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Alternative Donor Transplantation with High-Dose Post-Transplantation Cyclophosphamide for Refractory Severe Aplastic Anemia

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A B S T R A C T

Severe aplastic anemia (SAA) is a life-threatening hematopoietic stem cell disorder that is treated with bone marrow transplantation (BMT) or immunosuppressive therapy (IST). The management of patients with refractory SAA after IST is a major challenge. Alternative donor BMT is the best chance for cure in refractory SAA, but morbidity and mortality from graft failure and complications of graft-versus-host disease (GVHD) have limited enthusiasm for this approach. Here, we employed post-transplantation high-dose cyclophosphamide in an effort to safely expand the donor pool in 16 consecutive patients with refractory SAA who did not have a matched sibling donor. Between July 2011 and August 2016, 16 patients underwent allogeneic (allo) BMT for refractory SAA from 13 haploidentical donors and 3 unrelated donors. The nonmyeloablative conditioning regimen consisted of antithymocyte globulin, fludarabine, low-dose cyclophosphamide, and total body irradiation. Post-transplantation cyclophosphamide 50 mg/kg/day i.v. on days +3 and +4 was administered for GVHD prophylaxis. Additionally, patients received mycophenolate mofetil on days +5 through 35 and tacrolimus from day +5 through 1 year. The median age of the patients at the time of transplantation was 30 (range, 11 to 69) years. The median time to neutrophil recovery over $1000 \times 10^3/mm^3$ for 3 consecutive days was 19 (range, 16 to 27) days, to red cell engraftment was 25 (range, 2 to 58) days, and to last platelet transfusion to keep platelets counts over $50 \times 10^3/mm^3$ was 27.5 (range, 22 to 108) days. Graft failure, primary or secondary, was not seen in any of the patients. All 16 patients are alive, transfusion independent, and without evidence of clonality. The median follow-up is 21 (range, 3 to 64) months. Two patients had grade 1 or 2 skin-only acute GVHD. These same 2 also had mild chronic GVHD of the skin/mouth requiring systemic steroids. One of these GVHD patients was able to come off all IST by 15 months and the other by 17 months. All other patients stopped IST at 1 year. Nonmyeloablative alloBMT using post-transplantation cyclophosphamide allowed for safe expansion of the donor pool to include HLA-haploidentical donors. This approach appears promising in refractory SAA patients. Importantly, engraftment was 100%, pre-existing clonal disease was eradicated, and the risk of GVHD was low.

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INTRODUCTION

Acquired severe aplastic anemia (SAA) is an immune-mediated hematopoietic stem cell disorder that presents with a hypocellular marrow and pancytopenia [1,2]. The incidence of SAA is roughly 1 in 250,000 individuals per year [3,4]. Most newly diagnosed patients are managed with immunosuppressive therapy (IST) unless they are young and have a suitable HLA-matched sibling donor (MSD) for bone marrow transplantation (BMT). IST improves hematopoiesis and decreases the early mortality of the disease. Though SAA is not considered overtly malignant, it confers significant risk to the patient because of its late complications, which include relapse and secondary clonal disease [5-8]. Infection (usually fungal) is the most common cause of early death; however, hemorrhage, clonal disease (myelodysplastic syndromes [MDS] [9], leukemia, and paroxysmal nocturnal hemoglobinuria [PNH]), and transfusional iron overload are other causes of severe morbidity and mortality [10]. Improved

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supportive care has led to significant progress in controlling the acute aspects of the disease over the past 2 decades, but little progress has been made controlling the late complications of SAA, especially the risk for relapse and secondary clonal disorders. Allogenic (allo) BMT from an MSD is the standard of care for young newly diagnosed SAA patients [2,11] with long-term survival rates approaching 90% in patients under 20 years [12,13] and 76% for patients older than 20 years [13]. The less favorable transplantation outcomes in older (above ages 30 to 40 years) patients has been attributed to reduced engraftment or high rates of graft-versus-host disease (GVHD) [14]. BMT addresses both the acute and chronic complications of SAA by virtually eliminating the risk of relapse and secondary clonal disease. Older SAA patients and even young adults who lack an MSD often proceed to IST because of the perceived high risk of morbidity and mortality from alternative donor BMT.

Equine antithymocyte globulin (ATG) combined with cyclosporine is the standard front-line IST therapy for SAA [15]. The hematopoietic response rate after ATG/cyclosporine is about 70% and the probability of survival at 5 years ranges from 60% to 85% [2,15]. However, subsequent to this regimen, patients often develop late sequelae that impact quality of life [16]. Thus, event-free survival of acquired SAA patients treated with IST is only 30% to 40%, primarily as a result of relapse and secondary clonal disease [1]. Currently, the only approved therapy for these patients is eltrombopag, which has a 20% to 40% hematopoietic response rate; however, relapse and secondary clonal disease remain problematic [17,18]. Salvage BMT is considered for patients with refractory SAA if an HLA-matched unrelated donor (URD) is available, but many patients, especially minorities, are unable to find an URD in the registry [19]. Thus, the management of refractory SAA is the most vexing clinical problem in managing SAA and is in desperate need for novel approaches that can restore hematopoiesis and reduce the risk of secondary clonal disease.

Post-transplantation cyclophosphamide (PTCy) after HLA-haploidentical BMT has been shown to facilitate engraftment and yield rates of GVHD comparable to those of matched sibling BMT in hematologic malignancies [20-22]. Additionally, this platform to decrease GVHD has been especially effective in nonmalignant diseases, such as PNH and sickle cell disease [23,24] where a graft-versus-tumor effect is not necessary. Thus, we hypothesized that PTCy would improve outcomes for patients with refractory SAA by safely expanding the donor pool to include alternative bone marrow donors. Here, we present the results of the prospective phase II clinical trial of mismatched donor alloBMT with PTCy in refractory SAA performed at a single center.

METHODS

Patients

All patients included in this series were diagnosed with SAA as defined by the Camitta criteria [25]. SAA could be defined as acquired or inherited but Fanconi anemia was excluded. The protocol (Johns Hopkins trial J1424) was approved by the Johns Hopkins institutional review board (IRB), and patients signed an IRB-approved informed consent form before BMT. The study was registered at ClinicalTrials.gov number NCT02224872. Seven patients were treated according to but not on the protocol because of timing or insurance issues (when clinical trial participation was not allowed by patients' carrier). Permission to include these patients in the analysis of outcomes was granted by the Johns Hopkins IRB given uniform treatment of all patients. Race was self-identified. Patients with refractory SAA undergoing their first alloBMT were eligible if they lacked an available MSD. Additional eligibility criteria included good performance status (Eastern Cooperative Oncology Group 0 or 1; Karnofsky and Lansky 70% to 100%), ability to sign consent (or assent, if minors) forms, and the presence of an appropriate donor. Clonality was defined by presence of a PNH granulocyte clone >1% or a karyotypic abnormality.

Donors and Grafts

Eligible alternative donors included related family members who shared at least 1 HLA haplotype and unrelated matched/mismatched donors. We prioritized haploidentical donors over unrelated donors because of timing in acutely neutropenic and thrombocytopenic patients. The 3 patients in whom we did proceed with unrelated donor grafts had contraindications to their available related haploidentical donors; 1 had a presumed inherited SAA and the other 2 had families who were not able to support them in this way because of donor health limitations. The protocol initially only allowed for haploidentical donors and was then amended 2 years after approval to include matched and mismatched URDs, as our major goal was to expand the donor pool in refractory SAA. Donor bone marrow was harvested with a target yield of 4×10^8 nucleated cells/kg recipient ideal body weight and infused on day 0. The marrow was unmanipulated except that major incompatible ABO grafts were RBC depleted by buffy coat preparation and minor ABO incompatible grafts were plasma depleted as per institutional standards. Patients 2 and 3 did have mobilized donors per institutional preference at the time.

HLA Typing

HLA phenotyping was performed as described previously [22]. Potential family members were initially typed at the HLA-A, HLA-B, and HLA-DRB1 loci at an intermediate-resolution level. Family members selected as donors were then further typed at the HLA-C locus at an intermediate-resolution level. DRB1 and DQB1 alleles were typed at a high-resolution level. As needed, recipients and potential donors were typed at a high-resolution level for HLA-Cw alleles. Haplotypes were determined based on family studies whenever possible. URDs were selected in accordance with the standard National Marrow Donor Program policies.

Conditioning and GVHD Prophylaxis

Rabbit ATG was dosed at .5 mg/kg on day –9 and 2 mg/kg on days –8 and –7. Fludarabine was administered 30 mg/m^2 i.v. daily for 5 days, from day –6 to day –2 (total dose received 150 mg/m^2). Cyclophosphamide was given 14.5 mg/kg i.v. daily for 2 days from day –6 to day –5 and administered as a 1- to 2-hour infusion (total dose received, 29 mg/kg) and total body irradiation administered at delivered in a single dose of 200 cGy on day –1. The marrow graft was infused on day 0. PTCy was administered at 50 mg/kg/day i.v. on days +3 and +4 after transplantation. Granulocyte colony–stimulating factor was given subcutaneously starting on day +5 at 5 mcg/kg/day until the absolute neutrophil count was greater than 1.5×10^9/L for 3 days. Mycophenolate mofetil was given from day 5 through 35 and tacrolimus from day 5 through day 365.

Supportive Care

Blood product replacement and other supportive care measures were per institution practices. Standard oral antibiotic prophylaxis with a quinolone and an azole was begun on day 0. Patients received standard *Pneumocystis jiroveci* and anti-herpes and varicella prophylaxis for 1 year. Magnesium levels were kept above 1.5 mg/dL. All blood products, except for the allograft, were irradiated with 25 Gy before transfusion. The thresholds of RBC and platelet transfusions were hematocrit < 25% and platelet count < 20×10^3/mm^3. Cytomegalovirus (CMV)–seronegative patients with seronegative donors were given transfusions from CMV-seronegative donors or leukocyte-reduced blood products if CMV-negative products were unavailable. Patients were monitored for CMV reactivation by weekly measurement of CMV copy number by PCR of serum until day 60. Pre-emptive therapy with ganciclovir would have been initiated when ≥ 500 copies of CMV/mL serum were detected, but no patient had this metric met. Patients were monitored weekly for Epstein-Barr virus and therapy in these subjects was not required here.

Engraftment and Chimerism Analysis

Neutrophil engraftment was defined as an absolute neutrophil count $>1.0 \times 10^9$/L measured for 3 consecutive measurements on different days. Red cell engraftment was counted as days from last packed RBC transfusion and *platelet engraftment* defined as a platelet count greater than 50×10^3/mm^3 for 7 days without transfusion.

Patients had chimerism studies done on peripheral blood or bone marrow on days 30, 60, 180, and 360 and yearly thereafter. Chimerism was measured by PCR analysis of variable number of nucleotide tandem repeats unique to donors or recipients on total peripheral blood and isolated CD3$^+$ T cells. *Graft failure* was defined as undetectable DNA of donor origin on at least 2 occasions no less than 1 week apart.

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