

New Malignant Diseases After Allogeneic Marrow Transplantation for Childhood Acute Leukemia

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Purpose: To determine the incidence of and risk factors for second malignancies after allogeneic bone marrow transplantation (BMT) for childhood leukemia.

Patients and Methods: We studied a cohort of 3,182 children diagnosed with acute leukemia before the age of 17 years who received allogeneic BMT between 1964 and 1992 at 235 centers. Observed second cancers were compared with expected cancers in an age- and sex-matched general population. Risk factors were evaluated using Poisson regression.

Results: Twenty-five solid tumors and 20 posttransplant lymphoproliferative disorders (PTLDs) were observed compared with 1.0 case expected ($P < .001$). Cumulative risk of solid cancers increased sharply to 11.0% (95% confidence interval, 2.3% to 19.8%) at 15 years and was highest among children at ages younger than 5 years at transplantation. Thyroid and brain cancers ($n = 14$) accounted for most of the strong age trend; many of these patients received cranial irradiation before BMT.

Multivariate analyses showed increased solid tumor risks associated with high-dose total-body irradiation (relative risk [RR] = 3.1) and younger age at transplantation (RR = 3.7), whereas chronic graft-versus-host disease was associated with a decreased risk (RR = 0.2). Risk factors for PTLD included chronic graft-versus-host disease (RR = 6.5), unrelated or HLA-disparate related donor (RR = 7.5), T-cell-depleted graft (RR = 4.8), and antithymocyte globulin therapy (RR = 3.1).

Conclusion: Long-term survivors of BMT for childhood leukemia have an increased risk of solid cancers and PTLDs, related to both transplant therapy and treatment given before BMT. Transplant recipients, especially those given radiation, should be monitored closely for second cancers.

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ALLOGENEIC BONE marrow transplantation (BMT) from an HLA-identical sibling donor is generally considered the treatment of choice for consolidation therapy in children with acute myelogenous leukemia (AML).¹ In children with acute lymphoblastic leukemia (ALL), transplantation is often used for those who relapse after primary chemotherapy and, occasionally, as front-line treatment in patients with high-risk features, such as the t(9;22) or t(4;11) translocations, or in those who respond poorly to

conventional induction therapy.¹⁻³ However, there is growing concern about possible late consequences of BMT, particularly new cancers resulting from total-body irradiation (TBI) and high-dose chemotherapy used as the conditioning regimen for transplantation (reviewed in a report by Deeg and Socié⁴). Transplant recipients are known to have an increased risk of posttransplant lymphoproliferative disorders (PTLDs), and several studies have reported an elevated incidence of second malignancies.⁵⁻⁹ In a previous study, we identified an increased risk of solid tumors in BMT recipients and reported that risk was particularly high in patients who underwent transplantation before the age of 20 years.¹⁰ The current report provides an in-depth evaluation of the incidence of and risk factors for second malignancies among children who undergo transplantation for acute leukemia, the most frequent indication for allogeneic BMT in this age group.

PATIENTS AND METHODS

Patients

A total of 3,182 patients younger than 17 years who received allogeneic or syngeneic BMT for acute leukemia were identified through the International Bone Marrow Transplant Registry (IBMTR) database in Milwaukee, WI, and the Fred Hutchinson Cancer Research Center in Seattle, WA. The IBMTR database included patients who received transplants at 234 centers worldwide between 1964 and 1990, whereas Seattle included transplants between 1969 and 1992. More

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All support information is given in the Appendix.

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than 90% of patients were followed through the end date of the study (IBMTR, December 31, 1991; Seattle, December 31, 1992). The median duration of follow-up was 0.9 years (range, < 1 month to 20.7 years) for all patients and 3.6 years (range, 1 to 20.7 years) for 2,410 patients who survived at least 1 year after transplantation.

Pathology reports and selected slides were reviewed centrally for 95% of the patients with new solid tumors (W.D.T.). PTLDs were confirmed by centralized histopathologic review in 13 cases (E.S.J., D.W.K.), pathology report evaluation in four cases (P.M.B.), and published reports in the pathology literature in another two cases^{11,12}; one case was documented by transplant center report only. In situ hybridization was performed for Epstein-Barr virus (EBV)-encoded RNA (EBER1) expression in 12 of 13 PTLD cases with tissue available; one additional case was documented as EBV-positive in the literature using similar methods.¹³

Treatment and Risk Factors

Patients with ALL comprised 63.5% of the cohort, acute nonlymphocytic leukemia (ANLL) comprised 35.5%, and acute leukemia undifferentiated or not otherwise specified comprised 0.9% (Table 1). Classification of ALL according to French-American-British group or by immunophenotype was available only for patients registered within the IBMTR database. Sixty percent of the ALL cases reported to the IBMTR were common ALL antigen-positive, 25% were T-cell ALL, and 15% were other subtypes. The French-American-British classification for patients with ANLL was as follows: M1/M2, 50%; M4/M5, 34%; and other subtypes (M3, M6, or M7), 16%.

Most patients received bone marrow from an HLA-identical sibling (IBMTR, 83%; Seattle, 66%). Median age at transplantation was 10.1 years (range, 0.1 to 16.9 years). Conditioning regimens for 2,766 patients (87% of the cohort) consisted of TBI or limited-field irradiation combined with cyclophosphamide and/or other drugs. Only 13% of patients received conditioning without irradiation. Conditioning with high-dose TBI (defined as ≥ 10 -Gy single-dose TBI or ≥ 13 -Gy fractionated TBI) was used for 27% of IBMTR and 74% of Seattle patients. Prophylaxis against graft-versus-host disease (GvHD) varied during the time period; methotrexate, cyclosporine, or a combination of both drugs were the most commonly used regimens. T-cell depletion of the graft was used as prophylaxis against GvHD in 11% of patients (IBMTR, 15%; Seattle, 0.3%). Antithymocyte (or antilymphocyte) globulin was given as prophylaxis or therapy in 11% of patients (IBMTR, 7%; Seattle, 19%). The incidence of moderate to severe (ie, grades II to IV) acute GvHD and chronic GvHD among 90-day survivors was low (35% and 15%, respectively).

For patients with second malignancies, information on prior radiation therapy for the primary disease was abstracted from transplant center records, but such data were generally unavailable for other subjects.

Statistical Analyses

For each transplant recipient, the number of person-years at risk was calculated from the date of transplantation until the date of last contact, death, diagnosis of second malignancy, or study end date(s), whichever occurred first. Age-, sex-, calendar year-, and geographic region-specific incidence rates for all invasive solid tumors and non-Hodgkin's lymphoma combined and for invasive solid tumors at specific sites were applied to the appropriate person-years at risk to compute the expected numbers of invasive second malignancies. Ratios of observed to expected second cancer cases (O/E) and 95% confidence intervals (CIs) were calculated on the assumption that the observed number of malignancies followed a Poisson distribution.¹⁴ The absolute (excess)

Table 1. Characteristics of 3,182 Patients Younger Than 17 Years Who Underwent Transplantation for Acute Leukemia

Characteristic	No. of Patients	%
Cohort		
IBMTR	2,384	74.9
Seattle	798	25.1
Sex of the recipient		
Male	1,945	61.1
Female	1,237	38.9
Primary disease		
ALL	2,022	63.5
ANLL	1,130	35.5
Acute leukemia undifferentiated or not otherwise specified	30	0.9
Donor-recipient relationship and histocompatibility		
HLA-identical sibling	2,385	75.0
Twin	96	3.0
HLA-identical related, not sibling	53	1.7
HLA-mismatched related	493	15.5
Unrelated	125	3.9
Other or uncertain	30	0.9
Conditioning regimen		
TBI + cyclophosphamide \pm other drugs	2,311	72.6
TBI + other drugs (no cyclophosphamide)	443	13.9
LFI \pm cyclophosphamide \pm other drugs	12	0.4
Busulfan + cyclophosphamide \pm other drugs	315	9.9
Cyclophosphamide \pm other drugs	41	1.3
Other	60	1.9
Radiation-based conditioning regimen	2,766	86.9
Non-radiation-based conditioning regimen	416	13.1
Drugs given for GvHD prophylaxis		
Methotrexate, no cyclosporine	1,110	34.9
Cyclosporine, no methotrexate	772	24.3
Cyclosporine + methotrexate \pm other drugs	931	29.2
No drugs*	250	7.8
Other	119	3.8
T-cell depletion of donor marrow	361	11.3
Acute GvHD (grades II-IV)	1,122	35.3
Chronic GvHD (moderate, severe/extensive)†	361	14.5
TBI dose		
Single dose		
< 10 Gy	325	10.2
≥ 10 Gy	577	18.1
Fractionated		
< 12 Gy	287	9.0
13 Gy	845	26.6
14 Gy	175	5.5
≥ 14 Gy	487	15.3
Unknown	58	1.8

Abbreviation: LFI, limited-field irradiation.

*Category includes twins and patients with T-cell-depleted transplants.

†Percent chronic GvHD among 2,494 patients who survived at least 90 days.

risk was calculated as the observed minus the expected number of second cancers per 10,000 recipients per year. The cumulative probability of a new malignancy was estimated by the Kaplan-Meier method.¹⁵

Univariate and multivariate analyses were used to compare risk for various subgroups of transplant recipients. Because multivariate anal-

Table 2. Solid Cancers After Bone Marrow Transplantation Among Children With Acute Leukemia

Patient No.	Solid Cancer	Primary Disease	Donor/Age at TX (years)/Sex	TBI Dose (Gy)/Other RT (Gy)	Latency (years)	GvHD	Vital Status/Survival (years)/Death Caused by NM
1	Tongue, SCC	ALL	Identical sib/10.3/M	No TBI/brain 24	2.6	—	Alive/4.0/—
2	Tongue, SCC	ALL	Identical sib/6.8/M	FTBI 15/brain 24, testes 17	10.7	Chronic, moderate	Dead/6.5/no
3	Tongue, SCC	ALL	Identical sib/14.0/M	STBI 10/brain 24	7.1	Acute, grade 2	Dead/1.6/yes
4	Salivary gland, mucoepidermoid carcinoma	ANLL	Identical sib/4.5/M	FTBI 13.2	6.5	—	Alive/0.8/—
5	Salivary gland, mucoepidermoid carcinoma	ANLL	Identical sib/5.4/F	STBI 10	6.6	—	Alive/9.5/—
6	Osteosarcoma	ANLL	Identical sib/6.5/M	FTBI 13.2	6.6	—	Dead/2.4/yes
7	Osteosarcoma	ANLL	Identical sib/9.8/F	FTBI 12	2.5	Acute, grade 1	Alive/6.8/—
8	MFH	ANLL	Identical sib/11.6/M	FTBI 12	1.7	—	Alive/2.3/—
9	Melanoma (skin) level III	ANLL	Twin/4.2/M	STBI 7.5	0.4	—	Alive/12.3/—
10	Melanoma (skin) level III	ANLL	Identical sib/14.1/F	STBI 10	5.2	—	Alive/3.2/—
11	Melanoma (skin) in situ	ANLL	Identical sib/16.4/F	FTBI 12	4.7	Acute, grade 2	Alive/11.4/—
12	Melanoma (skin) level III	ALL	Identical sib/8.1/F	STBI 10/brain 18	1.8	Acute, grade 1	Alive/12.0/—
13	Thyroid, papillary carcinoma	ALL	Identical sib/9.2/F	STBI 10	10.9	Acute, grade 2	Alive/3.6/—
14	Thyroid, papillary carcinoma	AL	Twin/8.8/F	STBI 10/brain 26	14.3	—	Alive/8.8/—
15	Thyroid, papillary carcinoma	AL	Identical sib/7.7/F	STBI 10/brain 20, ovaries 20	10.4	—	Alive/7.7/—
16	Thyroid, papillary carcinoma	ALL	Identical sib/5.5/M	STBI 10/brain 24	4.5	Acute, grade 2	Alive/8.5/—
17	Thyroid, papillary carcinoma 9 Brain cancers*	ANLL ALL (6) ANLL (3)	Identical sib/15.6/M 6 identical sib, 1 twin, 2 mismatch related/ 1.0-9.7/6 M, 3 F	FTBI 15.8 STBI 10 (n = 4), FTBI 11-15.8 (n = 5)/brain ± other (n = 6)	6.5 0.98-9.3	— Acute, grade 1 (2), grade 2 (2)	Alive/4.6/— 9 dead/0.2-2.7/ yes (8), no (1)

Abbreviations: TX, transplant; GvHD, graft-versus-host disease; identical sib, HLA identically matched sibling; MFH, malignant fibrous histiocytoma; STBI, single-dose total-body irradiation; FTBI, fractionated total-body irradiation; brain, cranial irradiation ± spinal irradiation; RT, radiation; SCC, squamous cell carcinoma; NM, new second malignancy; AL, acute leukemia undifferentiated or not otherwise specified.

*Brain cancer case cell types: primitive neuroectodermal tumor (n = 1), glioblastoma multiforme (n = 5), and astrocytoma (n = 3).

yses for solid tumors assumed a minimum 1-year latent period, as in previous investigations,¹⁰ we excluded patients with less than 1 year of follow-up. Multivariate analysis for PTLD included all time periods because of the high risk of these malignancies during the first year after transplant. Poisson regression methods for grouped survival data were used; analyses were stratified according to the interval since transplantation and were adjusted for the cohort (Seattle or IBMTR). Occurrences of acute and chronic GvHD were entered as time-dependent covariates.

RESULTS

New Malignancies

Characteristics. Among the 3,182 children with acute leukemia who underwent BMT, 45 invasive second cancers (25 invasive solid cancers and 20 PTLDs) and one in situ cancer were observed. The characteristics of all patients with solid tumors are listed in Table 2. The underlying primary disease of the 25 patients with invasive solid malignancies was ALL in 12 patients, ANLL in 11 patients, and acute leukemia not otherwise specified in two patients.

The median age at transplantation was 8.2 years (range, 1 to 16.4 years). Fifteen patients were boys and 10 were girls. The median time from transplantation to diagnosis of a solid tumor was 6 years (range, 0.3 to 14.3 years). Two invasive solid tumors, a melanoma and a brain cancer, occurred in the first year after transplant. More than half of the 25 invasive solid tumors were cancers of the brain or thyroid; nine of these 14 patients had CNS irradiation before BMT (six of nine patients with brain cancer and three of five patients with thyroid cancer). Twelve patients with solid cancers died, 10 as a direct consequence of their new malignancies.

The 20 PTLDs (11 boys, nine girls) occurred in 11 patients who underwent transplantation for ALL and in nine who underwent transplantation for ANLL. The median age at transplantation was 5.8 years (range, 0.4 to 16.1 years). The median time from transplantation to diagnosis of PTLD was 1.5 years: 15 PTLDs occurred in the first year after transplant, four occurred between 12

Table 3. Ratio of Observed to Expected Cases of New Invasive Malignancies According to Time Since Transplantation

	Time After Transplantation (years)									
	< 1		1-4		5-9		≥ 10		Total	
	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E
No. of patients	3,182		1,658		602		150		3,182	
Person-years at risk	2,191		3,961		1,730		328		8,209	
All malignancies	17	77	12	29	12	46	4	50	45	45
PTLD	15	540	5	97	0	0	0	0	20	182
Solid tumors	2	12	7	23	12	63	4	60	25*	34
Tongue	0	0	1	2,888	1	2,582	1	5,369	3	2,765
Salivary	0	0	0	0	2	1,745	0	0	2	519
Melanoma	1	176	1	62	1	56	0	0	3	65
Brain/CNS	1	18	2	21	6	169	0	0	9	46
Thyroid	0	0	1	69	1	69	3	522	5	125
Bone, connective tissue	0	0	2	28	1	32	0	0	3	20

*In addition to these 25 cases of invasive solid tumors, 1 case of in situ malignant melanoma was observed.

and 18 months after transplant, and one occurred at 4.9 years after transplant. All 20 patients with PTLN died; in 18 cases, PTLN was the primary (n = 16) or contributing (n = 2) cause of death. EBV genome was detected in 13 of 13 assessable cases.

Overall incidence and tumor type. The risk of developing a new malignancy was significantly increased, with 45 invasive cancers observed compared with 1.0 case expected in an age- and sex-matched general population (O/E = 45; 95% CI, 33 to 61; $P < .001$; Table 3). Significantly elevated risks were observed for PTLN (O/E = 182), solid tumors overall (O/E = 34) and specifically for cancers of the tongue (O/E = 2,765), salivary glands (O/E = 519), brain and CNS (O/E = 46), thyroid (O/E = 125), bone and connective tissue (O/E = 20), and malignant melanoma (O/E = 65). The exceptionally high O/E ratios for cancers of the tongue and salivary gland result in part from the rarity of these neoplasms among children and young adults. The increase in risk for invasive solid tumors compared with the general population increased over time from 23-fold during the 1 to 4 years after transplant to more than 60 times the

expected risk in the 5 to 9 year and 10+ years after transplant. The Kaplan-Meier estimates of the probability of new invasive solid tumors at 5, 10, and 15 years after transplantation were 0.9% (95% CI, 0.3% to 1.5%), 4.3% (95% CI, 2.2% to 6.5%), and 11.0% (95% CI, 2.3% to 19.8%), respectively. In contrast, the risk of PTLN was highest during the first 5 years after transplant (< 1 year, O/E = 540; 1 to 5 years, O/E = 97) but then decreased sharply with no cases of PTLN reported among 5+-year survivors. The cumulative rate of PTLN was 1.0% (95% CI, 0.5% to 1.5%) at 5 years. In absolute terms, the excess cancer rate (PTLN and solid cancers) was 53 cancers/10,000/y over all time periods, and 120/10,000/y among 10+-year survivors.

Risk of a new malignancy did not vary by type of leukemia (Table 4; ALL, O/E = 44; ANLL, O/E = 48). However, there was a strong relationship between patient age at the time of transplantation and second cancer risk in both relative (O/E) and absolute (excess risk) terms. The excess risk in patients younger than 5 years was 117/10,000/y, whereas it was 68/10,000/y in patients between 5

Table 4. Ratio of Observed to Expected Cases of New Invasive Malignancies According to Age at Transplant and Primary Disease

	No. of Patients	Observed	Expected	O/E	95% CI	Excess Risk*
Primary disease						
ALL + AL	2,052	25	0.57	44	28-65	50
ANLL	1,130	20	0.42	48	29-74	60
Age at transplant						
< 5 years	487	14	0.12	115	63-193	117
5-10 years	1,071	20	0.27	75	46-115	68
10-16 years	1,624	11	0.59	18	9-33	25

*Excess risk = [(observed - expected)/person-years at risk] × 10,000.

Table 5. Risk Factors for New Invasive Solid Cancers Among 1,658 Children Who Survived at Least 1 Year After Transplantation for Acute Leukemia

Model Variables	PYR	Cases*	Relative Risk	95% CI	P
Multivariate Poisson regression model I: 23 solid tumors; 5,843 PYR					
Cohort					
IBMTR	4,248	10	1.0	Reference	.28
Seattle	1,595	13	1.7	0.7-4.4	
Transplant age					
0-9 years	2,893	18	3.7	1.5-11.2	.005
10-16 years	2,950	5	1.0	Reference	
Radiation					
No or low-dose TBI	3,679	5	1.0	Reference	
High-dose TBI†	2,164	18	3.1	1.1-10.3	.03
Chronic GvHD					
None, mild	4,880	22	1.0	Reference	
Moderate, severe	963	1	0.2	0.01-0.9	.03
Multivariate Poisson regression model II: 13 brain and thyroid cancers; 5,843 PYR					
Cohort					
IBMTR	4,248	4	1.0	Reference	
Seattle	1,595	9	2.3	0.7-9.8	.20
Transplant age					
0-9 years	2,893	12	12.2	2.4-223	.0009
10-16 years	2,950	1	1.0	Reference	
Radiation					
No or low-dose TBI	3,679	2	1.0	Reference	
High dose TBI†	2,164	11	3.6	0.8-25.9	.10
Chronic GvHD					
None, mild	4,880	13	1.0	Reference	
Moderate, severe	963	0	0.0	0.0-0.6	.01

Abbreviations: PYR, person-years at risk.

*Model I includes all solid tumors (n = 23); model II includes a subset of solid tumors (n = 13 brain and thyroid cancers).

†High dose TBI defined as ≥ 10 -Gy single-dose TBI or ≥ 13 -Gy fractionated TBI.

to 10 years of age, and 25/10,000/y in patients between 10 and 16 years (P for trend $< .0001$). Second cancers of the brain and thyroid, which tended to occur among the very young, accounted for much of the age difference.

Risk Factor Analyses

Solid tumors. The results of multivariate regression analyses of risk factors for the 23 invasive solid tumors occurring among patients who survived at least 1 year after transplantation are summarized in Table 5 (one brain cancer and one melanoma occurring in the first year after BMT were excluded). Patients who received pretransplantation conditioning with high-dose TBI (≥ 10 -Gy single-dose TBI or ≥ 13 -Gy fractionated TBI) had a higher risk of cancer than those who received lower-dose TBI or no radiation (relative risk [RR] = 3.1). Age at transplant was also a significant risk factor in multivariate analyses, with a nearly fourfold risk of solid tumors in patients who underwent BMT at an age younger than 10 years. No difference in solid cancer risk was detected for children younger than 5 years at transplantation versus those aged 5 to 9 years (RR = 3.9 v 3.6; $P = .87$). Patients with moderate to severe

chronic GvHD had a significantly lower risk of solid cancers (RR = 0.2).

We evaluated risk factors for the 13 brain and thyroid cancers that occurred among 1-year survivors separately from the 10 solid tumors of other types (tongue, salivary gland, melanoma, sarcomas). Younger age at transplantation was the strongest risk factor for developing cancer of the brain or thyroid (RR = 12.2; $P = .0009$; Table 5). Patients with chronic GvHD had a significantly lower risk in these analyses, whereas the risk associated with high-dose TBI remained elevated but was not statistically significant (RR = 3.6; $P = .10$). No significant factors were identified in models that evaluated other solid tumor types (n = 10; data not shown). Age at transplant had only a marginal association on risk of solid tumors of other types (RR = 1.6 for ages < 10 years v 10 to 16 years; $P = .49$), but higher-dose TBI was again associated with increased risk (RR = 2.8; $P = .16$). Thus, although the effects of high-dose TBI seemed to be consistent across solid tumor types, difference in risk by age at transplantation was confined to second brain and thyroid cancers alone.

Table 6. Risk Factors for PTLDs Among 3,182 Children Who Underwent Transplantation for Acute Leukemia

Model Variables	PYR	Cases (n = 20)	Relative Risk	95% CI	P
Multivariate Poisson regression model: 20 PTLDs; 8,213 PYR					
Chronic GvHD					
None, mild	7,070	14	1.0	Reference	
Moderate, severe	1,143	6	6.5	2.0-19.8	.003
HLA					
HLA-identical related, twin, or HLA 1-Ag-mismatched relative	7,788	9	1.0	Reference	< .0001
HLA 2+ Ag-mismatched relative, or unrelated	425	11	7.5	2.9-19.7	
T-cell depletion					
No	7,587	12	1.0	Reference	
Yes	626	8	4.8	1.7-12.4	.003
Antithymocyte globulin (prophylaxis or treatment for acute GvHD)					
No	7,391	14	1.0	Reference	
Yes	822	6	3.1	1.1-8.2	.04

Abbreviations: Ag, antigen; PYR, person-years at risk.

PTLD. The results of multivariate regression analyses for PTLT risk factors are summarized in Table 6. Patients who developed moderate/severe chronic GvHD had 6.5 times the risk of PTLT compared with patients who had no/mild chronic GvHD after transplant. Transplantation from an unrelated donor or \geq two HLA-antigen disparate family donors was associated with a 7.5-fold increased risk of PTLT. T-cell depletion of the marrow graft was also a significant risk factor (RR = 4.8), as was use of antithymocyte (or antilymphocyte) globulin for prophylaxis or treatment of acute GvHD (RR = 3.1).

DISCUSSION

This evaluation of second cancers after BMT for childhood acute leukemia showed that solid cancer risk increased over time to an estimated 11% (95% CI, 2.3% to 19.8%) at 15 years, and that children who had undergone transplantation when younger than 10 years had the highest risk. Major strengths of our study include the large numbers of children evaluated and the efforts made to ensure nearly complete follow-up throughout the period of study.

Ideally, the risk of second malignancy among patients who receive allogeneic transplantation should be compared with the subsequent cancer risk after "conventional" therapy. Because the incidence of PTLT is rare in persons with normal immune function, the comparison focuses on the risk of secondary solid tumors. Unfortunately, the literature on solid cancer risk after childhood ALL and AML with conventional therapy is sparse for individual solid tumor sites, with the exception of secondary cancers of the brain and CNS. To our knowledge, no studies have evaluated the risk of solid cancers after AML, most likely reflecting the generally poor prognosis for these patients and the small numbers of long-term survivors. In the largest ALL study to

date, Neglia et al¹⁶ evaluated 9,720 children treated for ALL and estimated the cumulative incidence of all second neoplasms at 2.5% at 15 years based on 10 new leukemias and lymphomas, 24 CNS tumors, and nine other solid tumors. A high 22-fold increased risk of brain cancer developed that was linked to cranial irradiation, but only a small, nonsignificant 1.8-fold excess of other solid neoplasms was observed. Other studies indicate that the cumulative incidence of secondary brain cancer after conventional therapy for ALL is typically between 0.5% and 2.0%,¹⁷⁻¹⁹ although risks as high as 12.8% at 8 years have been reported after intensive systemic antimetabolite therapy before and during radiotherapy.¹⁸ A recent study of 1,597 childhood ALL patients from a multicenter cohort reported an overall cumulative incidence of new malignancies similar to the study by Neglia et al¹⁶ (2.7% at 18 years; 13 malignancies), but only five nonbrain solid tumors were described.²⁰ Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program from 1973 to 1993, provide some evidence that children with ALL have a significantly increased risk of solid cancers at sites other than brain and CNS (O/E = 4.6; 95% CI, 1.8 to 9.4; seven cases; R. Curtis, personal communication, October 1999). Our current study of children with acute leukemia undergoing allogeneic transplantation found a 34-fold increased risk of solid cancers, including excesses of cancers of the tongue, salivary glands, brain, thyroid, bone and connective tissue, and malignant melanoma. Although statistical comparisons are limited by small numbers, these risks seem to be higher than that observed to date after conventional therapies.

A large proportion of the children in our study died and were censored during the early years after BMT, and only 150 of 3,182 recipients survived \geq 10 years after transplant.

Thus, the estimates of cumulative risk of solid cancers among long-term survivors should be viewed with caution. Other investigators have observed that when the majority of second cancer events occur at follow-up intervals beyond which most of the patients in the cohort were censored, the late events tend to magnify the percent change in the actuarial risk.²¹ Moreover, some investigators warn that the Kaplan-Meier method provides an inappropriate estimate of the probability of an event when end points are subject to competing risks, and that the cumulative incidence estimate is preferred.²² In our series, the cumulative incidence method gives substantially lower estimates of solid cancer risk at 10 years (1.7%; 95% CI, 0.8% to 2.5%) and 15 years (3.9%; 95% CI, 1.0% to 6.8%) as compared with the Kaplan Meier method (4.3% and 11.0%, respectively). Thus, studies with larger numbers of long-term survivors are needed to confirm the magnitude of late cancer risk after BMT.

Although several factors likely contributed to the solid tumor excess, our results indicate that high-dose irradiation at a young age played an important role. The elevations in risk for several second malignancies in our study seem compatible with a radiogenic effect, particularly cancers of the brain, thyroid, bone, connective tissue, and salivary gland (reviewed by Boice et al,²³ Parker,²⁴ and Holm²⁵). These results are consistent with the increased risk of malignancies found in previous investigations of second cancers after irradiation for childhood cancer.^{16,19,26-36} Our dose-response analyses found higher solid tumor risks associated with higher TBI doses, providing evidence for a radiation effect.

Brain and thyroid cancers accounted for more than one half of all solid tumors in our study. There was a strong relationship between age at transplantation and the risk of these tumors, suggesting that the brain and thyroid gland are highly sensitive to the effects of irradiation at very young ages. It is likely that prior therapy contributed to this excess because nine of the 14 children with second brain or thyroid cancer had received cranial irradiation as prophylaxis or therapy for acute leukemia before BMT. In previous studies of children who received conventional therapy, cranial irradiation for ALL was associated with 20- to 50-fold increased risks of CNS tumors.^{16,19} Irradiation of the developing brain before the age of 5 years was particularly hazardous in the series by Neglia et al¹⁶ and accounted for 23 of the 24 CNS tumors.

The thyroid gland is highly sensitive to the effects of ionizing radiation.³⁷ Increased risks of thyroid cancer are found after head and neck irradiation during childhood at doses as low as 0.10 Gy³⁷ and at high doses more than 10 Gy used in therapeutic radiation for cancer.³⁸ Age at exposure is known to be an important factor in radiogenic thyroid cancer, with the highest risk found for those exposed

when younger than 10 years; there is little evidence of increased risk among those who undergo irradiation at ages 15 to 20 years.³⁷ Recent reports of children who received mantle irradiation for Hodgkin's disease estimate the thyroid cancer risk to be 10- to 30-fold times that expected in the general population.³⁹⁻⁴¹ Although reports of thyroid cancer after ALL are infrequent,^{16,28,42-44} the absorbed dose to the thyroid gland after prophylactic cranial irradiation of 18 to 24 Gy can be substantial, in the range of 0.13 to 1.3 Gy,⁴⁵ and high doses are delivered to the thyroid when conditioning for transplant with TBI.

The patterns of excess cancers of the salivary gland, bone, and connective tissues in our series are also consistent with a radiation effect. Cancers of the parotid gland are rare among children. Case reports have noted this tumor developing 5 to 15 years after cranial irradiation for ALL,^{46,47} and a significantly increased risk of salivary gland cancer has been noted among children who undergo irradiation for Hodgkin's disease.^{39,40} An exceptionally strong dose response was found for mucoepidermoid carcinoma of the salivary gland in the atomic bomb survivor cohort.⁴⁸ Radiation-related excesses of second cancers of the bone have been reported in several studies of patients treated with high-dose radiation (> 10 Gy),⁴⁰ and sarcoma risk is significantly related to radiation dose among childhood cancer survivors.^{49,50}

Neither melanoma nor cancer of the tongue has been linked to ionizing radiation in previous studies.²³ Melanoma has been reported to occur in excess among immunosuppressed patients, such as renal transplant recipients⁵¹ and childhood survivors of Hodgkin's disease.⁴⁰ Tongue cancer is exceedingly rare among young children and is not observed in excess in other childhood cancer cohorts, which suggests that the transplant environment of severe immune dysfunction/immunosuppression likely contributes to the pathogenesis of these rare tumors. Cancers of the tongue have also been described in patients who undergo BMT for aplastic anemia, particularly those who had severe chronic GvHD.^{6,8}

The decreased risk of solid tumors after chronic GvHD in our study was unexpected because our previous investigation that evaluated BMT recipients (all ages and primary diseases) found that chronic GvHD was strongly associated with an increased risk of squamous cell cancers of the oral cavity and skin but negatively associated with risk of brain and CNS tumors.¹⁰ Although the deficit in risk of solid tumors among children with acute leukemia may be simply a chance finding, pretransplant factors not evaluated in our analysis may, in part, explain this result. In addition, very young children may not have had sufficient time to reach the age at which GvHD-induced squamous cell cancers of the oral cavity or skin typically develop, because no deficit in

risk of these solid tumor sites was observed for older patients with acute leukemia in this cohort.

We found a particularly high risk of EBV-related PTLD occurring during the first year after transplant that was strongly related to factors associated with immune dysfunction. PTLD represent a spectrum of clinically and morphologically heterogeneous proliferations that are typically associated with T-cell dysfunction and the presence of EBV.^{4,7} Twenty PTLDs occurred in our patients, and all but one occurred within 18 months after transplant. The presence of the EBV genome was detected in all cases tested. PTLDs were the first malignancies for which risk factors were described after BMT; however, past investigations have combined both childhood and adult BMT recipients in their reports,^{5,7,9} and some series have included patients with primary immune-deficiency diseases who have a predisposition to cancer.⁹ Prior studies have found significant associations in multivariate analysis with T-cell depletion of donor marrow, unrelated donor, or HLA-mismatched related donor and the use of antithymocyte globulin or anti-CD monoclonal antibody (64.1) to treat acute GvHD.^{4,7} Our results confirm the importance of these PTLD risk factors in children who undergo BMT and identify chronic GvHD as an additional strong risk factor.

Most children included in our study received treatment modalities that were commonly used in the 1980s or earlier. However, current treatment protocols for children with acute leukemia frequently exclude prophylactic CNS irradiation for low- and intermediate-risk patients, and when radiation is given, lower doses are often used.¹ Among very young children who require transplantation, conditioning regimens that include chemotherapy without TBI are now commonly given. Long-term follow-up of these children will be necessary to determine whether this change in treatment strategy results in a lower risk of second cancers.

Our results alert pediatricians to the increased risk of subsequent neoplasms after BMT for childhood acute leukemia and to the increasing risk over time. Patients with severely compromised immune function following T-cell-depleted marrow grafts, HLA-mismatched grafts, or moderate to severe chronic GvHD should be considered at high risk for development of PTLD, particularly within the first 2 years after transplant. Long-term surveillance of children undergoing BMT will be needed to detect late-developing solid tumors, particularly at sites most sensitive to radiation exposure such as the brain, thyroid, salivary gland, bone, and breast.

APPENDIX

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REFERENCES

1. Kersey JH: Fifty years of studies of the biology and therapy of childhood leukemia. *Blood* 90:4243-4251, 1997
2. Hongeng S, Krance RA, Bowman LC, et al: Outcomes of transplantation with matched-sibling and unrelated-donor bone marrow in children with leukaemia. *Lancet* 350:767-771, 1997
3. Barrett AJ, Horowitz MM, Pollock BH, et al: Bone marrow transplants from HLA-identical siblings as compared with chemotherapy for children with acute lymphoblastic leukemia in a second remission. *N Engl J Med* 331:1253-1258, 1994
4. Deeg HJ, Socié G: Malignancies after hematopoietic stem cell transplantation: Many questions, some answers. *Blood* 91:1833-1844, 1998
5. Witherspoon RP, Fisher LD, Schoch G, et al: Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. *N Engl J Med* 321:784-789, 1989

6. Deeg HJ, Socie G, Schoch G, et al: Malignancies after marrow transplantation for aplastic anemia and Fanconi anemia: A joint Seattle and Paris analysis of results in 700 patients. *Blood* 87:386-392, 1996
7. Curtis RE, Travis LB, Deeg HJ, et al: Risk of lymphoproliferative disorders following bone marrow transplantation: A multi-institutional collaborative study. *Blood* 94:2208-2216, 1999
8. Socié G, Henry-Amar M, Bacigalupo et al: Malignant tumors occurring after treatment of aplastic anemia. *N Engl J Med* 329:1152-1157, 1993
9. Bhatia S, Ramsay NK, Steinbuch M, et al: Malignant neoplasms following bone marrow transplantation. *Blood* 87:3633-3639, 1996
10. Curtis RE, Rowlings PA, Deeg HJ, et al: Solid cancers after bone marrow transplantation. *N Engl J Med* 336:897-904, 1997
11. Zutter MM, Durnam DM, Hackman RC, et al: Secondary T-cell lymphoproliferation after marrow transplantation. *Am J Clin Pathol* 94:714-721, 1990
12. Brion A, Cahn JY, Mougin C, et al: Herpes virus-related lymphoproliferative disorders following allogeneic bone marrow transplantation: Clinical and biological characteristics of six cases. *Nouv Rev Fr Hematol* 37:289-296, 1995
13. Verschuur A, Brousse N, Raynal B, et al: Donor B cell lymphoma of the brain after allogeneic bone marrow transplantation for acute myeloid leukemia. *Bone Marrow Transplant* 14:467-470, 1994
14. Breslow NE, Day NE: *Statistical Methods in Cancer Research, vol II: The Design and Analysis of Cohort Studies*. IARC scientific publication no. 82. Lyon, France, International Agency for Research on Cancer, 1987
15. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
16. Neglia JP, Meadows AT, Robison LL, et al: Second neoplasms after acute lymphoblastic leukemia in childhood. *N Engl J Med* 325:1330-1336, 1991
17. Walter AW, Hancock ML, Pui C-H, et al: Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. *J Clin Oncol* 16:3761-3767, 1998
18. Relling MV, Rubnitz JE, Rivera GK, et al: High incidence of secondary brain tumours after radiotherapy and antimetabolites. *Lancet* 354:34-39, 1999
19. Rosso P, Terracini B, Fears TR, et al: Second malignant tumors after effective end of therapy for a first cancer in childhood: A multicenter study in Italy. *Int J Cancer* 59:451-456, 1994
20. Dalton VMK, Gelber RD, Li F, et al: Second malignancies in patients treated for childhood acute lymphoblastic leukemia. *J Clin Oncol* 16:2848-2853, 1998
21. Donaldson SS, Hancock SL: Second cancers after Hodgkin's disease in childhood. *N Engl J Med* 334:792-794, 1996 (editorial)
22. Gooley TA, Leisenring W, Crowley J, et al: Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. *Stat Med* 18:695-706, 1999
23. Boice JD, Land CE, Preston DL: Ionizing radiation, in Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention* (ed 2). New York, NY, Oxford University Press, 1996, pp 319-354
24. Parker RG: Radiation-induced cancer as a factor in clinical decision making. *Int J Radiat Oncol Biol Phys* 18:993-1000, 1990
25. Holm LE: Cancer occurring after radiotherapy and chemotherapy. *Int J Radiat Oncol Biol Phys* 19:1303-1308, 1990
26. Kony SJ, de Vathaire F, Chompret A, et al: Radiation and genetic factors in the risk of second malignant neoplasms after a first cancer in childhood. *Lancet* 350:91-95, 1997
27. Jankovic M, Frascini D, Amici A, et al: Outcome after cessation of therapy in childhood acute lymphoblastic leukaemia. *Eur J Cancer* 29A:1839-1843, 1993
28. Gutjahr P: Nonleukemic second malignancies following childhood acute lymphocytic leukaemia. *Helv Paediatr Acta* 40:449-459, 1985
29. Hudson MM, Jones D, Boyett J, et al: Late mortality of long-term survivors of childhood cancer. *J Clin Oncol* 15:2205-2213, 1997
30. de Vathaire F, François P, Hill C, et al: Role of radiotherapy and chemotherapy in the risk of second malignant neoplasms after cancer in childhood. *Br J Cancer* 59:792-796, 1989
31. de Vathaire F, Schweisguth O, Rodary C, et al: Long-term risk of second malignant neoplasms after a cancer in childhood. *Br J Cancer* 59:448-452, 1989
32. Olsen JH, Garwicz S, Hertz H, et al: Second malignant neoplasms after cancer in childhood or adolescence. *BMJ* 307:1030-1036, 1993
33. Pratt CB, George SL, Green AA, et al: Carcinomas in children. *Cancer* 61:1046-1050, 1988
34. Hawkins MM, Draper GJ, Kingston JE: Incidence of second primary tumours among childhood cancer survivors. *Br J Cancer* 56:339-347, 1987
35. Blatt J, Olshan A, Gula MJ, et al: Second malignancies in very-long-term survivors of childhood cancer. *Am J Med* 93:57-60, 1992
36. Tucker MA, Meadows AT, Boice JD: Cancer risk following treatment of childhood cancer; in Boice JD Jr, Fraumeni JF Jr (eds): *Radiation Carcinogenesis: Epidemiology and Biological Significance*. New York, NY, Raven Press, 1984, pp 211-224
37. Ron E, Lubin JH, Shore RE, et al: Thyroid cancer after exposure to external radiation: A pooled analysis of seven studies. *Radiat Res* 141:259-277, 1995
38. Tucker MA, Morris Jones PH, et al: Therapeutic radiation at a young age is linked to secondary thyroid cancer. *Cancer Res* 51:2885-2888, 1991
39. Bhatia S, Robison LL, Oberlin O, et al: Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med* 334:745-751, 1996
40. Wolden SL, Lamborn KR, Cleary SF, et al: Second cancers following pediatric Hodgkin's disease. *J Clin Oncol* 16:536-544, 1998
41. Sankila R, Garwicz JH, Olsen JH: Risk of subsequent malignant neoplasms among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence: A population-based cohort study in the five Nordic countries. *J Clin Oncol* 13:1442-1446, 1996
42. Rovelli A, Cohen A, Uderzo C, et al: Follicular cell carcinoma of the thyroid in a child after bone marrow transplantation for acute lymphoblastic leukemia. *Acta Haematol* 97:225-227, 1997
43. Uderzo C, van Lint MT, Rovelli A, et al: Papillary thyroid carcinoma after total body irradiation. *Arch Dis Child* 71:256-258, 1994
44. Garcia-Boyer R, Sanz GF, Sanz MA: Two secondary malignancies following the successful treatment of a patient with acute lymphoblastic leukemia. *Ann Oncol* 7:322-323, 1996
45. Bessho F, Ohta K, Akanuma A, et al: Dosimetry of radiation scattered to the thyroid gland from prophylactic cranial irradiation for childhood leukemia. *Pediatr Hematol Oncol* 11:47-53, 1994

46. Pratt CB: Parotid carcinomas following the treatment of childhood acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 12:417-419, 1995
47. Atahan IL, Ayhan A, Özyar E, et al: A case of mucoepidermoid carcinoma of the parotid gland developing in a child after the treatment of acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 12:403-405, 1995
48. Land CE, Saku T, Hayashi Y, et al: Incidence of salivary gland tumors among atomic bomb survivors, 1950-87: Evaluation of radiation-related risk. *Radiat Res* 146:28-36, 1996
49. Tucker M, D'Angio GJ, Boice JD Jr, et al: Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med* 317:588-593, 1987
50. Hawkins MM, Wilson LM, Burton HS, et al: Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Natl Cancer Inst* 88:270-278, 1996
51. Greene MH, Young TI, Clark WH Jr: Malignant melanoma in renal-transplant recipients. *Lancet* 1:1196-1199, 1981