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Malignancies after Hematopoietic Cell Transplantation for Primary Immune Deficiencies: A Report from the Center for International Blood and Marrow Transplant Research

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We describe the incidence of malignancy in patients with primary immunodeficiency disorders (PIDD) following hematopoietic cell transplantation (HCT). From the Center for International Blood and Marrow Transplant Research, 2266 PIDD patients who had undergone allogeneic HCT between 1968 and 2003 were identified. Patient, disease, and transplant factors for development of malignancy were examined and pathology reports for reported malignancies reviewed independently by a pathologist for confirmation. The incidence of malignancy was highest for Wiskott-Aldrich syndrome (3.3%), with an overall incidence of 2.3% for PIDD. Post-HCT malignancy was confirmed for 52 of 63 reported cases. Forty-five of 52 patients developed posttransplant lymphoproliferative disorders (PTLD) at a median of 3 months post-HCT. Of these, 26 had received T cell-depleted (TCD) bone marrow. Three patients who developed myelodysplastic syndrome had received TCD marrow and total body irradiation. Three patients developed a solid tumor. Patients with PIDD are at a relatively low risk of developing malignancies post-HCT compared with their historic risk of cancer. The most frequent malignancy or lymphoproliferative disorder was early-onset PTLD. As in other HCT recipients, TCD appears to correlate with PTLD development. Our results lend support to the hypothesis that immune reconstitution in PIDD following HCT leads to a decrease in cancer risk.

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INTRODUCTION

Children with primary immune deficiency diseases (PIDD) such as severe combined immune deficiency (SCID) and Wiskott-Aldrich syndrome (WAS) die prematurely as a result of serious infections or malignancies. Although the number of children with PIDD who develop cancer every year is small, it has been estimated that the overall risk for cancer in these children is about 4%, or about 10,000 times greater than expected in age-matched healthy controls [1,2].

Allogeneic hematopoietic cell transplantation (HCT) is currently the only curative therapy available for a number of prematurely lethal PIDD. Since 1968, when the first successful allogeneic bone marrow transplantation was reported in a child with SCID [3], several thousand children with PIDD have undergone HCT. SCID and WAS represent the most frequent indications for allogeneic HCT among these patients. Complete reconstitution of the immune system with full donor hematopoietic chimerism can be achieved in patients with PIDD after myeloablative

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chemotherapy with or without irradiation and HCT. It is not known whether this impacts the risk of malignancies for these patients. We hypothesize that allogeneic HCT for PIDD results in a decreased risk of malignancy because of improved immune surveillance as a result of achieving immune competence.

There is little specific data in the published literature regarding the incidence of malignancies post-HCT in patients with PIDD. Posttransplant lymphoproliferative disorders (PTLD) have been reported in a number of patients with SCID following thymic epithelial transplants and haploidentical T cell-depleted (TCD) bone marrow transplants (BMTs) [4]. A retrospective analysis performed by Neudorf et al. [5] in 1984 had documented no cases of cancer in SCID patients following successful BMT.

Whether HCT decreases the risk of cancer in patients with PIDD is unknown. Little is known about the incidence of cancer or the risk factors associated with development of cancer in these HCT survivors. Here, we present a descriptive report of risk factors that may have contributed to the development of a malignancy after allogeneic HCT in a large cohort of children with PIDD reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

METHODS

Data Collection

The CIBMTR is a working group of over 500 transplant centers worldwide that voluntarily contribute detailed patient, disease, and, transplant characteristics and outcome data on HCT recipients to a Statistical Center at the Medical College of Wisconsin. Participating centers register consecutive transplants and provide relevant patient, disease, and transplant characteristics and outcome data including graft-versus-host disease (GVHD), development of malignancy post-HCT, survival, and for deceased patients, cause of death. Detailed demographic, disease, and transplant characteristics as well as outcome data are collected on allogeneic transplants. Patients are followed annually until death. Computerized error checks, physician review of submitted data, and on-site audits of participating centers ensure data quality. This study was approved by the institutional review board of the Medical College of Wisconsin.

Statistical Analysis

The incidence of malignancy post-HCT was determined using the cumulative incidence estimator with death as the competing risk. Ninety-five percent confidence intervals were calculated using standard techniques [6].

Patients

The study population consisted of 2266 patients with PIDD who had undergone allogeneic HCT between 1968 and 2003 and reported to the CIBMTR (Table 1). Included are recipients of matched and mismatched related donor and unrelated donor transplants. Patients' ages ranged from 1.2 months to 47 years, with a median age of 1 year. The 2 most common indications for transplantation for PIDD were SCID (47%) and WAS (16%). As a result, approximately 80% of patients were male.

Sixty-three patients reportedly developed a new malignancy after HCT. Because of the inclusive dates of the analysis, and the fact that the CIBMTR does not maintain a tissue bank, it was deemed impracticable to retrieve and review slides on biopsy/autopsy specimens to confirm the diagnosis of a malignancy. Therefore, post-HCT malignancy was confirmed in 52 patients using pathology reports and/or confirming with the transplant center. There was insufficient information to confirm the diagnosis of malignancy in 11 patients. To avoid reporting bias, patients transplanted at inactive centers or centers that did not respond to requests to participate were excluded from the analysis (n = 143 patients from 7 transplant centers).

RESULTS

Table 2 shows the characteristics of patients with PIDD who developed malignancy post-HCT compared with those who did not. Fifty-two of 2266 patients were confirmed to have developed posttransplantation malignancy. Patient, disease, and transplant characteristics of these patients are shown in Table 3. The 5-year, 10-year, and 15-year cumulative incidence of post-HCT malignancy was 2% (95% confidence interval [CI]: 2%-3%), 2% (95% CI:2%-3%), and 3% (95% CI:2%-5%), respectively. The corresponding cumulative incidence for patients with SCID was 2% (95% CI:1%-3%) at 5 and 10 years and 3% (95% CI:1%-6%) at 15 years; for WAS, 4% (95%

Table 1. Patients with PIDD Reported to CIBMTR (1968-2003)

Variable	N (%)
Patients	2266
Diagnosis	
Wiskott-Aldrich Syndrome	360 (16)
SCID	1075 (47)
Other	831 (37)
Patients with confirmed malignancy reported to CIBMTR	52
Wiskott-Aldrich Syndrome	12/360 (3.3)
SCID	25/1075 (2.3)
Other	15/831 (1.8)

PIDD indicates patients with primary immunodeficiency disorders; SCID, severe compromised immunodeficiency; CIBMTR, Center for International Blood and Marrow Transplant Research.

Table 2. Characteristics of Patients Undergoing Transplantation for a Primary Immune Deficiency and Registered with the CIBMTR before 2003

Characteristics	No Malignancy Post-tx N (%)	Malignancy Post-tx N (%)	P*
Number of patients	2214	52	
Disease			0.27
SCID	1050 (47)	25 (48)	
WAS	348 (16)	12 (23)	
Other ID †	816	15	
Phagocyte disorders	208 (9)	5 (10)	
Combined immunodeficiency disorders	278 (13)	6 (12)	
T cell disorders	28 (1)		
Other ID, not specified	302 (14)	4 (8)	
SCID Phenotype			0.83
SCID ADA deficiency	129 (12)	2 (8)	
SCID absent T and B cells	271 (26)	7 (28)	
SCID absent T, normal B cells	317 (30)	8 (32)	
Omenn syndrome	74 (7)	3 (12)	
Reticular dysgenesis	14 (1)	0	
SCID, not specified	245 (23)	5 (20)	
Donor			0.001
HLA-id sib	630 (28)	1 (2)	
Other relative	932 (42)	29 (58)	
Unrelated	519 (23)	19 (33)	
Fetal ‡	91 (4)	3 (5)	
Other/missing	42 (1)		
T cell depletion §			0.002
No	999 (45)	12 (23)	
Yes	1045 (47)	40 (77)	
Missing	170 (8)	0	
Type of malignancy posttransplantation			
PTLD		45 (87)	
AML/MDS		4 (8)	
Solid tumor		3 (6)	
Year of transplantation			0.14
≤1980	174 (8)	1 (2)	
1981-1990	510 (23)	18 (35)	
1991-1999	1073 (48)	23 (44)	
2000-2003	457 (21)	10 (19)	
Survival status			
Alive	1365 (62)	12 (23)	
Dead	849 (38)	40 (77)	
Median follow-up of survivors, years (range)	4.6 (<1-30)	7 (4-14)	

SCID indicates severe combined immunodeficiency; WAS, Wiskott-Aldrich Syndrome; PTLD, posttransplant lymphoproliferative disease; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.
*Chi-square test.
†Phagocyte disorders include chronic granulomatous disease, Chediak-Higashi syndrome, and leukocyte adhesion deficiencies; combined immunodeficiency disorders include X-linked lymphoproliferative syndrome, cartilage hair hypoplasia, immune deficiency plus neutropenia, CD40 ligand deficiency, common variable immunodeficiency, other combined immunodeficiencies, bare lymphocyte syndrome, and ataxia telangiectasia; T cell disorders include HIV infection and DiGeorge anomaly.
‡Fetal tissue refers to the use of fetal liver, thymus, or other fetal tissue (not cord blood).
§T cell depletion includes in vivo and/or ex vivo T cell depletion. The *P* values need to be interpreted with caution because data on TCD was missing in a large number of patients.

CI:2%-6%) at all 3 time points and for other PIDD, 2% (95% CI:1%-3%) at 5 years and 2% (95% CI:1%-4%) at 10 and 15 years. With a median follow-up of 6 years (range: 4-14), 12 patients were alive. Forty patients (77%) are dead; death was attributed to the posttransplantation malignancy in 29 patients. Other causes of death include GVHD (n = 3), infection without GVHD (n = 4), and the cause of death was not reported for 4 patients.

Lymphoproliferative disorders (LPD) ranging from PTLD to a non-Hodgkin lymphoma was the most common malignancy and occurred in 45 patients. Epstein-Barr virus (EBV)-induced LPD was confirmed in 17 of these patients. GVHD prophylaxis or treatment for the 45 patients with PTLD consisted of TCD in 35 (78%) patients. Of these, 12 received TCD bone marrow graft, 13 received TCD bone marrow graft and in vivo antithymocyte globulin (ATG), 1 patient received a TCD peripheral blood stem cell (PBSC) graft and in vivo ATG, and the remaining 9 patients received in vivo ATG only. Only 5 patients received total body irradiation (TBI). The median time to development of the LPD was 3 months from transplantation (range: 1-41 months).

Three patients developed myelodysplastic syndrome (MDS) and 1 patient, acute myeloid leukemia (AML); these developed in patients with non-SCID PIDD. All 3 MDS patients had received TBI (1320-1400 cGy) as part of their conditioning regimen and a TCD bone marrow graft. The patient who developed AML received ATG as part of the conditioning regimen, and 1 patient with MDS received ATG for treatment of acute GVHD (aGVHD). The median time to development of the MDS or AML was 34 months (range: 9-55 months). Patient ID #5 with WAS who underwent a sex-matched TCD unrelated donor HCT developed MDS 55 months post-HCT. Cytogenetics showed numerous structural abnormalities but was unable to resolve the source of the malignant clone. Patient ID #16 with Chediak-Higashi syndrome developed MDS 44 months after a TCD-unrelated donor transplant. Bone marrow showed multiple cytogenetic abnormalities (including del7q and del 20q) distributed among 4 independent clones whose origin could not be determined. Whether these were present pre-HCT could not be confirmed because the pretransplantation bone marrow failed to yield metaphases. The bone marrow did show rare mononuclear cells with abnormal Chediak granules, suggesting residual host cells. Patient ID #17 with WAS underwent a sex-mismatched TCD-unrelated donor HCT. He developed MDS 23 months post-HCT, and his bone marrow had 80% recipient and 20% donor cells, with 1 of the recipient clones showing a del(7) abnormality.

Three patients developed a solid tumor. One patient with Omenn syndrome developed desmoplastic squamous cell carcinoma of the right foot 170 months after unrelated donor HCT; 1 patient with CID developed hepatocellular carcinoma 84 months after unrelated donor HCT; and the remaining patient

Table 3. List of 52 Patients with Confirmed Malignancy/Lymphoproliferative Disorder

ID	Diagnosis	Age at Transplantation (Months)	Donor	Graft Source	Preparative Regimen	GVHD Prophylaxis	aGVHD	cGVHD	Interval* (Months)	Status	Posttransplantation Malignancy
1	SCID	12	MRD	BM	CY	T-depletion	No	No	38.9	Dead	EBV-PTLD
2	CID	18	Haplo Id	BM	None	T-depletion	No	No	2.9	Dead	Immunoblastic BCL
3	WAS	18	Haplo Id	BM	BU + CY+ATG	T-depletion	Gr 2	No	1.5	Dead	EBV-PTLD
4	SCID	6	Haplo Id	BM	None	T-depletion	No	No	16.4	Dead	Large cell lymphoma
5	WAS	32.4	1 Ag MM URD	BM	Cy + TBI	T-depletion	Gr 1	No	55.2	Dead	MDS
6	Immune-unclassified	6	Haplo Id	BM	BU + CY	T-depletion	Gr 2	No	26.9	Dead	PTLD
7	SCID	7.2	Haplo Id	BM	None	T-depletion	Gr 2	Yes	26.2	Dead	BLPD
8	SCID	7.2	Haplo Id	BM	Cy + TBI+ATG	T-depletion	No	No	2.5	Dead	PTLD
9	SCID	20.4	Haplo Id	BM	BU + CY+ATG	T-depletion	No	No	1.3	Dead	PTLD
10	SCID	18	1 Ag MM URD	BM	BU + CY+ATG	CSA + MTX	Gr 4	Yes	2.2	Dead	EBV-PTLD
11	SCID	8.4	Haplo Id	BM	BU + CY+ATG	T-depletion	Gr 1	No	2.2	Alive	B cell LPD
12	SCID	15.6	Haplo Id	BM	BU + CY+ATG	T-depletion	Gr 2	No	2.9	Dead	EBV-PTLD
13	WAS	12	Haplo Id	BM	BU + CY+ATG	T-depletion	Gr 3	No	3.7	Dead	PTLD
14	SCID	6	Haplo Id	BM	CY + ATG	T-depletion	Gr 3	No	2.7	Dead	Monoclonal BCL
15	Omenn syndrome	1.2	1 Ag MM RD	BM	None	None	No	No	3.7	Dead	Malignant lymphoma
16	CHS	14.4	MUD	BM	Cy + TBI	T-depletion	Gr 2	Yes	44.9	Alive	MDS
17	WAS	21.6	MUD	BM	Cy + TBI	T-depletion	Gr 2	Yes	23.2	Alive	MDS/AML
18	SCID	39.6	1 Ag MM URD	BM	BU + CY+ATG	T-depletion	No	No	3.7	Dead	EBV-PTLD
19	LAD	19.2	Haplo Id	BM	BU + CY	T-depletion	Gr 1	No	36.3	Dead	Immunoblastic BCL
20	SCID	1.2	MSD	BM	CY + ATG	CSA + other	No	No	2.1	Dead	EBV-PTLD
21	CVID	152.4	MUD	BM	Cy + TBI	T-depletion	Gr 3	Yes	1.9	Alive	BLPD
22	Kostmann	88.8	1 Ag MM URD	CB	Bu+Cy+ATG	CSA + other	Gr 2	No	7.4	Alive	BLPD-LBCL
23	SCID	14.4	1 Ag MM RD	BM	BU + CY+ATG	T-depletion	Gr 4	Yes	15.4	Alive	High Grade NHL
24	WAS	265.2	MUD	BM	Cy + TBI+ATG	CSA + MTX	Gr 1	No	1.6	Dead	EBV-PTLD
25	SCID	24	1 Ag MM URD	BM	Fludarabine	CSA + MTX	Gr 2	No	2.6	Dead	PTLD
26	SCID	195.6	2 Ag MM URD	CB	Cy + Flud + ATG	CSA + other	No	No	0.9	Dead	EBV-PTLD
27	WAS	55.2	URD	BM	BU + CY+ATG	CSA + MTX	No	Yes	3.6	Alive	Immunoblastic BCL
28	Omenn syndrome	7.2	MUD	BM	Cy	CSA + MTX	Gr 2	Yes	169.6	Alive	Desmoplastic squamous cell, R. foot
29	SCID	7.2	Haplo Id	BM	Cy	T-depletion	Gr 2	No	2.0	Alive	EBV-PTLD
30	SCID	4.8	Haplo Id	BM	None	NR	No	No	1.8	Dead	EBV-PTLD
31	WAS	93.6	RD	NR	NR	NR	NR	NR	19.7	Dead	Large cell malignant lymphoma EBV +
32	ID, NOS	20.4	RD	PBSC	Mel+Thio+Flud+ATG	T-depletion	NR	NR	1.0	Dead	Diffuse large B-cell Lymphoma EBV +
33	WAS	64.8	URD	BM	BU + CY+ATG	Corticosteroids + other	NR	NR	1.5	Dead	B cell lymphoma EBV positive
34	CID	20.4	RD	BM	BU + CY	None	NR	NR	14.2	Alive	EBV PTLD
35	WAS	15.6	URD	CB	BU + CY+ATG	CSA + other	NR	NR	9.4	Dead	PTLD
36	CHS	84	RD	BM	BU + CY	CSA + MTX	NR	NR	9.9	Dead	EBV PTLD
37	SCID	6	RD	BM	CY + ATG	T-depletion	NR	NR	1.3	Dead	Lymphoma, EBV undetermined
38	SCID	4.8	Fetal	Fetal	None	None	No	No	NR	Dead	Brain tumor
39	SCID	10.8	Fetal	Fetal	None	None	No	No	41.0	Dead	Hodgkin lymphoma
40	CID	4.8	Fetal	Fetal	None	None	No	No	NR	Dead	Lymphoma
41	SCID	4.8	Haplo Id	BM	Cy+ARAC	T-depletion	No	No	NR	Dead	EBV-PTLD
42	WAS	8.4	Haplo Id	BM	BU + CY	T-depletion	No	No	8.4	Dead	B cell lymphoma
43	WAS	40.8	Haplo Id	BM	Cy + TBI	T-depletion	No	No	1.1	Dead	EBV-PTLD
44	WAS	13.2	MUD	BM	BU + CY+ATG	T-depletion	Gr 2	No	19.4	Dead	B cell lymphoma
45	Immune-unclassified	111.6	1 Ag MM URD	BM	Cy + TBI+ATG	T-depletion	No	No	3.0	Dead	EBV-PTLD
46	X-linked lymphoproliferative syndrome	93.6	MUD	CB	BU + CY+ATG	CSA + other	Gr 4	Yes	5.4	Dead	EBV-PTLD

47	SCID	7.2	Haplo Id	BM	Mthpred+Campath	T-depletion	No	No	NR	Dead	EBV-PTLD
48	SCID	8.4	Haplo Id	BM	BU + CY+ATG	T-depletion	Gr 2	No	5.0	Dead	Lymphoma-EBV neg
49	Kostmann agranulocytosis	138	2 Ag MM URD	CB	BU + CY+ATG	CSA + other	No	No	9.6	Dead	AML
50	CID	99.6	URD	BM	BU + CY+ATG	NR	NR	NR	84.2	Alive	Hepatocellular carcinoma
51	Immune-unclassified	22.8	RD	NR	BU + CY+Etoposide	CSA + other	NR	NR	41.3	Alive	Mature B cell lymphoma
52	SCID	13.2	RD	PBSC	NR	NR	NR	NR	4.7	Dead	B-lymphoma

BU indicates busulfan; CY, cyclophosphamide; ATG, antithymocyte globulin; MTX, methotrexate; TBI, total body irradiation; MDS, myelodysplastic syndrome; AML, acute myelogenous leukemia; NR, not reported (data for acute/chronic GVHD not available); aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disease; BCL, B-cell lymphoma; BLPD, B-cell lymphoproliferative disease.
*Time from transplantation to onset of malignancy/lymphoproliferative disorder.

developed a brain tumor after HCT for SCID, although the time to tumor development was not reported.

DISCUSSION

The etiology of cancer in childhood is multifactorial. An important factor that contributes to an increased incidence of cancer in children is the presence of underlying immunodeficiency, either inherited or acquired [1]. Improved treatments and supportive care as well as allogeneic HCT for the PIDD have resulted in significant improvements in survival for these children. The Immunodeficiency-Cancer Registry was set up in 1973 to track the incidence of cancers in patients with PIDD. As of August 1986, 514 cases of malignancy had been registered in patients with PIDD. Of these, almost half were non-Hodgkin lymphoma, with leukemia or Hodgkin's disease accounting for another 20% of cases. Nine percent of the cases were adenocarcinomas, and other tumors accounted for the remainder. Although over one-half of these tumors occurred in patients with Ataxia-Telangiectasia (AT) (30%) and common variable immunodeficiency (24%), about 25% were seen in patients with WAS and SCID [7-9]. A recent analysis of data reported to the Australasian Society of Clinical Immunology and Allergy PID Registry showed that although there was a 1.6-fold excess relative risk of cancer observed for PID patients, the standardized incidence ratio (SIR) was 5.36 to 8.82 for non-Hodgkin lymphoma, leukemia, and stomach cancer. The SIRs for all cancers were significantly increased in patients with common variable immunodeficiency (CVID) and AT [10].

Patients with leukemia or aplastic anemia who have undergone BMT are at a significantly higher risk of developing a secondary cancer compared with age-matched healthy controls [11]. In a recent analysis of over 18,000 BMT recipients by Curtis et al. [12], the cumulative incidence of PTLD was 1.0 ± 0.3% at 10 years after HCT with the highest incidence in the first 5 months post-HCT. Patients with non-Hodgkin lymphoma, Fanconi anemia, and PIDD were excluded from this analysis.

Although our analysis can only serve to assess the risk factors that contribute to the development of a malignancy post-HCT for PIDD, the overall incidence of malignancies in transplanted PIDD patients (52 of 2266, or 2.3%) is lower than what has been reported in previous reports of patients with PIDD. LPD constitutes the most frequent malignancy in patients with PIDD, especially those with WAS, common variable immune deficiency, AT, and SCID. It has been estimated that the risk of malignancy in WAS, CVID, and AT may be 100 times that of the general population. Because patients with SCID

invariably die in infancy or early childhood without successful HCT, there is little data on the long-term incidence of malignancies in nontransplanted patients. However, the median survival of patients with WAS who do not undergo HCT has been estimated to be in the late teens. Two large analyses of WAS patients by Perry et al. [13] and Sullivan et al. [14] reported development of a malignancy in 12% and 13% among 301 and 154 WAS patients, respectively.

Of the 52 malignancies reported here, 45 (87%) were lymphoproliferative disorders. In the report by Curtis et al. [12] discussed above, the risk of early PTLD was strongly associated with TCD of donor marrow (relative risk [RR] = 12.7), and the use of ATG (RR = 6.4) or anti-CD3 monoclonal antibody (RR = 43.2) for prophylaxis or treatment of acute GVHD. In our analysis, TCD clearly contributed as a significant risk factor for the development of LPD. Because the most frequent malignancies/lymphoproliferative disorders reported in nontransplanted patients with PIDD are LPD [15,16], it is difficult to assess the relative contributions of the underlying immune deficiency, the preparative regimen, and the TCD to LPD development. However, the median time of 3 months between the HCT and the LPD is very similar to the findings of Curtis et al. [12] and suggests that the TCD was an important contributory risk factor. There was no correlation between incidence of PTLD and year of transplantation (data not shown). EBV monitoring was not routinely available for the majority of patients transplanted during the period covered by this report. Of the 52 patients reported here, 40 died after developing a malignancy/lymphoproliferative disorder, with the majority of the deaths being attributed to the malignancy. With routine monitoring for EBV reactivation with EBV polymerase chain reaction (PCR) and preemptive therapy, future analyses may allow us to assess the impact of these approaches on the incidence and survival of PTLD in these patients.

An analysis of 19,229 patients who had received allogeneic or syngeneic transplantations for acute and chronic leukemias and a number of nonmalignant diseases identified a cumulative incidence of new solid cancers of 2.2% at 10 years and 6.7% at 15 years. The use of TBI and the presence of chronic GVHD (cGVHD) were associated with a higher risk of solid cancers, and there was a trend toward an increased risk of solid cancers over time, with younger patients having the greatest risk of developing solid cancers post-HCT [17]. However, patients with Fanconi anemia and primary immune deficiencies were excluded from this analysis because of their inborn susceptibility to cancer. In a separate analysis of 700 patients with severe aplastic anemia including 79 with Fanconi anemia, Deeg et al. [18] reported 23 malignancies post-HCT. There were 5 cases of lymphoid malignancies at a median of 3 months posttransplantation and 18 cases of solid tumors at a median of 99 months post-HCT. In this analysis, the most significant risk factor for solid tumors was Fanconi anemia, consistent with the known risk of solid tumors in nontransplanted Fanconi anemia patients.

There are a number of limitations to our analysis that need to be acknowledged. Centralized histopathologic examination of archived tissue or slides on each of the patients would have been the ideal way to confirm the occurrence of a malignancy. Because a large number of these patients had been diagnosed over 20 years earlier, it was considered impracticable to retrieve these specimens, and we chose to review clinical and pathology reports to confirm the malignancy. Second, although data are available for the risk of malignancy in a cohort of age-matched healthy children, the true comparator for our cohort of patients with primary immune deficiencies would have been a similarly sized cohort of patients with PIDD who had not undergone transplantation. Unfortunately, reliable data on such a cohort are not available. For assessment of the impact of HCT on the risk of malignancy in PIDD, one has to thus rely on early data from the Immunodeficiency-Cancer Registry and data compiled through multiinstitutional surveys of patients with WAS.

We conclude from this analysis that patients with primary immune deficiencies who undergo HCT appear to be at a relatively low risk of developing malignancies compared with the historic risk of cancer in these patients. The most frequent malignancy/lymphoproliferative disorder seen in this cohort of patients is that of early-onset PTLD, and as has been noted for other HCT recipients, the use of TCD appears to correlate with the development of PTLD posttransplantation.

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AUTHORSHIP CONTRIBUTIONS

Naynesh Kamani had full access to all of the data in the study and had final responsibility for the integrity of the data, the accuracy of the data analysis, and the responsibility for the decision to submit for publication. Authors designed research (N.K., M.E., A.H.F.), collected data (N.K., J.C., M.C., J.S., A.F., P.S., J.W., E.H., A.H.F.), reviewed pathology reports (S.K.) performed statistical analyses (N.K., A.H., J.L.R., M.E.), interpreted data (N.K., S.K., A.H., J.L.R., M.E., J.C., M.C., J.S.T.C., A.F., P.S., J.W., E.H., A.H.F.), drafted the manuscript (N.K., M.E., A.H.F.), and critically revised the manuscript (all authors).

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