Comparable Outcomes of Matched-Related and Alternative Donor Stem Cell Transplantation for Pediatric Severe Aplastic Anemia


Center for Cell and Gene Therapy, Baylor College of Medicine, The Methodist Hospital and Texas Children’s Hospital, Houston, Texas

Correspondence and reprint requests: Alana A. Kennedy-Nasser, MD, Center for Cell and Gene Therapy, Baylor College of Medicine, The Methodist Hospital and Texas Children’s Hospital, Houston, TX 77030 (e-mail: aakenned@txccc.org).

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ABSTRACT

Matched sibling donor (MSD) bone marrow transplantation is the treatment of choice for pediatric patients with severe aplastic anemia (SAA); however, only about 33% of patients will have an HLA-identical sibling. Alternative donor (AD) transplants may be an option for these patients, but such therapies have been associated with greater incidence of graft failure and graft-versus-host disease (GVHD). We retrospectively analyzed 36 pediatric patients who received 38 bone marrow or peripheral blood stem cell transplants (15 MSD and 23 AD) for SAA at our institution from April 1997 to October 2005. Nineteen AD recipients received reduced intensity conditioning with cyclophosphamide, low-dose total body irradiation, and antithymocyte globulin (ATG) or Campath. The 4-year overall survival for MSD recipients was 93% versus 89% for AD recipients treated with reduced intensity conditioning regimens at a median follow-up of 52 months (range, 6-99 months). No patient receiving Campath, compared with 3 of 9 patients receiving ATG, developed extensive, chronic GVHD. We conclude that, for children with SAA, AD transplantation is as effective as MSD transplantation. Further, compared with ATG, preparatory regimens containing Campath may be associated with a lower incidence of extensive, chronic GHVD.

INTRODUCTION

HLA-identical matched sibling donor (MSD) hematopoietic stem cell transplantation (HSCT) is the treatment of choice for pediatric patients with severe aplastic anemia (SAA). Storb et al [1] reported an 88% event-free survival for 81 patients with SAA receiving MSD transplantation after conditioning with cyclophosphamide and antithymocyte globulin (ATG). Unfortunately, only about 33% of patients have a suitably HLA-matched sibling [1-4]. Results from alternative donor (AD) transplantsations have been less encouraging, mainly because of high rates of graft failure and severe graft-versus-host disease (GVHD) [3-5]. Data from the International Bone Marrow Transplant Registry for 732 pediatric patients who underwent transplantation with MSD grafts between 1996 and 2001 showed a 3-year survival of 82% but only 53% survival for 218 pediatric patients who received transplants from unrelated donors [6]. The Center for International Blood and Marrow Transplant Research reported a 30% to 49% 5-year overall survival for 318 AD grafts [7]. Thus, the trend has been to offer immunosuppressive therapy (IST) to pediatric patients with SAA who do not have an MSD and to offer AD transplants only if immunosuppression fails.

Although survival rates after IST in children with SAA have been reported to be as high as 80% [8,9],
treatment failure occurs in 40% to 50% of cases [10]. Further, late clonal complications including myelodysplasia and paroxysmal nocturnal hemoglobinuria may develop in 25% to 45% of patients undergoing IST by 7 to 11 years after therapy [11-14].

Reports for patients who underwent AD transplantation by European groups and the National Marrow Donor Program suggest that high-dose total body irradiation (TBI) regimens, although effective in achieving engraftment, also increase toxicity, so that survival is not improved [15-18]. Deeg et al [19] reported the results of a multicenter, prospective, phase I study in which the minimum effective dose of TBI was determined in patients with SAA undergoing unrelated donor HSCT. They concluded that a TBI dose of 200 cGy in combination with cyclophosphamide and ATG was sufficient for engraftment in matched unrelated donor (MUD) grafts without incurring unacceptable toxicities.

At our institution, all patients with SAA and matched siblings receive HSCT. Other patients initially receive IST and, if this fails, they receive AD transplants. We report that MSD and AD HSCT using reduced intensity conditioning regimens have essentially identical outcomes in pediatric patients with SAA.

METHODS

Patients

Between April 1997 and October 2005, 36 consecutive pediatric patients with SAA underwent allogeneic HSCT at Texas Children’s Hospital (n = 35) and The Methodist Hospital (n = 1) in studies approved by the institutional review boards. SAA was defined as any 2 of the following: neutrophil count <0.5 × 10⁹/L, platelet count <20 × 10⁹/L, or reticulocytes <1% and marrow features of severe hypocellularity or moderate hypocellularity (<35% cellularity) [20]. All patients had acquired SAA (Table 1). Fanconi anemia was excluded in all patients by using chromosomal breakage studies.

The median age at time of transplantation was 9.4 years (range, 1.3-18.4 years; 20 boys and 16 girls). Median times from diagnosis to transplantation were 4.8 months for all patients (range, 1.2-51.6 months), 2.4 months for MSD recipients, and 6 months for AD recipients. This difference reflects that all but 1 of the AD recipients received and failed IST before transplantation.

Bone Marrow Donor Selection

Donor characteristics for all transplants are listed in Table 1. Unrelated donors were recruited through the National Marrow Donor Program. DNA-based allele typing for class II DR has been performed since 1997. Class I A and B typing was antigen specific until March 2005, when allele typing was instituted. The median age of ADs was 35 years (range, 23-50 years). The median age of MSDs was 11 years (range, 0.3-22 years).

Transplants

Thirty-six consecutive patients with acquired SAA received 38 allogeneic transplants. Fifteen patients initially received MSD transplants and 21 received AD transplants: 11 MUD, 7 mismatched unrelated donor (MMUD), and 3 mismatched related donor. Two of these 36 patients received a second transplant: 1 MSD recipient had late graft failures despite several additional donor cell infusions and 8 years later received a MUD graft after reduced intensity conditioning (for the purpose of statistical analysis, this patient was censored at the time of undergoing MUD transplantation). One patient had a failed engraftment after MMUD transplantation at 17 years of age, and 2 months later received a peripheral blood stem cell transplant from a haploidentical parent.
Stem Cell Products

The source of stem cells was unmanipulated bone marrow (n = 34) or CD34+–selected peripheral blood (Isolex [Baxter, Irvine, California]; n = 4; 1 mismatched related donor, 1 MUD, 1 MSD, and 1 haploidentical graft) collected after granulocyte colony-stimulating factor mobilization. For marrow a median of 4.97 total nucleated cells/kg (range, 0.79-14.94) and for CD34+–selected products a median of 8.02 CD34+/kg (range, 6.53-10.10) were infused.

Transplantation Protocol for MSD HSCT

Fourteen of 15 MSD recipients received cyclophosphamide 50 mg/kg for 4 days (days −5 to −2) and equine ATG (ATGAM) 30 mg/kg for 3 days (days −5 to −3) in accord with the Seattle regimen [1]. One MSD recipient with paroxysmal nocturnal hemoglobinuria received busulfan for 4 days (days −7 to −4) and cyclophosphamide 50 mg/kg for 2 days (days −3 and −2).

Transplantation Protocol for AD HSCT

Nineteen of 23 AD recipients received a reduced intensity conditioning regimen consisting of cyclophosphamide 50 mg/kg for 4 days (days −6 to −3) and low-dose TBI (200 cGy for MUD on day −2 and 200 cGy for MMUD recipients on days −2 and −1). Patients who underwent transplantation from 1997 to 2000 received equine ATG (ATGAM) 30 mg/kg for 3 days (days −5 to −3). After 2000, patients received humanized anti-CD52 monoclonal antibodies and Campath-1H (alemtuzumab) in a weight-dependent dose (3 mg for patients 5-15 kg, 5 mg for patients 16-30 kg, and 10 mg for patients >30 kg) daily for 4 days (days −4 to −1). Three patients received fully myeloablative preparative regimens and 1 patient received a subablative regimen of fludarabine 30 mg/m2 daily for 10 days (days 1-2, Campath 10 mg on days −5 to −2, and low-dose TBI conditioning for a haploidentical peripheral blood stem cell transplant 2 months after failing to engraft from an initial MMUD transplant. In all, 9 AD grafts included ATG in the preparative regimen and 14 included Campath.

GVHD and Infectious Prophylaxis

All patients received FK506 or cyclosporine, with or without methotrexate for GVHD prophylaxis. All patients received bacterial and fungal prophylaxis during the peri-transplantation period and all patients received pneumocystis carinii pneumonia prophylaxis. Monitoring of viral and fungal infections was carried out as per institutional standard of care [21].

Statistical Methods

Engraftment rates and incidences of acute and chronic GVHD are reported for each patient group. Survival time was calculated from date of transplantation to date of death or date of final patient follow-up in March 2006. Kaplan-Meier survival curves and estimates of survival rates at specific time points in addition to 95% confidence intervals are estimated for each group of patients.

RESULTS

Tables 2 and 3 list the transplant characteristics and outcomes of MSD and AD recipients.

Engraftment

Engraftment was defined as a sustained (3-day) neutrophil count >0.5 × 109/L and unsupported platelet count >20 × 109/L. Thirty-seven of 38 transplants were evaluable for engraftment. One patient (no. 11) died of a pre-existing Pseudomonas aeruginosa infection only 6 days after MSD transplantation and was therefore unevaluable for engraftment. Thirty-six of 37 (97%) evaluable transplants engrafted. Median time to neutrophil engraftment was 17 days (range, 11-44 days) and median time to platelet engraftment was 32 days (range, 11-282 days). One patient’s engraftment failed (no. 34) after MMUD transplantation using reduced intensity conditioning but was later successful after haploidentical transplantation using a different reduced intensity conditioning regimen.

Chimerism Studies

Chimerism was determined on blood and/or bone marrow using fluorescence in situ hybridization probes for sex chromosomes or polymerase chain reaction amplification of specific polymorphic DNA sequences (short tandem repeats). Thirty-four of 36 (94%) evaluable transplant patients had >95% donor chimerism. Seven of 14 (50%) MSD recipients and 17 of 22 (77%) AD recipients were 100% chimeric. One patient had autologous recovery (MSD recipient) and is transfusion independent with 100% recipient cells and 50%-70% bone marrow cellularity with normal cytogenetics.

Survival

Thirty-one of 36 (86.1%) patients have survived to date as transfusion independent, at a median follow-up of 52 months (range, 6-99 months). The 4-year overall survival was 93% in the MSD group compared with 89% in the AD group of patients receiving this reduced intensity regimen. There was no statistical difference between these 2 groups of patients (Figure 1).

Five patients died at a median of 52 days after transplantation (range, 6 days to 5.5 years). Four patients died of infection soon after transplantation and 1 patient (no. 16) died 5.5 years after MUD transplantation from chronic GVHD pulmonary complications.
resulting in pulmonary failure (Table 4). For patients dying from infection, the causes of death were pre-existing pseudomonas (n = 2), idiopathic pneumonia (n = 1), and adenovirus complicated by acute GVHD (n = 1).

Ten patients (3 MSD, 7 AD) developed cytomegalovirus (CMV) reactivation without CMV disease. Five patients received ATG or Campath in the conditioning regimen, and frequencies of CMV infection were 36% with Campath and 23% with ATG. Two of these patients died; 1 MUD recipient who received ATG as a result of pre-existing pseudomonas infection and 1 MUD recipient who received Campath died from adenoviral infection. An additional patient who received Campath developed Epstein-Barr viral reactivation, which was treated successfully with rituximab.

**Graft-versus-Host Disease**

Severe, acute GVHD (grade III or IV) developed in 0 of 15 MSD recipients and 4 of 23 AD recipients. Specifically, 2 of 9 AD recipients who received ATG developed severe, acute GVHD compared with 2 of 14 Campath recipients. Extensive, chronic GVHD developed in 0 of 15 MSD recipients and 3 of 23 AD recipients, all 3 of whom received ATG in the preparative regimen. No patient treated with Campath developed extensive, chronic GVHD. One MMUD recipient (no. 23) with hepatitis-associated SAA developed grade IV acute GVHD and extensive, chronic GVHD of the liver, received a liver transplant, and is now well and disease free.

**DISCUSSION**

Although the outcomes after MSD transplantation for pediatric SAA have improved over the years, the results using AD transplants have been less satisfactory. Margolis and Casper [5] reported 55% survival at 33 months for 28 heavily transfused adult and pediatric patients with SAA undergoing AD HSCT using an intensive conditioning regimen. Because of these and similar results [3-7], immunosuppression has remained first-line therapy for patients lacking an HLA-matched sibling. Unfortunately, IST has achieved limited improvement in survival, with high rates of clonal evolution and relapse [8,11-13,22,23]. In addition, delayed time to transplantation presumably due to IST administration has been associated with a poorer outcome in several studies [7,24]. This has led to the use of nonmyeloablative or reduced intensity preparative regimens to improve survival for recipients of AD transplants. The European Group for Blood and Marrow Transplantation Working Party reported 73% survival for 38 adult and pediatric patients when using a reduced intensity conditioning regimen.
<table>
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<th>Time to HSCT (mo)</th>
<th>Conditioning Regimen</th>
<th>ATG or Campath</th>
<th>Acute GVHD</th>
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</table>

NA indicates not available or applicable; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; D, donor; R, recipient; M, male; F, female; HLA, human-leukocyte antigens; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; MMRD, mismatched related donor; Haplo, haploidentical; Cy, cyclophosphamide; TBI, total body irradiation; AraC, cytarabine arabinoside; Flu, fludarabine; Bu, busulfan; ATG, antithymocyte globulin; Ext, extensive; Lim, limited; RFLP, restriction fragment length polymorphism; FISH, fluorescence in situ hybridization; STR, short tandem repeats; Ag, antigen.

*Patients 34 and 35 are the same patient.
†Patient 36 is also patient 1 in Table 2.
regimen of fludarabine, cyclophosphamide, and ATG [25]. Another study reported 75% survival with durable engraftment using non-TBI preparative regimens for 13 mostly young adult patients with SAA who received AD transplants [26]. Vassiliou et al [27] reported 100% survival with AD HSCT using Campath, low-dose TBI, and cyclophosphamide as reduced intensity conditioning in 8 patients. In addition, low-dose TBI with cyclophosphamide and ATG has been shown to be effective in securing durable grafts with acceptable toxicities in MUD grafts [2].

We find that this reduced intensity conditioning regimen with low-dose TBI achieves stable engraftment and excellent survival. There is concern that these patients may be at risk for secondary malignancies but none has occurred up to 86 months after AD transplantation. After irradiation, the risk for thyroid cancer is expected to be highest in children exposed at an age <5 years [28]. For patients with SAA excluding Fanconi anemia undergoing MSD and AD transplantation [29], the estimated risk for developing any malignancy by 20 years (range, 1.4-221 months) was reported as 14%. The risk of malignancy likely has a linear relation to radiation doses up to 7-8 Gy. Although the risk of malignancy after conditioning regimens that include radiation are of obvious concern, these risks may be little different from those incurred after IST alone or after transplant-preparative regimens that use only chemotherapy. Lifelong follow-up for all these patients is therefore necessary.

Fludarabine has been used in preparative regimens without TBI. Although a survival of 71% to 84% has been noted for patients who received AD transplants [25,30-33], this regimen has led to a reportedly higher incidence of graft failure and GVHD in some studies [30,32]. Although fludarabine-based conditioning regimens remain promising, the incidence of GVHD using our conditioning regimen (especially in the patients who received Campath) appears lower than that in other reported series. Certainly, the long-term (>20-year) effects of a fludarabine-based or low-dose TBI-based preparatory regimen have yet to be determined.

Campath was substituted for ATG because it allows for predictable depletion of T and B lymphocytes [34,35]. As previously published by our group and others, Campath may be associated with higher rates of viral infections such as CMV and adenovirus [36-38]; however, in our patients, there was no CMV disease.

Previous studies have shown that AD transplants result in an increased incidence of graft rejection and an increased risk of death from acute GVHD, infection, and pneumonitis when compared with MSD transplantation [25]. However, other groups have noted an association with lower rates of GVHD using Campath [39,40]. Although graft failure has been an ongoing concern in patients with SAA undergoing AD HSCT, in our experience only 1 patient’s engraftment failed and GVHD was minimal in this cohort of patients. None of the patients who received Campath developed extensive, chronic GVHD compared with 3 of 9 ATG recipients in the AD group; however, the sample was too small to determine significance.

Many studies have shown that survival after HSCT is improved by shortening the time to transplantation, thereby decreasing blood product exposures and minimizing prior therapy [24,25,41]. In our report, the median time to transplantation was notably longer in the AD than in the MSD group (6 versus 2.4 months). This delay was attributed to the fact that all but 1 of the AD recipients received and failed IST

<table>
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<th>Patient No.</th>
<th>Age (y) at Time of HSCT</th>
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<th>Conditioning Regimen</th>
<th>ATG or Campath</th>
<th>Time of Death after HSCT</th>
<th>Cause of Death</th>
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RI indicates reduced intensity; HSCT, hematopoietic stem cell transplantation; MSD, matched sibling donor; MMRD, mismatched related donor; MUD, matched unrelated donor; Cy, cyclophosphamide; GVHD, graft-versus-host disease; ATG, antithymocyte globulin.
before transplantation. However, we observed no effect of time from diagnosis to transplantation on survival, even though AD transplantation was performed later after diagnosis than MSD transplantation. Some preceding IST for these patients may have favored subsequent engraftment when low-intensity conditioning was used.

We have shown that a reduced intensity conditioning regimen of cyclophosphamide, low-dose TBI, and ATG or Campath achieves sustained engraftment and excellent survival in pediatric patients with SAA who receive AD transplants. These results are comparable to the outcome for pediatric patients with SAA who received MSD transplants.

REFERENCES


27. Vassiliou GS, Webb DK, Pamphilon D, Knapper S, Veyes PA. Improved outcome of alternative donor bone marrow transplantation in children with severe aplastic anaemia using a conditioning regimen containing low-dose total body irra-


