after diagnosis than those with early-onset tumors (P = .03). Eleven of 14 patients (79%) with late-onset PTLD died; in 9 cases the lymphoma was either the primary (n = 8) or contributing (n = 1) cause of death. Two PTLD cases were diagnosed after death; median survival for the 9 patients diagnosed before death was 6 months (range, 1 to 22 months). Three patients are alive at 37, 46, and 112 months after developing PTLD.

Table 3 presents results from multivariate models evaluating risk factors for PTLD diagnosed less than 1 year and ≥1 year posttransplant and for all time periods combined. The risk of early-onset PTLD was strongly associated (P < .0001) with T-cell depletion of the graft (RR = 12.7), unrelated donor or ≥2 HLA-antigen mismatched related donor (RR = 4.1) and use of anti-CD3 monoclonal antibody 64.1 (RR = 43.2) or antithymocyte globulin (RR = 6.4) as prophylaxis or treatment of acute GVHD. A weaker association was observed with the occurrence of acute GVHD grades II-IV (RR = 1.9, P = .02). Recipients of transplants from 1 HLA-antigen mismatched related donors (RR = 1.9, P = .20) were not significantly different in PTLD risk from those with HLA-identical sibling grafts. Patients who received unrelated donor grafts (RR = 3.3) had risks similar to

those with ≥2 HLA-antigen mismatched related transplants (RR = 4.8), and thus were grouped for analyses.

Among patients who survived more than 1 year posttransplant, the relationship between PTLD risk and previously identified risk factors (T-cell depletion, HLA disparity, use of antithymocyte globulin or monoclonal antibody CD3 therapy) was greatly diminished (Table 3). The only risk factor identified for late-onset PTLD was extensive chronic GVHD (RR = 4.0, P = .01).

For all time intervals combined, conditioning regimens with radiation were associated with risk of PTLD (RR = 2.9, P = .02). However, only small numbers of PTLD patients (n = 4) did not receive radiation and risk was inconsistent across geographic regions. Risk appeared to vary by dose of fractionated TBI with 3.5- to 4.3-fold risks seen for doses ≥13 Gy.

We compared the risk of PTLD associated with 5 different methods of T-cell depletion of bone marrow (Table 4), while controlling for other major risk factors. Significant differences among T-cell depletion techniques were detected (test of homogeneity, P = .009). Particularly high risks were seen for methods using monoclonal antibodies specifically directed against T cells or T plus NK cells (RR = 12.3) and for sheep red blood cell E-rosetting techniques (RR = 15.6). Only 4 PTLD developed in recipients of grafts depleted of T cells using CAMPATH-1 monoclonal antibodies, elutriation, or lectins, all of which remove both T and B cells.

We assessed the risk of PTLD related to the number of risk factors for PTLD. Four major risk factors were defined: (1) T-cell depletion using monoclonal antibodies directed at T cells or T plus NK cells, or E-rosetting; (2) unrelated or ≥2 HLA-antigen mismatched related donor; (3) prophylaxis or therapy for acute GVHD with antithymocyte globulin; and (4) treatment of acute GVHD with anti-CD3 monoclonal antibody 64.1. Patients with unclassified or other methods of T-cell depletion were excluded (84 patients and 2 PTLD cases). Figure 2 shows 10-year cumulative incidence rates of PTLD in patients with 0, 1, 2, or 3 to 4 major risk factors, with incidences ranging from 0.5% ± 0.3% in those with no major risk factors to high rates among recipients with 2 and ≥3 major risk factors (8.0% ± 2.9% and 22.3% ± 17.9%, respectively). We observed

Table 3. Risk Factors for PTLD, by Time Since Transplantation

Variable	Time Since Transplantation								
	All Periods (78 PTLD, 42,349 PYR)			<1 yr (64 PTLD, 11,696 PYR)			≥1 yr (14 PTLD, 30,653 PYR)		
	No. of PTLD	RR	95% CI	No. of PTLD	RR	95% CI	No. of PTLD	RR	95% CI
Conditioning radiation (TBI or LFI), yes v no	74	2.9*	1.1-10.1	61	2.8	0.9-11.8	13	2.4	0.4-49.6
Unrelated or ≥2 HLA-Ag mismatched related donor v matched sibling or 1 HLA-Ag mismatched relative	30	3.7*	2.2-6.0	30	4.1*	2.4-6.9	0	0.0	0.0-2.4
T-cell depletion, yes v no	42	9.1*	5.5-15.1	40	12.7*	7.2-23.0	2	1.7	0.3-6.5
Acute GVHD: grade II-IV v grade I or no acute GVHD	42	1.6	1.0-2.7	36	1.9*	1.1-3.3	6	1.1	0.3-3.3
ATG/ALG for acute GVHD, prophylaxis or therapy, yes v no	25	5.5*	3.2-9.1	23	6.4*	3.6-11.0	2	2.1	0.3-8.2
Anti-CD3 MoAb (64.1) for acute GVHD therapy yes v no	3	35.9*	8.4-107	3	43.2*	9.8-134	0	0.0	—
Chronic GVHD, extensive v none, limited	16	1.9*	1.0-3.6	7	1.2	0.5-2.7	9	4.0*	1.3-13.5

Abbreviations: PYR, person-years at risk; CI, confidence interval; Ag, antigen; ATG/ALG, antithymocyte globulin or serum, antilymphocyte globulin or serum; RR, relative risk; TBI, total body irradiation; LFI, limited field irradiation.

Poisson regression models stratified by time since transplantation (14 groups) and primary disease group (5 groups).

*Denotes relative risks that are statistically significant (P < .05).

Table 4. Relative Risk (RR) of PTLD by Method of T-Cell Depletion of the Bone Marrow

Method of T-Cell Depletion	No. of PTLD	RR*	95% CI
No T-cell depletion	36	1.0	Reference
Anti-T or anti-T + NK MoAb†	31	12.3	7.1-21.3
SRBC rosetting‡	5	15.6	5.3-37.5
Lectins§	1	4.1	0.2-19.8
CAMPATH-1 MoAb	2	2.0	0.3-6.7
Elutriation/density gradient centrifugation	1	2.6	0.1-12.4
Unclassified/unknown	2	12.7	2.0-43.1

*Relative risks were adjusted for HLA disparity, use of ATG or MoAb anti-CD3 A641 for acute GVHD, occurrence of acute GVHD II-IV, occurrence of extensive chronic GVHD, and radiation conditioning.

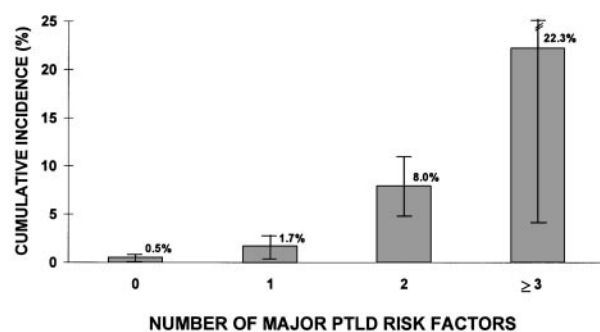
†Anti-T methods include monoclonal antibodies directed against T-cell-specific epitopes (including single antibodies or combinations): CD3, CD3/CD7, CD4, CD4/CD8, CD4/CD5/CD8, CD5, CD5/CD8, CD5/ricin, T10 B9, CD6/CD7/CD8, CD6/CD7, CD6/CD8, CD8, CD7/CD8. Anti-T and anti-NK methods include monoclonal antibodies directed against T-cell- and NK-cell-specific epitopes (including single antibodies or combinations): CD2, CD2/CD3, CD2/CD8, CD2/CD4/CD8, CD2/CD6/CD8/CD28, CD2/CD7, CD2/CD5/CD7, CD2/CD5, CD8, CD2/CD3/CD8, CD2/CD8, ATG incubation.

‡SRBC (sheep red blood cell) rosetting methods includes SRBC rosetting + density gradient centrifugation.

§Lectin methods include lectin or lectin and E-rosetting (n = 126), and lectin and MoAb CD5/CD8 (n = 7).

||Elutriation methods include elutriation, density gradient centrifugation, and elutriation/density gradient centrifugation.

significant heterogeneity among patients with only 1 major risk factor ($P = .0001$). No PTLD developed among 1,240 patients (1,412 person-years) with unrelated or ≥ 2 HLA-antigen mismatched related donor grafts who did not have other major risk factors, and this group was not significantly different in PTLD risk ($P = .08$) from those with no major risk factors (21 cases, 6/10,000/yr). This result contrasted with the substantial in-



	0	1	2	≥3
No. Patients	13,758	3,493	642	37
No. PTLD	21	22	28	5

Fig 2. Cumulative incidence (%) of PTLD for patients with 0, 1, 2, or 3 to 4 major risk factors for PTLD. The 4 risk factors were defined as: (1) T-cell depletion methods that selectively target T cells or T + NK cells or E-rosetting; (2) unrelated or ≥ 2 HLA antigen mismatched related donor; (3) antithymocyte globulin used as prophylaxis or therapy for acute GVHD; and (4) anti-CD3 monoclonal antibody 64.1 given as therapy for acute GVHD (Seattle only). Analysis excludes 2 PTLD and 84 patients with unclassified or other methods of T-cell depletion.

creased risk seen among patients in other single-risk factor groups: T-cell-depleted graft alone (14 cases, 71/10,000/yr) or antithymocyte globulin therapy alone (7 cases, 27/10,000/yr). Of the 21 PTLD patients with no major risk factors, 20 received radiation for conditioning, 11 had acute or chronic GVHD (or both), and 3 received a graft that was T-cell-depleted with CAMPATH-1 monoclonal antibodies or lectin techniques.

Disease for which the transplant was performed and age at transplantation had no significant association with risk of PTLD in multivariate regression analyses. Drugs used for conditioning, evaluated singly and in combination, were also not significantly related to PTLD risk, and no increase in risk was observed for patients who received antithymocyte globulin for conditioning (RR = 0.8, $P = .68$), as previously reported.² There were no significant associations with specific immunosuppressive drugs used to prevent or treat acute GVHD, other than those described above.

DISCUSSION

Lymphoproliferative disorders after bone marrow and organ transplantation and among patients infected with AIDS are believed to result from uncontrolled proliferation of EBV-transformed B-lymphocytes in the setting of immune dysfunction.^{1,22-28} Recent evidence suggests that most of the latent EBV proteins, including EBNA-1, -2, and -3, and LMP-1, are expressed on the malignant cells in EBV-induced PTLD^{1,4} and that LMP-1 functions as a signaling protein in these tumors.²⁹ PTLD in the solid-organ transplant setting have been extensively studied over the last 3 decades. A wide range of tumors, from lymphoid hyperplasias that resolve after withdrawal of immunosuppression to aggressive monoclonal lymphomas with poor outcomes, are reported.^{9,30,31} In contrast, lymphoproliferative disorders after allogeneic BMT have been studied more recently.^{11,32} Most tumors after BMT appear to be rapidly fatal, monoclonal or oligoclonal B-cell lymphomas that occur early after transplant. Recent advances in the therapy of EBV-related lymphomas following BMT offer hope for improved survival following this complication, and efforts have intensified to identify and monitor patients at highest risk.³³⁻³⁵ Our current study evaluated 78 lymphoproliferative disorders occurring in a large cohort of 18,000 BMT recipients, and assessed incidence and risk factors for early-onset versus late-onset PTLD.

Our 1.0% cumulative incidence of PTLD at 10 years after BMT is comparable to rates of 0.5% to 1.8% reported from single centers.^{2,11,36} Data from our study also demonstrate that PTLD incidence varies markedly with time after transplantation, with particularly high rates occurring during the first 5 months, followed by a steep decline in incidence between 6 and 12 months posttransplant. A significantly increased risk of PTLD continues among longer term survivors, although the rate is greatly diminished. The high incidence of PTLD during the first few months after transplant is consistent with clinical investigations of the temporal pattern of immune reconstitution in marrow transplant recipients. Lucas et al reported that levels of anti-EBV cytotoxic T-lymphocyte precursors (CTLp) appear to return to normal by 6 months posttransplant in most patients, and that this interval of low CTLp frequency corresponds to the period of highest risk of EBV-related PTLD.³⁷ Although T-cell immunity can be impaired in some patients for a prolonged

interval, most transplant recipients without chronic GVHD have substantial recovery of T-cell function within 1 year.^{38,39} It is perhaps not surprising then that PTLD incidence declines during the first 12 months posttransplant from a high of 210 cases/10,000/yr to less than 5 cases/10,000/yr.

Previous investigations of risk factors for lymphomas after BMT were limited mostly to early-onset tumors.^{1-3,35,40} The 2 largest series evaluated 22 PTLD occurring among 2,150 BMT recipients at the University of Minnesota² and 16 PTLD among 2,246 patients at Seattle.³ In those studies and the current study, factors associated with severe immune dysfunction and altered T-cell regulatory mechanisms were major predictors of early-onset lymphomas. Significantly increased risks were seen with T-cell depletion of the graft,^{2,3} unrelated donor or donor-recipient HLA disparity,^{2,3} anti-CD3 monoclonal antibody 64.1 therapy for acute GVHD,³ use of antithymocyte globulin,^{2,3} and transplantation for primary immunodeficiency.² New findings in the current study indicate that the occurrence of acute GVHD of grades II to IV is significantly related to risk of early-appearing PTLD and that patients who receive 1 HLA-antigen mismatched related donor marrow are not significantly different in risk from recipients of an HLA-identical sibling graft. Radiation given as part of the conditioning regimen may be an additional risk factor for PTLD, although there was inconsistency in risk estimates across geographic areas. The mechanism by which pretransplant radiation might contribute to the development of PTLD is unclear. Higher TBI doses have been reported to increase GVHD severity,⁴¹ and exaggerated acute GVHD may trigger the need for prolonged immunosuppressive therapy, making it difficult to quantify the relative contributions of these effects to PTLD risk.

Our study is the first to evaluate risk factors for late-onset PTLD following allogeneic BMT, although case reports have described late-occurring lymphomas.^{3,12,13,15,42-44} Risk factors for early-onset PTLD in our study did not predict late-onset PTLD. However, chronic GVHD, an established correlate of immune dysregulation in long-term survivors, was identified as a strong risk factor. Patients with chronic GVHD may also require long-term treatment with immunosuppressive drugs, which is linked to an excess of PTLD following solid-organ transplants.⁴⁵ Thus, it is likely that immune dysfunction and immunosuppressive mechanisms continue to play a role in the development of PTLD among long-term survivors of BMT, although different risk factors may be involved.

We found significant heterogeneity in PTLD risk among the nearly 2,500 patients who received T-cell-depleted grafts. Particularly high risks were observed among recipients of grafts T-cell-depleted with monoclonal antibodies or E-rosetting techniques that selectively target T (or T plus NK) cells, whereas lower rates were associated with methods that remove both T and B cells (CAMPATH-1 monoclonal antibodies, elutriation, lectins). Similarly, reports from single centers have described PTLD incidence rates as high as 25% in patients depleted with T-cell-specific monoclonal antibodies or E-rosetting.^{2,5,11,40,46-48} In a recent multicenter study of 2,401 recipients T-cell-depleted with CAMPATH-1M or 1G, Hale et al⁴⁹ reported a low 1.1% cumulative risk of PTLD and hypothesized that depletion of B cells, as well as T cells, may reduce the viral load or virus target tissue in the interval before full recovery of

the T-cell population. Low PTLD rates have been observed also after transplants using marrow that was T-cell-depleted with counterflow centrifugal elutriation⁵⁰ or with lectin agglutination/E-rosette-depleted grafts without additional immunosuppression.^{4,35} Thus, the risk of PTLD appears much less with T-cell depletion techniques removing both T and B lymphocytes, possibly related to the reduced numbers of EBV-transformed B lymphocytes.⁴

Although PTLD incidence is reported to increase to high levels (up to 25%) among patients with multiple risk factors,^{4,35} few data are available to evaluate the individual and combined effects of each of the PTLD risk determinants. Our results indicate a steep increase in cumulative incidence with greater numbers of major risk factors, each of which are markers of altered immunity or T-cell function. In previous studies, patients receiving unrelated or HLA-mismatched related donor transplants were reported to be at higher risk of PTLD than those with HLA-identical sibling donors,^{2,3,32,37,46,47} although most patients in these investigations received a T-cell-depleted graft or other T-cell manipulation. Our study evaluated recipients of an unrelated or ≥ 2 HLA-antigen mismatched related graft who had no other major risk factors and found a low PTLD risk. This result contrasts with elevated PTLD rates among patients who received antithymocyte globulin alone or T-cell-depleted grafts alone (no other major risk factors). Although caution is indicated due to the high early mortality rate after HLA mismatched transplants and the strong correlation between HLA disparate donors and other risk factors, such as acute GVHD, these results suggest that HLA incompatibility by itself may be less important than other variables affecting PTLD risk. Along with the factors considered in the current study are other variables that appear to influence susceptibility to EBV-related lymphoproliferative disorders in solid-organ and marrow transplants, such as EBV viral burden, specific EBV strain (EBER A v EBER B), and deficiencies in cellular immunity to EBV.^{4,33,37,51} Even patients with no identifiable risk factors, except possibly radiation, may develop PTLD, although the risk is relatively low, reflecting variability in immune reconstitution not accounted for by known determinants.

Early-onset PTLD in our series were uniformly EBV-positive and most developed progressive disease that proved rapidly fatal. The 14 patients with late-onset PTLD had a significantly longer survival postdiagnosis than those with early-onset tumors. In addition, 3 of the late-onset PTLD cases in our series were described in published reports to be EBV-negative and 2 were T-cell PTLD.^{12,13} Recent evidence from solid-organ transplants suggests that EBV-negative PTLD are morphologically and clinically distinct from EBV-positive PTLD; EBV-negative PTLD after organ transplants tended to have later onset (median, 4.9 years), a higher prevalence of monomorphic lymphomas, and a greater proportion derived from T cells.⁵² These differences indicate the need for further research to fully characterize the clinicopathologic features of late-onset PTLD following BMT.

Most patients in our study developed PTLD during the 1980s and early 1990s, when available treatments (ie, antiviral and chemotherapeutic agents) were largely ineffective. Underreporting of PTLD during this period may be substantial due to difficulties in diagnosis, so that our estimates of PTLD inci-

dence are likely to be conservative. In recent years, considerable progress has been made in the diagnosis, prevention, and treatment of PTLD among allogeneic BMT recipients. Immunovirologic assays are available to detect high levels of EBV DNA, which strongly correlates with increased risks of EBV-related PTLD.^{33,53,54} New approaches for prophylaxis and treatment have been reported, including successful therapy with infusions of donor leukocytes.³⁵ Recent promising strategies include antiviral prophylaxis and treatment with gene-marked EBV-specific T lymphocytes,^{34,55} and the use of specific anti-CD21 and anti-CD24 murine monoclonal antibodies to control severe PTLD.⁵⁶ These advances may improve the prognosis for patients at increased risk of PTLD.

We conclude from these analyses in a large cohort of BMT recipients that the risk of PTLD persists among patients surviving more than 1 year after transplant, although it is greatly decreased compared with the early posttransplant period. Moreover, our data indicate that risk factors associated with altered immunity and T-cell regulatory mechanisms are predictors of both early- and late-onset PTLD. Patients at highest risk of PTLD are candidates for trials of prophylactic or preemptive therapies.

ACKNOWLEDGMENT

We are indebted to all collaborating investigators and staff from the participating transplant centers who contributed data to this study. We wish to thank Muriel Siadek, K. Erne, and Gary Schoch from Fred Hutchinson Cancer Research Center, Seattle, and Diane Knutson and Sharon Nell from the IBMTR, Milwaukee, for support in data collection. We acknowledge Kathy Chimes, Elena Adrianza, Andy Singer, and Diane Fuchs from Westat, Inc for coordination of field studies, George Geise and Christel McCarty from Information Management Services for computing support, and Denise Duong and Rebecca Albert for manuscript preparation.

APPENDIX

This research is supported by Contracts No. CP-51027 and CP-51028 from the National Cancer Institute. The International Bone Marrow Transplant Registry is supported by Public Health Service Grant no. P01-CA-40053 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung and Blood Institute of the US Department of Health and Human Services; and grants from Alpha Therapeutic Corp; Amgen, Inc; Anonymous; Baxter Healthcare Corporation; Bayer Corp; Berlex Laboratories; Blue Cross and Blue Shield Association; Lynde and Harry Bradley Foundation; Bristol-Myers Squibb Co; Cell Pro, Inc; Centeon; Center for Advanced Studies in Leukemia; Chimeric Therapies; Chiron Therapeutics; Charles E. Culpeper Foundation; Eleanor Naylor Dana Charitable Trust; Eppley Foundation for Research; Genentech, Inc; Glaxo Wellcome Co; ICN Pharmaceuticals; Immunex Corp; Kettering Family Foundation; Kirin Brewery Company; Robert J. Kleberg, Jr and Helen C. Kleberg Foundation; Herbert H. Kohl Charities, Inc; Nada and Herbert P. Mahler Charities; Milstein Family Foundation; Milwaukee Foundation/Elsa Schoeneich Research Fund; NeXstar Pharmaceuticals, Inc; Samuel Roberts Noble Foundation; Novartis Pharmaceuticals; Ortho Biotech, Inc; John Oster Family Foundation; Jane and Lloyd Pettit Foundation; Alirio Piffier Bone Marrow Transplant Support Association; Pfizer, Inc; Pharmacia and Upjohn; Principal Mutual Life Insurance Co; RGK Foundation; Rockwell Automation Allen Bradley Co; Roche Laboratories; SangStat Medical Corp; Schering-Plough Oncology; Searle; Stackner Family Foundation; Starr Foundation; Joan and Jack Stein Foundation; SyStemix; United Resource Networks; and

Wyeth-Ayerst Laboratories. The Fred Hutchinson Cancer Research Center investigators are supported by Grants No. P01-CA 18029, P01-CA-18221 and P01-CA-15704 from the National Cancer Institute, and P01-HL-36444 from the National Heart, Lung, and Blood Institute.

REFERENCES

- Deeg HJ, Socié G: Malignancies after hematopoietic stem cell transplantation: Many questions, some answers. *Blood* 91:1833, 1998
- Bhatia S, Ramsay NK, Steinbuch M, Dusenbery KE, Shapiro RS, Weisdorf DJ, Robison LL, Miller JS, Neglia JP: Malignant neoplasms following bone marrow transplantation. *Blood* 87:3633, 1996
- Witherspoon RP, Fisher LD, Schoch G, Martin P, Sullivan KM, Sanders J, Deeg HJ, Doney K, Thomas D, Storb R, Thomas ED: Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. *N Engl J Med* 321:784, 1989
- O'Reilly RJ, Lacerda JF, Lucas KG, Rosenfield NS, Small TN, Papadopoulos EB: Adoptive cell therapy with donor lymphocytes for EBV-associated lymphomas developing after allogeneic marrow transplants, in De Vita TD, Helman S, Rosenberg SA (eds): *Important Advances in Oncology 1996*. Philadelphia, PA, Lippincott-Raven, 1996, p 149
- Orazi A, Hromas RA, Neiman RS, Greiner TC, Lee CH, Rubin L, Haskins S, Heerema NA, Gharpure V, Abonour R, Srour EF, Cornetta K: Posttransplantation lymphoproliferative disorders in bone marrow transplant recipients are aggressive diseases with a high incidence of adverse histologic and immunobiologic features. *Am J Clin Pathol* 107:419, 1997
- Lustig JP, Lugassy G, Neder A, Sigler E: Head and neck carcinoma in Fanconi's anaemia—Report of a case and review of the literature. *Eur J Cancer B Oral Oncol* 31B:68, 1995
- Filipovich AH, Mathur A, Kamat D, Shapiro RS: Primary immunodeficiencies: Genetic risk factors for lymphoma. *Cancer Res* 52:5465s, 1992 (suppl 19)
- Martin PJ, Shulman HM, Schubach WH, Hansen JA, Fefer A, Miller G, Thomas ED: Fatal Epstein-Barr-virus-associated proliferation of donor B cells after treatment of acute graft-versus-host disease with a murine anti-T-cell antibody. *Ann Intern Med* 101:310, 1984
- Knowles DM, Cesarman E, Chadburn A, Frizzera G, Chen J, Rose EA, Michler RE: Correlative morphologic and molecular genetic analysis demonstrates three distinct categories of posttransplantation lymphoproliferative disorders. *Blood* 85:552, 1995
- d'Amore ESG, Manivel JC, Gajl-Peczalska KJ, Litz CE, Copenhagen CM, Shapiro RS, Stricker JG: B-cell lymphoproliferative disorders after bone marrow transplant. An analysis of ten cases with emphasis on Epstein-Barr virus detection by in situ hybridization. *Cancer* 68:1285, 1991
- Zutter MM, Martin PJ, Sale GE, Shulman HM, Fisher L, Thomas ED, Durnam DM: Epstein-Barr virus lymphoproliferation after bone marrow transplantation. *Blood* 72:520, 1988
- Zutter MM, Durnam DM, Hackman RC, Loughran TP Jr, Kidd PG, Ashley RL, Petersdorf EW, Martin PJ, Thomas ED: Secondary T-cell lymphoproliferation after marrow transplantation. *Am J Clin Pathol* 94:714, 1990
- Trimble MS, Wayne JS, Walker IR, Brain MC, Leber FB: B-cell lymphoma of recipient origin 9 years after allogeneic bone marrow transplantation for T-cell acute lymphoblastic leukaemia. *Br J Haematol* 85:99, 1993
- Brion A, Cahn JY, Mougin C, Angonin R, Flesch M, Deschaseaux ML, Plouvier E, Deconinck E, Voillat L, Racadot E, Carbillet JP, Herve P: Herpes virus-related lymphoproliferative disorders following allogeneic bone marrow transplantation: Clinical and biological characteristics of six cases. *Nouv Rev Fr Hematol* 37:289, 1995
- Verschuur A, Brousse N, Raynal B, Brison O, Rohrlisch P, Rahimy C, Vilmer E: Donor B cell lymphoma of the brain after

allogeneic bone marrow transplantation for acute myeloid leukemia. *Bone Marrow Transplant* 14:467, 1994

16. Kingma DW, Medeiros LJ, Barletta J, Raffeld M, Mann RB, Ambinder RF, Jaffe ES: Epstein-Barr virus is infrequently identified in non-Hodgkin's lymphomas associated with Hodgkin's disease. *Am J Surg Pathol* 18:48, 1994
17. Breslow NE, Day NE: *Statistical Methods in Cancer Research. Vol II—The Design and Analysis of Cohort Studies*. Lyon, France, International Agency for Research on Cancer, 1987 (IARC scientific publication no. 82)
18. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457, 1958
19. Preston DL, Lubin JH, Pierce DA: *Epicure User's Guide*. Seattle, WA, HiroSoft Intl Corp, 1993
20. Cox DR: Regression models and life-tables (with discussions). *J R Stat Soc B* 34:187, 1972
21. Curtis RE, Rowlings PA, Deeg HJ, Shriner DA, Socié G, Travis LB, Horowitz MM, Witherspoon RP, Hoover RN, Sobocinski KA, Fraumeni JF Jr, Schoch HG, Sale GE, Storb R, Travis WD, Kolb HJ, Gale RP, Passweg JR, Boice JD Jr: Solid cancers after bone marrow transplantation. *N Engl J Med* 336:897, 1997
22. Goedert JJ, Cote TR, Virgo P, Scoppa SM, Kingma DW, Gail MH, Jaffe ES, Biggar RJ: Spectrum of AIDS-associated malignant disorders. *Lancet* 351:1833, 1998
23. Newell KA, Alonso EM, Whittington PF, Bruce DS, Millis JM, Piper JB, Woodle ES, Kelly SM, Koeppen H, Hart J, Rubin CM, Thistlethwaite JR Jr: Posttransplant lymphoproliferative disease in pediatric liver transplantation. Interplay between primary Epstein-Barr virus infection and immunosuppression. *Transplantation* 62:370, 1996
24. Opelz G, Henderson R: Incidence of non-Hodgkin's lymphoma in kidney and heart transplant recipients. *Lancet* 342:1514, 1993
25. Hoover RN: Lymphoma risks in populations with altered immunity—A search for mechanism. *Cancer Res* 52:5477s, 1992 (suppl 19)
26. Kinlen LJ: Immunologic factors, including AIDS, in Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention* (ed 2). New York, NY, Oxford University Press, 1996, p 532
27. Cohen JI: Epstein-Barr virus lymphoproliferative disease associated with acquired immunodeficiency. *Medicine (Baltimore)* 70:137, 1991
28. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, O'Sullivan EJ, Johnson MR, Heroux AL, Dizikes GJ, Pifarre R, Fisher RI: Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. *N Engl J Med* 323:1723, 1990
29. Liebowitz D: Epstein-Barr virus and a cellular signaling pathway in lymphomas from immunosuppressed patients. *N Engl J Med* 338:1413, 1998
30. Nalesnik MA, Makowka L, Starzl TE: The diagnosis and treatment of posttransplant lymphoproliferative disorders. *Curr Probl Surg* 25:367, 1988
31. Frizzera G, Hanto DW, Gajl-Peczalska KJ, Rosai J, McKenna RW, Sibley RK, Holahan KP, Lindquist LL: Polymorphic diffuse B-cell hyperplasias and lymphomas in renal transplant recipients. *Cancer Res* 41:4262, 1981
32. Shapiro RS, McClain K, Frizzera G, Gajl-Peczalska KJ, Kersey JH, Blazar BR, Arthur DC, Patton DF, Greenberg JS, Burke B, Ramsay NKC, McGlave P, Filipovich AH: Epstein-Barr virus associated B cell lymphoproliferative disorders following bone marrow transplantation. *Blood* 71:1234, 1988
33. Lucas KG, Burton RL, Zimmerman SE, Wang J, Cornetta KG, Robertson KA, Lee CH, Emanuel DJ: Semiquantitative Epstein-Barr virus (EBV) polymerase chain reaction for the determination of patients at risk for EBV-induced lymphoproliferative disease after stem cell transplantation. *Blood* 91:3654, 1998
34. Rooney CM, Smith CA, Ng CY, Loftin SK, Sixbey JW, Gan Y, Srivastava DK, Bowman LC, Krance RA, Brenner MK, Heslop HE: Infusion of cytotoxic T cells for the prevention and treatment of Epstein-Barr virus-induced lymphoma in allogeneic transplant recipients. *Blood* 92:1549, 1998
35. Papadopoulos EB, Ladanyi M, Emanuel D, Mackinnon S, Boulard F, Carabasi MH, Castro-Malaspina H, Childs BH, Gillio AP, Small TN, Young JW, Kernan NA, O'Reilly RJ: Infusions of donor leukocytes to treat Epstein-Barr virus-associated lymphoproliferative disorders after allogeneic bone marrow transplantation. *N Engl J Med* 330:1185, 1994
36. Bhatia S, Krishnan A, Niland J, Forman S: Second malignant neoplasms (SMN) following bone marrow transplantation (BMT) for hematologic malignancies: City of Hope experience. *Blood* 90:378a, 1997 (suppl 1, abstr)
37. Lucas KG, Small TN, Heller G, Dupont B, O'Reilly RJ: The development of cellular immunity to Epstein-Barr virus after allogeneic bone marrow transplantation. *Blood* 87:2594, 1996
38. Roux E, Helg C, Dumont-Girard F, Chapuis B, Jeannot M, Roosnek E: Analysis of T-cell repopulation after allogeneic bone marrow transplantation: Significant differences between recipients of T-cell depleted and unmanipulated grafts. *Blood* 87:3984, 1996
39. Keever CA, Small TN, Flomenberg N, Heller G, Pekle K, Black P, Pecora A, Gillio A, Kernan NA, O'Reilly RJ: Immune reconstitution following bone marrow transplantation: Comparison of recipients of T-cell depleted marrow with recipients of conventional marrow grafts. *Blood* 73:1340, 1989
40. Davey DD, Kamat D, Laszewski M, Goeken JA, Kemp JD, Trigg ME, Purtilo DT, Davis J, Dick FR: Epstein-Barr virus-related lymphoproliferative disorders following bone marrow transplantation: An immunologic and genotypic analysis. *Mod Pathol* 2:27, 1989
41. Hill GR, Crawford JM, Cooke KR, Brinson YS, Pan L, Ferrara JLM: Total body irradiation and acute graft-versus-host disease: The role of gastrointestinal damage and inflammatory cytokines. *Blood* 90:3204, 1997
42. Meignin V, Devergie A, Brice P, Brison O, Parquet N, Ribaud P, Cojean I, Gaulard P, Gluckman E, Socié G, Janin A: Hodgkin's disease of donor origin after allogeneic bone marrow transplantation for myelogenous chronic leukemia. *Transplantation* 65:595, 1998
43. Schouten HC, Hopman AH, Haesevoets AM, Arends JW: Large-cell anaplastic non-Hodgkin's lymphoma originating in donor cells after allogeneic bone marrow transplantation. *Br J Haematol* 91:162, 1995
44. O'Riordan JM, Molloy K, O'Briain DS, Corbally N, Devaney D, McShane D, Considine N, McCann SR: Localized, late-onset, high-grade lymphoma following bone marrow transplantation: Response to combination chemotherapy. *Br J Haematol* 86:183, 1994
45. Armitage JM, Kormos RL, Stuart RS, Fricker FJ, Griffith BP, Nalesnik M, Hardesty RL, Dummer JS: Posttransplant lymphoproliferative disease in thoracic organ transplant patients: Ten years of cyclosporine-based immunosuppression. *J Heart Lung Transplant* 10:877, 1991
46. Antin JH, Bierer BE, Smith BR, Ferrara J, Guinan EC, Sieff C, Golan DE, Macklis RM, Tarbell NJ, Lynch E, Reichert TA, Blythman H, Bouloux C, Rapoport JM, Burakoff SJ, Weinstein HJ: Selective depletion of bone marrow T lymphocytes with anti-CD5 monoclonal antibodies: Effective prophylaxis for graft-versus-host disease in patients with hematologic malignancies. *Blood* 78:2139, 1991
47. Gerritsen EJ, Stam ED, Hermans J, van den Berg H, Haraldsson A, van Tol MJD, van den Bergh RL, Waaijer JLM, Kroes ACM, Kluijn PM, Vossen JM: Risk factors for developing EBV-related B cell lymphoproliferative disorders (BLPD) after non-HLA-identical BMT in children. *Bone Marrow Transplant* 18:377, 1996
48. Jabado N, Le Deist F, Cant A, De Graeff-Meesters ER, Fasth A, Morgan G, Vellodi A, Hale G, Bujan W, Thomas C, Cavazzana-Calvo M, Wijdenes J, Fischer A: Bone marrow transplantation from geneti-

cally HLA-nonidentical donors in children with fatal inherited disorders excluding severe combined immunodeficiencies: Use of two monoclonal antibodies to prevent graft rejection. *Pediatrics* 98:420, 1996

49. Hale G, Waldmann H: Risks of developing Epstein-Barr virus-related lymphoproliferative disorders after T-cell-depleted marrow transplants. *CAMPATH Users. Blood* 91:3079, 1998

50. Flinn I, Orentas R, Noga SJ, Marcellus D, Vogelsang GB, Jones RJ, Ambinder RF: Low risk of Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disease (PTLD) in patients receiving elutriated allogeneic marrow transplants may reflect depletion of EBV infected lymphocytes from the graft. *Blood* 86:626a 1995 (suppl 1, abstr)

51. Frank D, Cesarman E, Liu YF, Michler RE, Knowles DM: Posttransplantation lymphoproliferative disorders frequently contain type A and not type B Epstein-Barr virus. *Blood* 85:1396, 1995

52. Leblond V, Davi F, Charlotte F, Dorent R, Bitker MO, Sutton L, Gandjbakhch I, Binet JL, Raphael M: Posttransplant lymphoproliferative disorders not associated with Epstein-Barr virus: a distinct entity? *J Clin Oncol* 16:2052, 1998

53. Riddler SA, Breinig MC, McKnight JL: Increased levels of circulating Epstein-Barr virus (EBV)-infected lymphocytes and decreased EBV nuclear antigen antibody responses are associated with the development of posttransplant lymphoproliferative disease in solid-organ transplant recipients. *Blood* 84:972, 1994

54. Savoie A, Perpète C, Carpentier L, Joncas J, Alfieri C: Direct correlation between the load of Epstein-Barr virus-infected lymphocytes in the peripheral blood of pediatric transplant patients and risk of lymphoproliferative disease. *Blood* 83:2715, 1994

55. Rooney CM, Smith CA, Ng CY, Loftin S, Li C, Krance RA, Brenner MK, Keslop HE: Use of gene-modified virus-specific T lymphocytes to control Epstein-Barr-virus-related lymphoproliferation. *Lancet* 345:9, 1995

56. Benkerrou M, Jais JP, Leblond V, Durandy A, Sutton L, Bordigoni P, Garnier JL, Le Bidois J, Le Deist F, Blanche S, Fischer A: Anti-B-cell monoclonal antibody treatment of severe posttransplant B-lymphoproliferative disorder: Prognostic factors and long-term outcome. *Blood* 92:3137, 1998