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Report

Outcomes of Hematopoietic Stem Cell Transplantation in Primary Immunodeficiency: A Report from the Australian and New Zealand Children's Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry

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A B S T R A C T

We performed a retrospective analysis on the outcomes of 135 hematopoietic stem cell transplantations (HSCTs) for primary immunodeficiency disorders in Australian and New Zealand Children's Haematology Oncology Group transplantation centers between 1992 and 2008. The most common indications for HSCT were severe combined immunodeficiency, Wiskott-Aldrich syndrome, and chronic granulomatous disease. Five-year overall survival (OS) was 72% for the entire cohort. Disease-specific 5-year OS was 70% for severe combined immunodeficiency, 81% for Wiskott-Aldrich syndrome, and 69% for chronic granulomatous disease. Transplantation-related mortality (TRM) was 10% at day +100. TRM and OS were equivalent in recipients of related and unrelated donor transplants. Source of stem cells had no impact on TRM or OS with outcomes following unrelated umbilical cord blood similar to unrelated bone marrow. The presence of interstitial pneumonitis, active cytomegalovirus infection, or veno-occlusive disease were all independent variables that significantly decreased OS. This large series supports the use of HSCT as curative therapy for a range of primary immunodeficiency disorders, demonstrating excellent survival after both related and unrelated donor transplantation.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has been the standard of treatment for primary immunodeficiency disorders (PIDs) in the pediatric population for decades. The first successful pediatric bone marrow transplantation was performed in 1968 on a child with severe combined immunodeficiency (SCID) using a histocompatible sibling donor [1]. HSCT has proven to be an effective treatment for a range of PIDs [2-6]. The initial success with matched sibling donors has been expanded to include the use of both unrelated marrow and umbilical cord blood grafts [7,8]. The use of cord blood in HSCT is increasing, and the advantages of rapid availability, decreased risk of viral transmission, and decreased rates of GVHD make cord blood an appealing source of donor stem cells for this population.

The use of reduced-intensity conditioning (RIC) regimens has been explored, and some support the use of RIC in selected subsets in this group [9,10]. The benefit of reduced late effects with RIC is balanced by the challenge of achieving durable long-term engraftment.

Advancements in donor selection, pretransplantation conditioning, and supportive care have contributed to excellent outcomes in recent years. A 5-year overall survival (OS) of 84% has been reported in patients with Wiskott-Aldrich syndrome (WAS) [11]. Outcomes for patients with SCID appear to be dependent on subtype. Gennery et al. [12] reported a 10-year survival of 70% for B(+) SCID, as opposed to only 51% for the B(−) subtype. A recent multicenter study of ADA-SCID outcomes reported a 5-year OS of 67% [13].

In this retrospective review, we analyzed the outcomes of 135 HSCTs performed in patients with PIDs at 6 Australian and New Zealand Children's Haematology Oncology Group pediatric transplantation centers between 1992 and 2008 using both related and unrelated donors (including unrelated marrow and cord blood). We examined transplantation outcomes (engraftment, graft-versus-host disease [GVHD], transplantation-related mortality [TRM], and OS) and tested variables for significant effects on these outcomes.

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METHODS

All patients were selected from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), which has recorded more than 95% of all HSCT activity in Australia since 1992 and in New Zealand since 1998 [14]. Patient consent for data reporting to ABMTRR was obtained by individual participating institutions. Patient consent for HSCT was obtained by individual institutions based on local Ethics Board requirements.

Recipients and donors were initially matched at HLA-A and -B loci by serologic methods and at -DR loci by molecular techniques. Since 2000, high-resolution allele typing at a minimum of 8 loci (HLA-A, -B, -C, -DRB1) has been performed in the majority of donor–recipient marrow pairs. Cord blood recipients were matched serologically or, more recently, by low/intermediate molecular resolution for -A and -B and at high molecular resolution for -DRB1.

All patients were cared for in single rooms ventilated with a high-efficiency particulate air filtration system. Patients at high risk for cytomegalovirus (CMV) infection received prophylactic ganciclovir up to day +100 once neutrophil engraftment had occurred or as preemptive therapy together with surveillance testing using CMV antigenemia or CMV PCR screening. Patients with a history of herpes simplex infection received prophylactic i.v. acyclovir. After engraftment, all patients received *Pneumocystis carinii* prophylaxis with co-trimoxazole or an appropriate alternative in cases of allergy. Episodes of fever were treated with broad-spectrum empiric antibiotics and antifungal therapy in accordance with individual institutional protocols.

Neutrophil engraftment was defined as the first of 3 consecutive days of an absolute neutrophil count of $\geq 0.5 \times 10^9$/L. Platelet engraftment was defined as a platelet count of $\geq 20 \times 10^9$/L measured a minimum of 7 days after the last platelet transfusion. Assessment and grading of acute GVHD (aGVHD) and chronic GVHD (cGVHD) were done using established standardized criteria [15,16]. TRM was defined as death from any cause other than persistent disease.

Various conditioning regimens were used, reflecting the differing underlying diagnoses, donor sources, transplantation center preferences, and era of transplantation (Table 1). The majority of patients received a myeloablative regimen (58%), and 25% received RIC regimen. Twenty-three patients with SCID (17%) received no conditioning. The most common myeloablative regimen used was busulfan (Bu) 16 mg/kg and cyclophosphamide (Cy) 200 mg/kg (32%). Melphalan, etoposide, or fludarabine was added to Bu/Cy in 21 patients (15%). A further 10% of patients received a myeloablative regimen using Cy with cytarabine, thiotepa, or melphalan, with 3 patients also receiving total body irradiation or total lymphocyte irradiation. Myeloablative conditioning included in vivo T cell depletion using either antithymocyte globulin or alemtuzumab in 33 patients (43%). All RIC regimens (34 patients; 25%) included fludarabine, with antithymocyte globulin or alemtuzumab added in 26 (76%) of these patients. Fludarabine was used alone or in combination with reduced-dose Bu, Cy, melphalan, or treosulphan. Ex vivo T cell depletion was performed in 29% of HSCTs, using either RBC rosette or positive $CD34^+$ cell selection, depending on the year of transplantation.

GVHD prophylaxis varied depending on stem cell source and institution. A combination of cyclosporin and methotrexate was the most common regimen used and was standard for all matched sibling/family donor and T cell–replete unrelated donor transplants. Recipients of an ex vivo T cell–depleted donor graft received cyclosporin alone. Some cord blood recipients received cyclosporin and methotrexate in combination with steroids before 2000, after which time cyclosporin and steroids or cyclosporin and mycophenolate combinations were used. A minority of patients received tacrolimus as an alternative to cyclosporin, as a single agent or in combination with mycophenolate.

The close-out date for this study was June 30, 2011, and survival statistics are based on that date. OS curves were produced using the method of Kaplan and Meier, and the Cox proportional hazards model was used to perform univariate and multivariate analysis of risk factors and their influence on outcomes. The following variables were tested for their association with time to neutrophil engraftment, incidence of aGVHD, TRM, and OS: sex, age, year of HSCT, time from diagnosis to HSCT, donor–recipient relationship, donor–recipient HLA compatibility, stem cell source, donor and recipient CMV seropositivity, pretransplantation conditioning, GVHD and CMV prophylaxis, and incidence of adverse events immediately post-transplantation, which were entered as time-dependent variables. Statistical analyses were performed using SPSS version 19 (IBM, Armonk, NY).

Table 1
Patient Characteristics

Characteristic	n (%)
Total patients	135
Recipient sex	
Male	107 (79)
Female	28 (21)
Year of HSCT	
1992-1999	53 (39)
2000-2008	82 (61)
Indication for transplant	
Chediak-Higashi syndrome	2 (1)
CGD	16 (12)
Congenital neutropenia/Kostmann syndrome	7 (5)
Di George syndrome	2 (1)
Leukocyte adhesion disorder	3 (3)
Omenn syndrome	6 (5)
SCID	65 (48)
WAS	27 (20)
X-linked hyper-IgM syndrome	2 (1)
X-linked lymphoproliferative syndrome	5 (4)
Conditioning regimen	
Bu + Cy with or without antithymocyte globulin	44 (32)
Bu + Cy + other	21 (15)
Fludarabine + other (RIC)	34 (25)
Cy + other	13 (10)
None	23 (17)
Unknown	1 (1)
Donor relation	
HLA-identical sibling	28 (21)
HLA-mismatched sibling	6 (5)
HLA-identical other related	10 (7)
HLA-mismatched other related	31 (23)
HLA-identical unrelated	42 (31)
HLA-mismatched unrelated	18 (13)
Cell source	
Bone marrow	92 (68)
Peripheral blood	9 (7)
Cord blood	33 (24)
Bone marrow and cord blood	1 (1)
GVHD prophylaxis	
T cell depletion	20 (15)
Cyclosporin only	27 (20)
Cyclosporin + methotrexate	42 (31)
Cyclosporin + mycophenolate	15 (11)
Cyclosporin + other	19 (14)
Other	4 (3)
None	6 (5)
Unknown	2 (1)

RESULTS

A total of 135 children underwent initial HSCT for a PID. Table 1 summarizes patient characteristics. Indications for HSCT included a diagnosis of SCID, WAS, chronic granulomatous disease (CGD), congenital neutropenia/Kostmann syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, leukocyte adhesion deficiency, X-linked hyper-IgM syndrome, Di George syndrome, or Chediak-Higashi syndrome. The median age at transplantation was 1 year (range, 0-15 years), and the cohort was 79% male. The median age of donors was 13 years (range, 0-51 years). Of the donors, 28% were HLA-matched related (21% matched sibling, 7% other matched related), 28% were mismatched related, and 44% were unrelated. Cord blood was used in 54% of unrelated donor transplantations. The median cryopreserved cord blood cell dose was 8.0×10^7/kg (range, 1.3-138.0×10^7/kg) for total nucleated cells and 3.1×10^5/kg (range, 0.9-57.0×10^5/kg) for $CD34^+$ cells.

The median time from diagnosis to HSCT for the entire cohort was 6 months (range, 0-163 months). A greater number of transplantations were performed in the more recent time period, with 82 in 2000-2008 compared with 53 in 1992-1999. The median patient follow-up for the entire cohort was 6.03 years (range, 0.39-17.31 years).

Engraftment

The median time to neutrophil and platelet engraftment was 16 days (range, 1-62 days) and 30 days (range, 1-112