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A study assessing the feasibility of randomization of pediatric and young adult patients between matched unrelated donor bone marrow transplantation and immune-suppressive therapy for newly diagnosed severe aplastic anemia: A joint pilot trial of the North American Pediatric Aplastic Anemia Consortium and the Pediatric Transplantation and Cellular Therapy Consortium

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Abstract

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CONFLICTS OF INTEREST

MAP is a member of a Novartis Steering Committee for a CART protocol; DAW is chair of the Steering Committee, Novartis ETB115E2201 (eltrombopeg in pediatric aplastic anemia). JH is a site PI for Novartis ETB115E2201.

Background: Recent data show survival after matched unrelated donor (MUD) bone marrow transplantation (BMT) is similar to matched sibling procedures for young patients with severe aplastic anemia (SAA). Donor delays, risk of transplant-related mortality (TRM), and concern about chronic graft versus host disease raise questions about whether MUD BMT or immune suppression therapy (IST) should be preferred initial therapy for young patients lacking matched sibling donors.

Procedure: We performed a pilot trial to assess the feasibility of randomizing patients under age 26 with newly diagnosed SAA to receive IST versus MUD BMT. Primary aims assessed the acceptability of randomization and timing of BMT. Secondary aims measured toxicities, response, and survival.

Results: Sixty-seven patients with possible SAA were screened at nine centers. Of 57 with confirmed SAA, 23 underwent randomization and received therapy with a median follow-up of 18 months. Of 12 randomized to BMT, 10 started BMT as initial therapy at a median of 36 days after randomization. One BMT recipient experienced secondary graft failure, requiring a second procedure. Six of 11 randomized to IST responded, whereas five with refractory disease underwent successful salvage BMT. One patient achieving complete response relapsed after discontinuation of immune suppression and died of infection after salvage BMT.

Conclusions: This feasibility study showed that a high percentage of patients underwent randomization and received up-front MUD BMT. Our study lays the groundwork for a larger randomized trial that will define best initial therapy for young patients with SAA who have an available MUD.

Keywords

immune suppression therapy; matched unrelated donor transplant; neutropenia; pediatric; randomized; severe aplastic anemia

1 | INTRODUCTION

Acquired severe aplastic anemia (SAA) is a rare bone marrow failure disorder with an estimated annual incidence of 2 per million in North America (600 new diagnoses in the US yearly).[1] The majority of cases have been attributed to autoimmune destruction of hematopoietic stem cells (HSCs); accordingly, the disease has been treated with either immune suppression therapy (IST) or hematopoietic stem cell (HSC) replacement through bone marrow transplantation (BMT).[2,3] When a matched sibling donor (MSD) is available, five-year survival rates exceeding 90%–95% have been reported in children and young adults, resulting in a consensus that MSD BMT is the preferred initial therapy.[2,4] For the large majority of young patients without MSDs, the combination of horse (h) antithymocyte globulin (ATG) and cyclosporine (CsA) developed in the 1990s remains the initial therapeutic approach of choice.[5] Younger patients have a similar response rate to hATG/CsA compared with adults with SAA but more frequently have a complete response (CR) or very good partial response (VGPR), as shown by a recent study by the North American Pediatric Aplastic Anemia Consortium (NAPAAC).[6]

From the initiation of IST, it takes an average of two to six months to see hematologic response, with 20%–25% of patients being refractory to initial therapy, and 3%–15% achieving a partial response, reaching transfusion-independence but with continued cytopenias that may limit lifestyle.[2,6,7] Of those who respond to IST therapy initially, as many as ~30% of patients eventually relapse up to 15 years posttreatment.[3,8] In spite of early failure of therapy in a portion of patients, five-year survival after IST in young patients exceeds 90%, as many refractory or relapsed patients respond to other forms of salvage IST or go on to receive BMT if they have a donor and are eligible. Unfortunately, between 10% and 15% of individuals treated with IST will develop clonal abnormalities, secondary myelodysplastic syndrome (MDS), or acute myeloid leukemia within 2–20 years after treatment.[3,7,9]

The outcomes of matched unrelated donor (MUD) BMT for SAA have improved significantly over the past two decades, with many studies reporting similar outcomes for BMT using highly HLA-matched MUD compared to MSD.[3,10–14] Improvements in MUD BMT outcomes for SAA have been attributed to reduced doses of total body irradiation (TBI),[15] the use of fludarabine with concomitant reduction in the dosage of cyclophosphamide, and improvements in supportive care.[16,17] Improved selection of histocompatibility locus antigen (HLA)-matched donors using molecular typing has reduced the incidence of graft failure and graft versus host disease (GVHD), and lowered the overall mortality of MUD transplants.[18] One recent BMTCTN trial reported a 97% one-year overall survival (OS) (95% CI 82.8–99.6) in patients receiving a reduced-dose cyclophosphamide regimen.[16] A single-center, nonrandomized pediatric study of 44 patients from the UK reported a five-year OS for up-front MUD recipients of 95% (95% CI 81.4–98.7),[17] and a retrospective comparison showed a marked difference in two-year EFS between young patients treated with up-front MUD BMT versus IST (92% ± 5% vs 40% ± 7%, $P = 0.0001$).[19]

Given these data and the fact that no standard of care has been defined by randomized trials in pediatric SAA for patients lacking an HLA-identical sibling, NAPAAC and the Pediatric Transplantation and Cellular Therapy Consortium (PTCTC) conducted an NIH-funded pilot trial to determine the feasibility and safety of randomization between IST and up-front MUD BMT at a limited number of centers nationwide. This report describes the initial outcomes of our pilot trial.

2 | METHODS

2.1 | Screening protocol and eligibility

All patients with a possible diagnosis of SAA (pancytopenia, no blasts present in the peripheral blood) at participating centers were asked to enroll in a screening protocol in order to track time to diagnosis, obtain biological samples, and participate in a uniform screening approach for SAA. The diagnosis of SAA was based on the Camitta criteria[20]: (a) BM cellularity < 25%, or < 30% if only hematopoietic cells are considered; and (b) two out of three of the following (in peripheral blood): neutrophils $< 0.5 \times 10^9$/L, platelets $< 20 \times 10^9$/L, reticulocyte count $< 60 \times 10^9$/L with hemoglobin < 8 g/dL. Inherited bone marrow failure (iBMF) syndromes were excluded by a detailed evaluation of patients for

phenotypes of iBMF and required diepoxybutane (DEB) (or equivalent) testing for Fanconi anemia, along with telomere length testing. Patients were excluded if they had cytogenetics, fluorescence in situ hybridization (FISH), or morphology suggestive of MDS or refractory cytopenia of childhood (RCC) with both local and central pathology reviews at Boston Children's Hospital. Exclusions also included prior hematopoietic stem cell transplantation (HSCT) from any donor or solid organ transplant, an allergy to hATG, HIV, or active hepatitis B or C, pregnancy or breast feeding, or a history of prior malignancies. Once local centers determined a final diagnosis of SAA, patients were approached for consent to the randomized trial if they were: (1) ≤ 25 years old; (2) had no sibling donors willing and eligible to donate; (3) had at least two identified donors in the unrelated donor registry matched at 9–10/10 HLA alleles (A, B, C, DRB1, DQB1); and (4) had organ function sufficient that they could be eligible for BMT within six to eight weeks after randomization. The reasons for ineligibility or refusal to randomize, treatment, and outcome were reported for those patients who were not consented for randomization.

2.2 | Treatment approach

Patients randomized to IST received hATG at a dose of 40 mg/kg i.v. daily for four days. CsA i.v. or p.o. was started on the first day of treatment and administered per institutional standards to maintain a level of 150–400 ng/mL by HPLC or 200–500 ng/mL by TDx (automatic clinical analyzer [Abbott] based on fluorescence polarization immunoassay). CsA was continued as tolerated for 12 months and tapered over the subsequent 40 weeks. Patients with disease refractory to IST at four to six months were treated per center preference. Those randomized to BMT received fludarabine 30 mg/m^2 i.v. daily for four days from days −5 to −2, rabbit ATG (thymoglobulin) 3 mg/kg i.v. daily for three days from days −4 to −2, cyclophosphamide 50 mg/kg i.v. once on day −2, and TBI in a single dose of 200 cGy on day −1. GVHD prophylaxis included CsA starting on day −1 targeting levels of 200–400 ng/mL by HPLC or 250–500 ng/mL by TDx. Methotrexate 10 mg/m^2 i.v. was given on days +1, +3, +6, and +11.[16]

2.3 | Response to IST and GVHD grading

CR: Hb ≥10 g/dL and ANC ≥1 × 109/L and Plts ≥100 × 109/L; VGPR: Hb ≥8 g/dL and ANC ≥0.5 × 109/L and Plts ≥50 × 109/L; partial response (PR): Hb ≥8 g/dL and ANC ≥0.5 × 109/L and Plts ≥20 × 109/L (without transfusion support); refractory or no response (NR): Hb < 8 g/dL or ANC < 0.5 × 109/L or Plts < 20 × 109/L. GVHD was graded by standard criteria.[21]

2.4 | Rapid acquisition of donors

With the intent to minimize delays in donor clearance, we arranged for expedited screening and clearance through the National Marrow Donor Program (NMDP). HLA typing of the patient and siblings was obtained on an expedited basis, and once completed if no familial match was found typing was submitted to the NMDP, who performed a search strategy consultation, forwarding all possible 9–10/10 HLA-matched donors to the transplant center. Centers selected up to five donors, who were then contacted and screened for the availability for donation within two to five weeks of randomization. This allowed centers to choose from a number of donors knowing their availability and potential timing of a BMT procedure

prior to offering consent to the family. If NMDP donors were not available for the patient, the presence of a minimum of two donors in international registries was sufficient for randomization. If patients enrolled on the trial and were randomized to BMT, donors were formally requested for clearance. If patients randomized to BMT were not able to start their preparative regimen for BMT within eight weeks of randomization, the protocol recommended that they proceed with IST.

2.5 | Statistical approach

The primary objective of this pilot study is to determine the feasibility of comparing outcomes of patients treated de novo with IST versus MUD BMT for pediatric acquired severe aplastic anemia by determining the proportion of patients randomized who accepted the randomization and received MUD BMT as primary therapy (feasibility outcome). Secondary outcomes were (a) time from randomization to the initiation of preparative regimen for MUD BMT; (b) rates of bacteremia, fungal infection, and GVHD; (c) proportion of subjects with count recovery at one and two years; and (d) proportion of subjects alive at one and two years following randomization.

Summary statistics include median and range for continuous variables and frequency and proportion for binary variables. Fisher exact test and Wilcoxon rank sum test were used to compare proportions and medians, respectively. The proportion of subjects is reported along with the exact binomial 95% confidence interval (CI). The Kaplan-Meier method was used to estimate the survival distribution. The R language was used for analysis (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

3 | RESULTS

3.1 | Diagnosis and screening

Between October 1, 2016, and October 31, 2019, 67 patients with possible SAA consented to the screening protocol. Ten of these patients did not have SAA, and of the 57 patients with SAA, 36 (63%) were eligible for randomization and 23 (40%; 95% CI: 28–54) were enrolled in the randomized trial. Table 1 shows the screening outcomes among the 57 subjects. Nineteen percent of patients had an MSD and were not eligible for randomization. Twelve percent of patients did not have the minimum two potential MUDs available (a protocol requirement) and a small percentage (6%) had medical issues that precluded randomization based on site investigator preferences. One of these patients had a nonspecified infection whereas two patients had telomeres < 1% but without molecular mutations consistent with dyskeratosis congenita. Six (11%) of patients did not favor going to randomization and another 7 (12%) expressed an up-front preference for either BMT or IST as their primary therapy.

3.2 | Demographics of patients on the randomized trial

Table 2 shows the clinical characteristics of patients entering the randomized trial. Patients varied from age 1 to 19 and were similar in age, sex, ethnic, and racial makeup between the

two arms of the trial. Although the majority of those enrolled described themselves as white, about a third were Hispanic, Asian, Black, or "Other."

3.3 | Time to initiation of therapy and feasibility of receiving BMT as initial therapy

At the cutoff date for this analysis (November 1, 2019), 11 patients had been randomized to IST and 12 to BMT. The median time from the initiation of screening to the finalization of diagnosis/randomization was 16 days (maximum 31 days with 77% of patients enrolled at or under our target time in the protocol of 3 weeks for ruling out inherited bone marrow failure syndromes/MDS and completing HLA typing). All patients randomized to IST received their intended therapy and began treatment at a median of seven days (range, 2–12 days) after randomization. Of the 12 patients randomized to BMT, 10 (83%; 95% CI: 52–98) initiated their BMT preparative regimen at a median of 36 days (range, 24–72 d) after randomization. One outlier patient took 72 days to initiate the preparative regimen due to a scheduling issue with the donor, which could not be resolved within eight weeks of randomization. Because the donor was available shortly after the deadline and the patient had medically challenging issues, the center PI elected to continue to transplant. The patient engrafted without incident and currently has normalized counts, off all immune suppression. One patient was unable to proceed to BMT within eight weeks due to a scheduling issue with the donor. The site investigator and family elected to give IST. A second patient had persistently high LFTs and was not eligible for BMT within the recommended eight-week timeframe for moving to BMT. LFTs eventually normalized after treatment with IST.

3.4 | Safety, severe adverse events

A total of 12 serious adverse events (SAEs) were reported on the IST arm from eight patients and six SAEs were reported on the BMT arm from two patients (Table 3). No unexpected events occurred, with the majority (11, 61%) of the SAEs being unplanned hospitalizations for fever and neutropenia, a complication that is common in SAA patients. One death from disseminated toxoplasmosis occurred on the IST arm on day +95 after a 9/10 HLA-matched rescue BMT for recurrent pancytopenia after a CR and subsequent to discontinuation of IST. Three other SAEs on the IST arm were considered life-threatening, all episodes of sepsis. One of these patients had acute respiratory failure due to pulmonary and sinus aspergillosis requiring intubation, chest tube placement, and debridement. This patient improved as her neutrophils recovered but remained transfusion dependent and went on to require a BMT for failure of IST. One patient on the IST arm who did not respond to therapy developed hepatosplenic candidiasis. This patient recovered; although the event was not reported as an SAE, it was considered significant by the study team. The patient went on to have successful salvage BMT. Two SAEs on the BMT arm were reported as life-threatening: one episode of sepsis prior to BMT and an acute rejection of the graft after BMT. One of the SAEs occurred after randomization while waiting for IST begin and three SAEs during the interval waiting for BMT conditioning to begin. These SAEs are due to the underlying SAA rather than the intervention, but the delay of therapy may have increased the risk of these events occurring.

In the BMT cohort, all patients demonstrated primary engraftment. Grade 1–2 acute GVHD with skin only stages 1–3 occurred in 3 of 10 (30%, 95% CI: 7–65) evaluable patients.

None of the 10 patients receiving initial BMT developed cGVHD. One patient engrafted on day +16, but then experienced secondary graft failure confirmed on day +34 through lack of chimerism on peripheral blood with no donor cells detected. This patient successfully underwent a rescue graft procedure from a second donor and has normal counts to normal levels with full donor chimerism five months out from the second infusion.

3.5 | Response to IST therapy

Of the 11 patients treated with IST, six (55%, 95% CI: 23–83) responded, with four achieving a CR and two a VGPR. Five (45%; 95% CI: 17–77) did not respond to initial treatment at four months. All five nonresponders went on to rescue BMT, experienced primary engraftment, and are alive at the time of this report. One patient who achieved CR lost response and died of complications after rescue BMT as outlined in the Safety, Severe Adverse Events section.

3.6 | Time to resolution of neutropenia

Of the 11 patients randomized to IST, one never developed ANC < 500, and six patients (55%; 95% CI: 23–83) had resolution of neutropenia (ANC > 500) at a median of 82.5 days from randomization (range, 28–95 days). One patient who resolved their neutropenia at day +81 did not become transfusion independent and went on to salvage BMT for lack of response. The four additional patients with IST-refractory disease resolved their neutropenia after BMT between 149 and 276 (median 188) days after randomization. Patients enrolled on the BMT arm receiving BMT as first therapy resolved their neutropenia at a median of 62 days after randomization (52–194 days—the outlier was the patient who rejected and required a rescue BMT procedure). The two patients randomized to BMT who received up-front IST resolved their neutropenia at days 123 (after IST alone) and 343 (failure of IST followed by rescue BMT) days after randomization.

DISCUSSION

The primary aim of this study was to determine the feasibility of a randomized trial comparing IST versus MUD BMT as initial therapy for pediatric SAA. The context of this pilot study was to plan a larger, multicenter phase 3 trial defining responses and outcomes in order to establish a standard of care in this rare disease. Because time to definitive treatment has been shown to be an important component of success in some studies,[22] we hypothesized that using an expedited donor acquisition protocol, at least 60% of patients randomized to the BMT arm would receive transplant as randomized. With 23 subjects randomized, 10/12 evaluable patients on the transplant arm received BMT as primary therapy (83%; 95% CI: 52–98). Ten of 12 donors were cleared and scheduled within the intended eight-week time frame. One donor was not available until after the eight-week cutoff and the center elected to move forward with IST, whereas a second donor became available at 10 weeks after randomization and the center elected to proceed with BMT using this donor based on the treating physician preference. Overall, 21 patients (36%) were randomized and proceeded to the planned therapy. Although our numbers are small, the high percentage of patients being able to be treated with BMT as randomized appears promising.

Secondary endpoints included reasons for not receiving therapy as randomized, time to and extent of count recovery, rates of SAEs, serious infections, and rates of acute and chronic GVHD. Notably, SAEs that occurred were mainly unplanned hospitalizations for fever, with occasional serious complications involving sepsis, respiratory failure, and other results of infections known to occur in this population. The SAEs reported in both arms were expected and consistent with the degree of immune suppression that occurs in SAA patients receiving BMT or IST therapy. Of note, at four months post-randomization, the number of subjects with ANC > 500 was not statistically significantly different in the two treatment arms [IST: (7/11) BMT: (9/10)], Fisher exact $P = 0.31$. However, patients (5/11) with IST-refractory disease or who did not get BMT as initial therapy as randomized (2/12) had prolonged neutropenia (81–348 days, median 180). Rates of acute and chronic GVHD were low in this cohort, but our numbers are too small to provide more definitive information about GVHD complications.

Notably, 40% of the SAA patients we screened were willing to enroll in a randomized trial testing IST versus MUD BMT. Thirty-seven percent of SAA patients were not approached for consent (Table 1), as they either had a matched sibling (19%) or did not have 9–10/10 HLA MUD (12%), or randomization was not deemed medically appropriate due to concomitant medical issues (4%). Randomization was presented to 36 patients, and 23 of them (64%) consented. We conducted a survey of NAPAAC and PTCTC centers and 45 centers expressed a commitment to participate in a large randomized phase 3 trial. Detailed numbers of newly diagnosed SAA patients presenting to each center for the past three years were reported in a survey of these centers and the yearly totals of confirmed newly diagnosed SAA patient from these centers exceeded 180 patients. If, similar to this feasibility study, 40% were enrolled, 72 patients/year could be randomized. Assuming the lower end of the standard deviation of our results were to enroll (28%) 50 patients/year could be randomized. With these numbers, it is likely that a trial to address this critical question could accrue more than 200 patients in three to four years.

We found that over time, centers increased in the percentage of patients they screened who accepted enrollment on the randomized trial. A careful review with our centers defined the following as best practices: (1) Attempt to minimize bias introduced by caregivers in initial conversations prior to final diagnosis via information sessions given to study personnel. Patients and parents can be strongly influenced by opinions of all types of caregivers (nurses, residents, fellows, non-study attendings); therefore, we worked to make sure that all caregivers were consistent in encouraging patients/parents to hear in detail the risks and benefits of study participation as presented by knowledgeable experts from the centers prior to making a judgment about participation, with the overriding message that no standard of care currently exists. (2) Allow full participation of experts in both IST and BMT as part of the study education and consent process. In-depth discussion with IST experts is necessary to understand the risks of this therapy, how often it succeeds, expected complications, what treatments will occur if primary IST failure occurs, and the likelihood of success of secondary therapies. The same issues regarding BMT need to be discussed, along with estimates of the timing of definitive therapy in the BMT arm, including risks that donors will not clear as well as risks of GVHD or nonengraftment. A balanced discussion emphasizes the fact that data supporting MUD BMT as primary therapy for SAA are based

upon very small numbers of patients, BMT risks are substantial, and thus the choice of BMT as primary therapy off study is not yet advisable. (3) Support the study approach by not offering MUD BMT as standard therapy. Each family going through the consent process may develop preferences, possibly due to presentation bias. Although British guidelines allow up-front MUD BMT as an option in young children with fully matched donors, the large majority of consensus opinions still concludes that IST should be considered standard of care when an MSD is not available until a definitive study shows otherwise. Our data clearly show that of patients who refused the trial due to a preference of one therapy, the number who preferred IST was similar to the number who preferred BMT. A roughly equal number of patients did not want to participate in randomization. With this in mind, a clear message from centers by not allowing MUD BMT as standard of care facilitates appropriate consideration of a randomized trial between the two therapies. Centers willing to adopt this standard have been challenged by other centers nearby being willing to do a MUD BMT as a standard-of-care procedure. We recommend that without an appropriately powered, randomized controlled trial, MUD BMT for SAA at initial diagnosis is not appropriate to offer this therapy as standard of care. For any future randomized trial, we plan to develop patient and caregiver educational materials that would include both printed material and videos that will explain the treatments, the lack of robust data that informs which therapy is optimal (and thus the need for a randomized trial), and FAQs.

An important consideration for any future randomized trial comparing IST with BMT is whether eltrombopag (EPAG) should be used as standard of care in children for up-front IST therapy. Data from the NIH study showed a significant improvement in response rates in adult patients with SAA compared with historical controls.[23] This led to FDA approval for use in the initial therapy of SAA for both children and adults (children were part of the initial NIH cohort). Notably, a more recent analysis of the NIH data in children which compared IST + eltrombopag with their own pediatric historical controls showed no difference in response rates and outcomes. Specifically, 39 patients < 18 years old treated with EPAG + hATG/CsA were compared with a historical control of 87 patients given hATG/CsA. Response at six months in the pediatric EPAG group was 72% and was not different from the pediatric historical control (74%). Notably, of the 28 responding patients in the pediatric EPAG group, 43% relapsed (median time to relapse 565 days from IST) versus 28% in the pediatric historical control IST group ($P = 0.252$).[24] Although additional studies are warranted in children and are under way, because there is no clear advantage in pediatric patients, and there is a possible risk of clonal evolution using eltrombopag,[25] it appears premature to include eltrombopag from up-front planned therapy in children off a clinical trial.

Our pilot trial demonstrates that in a multicenter setting, patients and families are willing to undergo randomization in reasonable numbers, and the large majority of patients can be treated as randomized. Using an approach to donor acquisition that focuses on expediting the process, time to BMT has been relatively quick, approximating count recovery of patients successfully undergoing IST therapy. In addition, although one small nonrandomized study of selected patients showed very good outcomes with up-front MUD BMT, because of the risks of GVHD, early mortality, or decreased fertility, and the fact that rescue BMT or other therapies can occur in many patients with IST-refractory disease, it is not clear that up-front

MUD BMT should be preferred as primary initial therapy. With that in mind, we feel that there is equipoise on this question, and a large randomized trial comparing outcomes of IST versus MUD BMT for up-front therapy for SAA in young patients is warranted and currently being planned.

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Abbreviations:

ANC	absolute neutrophil count
ATG	antithymocyte globulin
BMT	bone marrow transplant
CI	confidence interval
CR	complete response
CsA	cyclosporine A
CTN	Clinical Trials Network
DEB	diepoxybutane
EPAG	eltrombopag
FISH	fluorescent in situ hybridization
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HPLC	high-performance liquid chromatography
HSC	hematopoietic stem cells
HSCT	hematopoietic stem cell transplant
iBMF	inherited bone marrow failure
IST	immune suppression therapy
MDS	myelodysplastic syndrome
MUD	matched unrelated donor

NAPAAC	North American Pediatric Aplastic Anemia Consortium
NMDP	National Marrow Donor Program
OS	overall survival
PR	partial response
PTCTC	Pediatric Transplantation and Cellular Therapy Consortium
RCC	refractory cytopenia of childhood
SAA	severe aplastic anemia
SAE	serious adverse event
TBI	total body irradiation
TRM	transplant-related mortality
VGPR	very good partial response

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TABLE 1

Outcome of screening

67 Patients consented for screening at eight centers: 57 patients had SAA	
Outcome of screening	**Number (%)**
Ineligible for randomization	**21 (37%)**
Sibling donor available	11 (19%)
9–10/10 HLA-matched donor not available	7 (12%)
Medical issues: “too sick to wait for BMT”	1 (2%)
Medical issues: “telomeres too low”	2 (4%)
Eligible for randomization	**36 (63%)**
Consented and randomized	23 (40%)
Not interested in randomization	6 (11%)
Did not want BMT	4 (7%)
Did not want IST	3 (5%)

TABLE 2

Patient demographics (as randomized)

Clinical characteristics	**IST cohort *N* = 11**	**BMT cohort *N* = 12**	***P***
Age: median (range)	10 years (1–19)	11 years (1–18)	0.82
Sex: # of females (%)	5 (45%)	6 (50%)	0.99
Ethnicity			0.56
Non-Hispanic (%)	7 (64%)	9 (75%)	
Hispanic (%)	1 (9%)	2 (17%)	
Unknown/not	3 (27%)	1 (8%)	
Reported (%)			
Race			0.99
White (%)	7 (64%)	8 (67%)	
Asian (%)	1 (9%)	2 (17%)	
Black (%)	1 (9%)	1 (8%)	
Other (%)	2 (18%)	1 (8%)	
Presenting counts			
ANC median/μL (range)	320 (0–7000)	440 (0–1080)	0.83
Hgb median g/dL (range)	8.7 (6–10.6)	8.6 (3.5–12.9)	0.72
Plt median K/μL (range)	8 (2–49)	12 (5–77)	0.16

TABLE 3

SAEs by treatment arm

Patient number	Type of SAE	Study arm: Brief description of the event	Relationship to therapy
01–0001	Hospitalization—initial or prolonged	IST: After therapy-febrile neutropenia, prior to count recovery	Possible
01–0001	Hospitalization—initial or prolonged	IST: After therapy—fever on cyclosporine, after count recovery	Probable
01–0009	Hospitalization—initial or prolonged	IST: After therapy, febrile neutropenia, prior to count recovery	Possible
02–0014	Life-threatening; hospitalization—initial or prolonged	IST: After therapy—acute respiratory failure and pulmonary and sinus aspergillosis requiring intubation, chest tube placement, and debridement, prior to count recovery	Possible
04–0001	Hospitalization—initial or prolonged	IST: Prior to therapy—cellulitis	Unrelated
04–0001	Hospitalization—initial or prolonged	IST: After therapy—fever and bacteremia, prior to count recovery	Possible
07–0002	Hospitalization—initial or prolonged	IST: After therapy—serum sickness	Definite
07–0003	Life-threatening; hospitalization—initial or prolonged	IST: After therapy—sepsis, febrile neutropenia after therapy	Possible
07–0003	Life-threatening; hospitalization—initial or prolonged	IST: After therapy—sepsis, febrile neutropenia after therapy (1 week after hospitalization listed above)	Possible
07–0003	Hospitalization—initial or prolonged	IST: After therapy—syncope in the presence of major anemia, mild swelling of tongue	Unrelated
08–0001	Death	IST: CR to initial IST with relapse after weaning nonresponsive to salvage IST. Died day +95 after 9/10 salvage BMT due to disseminated toxoplasmosis	Unrelated (was no longer on study therapy)
09–0003	Hospitalization—initial or prolonged	IST: After therapy—dehydration, acute kidney injury, elevated CsA level, fever	Definite
01–0002	Hospitalization—initial or prolonged	BMT: Prior to therapy—febrile neutropenia, adenopathy	Unrelated
01–0002	Life-threatening; hospitalization—initial or prolonged	BMT: Prior to therapy—febrile neutropenia, hypotension/sepsis, rash—presumed DRESS syndrome, EBV viremia, pulmonary nodules, candidemia with *Candida parapsilosis*, and bacteremia with *Stenotrophomonas maltophilia*	Unrelated
01–0002	Hospitalization—initial or prolonged	BMT: Prior to therapy—febrile neutropenia, mouth ulcers, lung nodules	Unrelated
01–0002	Hospitalization—initial or prolonged	BMT: After therapy—recurrence of *Stenotrophomonas* bacteremia, acute kidney injury, persistent EBV viremia, biopsy of lymphadenopathy not consistent with lymphoproliferative disease	Possible
07–0012	Hospitalization—initial or prolonged	BMT: After therapy—febrile neutropenia, decreasing blood counts, possible graft rejection	Possible
07–0012	Life-threatening	BMT: After therapy—graft rejection: initial engraftment followed by chimerism confirmed rejection on day +34	Definite

CsA, cyclosporine; DRESS, drug rash with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus. SAE, severe adverse event.