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Long-Term Survival and Late Deaths after Hematopoietic Cell Transplantation for Primary Immunodeficiency Diseases and Inborn Errors of Metabolism

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It is uncertain whether late mortality rates after hematopoietic cell transplantation for severe combined immunodeficiency (SCID), non-SCID primary immunodeficiency diseases (non-SCID PIDD), and inborn errors of metabolism (IEM) return to rates observed in the general population, matched for age, sex, and nationality. We studied patients with SCID (n = 201), non-SCID PIDD (n = 405), and IEM (n = 348) who survived for at least 2 years after transplantation with normal T cell function (SCID) or >95% donor chimerism (non-SCID PIDD and IEM). Importantly, mortality rate was significantly higher in these patients compared with the general population for several years after transplantation. The rate decreased toward the normal rate in patients with SCID and non-SCID PIDD beyond 6 years after transplantation, but not in patients with IEM. Active chronic graft-versus-host disease at 2 years was associated with increased risk of late mortality for all diseases (hazard ratio [HR], 1.87; $P = .05$). In addition, late mortality was higher in patients with non-SCID PIDD who received T cell–depleted grafts (HR 4.16; $P = .007$) and in patients with IEM who received unrelated donor grafts (HR, 2.72; $P = .03$) or mismatched related donor grafts (HR, 3.76; $P = .01$). The finding of higher mortality rates in these long-term survivors for many years after transplantation confirms the need for long-term surveillance.

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INTRODUCTION

Severe combined immunodeficiency (SCID), non-SCID primary immunodeficiency diseases (non-SCID PIDD), and inborn errors of metabolism (IEM) are fatal disorders, and for many years, allogeneic hematopoietic cell transplantation was the only known definitive treatment available [1]. In recent years, enzyme replacement therapy and gene therapy have been

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used successfully for some, but not all, primary immunodeficiency and metabolic diseases. Transplantation remains the standard of care for the majority of children with these diseases [2-8].

Patients with SCID have been studied by several groups, with reports detailing immune reconstitution, complications, and survival after matched or mismatched related donor transplantation [2,6-8]. However, most patients in those studies received allografts from related donors and did not receive pretransplantation conditioning chemotherapy. Neven et al. [7] reported a 2-year survival rate of 63% in 149 patients with SCID who received allografts from related donors (except for 2 patients who received allograft from unrelated donors), only one-half of whom received pretransplantation conditioning. An additional 8 deaths occurred beyond 2 years after poor immune reconstitution, chronic graft-versus-host disease (GVHD) and related complications, and endocrine, autoimmune, and inflammatory complications [7]. In the study of Railey et al. [8], in which all patients received an allograft from a related donor and none received pretransplantation conditioning, the timing of transplantation was predictive of outcome. Transplantation within the first 3.5 months of life was associated with improved long-term survival, better nutritional status, and fewer subsequent cellular infusions to boost engraftment.

Antoine et al. [2] examined long-term survival after transplantation for SCID and non-SCID PIDD and reported better long-term survival in recipients of grafts from HLA-matched sibling donors. More than 90% of the SCID patients and 80% of non-SCID PIDD patients received their allografts from an HLA-matched or HLA-mismatched related donor [2]. A more recent report on long-term outcome after transplantation for Wiskott-Aldrich syndrome reported a 7-year event-free survival rate of 75% in 96 patients who survived for at least 2 years after transplantation [3]. Two-thirds of patients in that study received an allograft from matched or mismatched donors, and late complications included GVHD, autoimmunity, and infections.

Data are sparse on long-term survival after transplantation for IEM and non-SCID PIDD, particularly after unrelated donor transplantation. Furthermore, previous reports [2,3,6-8] did not compare the mortality rate in long-term transplantation survivors with immune deficiency diseases (SCID or non-SCID PIDD) and IEM with that in the general population. In contrast, late mortality rates in long-term survivors with severe aplastic anemia and hematologic malignancies are well documented, and increased rates are known to persist for years after transplantation [9-11]. Socié et al. [9] reported no significant differences in the risk of death compared with the normal population by the sixth year after transplantation for severe aplastic anemia and by the ninth year after transplantation for acute myelogenous leukemia (AML). These data stand in contrast to findings of Bhatia et al. [10], who reported that the risk of late mortality remained significantly higher in long-term survivors after transplantation compared with the normal population. Similarly, a recent CIBMTR study of patients with hematologic malignancies and severe aplastic anemia also confirmed a lower life expectancy in long-term survivors of transplantation compared to the general population [11]. Although the study population of Socié et al. [9] included fewer than 5% of unrelated donor transplant recipients, the more recent reports have included higher proportions of unrelated donor transplant recipients, possibly explaining the observed differences between the earlier and later reports.

We report on late mortality in patients with SCID, non-SCID PIDD, and IEM who survived at least 2 years after transplantation with normal T cell function (SCID) and >95% donor chimerism (non-SCID PIDD and IEM). Including only long-term survivors allowed us to determine mortality rates in these patients relative to mortality rates in an age-, sex-, and nationality-matched general population, as well as to identify risk factors for late mortality in patients considered cured of their disease.

METHODS

Data Collection

Data were collected by the Center for International Blood and Marrow Transplant Research (CIBMTR), a voluntary organization of more than 450 transplantation centers worldwide that report consecutive transplantations facilitated at their centers to a statistical center located at the Medical College of Wisconsin. The CIBMTR database includes detailed patient, disease, and transplantation characteristics and their outcome data on approximately 60% of all transplantations performed. All patients are followed longitudinally annually, and compliance is monitored by onsite audits. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Eligibility Criteria

Eligibility for participation was limited to transplantation centers that provided extended follow-up data on >85% of their surviving patients with SCID, non-SCID PIDD, and IEM. All patients had to be alive for longer than 2 years after their transplantation and demonstrate sustained immunologic recovery or donor chimerism. Patients with SCID had normal T cell function, and those with non-SCID PIDD and IEM had >95% donor chimerism at study entry (ie, 2 years after transplantation). It was expected that

deaths due to the early complications of transplantation would occur before the 2-year period. A total of 954 patients were eligible, and data were reported by 114 transplantation centers. An additional 847 patients (SCID, n = 180; non-SCID PIDD, n = 327; IEM, n = 340) underwent transplantation at a participating center but died within 2 years after transplantation, had autologous recovery, or failed to attain normal T cell function within 2 years after transplantation, making them ineligible for this analysis.

Statistical Methods

The SCID, non-SCID PIDD, and IEM disease groups were analyzed separately because of differences in biological features and transplant strategies. Late deaths were defined as any death occurring beyond 2 years after transplantation. Reported causes of death were reviewed and categorized. Patients who died with active chronic GVHD were considered to have died of this complication. Deaths due to infection included only those patients without active GVHD.

The probability of long-term survival was calculated using the Kaplan-Meier estimator, and 95% confidence intervals (CIs) were estimated using Greenwood's formula [12]. Death from any cause was considered an event, and surviving patients were censored at last follow-up. Cox proportional hazards regression was used to identify risk factors associated with late deaths for each disease group [13]. Multivariate models were built with the use of stepwise forward selection, with a P value of $\leq .05$ indicating statistical significance; all variables met the proportional-hazards assumption. The variables considered in multivariate analysis were age at transplantation, race, sex, donor type, graft type, conditioning regimen, use of antithymocyte globulin, recipient cytomegalovirus serostatus, GVHD prophylaxis, donor–recipient sex match, history of grade II-IV GVHD, chronic GVHD (none versus resolved by 2 years after transplantation versus active chronic at 2 years after transplantation), and year of transplantation (Table 1).

Estimates of relative mortality (ie, excess risk of mortality) were calculated as described by Andersen and Vaeth [14], taking into account differences among the patients in terms of age, sex, and nationality. Relative mortality is the relative risk of dying at a given time after transplantation compared with a person of similar age, sex, and nationality in the general population. Age-, sex-, and nationality-specific rates for all countries from which transplantations were reported were used to calculate the relative mortality. The ratio of observed to expected cancers and the absolute excess risk (AER) were estimated. AER is the number of observed cases minus the number of expected cases per 10,000 person-years at risk. The number of person-years at risk was calculated from the date of transplantation to date of diagnosis of solid tumors, date of death, or date of last contact, whichever occurred first. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patients

The characteristics of the study population are summarized in Table 1. The cohort included 201 patients with SCID, 405 with non-SCID PIDD, and 348 with IEM. Transplantations occurred between 1980 and 2003, and the median follow-up of surviving patients was 83 months (range, 25-283 months). The median age at last contact was 7 years for patients with SCID, 9 years for those with non-SCID PIDD, and 10 years for those with IEM. Age at transplantation varied depending on the disease for which transplantation was performed; the SCID group was younger than the non-SCID PIDD and IEM groups. Transplantation was performed before age 2 years in 97% of the patients with SCID, compared with 65% of patients with non-SCID PIDD and IEM. In the SCID group, 70% of patients received an allograft from an HLA-matched sibling or HLA-mismatched relative. Transplantation of allografts from an unrelated donor was more common in the non-SCID PIDD and IEM groups, accounting for 55% of the transplants. Bone marrow was the predominant stem cell source. All but 27 patients in the SCID group received pretransplantation conditioning, and 84% received a conditioning regimen not including total body irradiation. The majority of patients in the non-SCID PIDD (86%) and IEM (90%) groups received a myeloablative conditioning regimen. Acute and chronic GVHD were assessed using standard criteria [15,16]. Grade II-IV acute GVHD developed in 383 of 954 patients (40%); most patients with GVHD had grade II or III acute GVHD. Chronic GVHD developed in 209 patients (22%), 119 of whom had active chronic GVHD at 2 years after transplantation. One hundred forty-eight of the 209 patients (70%) with chronic GVHD had grade II-IV acute GVHD before the onset of chronic GVHD. Chronic GVHD was limited in 118 patients and extensive in 88 patients.

Long-Term Survival and Late Mortality

Fourteen patients with SCID (7%), 15 patients with non-SCID PIDD (4%), and 37 patients with IEM (11%) died beyond 2 years after transplantation. The 7-year probabilities of overall survival were 93% (95% CI, 89%-97%) in the SCID group, 96% (95% CI, 94%-98%) in the non-SCID PIDD group, and 90% (95% CI, 86%-93%) in the IEM group (Figure 1). Active chronic GVHD was associated

Table 1. Patient, Disease, and Transplantation Characteristics

Characteristic	SCID*	Non-SCID PIDD†	IEM‡
Number of patients	201	405	348
Age at transplantation, years, n (%)			
<1	159 (79)	108 (27)	81 (23)
1-2	36 (18)	144 (36)	142 (41)
3-5	3 (1)	79 (19)	54 (15)
6-9	3 (1)	34 (8)	38 (11)
10-15	1 (<1)	29 (7)	16 (5)
>15	0	11 (3)	17 (5)
Male sex, n (%)	118 (59)	296 (73)	201 (58)
Donor type, n (%)			
HLA-matched sibling	51 (25)	137 (34)	108 (31)
Mismatched related	93 (46)	50 (12)	41 (12)
Unrelated	57 (28)	218 (54)	199 (57)
Graft type, n (%)			
Bone marrow	161 (80)	324 (80)	260 (75)
Peripheral blood progenitor cells	18 (9)	23 (6)	10 (3)
Umbilical cord blood	22 (11)	58 (14)	78 (22)
Conditioning regimen, n (%)			
Total body irradiation + cyclophospahmide ± other	5 (2)	42 (11)	85 (25)
Busulfan + cyclophosphamide ± other	92 (46)	333 (82)	252 (72)
Busulfan + other	10 (5)	7 (2)	4 (1)
Busulfan alone	7 (3)	1 (<1)	–
Cyclophosphamide + other	21 (10)	10 (2)	2 (<1)
Cyclophosphamide alone	20 (10)	4 (1)	1 (<1)
Fludarabine + other	5 (2)	7 (2)	4 (1)
Antithymocyte globulin	11 (5)	1 (<1)	–
None	27 (13)	–	–
GVHD prophylaxis, n (%)			
T cell depletion	79 (39)	61 (15)	77 (22)
Cyclosporine + methotrexate	56 (28)	211 (52)	127 (36)
Cyclopsorine ± other agents	55 (27)	114 (28)	128 (36)
Tacrolimus ± other agents	2 (<1)	8 (1)	5 (1)
Methotrexate ± other agents	7 (3)	8 (2)	11 (3)
Other agents	2 (1)	3 (1)	0
Year of transplantation, n (%)			
1980-1989	32 (15)	33 (8)	53 (15)
1990-2000	112 (56)	226 (56)	172 (49)
2001-2003	57 (28)	146 (36)	123 (36)
History of grade II-IV acute GVHD, n (%)			
None	125 (62)	239 (59)	207 (59)
Yes	76 (38)	166 (41)	141 (41)
Acute GVHD grade, n (%)			
0	105 (52)	193 (48)	153 (44)
I	20 (10)	46 (11)	54 (15)
II	46 (23)	85 (21)	75 (22)
III	27 (13)	72 (18)	54 (15)
IV	3 (1)	9 (2)	12 (4)
Chronic GVHD, n (%)			
None	163 (81)	310 (77)	272 (78)
Chronic GVHD resolved by 2 years after transplantation	11 (5)	36 (9)	28 (8)
Chronic GVHD active for at least 2 years after transplantation	23 (11)	54 (13)	42 (12)
Chronic GVHD resolved by 2 years, not reported	4 (2)	5 (1)	6 (2)
Age at last contact, years, n (%)			
2-5	67 (33)	79 (20)	63 (18)
6-9	61 (30)	143 (35)	101 (29)
10-15	57 (28)	111 (27)	101 (29)
16-20	15 (7)	46 (11)	48 (14)
21-25	1 (<1)	14 (3)	18 (5)
>25	0	13 (3)	17 (5)
Follow-up of survivors, months, median (range)§	93 (29-244)	75 (25-284)	90 (25-269)

*SCID: ADA deficiency, n = 9 (4%); $T^- B^-$ ± NK activity, n = 76 (38%); $T^- B^+$ ± NK activity, n = 87 (43%); $T^+ B^-$ ± NK activity, n = 20 (10%); $T^+ B^+$ ± NK activity, n = 6 (3%); unknown, n = 3 (2%).

†Non-SCID PIDD: Wiskott-Aldrich syndrome, n = 144 (35%); hemophagocytic lymphohistiocytosis, n = 91 (25%); Langerhan's cell histiocytosis, n = 12 (3%); Chediak-Higashi syndrome, n = 21 (4%); chronic granulomatous disease, n = 17 (4%); Kostmann agranulocytosis, n = 18 (4%); leukocyte adhesion deficiency, n = 15 (4%); X-linked lymphoproliferative disease, n = 12 (3%); other non-SCID PIDD, n = 75 (18%).

‡IEM: osteopetrosis, n = 59 (17%); Hurler syndrome, n = 111 (32%); other mucopolysaccharidosis, n = 48 (12%); adrenoleukodystrophy, n = 36 (10%); metachromatic leukodystrophy, n = 33 (9%); globoid cell leukodystrophy, n = 20 (6%); Gaucher's disease, n = 13 (4%); other IEM, n = 33 (10%).

§645 patients were followed for at least 5 years, 440 were followed for at least 7 years, and 235 were followed for at least 10 years.

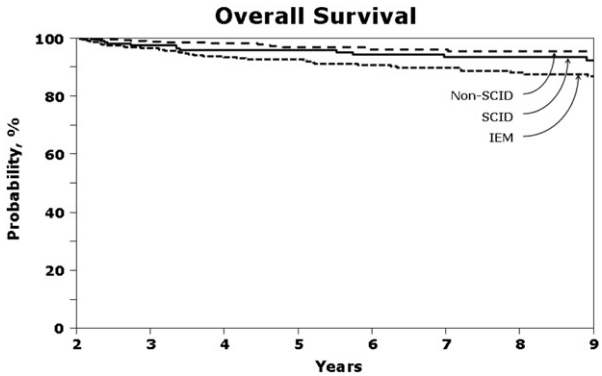

Figure 1. The 7-year probability of overall survival for patients who survived longer than 2 years after transplantation with normal T cell function (SCID patients) and >95% donor chimerism (non-SCID PIDD and IEM patients) was 93% for SCID patients, 96% for non-SCID PIDD patients, and 90% for IEM patients. The 9-year probability of overall survival was 92% for SCID patients, 96% for non-SCID PIDD patients, and 88% for IEM patients.

with a higher risk of mortality in all patients (HR, 1.87; 95% CI, 0.99-3.53; $P = .05$). Other risk factors associated with late mortality differed by disease type. Late mortality was greater in recipients of T cell–depleted allografts (HR, 4.16; 95% CI, 1.49-11.76; $P = .007$) in patients with non-SCID PIDD and for patients with IEM who received allografts from unrelated donors (HR, 2.72; 95% CI, 1.11-6.71; $P = .03$) and mismatched related donors (HR, 3.76; 95% CI, 1.34-10.52; $P = .01$) compared with HLA-matched sibling donors. Late mortality risk did not differ between patients with B^- SCID and those with B^+ SCID (HR, 1.60; 95% CI, 0.31-8.33; $P = .57$). The primary causes of late mortality are listed in Tables 2 and 3. There were 66 late deaths, including 49 deaths occurring 2-6 years after transplantation and 17 deaths after 6 years. The most common causes of late death were chronic GVHD, infections not associated with chronic GVHD, and organ failure.

Malignancy accounted for 5% of the late deaths (n = 3). Eight malignancies occurred 2 years after transplantation, excluding 2 patients with nonmelanoma skin cancer and 2 patients with posttransplantation lymphoproliferative disorder positive for Epstein-Barr virus (PTLD-EBV), which occurred at 36 months and 39 months after transplantation, respectively. Two patients developed AML, 1 patient had myelodysplastic syndrome (MDS), and 5 patients had solid tumors (1 each with Hodgkin's lymphoma, kidney tumor, brain stem glioma, melanoma, and mucoepidermoid carcinoma) (Table 4). The median time to development of leukemia, MDS, and solid tumors was 72 months (range, 45-240 months) in patients with non-SCID PIDD. AML and MDS developed in patients who had received total body irradiation (>1000 cGy dose). All malignancies but 1 occurred in patients age <10 years at transplantation.

Table 2. Primary Causes of Death in Children Age 2-6 Years

Cause of Death	SCID (n = 10)	Non-SCID (n = 12)	IEM (n = 27)	Total (n = 49)
Chronic GVHD	2	5	7	14
Infection without GVHD*	3	2	6	11
Organ failure†	3	–	10	13
PTLD-EBV positive	1	1	–	2
AML	–	2	–	2
Graft failure	–	1	–	1
Seizure	–	–	1	1
Accidental death	–	1	1	2
Acute abdomen	–	–	1	1
Not reported	1	–	1	2

*Infection without GVHD: bacterial, n = 8; viral, n = 1; no isolate, n = 2.
†Organ failure: multiorgan failure (IEM, n = 1), cardiac (SCID, n = 2; IEM, n = 3), and pulmonary (SCID, n = 1; IEM, n = 5).

Table 3. Primary Causes of Death in Children Age >6 Years

Cause of Death	SCID (n = 4)	Non-SCID (n = 3)	IEM (n = 10)	Total (n = 17)
Chronic GVHD	–	–	2	2
Infection without GVHD*	2	1	2	5
Organ failure†	1	–	2	3
Brain stem glioma	–	1	–	1
Not reported	1	1	4	6

*Infection without GVHD: bacterial infection, n = 3; viral infection, n = 1; no isolate, n = 1.
†Organ failure: cardiac failure (SCID, n = 1), pulmonary failure (IEM, n = 1), and progressive neurologic deterioration (Gaucher's disease, n = 1).

The relative mortality rate for each disease category was calculated to compare mortality in the transplant recipients and an age-, sex- and nationality-matched general population (Table 5). The risk of mortality at 2-6 years after transplantation exceeded that for the general population in all patients. Beyond 6 years, the mortality risk was not different from that for the general population in patients with SCID and non-SCID PIDD; however, in patients with IEM, the risk remained higher than that for the general population, even beyond 6 years after transplantation.

DISCUSSION

Patients are at high risk of dying from a transplantation-related complication or recurrence of primary disease within the first 2 years after transplantation. Thereafter, the risk is substantially lower, with the survival curve reaching a plateau. However, the risk for late mortality persists for several years after transplantation and is linked to several factors, including pretransplantation treatment, transplantation conditioning regimen, chronic GVHD, infections, and autoimmunity [2-11]. We examined late mortality in a large group of patients with SCID, non-SCID PIDD, and IEM who survived longer than 2 years after transplantation with normal T cell function (SCID) and >95% donor chimerism (non-SCID PIDD and IEM). There are important differences in the patient characteristics between our study population and the

Table 4. Ratio of Observed to Expected Cases and Absolute Excess Risk of New Malignancy Occurring 2 Years after Transplantation

Primary Disease	New Malignancy	Observed	Expected	Observed:Expected (95% CI)	*P* Value	AER*
Chronic granulomatous disease	Melanoma of skin	1	0.0027	370.33 (9.37-2063)	.005	1.40
Wiskott-Aldrich syndrome	Kidney	1	0.0656	15.23 (0.39-84.85)	.127	1.31
Hemophagocytic lymphohistiocytosis	Brain stem glioma	1	0.0212	46.98 (1.19-262)	.042	1.37
Hemophagocytic lymphohistiocytosis	Hodgkin's lymphoma	1	0.0727	13.75 (0.35-76.63)	.140	1.30
Wiskott-Aldrich syndrome	AML	2	0.0533	37.55 (4.55-135.66)	.003	2.72
Chediak-Higashi syndrome	MDS	1	0.0516	19.38 (0.49-108)	.101	1.33
Langerhan cell histiocytosis	Mucoepidermoid cancer	1	0.2043	4.89 (0.12-27.27)	.369	1.11

*Absolute excess risk; number of observed cases minus number of expected cases per 10,000 person-years at risk.

populations of previous reports [2-8]. In this analysis, (1) patients were alive longer than 2 years after transplantation, with sustained immunologic recovery or donor chimerism; (2) the majority of patients with SCID received chemotherapy for pretransplantation conditioning, and one-third received an allograft from an unrelated donor; and (3) more than one-half of all patients with non-SCID PIDD and IEM received an allograft from an unrelated donors.

The majority of the patients in the current analysis were long-term survivors, with 7-year posttransplantation survival rates of 93% for the SCID group, 96% for the non-SCID PIDD group, and 90% for the IEM group. Overall, 7% of surviving patients died of a transplantation-related complication more than 2 years after the procedure, confirming that the risk of late mortality after transplantation is not negligible. High relative mortality in transplant recipients compared with an age-, sex-, and nationality-matched general population was observed in all patients for as long as 6 years after transplantation. Excess mortality beyond 6 years was seen only in the IEM group. This high mortality risk in the IEM group may reflect failure of the transplantation procedure to prevent progression of end-organ damage or to fully correct organ dysfunction that might have occurred as a consequence of the disease process before or shortly after transplantation [4].

Active chronic GVHD was associated with higher mortality in all 3 disease groups. Previous studies also identified active chronic GVHD as a significant contributor to long-term morbidity and mortality after transplantation for malignant diseases, aplastic anemia, SCID, and Wiskott-Aldrich syndrome [3,6,7,9-11,17]. In our analysis, the risk of late mortality was not associated with transplant donor source in the SCID and non-SCID PIDD groups, in contrast to a previous report [2]. However, donor source was associated with late mortality in the patients with IEM; the risk of mortality was greater after mismatched related and unrelated donor transplantation compared with HLA-matched sibling transplantation. Changes in transplantation strategies, including donor selection (donor–recipient HLA matching at the allele level at HLA-A, -B, -C, DRB1) and improvements in supportive care, have resulted in fewer early deaths from transplantation-related complications and may result in comparable improvement in late outcomes after alternative donor transplantations in the current era. The current analysis is limited to those who survived for 2 years or longer after transplantation. We hypothesize donor source might not be associated with survival beyond 2 years after transplantation as the majority of complications attributed to donor source would have occurred earlier post-transplant.

Table 5. Estimated Excess Deaths per 1000 Compared with an Age-, Sex-, and Nationality-Matched General Population

	Excess Deaths per 1000 (95% CI)		
	SCID	Non-SCID	IEM
2-6 years after HSCT	54 (28-79)*	38 (25-51)*	90 (77-103)*
6-10 years after HSCT	25 (−2-51)	16 (−6-39)	33 (15-50)*

*Significant difference in excess deaths compared with an age- and sex-matched general population.

Consistent with previous reports, the most frequent causes of death in our series were chronic GVHD, infection without chronic GVHD, and organ failure [3,7,9-11]. In patients with chronic GVHD, death may occur as a direct complication of GVHD, such as bronchiolitis obliterans, or as a consequence of the immunodeficiency associated with chronic GVHD, which increases the susceptibility to infection and death [17,18]. Information on the burden of morbidity in patients with chronic GVHD is not available [19]; this is a limitation when using data collected by an observational registry.

Death from infection in the absence of chronic GVHD was also frequent in our series. Approximately 75% of late infections were bacterial, indicating persistent immunodeficiency after transplantation [20]. Organ failure was common, especially in the SCID and IEM groups. Cardiopulmonary failure was the most frequently cited cause of organ failure. Death from organ failure might be related to the transplantation procedure, organ toxicity from radiation or chemotherapeutic agents used for pretransplantation conditioning, or the underlying disease. Patients with immunodeficiency are susceptible to bronchopulmonary infection before transplantation, and patients

with IEM may have cardiopulmonary end-organ dysfunction at the time of transplantation. The majority (90%) of our patients with IEM received a myeloablative conditioning regimen, and it remains to be seen whether recent strategies aimed at reducing transplantation-related complications, such as substitution of treosulfan for busulfan [21], reduces the risk of fatal organ toxicity in long-term survivors. Organ failure also can be autoimmune-mediated, and autoimmunity without chronic GVHD has been documented in long-term survivors with SCID and non-SCID PIDD [3,6,7].

Malignancy excluding PTLD-EBV accounted for 5% of the late deaths in our series; malignancy occurred only in patients with non-SCID PIDD. The increased risk of malignancy compared with the general population matched for age, sex, and nationality was confined to melanomas, brain stem gliomas, and AML. Our study population is relatively small, and the cancers noted to occur in excess limited by 1 or 2 events compared to an age, sex-matched general population. The occurrence of solid tumors after allogeneic transplantation is well documented, and the risk increases with longer follow-up [22-24]. Posttransplantation malignancy has been associated with altered immune system/function after transplantation, very young age at transplantation, irradiation-containing pretransplantation conditioning regimens, and transplantation of T cell–depleted allografts, all of which are known risk factors [22-24].

Transplantation strategies have evolved, and in recent years, more aggressive measures have been instituted with respect to defining suitably matched related or unrelated donors, GVHD prevention, and infection surveillance and treatment. Thus, several of the late complications that resulted in death in our series may no longer be as relevant for patients undergoing transplantation today. Only 25% of our surviving patients had more than 10 years of follow-up, and complications occurring beyond this period are underreported. Curtis et al. [22] reported a sharp increase in new solid malignancies at 15 years after bone marrow transplantation for hematologic malignancies, and Baker et al. [25] reported increases in diabetes, hypertension, and cardiovascular events after transplantation in very long-term survivors.

Although the probability of long-term survival after transplantation for SCID, non-SCID PIDD, and IEM is high, the risk of mortality is substantially greater than that expected for a normal general population for several years after transplantation. Allogeneic transplantation is unlikely to reverse any end-organ damage occurring before transplantation, and for some of the IEM diseases, progressive end-organ damage persists despite adequate engraftment. Furthermore, this treatment might not fully correct the immunologic or metabolic defect, resulting in continued interplay between inflammatory process and poorly regulated cellular repair. Consequently, late mortality could be attributed to the primary disease, as well as to the transplantation procedure. We recommend life long surveillance to prevent and treat life-threatening late complications and better define the long-term risks of transplantation for SCID, non-SCID PIDD, and IEM. This surveillance should include assessment for chronic GVHD, pulmonary function, and cardiovascular risk (including echocardiography and lipid profile), diabetes, obesity, and renal function, in addition to other recommended tests [26]. Others have reported that survivors experience considerable difficulty in holding jobs and obtaining health insurance [10], which likely will hinder life long surveillance of survivors of transplantation in countries without national health insurance.

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