Published in final edited form as:

Pediatr Hematol Oncol. 2016 September ; 33(6): 347–358. doi:10.1080/08880018.2016.1204399.

Allogeneic hematopoietic stem cell transplantation for non-malignant hematologic disorders using chemotherapy-only cytoreductive regimens and T cell depleted grafts from HLA-matched or mismatched donors

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Abstract

Non-malignant hematologic disorders (NMHD) of childhood comprise a variety of disorders including acquired severe aplastic anemia, and inherited marrow failure syndromes. Patients with high risk NMHD without matched related donors fare poorly with allogeneic hematopoietic alternative donor stem cell transplantation (allo-HSCT) and are at high risk for developing graft versus host disease following unmodified grafts. We retrospectively analyzed data on 18 patients affected by NMHD, lacking an HLA-identical sibling donor, who underwent an alternative donor allo-HSCT at our institution between April 2005 and May 2013. 50% had received prior immunosuppressive therapy, 72% had a history of infections, and 56% were transfusion-dependent at the time of transplant. Cytoreduction included a combination of three of five agents: fludarabine, melphalan, thiotepe, busulfan and cyclophosphamide. Grafts were T-cell depleted. All evaluable patients engrafted. Five died of transplant complications. The cumulative incidence of graft versus host disease was 6%. No patient had recurrence of disease. 5-year overall survival was 77%. Age at transplant <6 years was strongly associated with better survival. Based on these results, transplant with chemotherapy-only cytoreductive regimens and T-cell depleted stem cell transplants could be recommended for patients with high risk NMHD especially at a younger age.

Keywords

anemias; bone marrow failure; bone marrow transplant; chemotherapy

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Conflict of interest statement:

The authors declare no conflict of interest.

INTRODUCTION

Non-malignant hematologic disorders (NMHD) of children comprise a broad spectrum of clinical entities and include inherited and acquired marrow failure disorders, as well as specific lineage disorders. For NMHDs refractory to immune suppression or those that are progressive, the only curative therapeutic option is allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1]. However, HSCT may be associated with acute and chronic morbidity and mortality secondary to both the cytoreductive regimens and the transplant related complications, primarily graft versus host disease (GVHD). Allo-HSCT from donors other than HLA-matched siblings has been performed primarily using unmodified grafts, while T-cell depleted transplants have traditionally required a conditioning regimen that includes total body irradiation (TBI) especially for recipients of related mismatched or unrelated donors, [2] due to the higher risk of graft rejection in multiply transfused patients. However, patients treated with this approach remain at high risk for GVHD and for late effects of TBI [3]. Whereas for malignant disorders, there may be an advantage for a myeloablative regimen (including TBI) and for graft versus leukemia effect, this is not the case in the context of NMHD. Therefore, reducing the toxicity of the cytoreduction using chemotherapy only, and reducing the chances to develop GVHD by using T-cell depleted grafts, are fundamental in patients with NMHD in order to decrease transplant related acute and late complications [4–6].

We present results of allo-HSCT in a population of pediatric patients with NMHD using chemotherapy-only cytoreductive regimens followed by T-cell depleted grafts from HLA matched and mismatched, related and unrelated donors.

PATIENTS AND METHODS

Patient characteristics

We retrospectively analyzed data on 18 patients affected by NMHD, lacking an HLA-identical sibling donor, who underwent an alternative donor allo-HSCT at Memorial Sloan Kettering Cancer Center (MSK) between April 2005 and May 2013. Approval of the Institutional Review Board/Privacy Board was obtained. The patient cohort included 10 males and 8 females with a median age at transplant of 5.8 years (range 0.7–18.1).

Disease and pretransplant characteristics

Table 1 details patient characteristics. The diagnoses of these patients included severe aplastic anemia (n=5), paroxysmal nocturnal hemoglobinuria (n=1), dyskeratosis congenita (n=3), congenital amegakaryocytic thrombocytopenia (n=2), severe chronic neutropenia (n=2), Shwachman Diamond Syndrome (n=1), chronic granulomatous disease (n=2), familial hemophagocytic lymphohistiocytosis (n=1), and severe refractory autoimmune hemolytic anemia (n=1). Patient pre-transplant course including treatment, infections and transfusion dependence is detailed in Table 1.

Donor characteristics

Table 2 details transplant characteristics. HLA typing was performed with DNA sequence-specific oligonucleotide typing for HLA A, B, C, DRB1 and DQB1 loci. Three patients received transplants from related donors: one HLA-compatible uncle, one 7/10 HLA-antigen matched mother and one 5/10 HLA-matched mother. Fifteen patients received grafts from unrelated donors who were 10/10 HLA-antigen matched (N=7), 9/10 HLA-antigen matched (N=3) or 8/10 HLA-antigen matched (N=5).

Transplant Characteristics

All patients in this cohort received one of four chemotherapy-only, fludarabine-based cytoreductive regimens varying based on greater need for immuno- or myelo-suppression. These included (1) thiotepa 10mg/kg, melphalan 140mg/m², fludarabine 150 mg/m² (n=10 – including the 8 patients treated most recently chronologically); (2) thiotepa 10 mg/Kg, cyclophosphamide 120 mg/Kg, fludarabine 150 mg/m² (n=3 – used in the patients requiring the highest level of immune suppression), (3) busulfan 10–12 mg/kg, melphalan 140 mg/m², fludarabine 125 mg/m² (n=2 – used in patients with most cellular marrow for increased myeloablation) and (4) low dose busulfan 4 mg/kg. Low dose cyclophosphamide 40–80 mg/kg, fludarabine 140 mg/m² was used in all 3 patients with dyskeratosis congenita. Rabbit ATG was used in all the patients as graft rejection prophylaxis at 2.5 mg/kg X 2–4 doses.

Preferred grafts were peripheral blood stem derived when available; marrow grafts were used based on donor preference. Mobilization was performed according to institutional and NMDP guidelines. T-cell depletion was based on the techniques available at the time of transplant. It was performed as previously described and included sequential soybean lectin agglutination with sheep red blood cell rosette depletion (SBA-E) bone marrow grafts (BM) [7] in five patients, CD34+ *in vitro* positive selection from peripheral blood stem cells (PBSC) in fourteen patients using ISOLEX 300i Magnetic Cell Separator [8] (Baxter Health care Corporation, Deerfield, IL, USA) with sheep RBC rosette depletion (N=6) and CliniMACS device [9] (Miltenyi Biotec, Bergisch Gladbach, Germany) (n=7). A calcineurin inhibitor was added for GVHD prophylaxis for patients with higher doses of T cells in the grafts ($>5 \times 10^4$ CD3+ cells/kg) (N=3), and for patients affected with dyskeratosis congenita because of increased DNA fragility and potential higher risk for GVHD.

The grafts were infused intravenously 36 to 48 hours after the last dose of chemotherapy. For the five marrow grafts, the median CD34+ cell dose was 1.8×10^6 cells/kg and the median CD3+ cell dose was 6.3×10^4 cells/kg. For the fourteen peripheral blood stem cell grafts, the median CD34+ cell dose was 14.9×10^6 cells/kg, and the median CD3+ cell dose was 3.39×10^3 cells/kg.

Patient immune status was studied regularly post allo-HSCT until 12–24 months and afterward based on immune recovery status as per institutional guidelines. Patients were evaluated with flow cytometry for quantitation of T and B cell subtypes and *in vitro* lymphocyte proliferation assays (PHA) as previously described [10].

Supportive care

Supportive care and anti-microbial prophylaxis was performed in accordance with standard institutional guidelines as previously reported [11].

Definitions

Neutrophil and platelet engraftments were defined as the first of three consecutive days on which the absolute neutrophil count was $\geq 500/\text{ml}$ and the platelet count was $\geq 20,000/\text{ml}$ (without platelets transfusions for seven days before the first measurement) respectively. Primary graft failure was defined as the absence of neutrophil recovery ($<500/\text{ml}$) by day +28 and $<5\%$ cellularity in the bone marrow biopsy analysis. Secondary graft failure was defined as neutrophil count $<500/\text{ml}$ after primary engraftment with a hypocellular bone marrow. Graft rejection and poor graft function were defined as single or multi-lineage cytopenia with loss of donor cells or full donor chimerism respectively. GVHD diagnosis was performed on clinical assessment and confirmed pathologically. Staging and classification were performed according to National Institutes of Health criteria [12]. Transplant related mortality was defined as any cause of death other than recurrent disease.

Statistical analysis

Analysis was performed on February 29th 2016. Overall survival (OS) and disease free survival (DFS) were calculated from the time of allo-HSCT. The Kaplan-Meier method was used to evaluate these outcomes. The following variables were considered for their possible association with OS and DFS: gender, recipient age at allo-HSCT <6 years (median age of the study population), type of disease (only for aplastic anemia and dyskeratosis congenita), prior transfusions before allo-HSCT, infections before allo-HSCT, cytomegalovirus (CMV) serologic status (for donor and/or recipient), time from diagnosis to allo-HSCT >46 months (median time of the study population), HLA-matching (identical versus non-identical), and graft source (PBSC versus BM). Univariate analyses were performed using a permutation log rank test. No multivariate analysis was performed due to the low number of events. Neutrophil engraftment, platelet engraftment and GVHD incidence were calculated using the cumulative incidence function.

RESULTS

Hematopoietic recovery

All eighteen evaluable patients engrafted, while one patient died of presumed sepsis prior to engraftment. Median neutrophil recovery time was 12 days post allo-HSCT (range day +9 to +15 days). All 15 evaluable patients who survived the first three months after allo-HSCT achieved platelet engraftment post allo-HSCT (range +13 to +104 days). Three patients received a T-cell depleted stem cell boost for poor graft function or worsening host chimerism, without GVHD. Patient #8 received a boost 6 months post allo-HSCT with successful reversal of mixed chimerism. Patient #1 received a boost 8 months post allo-HSCT for moderate pancytopenia but died a few weeks later in the context of multi organ failure. Patient #14 received a boost 13 months after allo-HSCT with resolution of mild pancytopenia.

Graft versus host disease

The cumulative incidence of grade II-IV acute GVHD at 1 year in the 12 evaluable patients was 6% (95% confidence interval [CI], 0.00–0.23). The cumulative incidence of chronic GVHD at 2 years in the 11 evaluable patients was 6% (95% confidence interval [CI], 0.00–0.23). Patient #15 developed late onset grade 3 acute GVHD 4 months after transplant with biopsy proven skin and gut involvement, was treated with high dose steroids and tacrolimus with complete resolution of the clinical picture, but developed severe chronic skin GVHD 9 months post allo-HSCT (overlap syndrome) and is currently being treated with high dose steroids and mesenchymal stem cells.

Peri-transplant toxicity

These regimens were relatively well tolerated with no grade 4 mucositis reported. Patients received analgesic therapy and parenteral nutrition support based on clinical status. Other relevant treatment related toxicity and early mortality included fulminant sepsis one day post allo-HSCT (patient #4) and hepatic veno-occlusive-disease two months post allo-HSCT (patient #3).

Vancomycin-resistant *Enterococcus* bacteremia was reported in three patients and *Clostridium difficile* colitis was reported in six patients. Patient #12 had early post allo-HSCT pneumonia related to *Aspergillus*, and patient #2 had radiological evidence of pneumonia, pyelonephritis and pancreatitis that resolved after broad spectrum antibiotic therapy. Post infectious Bronchiolitis Obliterans Organizing Pneumonia was reported in one patient (#18) five months post allo-HSCT and resolved following treatment with systemic steroids and anti-infective prophylaxis.

Four patients had CMV viremia post allo-HSCT. In all cases, pre transplant CMV serology was positive in both patient and donor. Patients were treated with anti-viral agents and/or adoptive CMV-specific cytotoxic T-cells with no subsequent progression to CMV disease. Post transplant Epstein-Barr virus (EBV) reactivation was observed in 6 patients: four patients had low grade EBV viremia that resolved spontaneously. One patient (#2) had localized lymphoproliferative disease (LPD) involving Waldeyer's ring treated with tonsillectomy with resolution of symptoms and viremia, and one patient (#8) developed EBV-LPD which was treated successfully with rituximab and adoptive EBV-specific cytotoxic T-cells.

Other post allo-HSCT viral infections included adenovirus viremia (N=2), BK viruria (N=3) including one patient with severe hemorrhagic cystitis, HHV6 viremia (N=1) and recurrent HSV stomatitis (N=1).

One patient affected by chronic granulomatous disease (#9) developed persistent high fever with lymphocytosis resistant to antimicrobial therapy 3 months after allo-HSCT and was diagnosed with acute immune reconstitution inflammatory syndrome which was successfully treated with steroids. He also received rituximab for hemolytic anemia. These complications have resolved.

One patient (#1) transplanted for severe refractory auto-immune hemolytic anemia was found to have myocarditis of unknown etiology five months after allo-HSCT associated with anti-donor red cell auto-antibodies and hemolytic anemia. She was treated with supportive therapy and high dose steroids with slow improvement of both cardiac and hemolytic parameters, but eventually followed by decompensation and mortality from infections related to her immunosuppression.

Overall Survival and Disease Free Survival

The median follow up for the 13 patients alive and disease-free was 66 months (range 4–115 months). None of the patients had disease recurrence. Five-year OS was 77% (95% CI: 50–91) as shown in figure 1. Four patients died. The primary cause of death was late primary disease complications of dyskeratosis congenita (hepatopulmonary syndrome 5 years post-HSCT) for 1 patient, and transplant related mortality for 4 patients including veno-occlusive disease (N=1), and infections (N=2). This represents the overall survival of a cohort of patients with heterogeneous and rare disorders.

Immune reconstitution

The recovery of CD4+ lymphocytes and PHA was studied at the following time intervals post allo-HSCT: 0–3 months (n=16); 3–6 months (n=15); 6–12 months (n=11); 12–18 months (n=4). Eight of 15 evaluable patients reached a CD4 lymphocyte count of >200 cells/ μ L by 6 months post allo-HSCT. At 6 months post allo-HSCT, a 50th percentile of PHA proliferation level was achieved in 10 out of 14 evaluable patients. Of note, two patients (#12, #14), both with dyskeratosis congenita, had a normalization of PHA response without achieving a CD4+ count >200 cells $\times 10^7$ /L.

Variables

Within the variables considered for the analysis, we found a significantly strong association between age at allo-HSCT ≥ 6 years and a better OS (p=0.02) as shown in figure 2. None of the patients younger than 6 years died. Because no events were censored in this group it was not possible to compute statistics regarding survival for this variable. We did not find any statistically significant association for the other variables analyzed.

DISCUSSION

In this report, we have analyzed the treatment of 18 patients with NMHD transplanted with chemotherapy-only regimens and T-cell depleted grafts. Patients with Fanconi anemia were excluded as they were described in a previous report using a TBI based regimen with T-cell depletion and are presently undergoing transplantation based on a multi-center protocol. The results will be reported as part of the multicenter study.

Several reports of allo-HSCT from alternative donors have been previously published for most of these disorders. Few reports have described results for children transplanted for severe aplastic anemia using unrelated donors. These results have shown overall survival rates of 30–90% but with a 10–80% risk of grade 2–4 acute GVHD and 30–40% risk of chronic GVHD [13]. Recently, a large registry study described results of allo-HSCT for

patients with dyskeratosis congenita, showing a 10-years OS of 30%, and risks of acute GVHD and chronic GVHD of 24% and 37% respectively; of note, 50% of allo-HSCTs in this series included grafts from HLA-matched related donors. The survival of this group exceeded those of the non-HLA-matched donor due to lower incidences of transplant related mortality and GVHD [14]. Less than thirty case reports of allo-HSCT for congenital amegakaryocytic thrombocytopenia have been reported. The two largest studies including 8 and 15 patients reported good results for recipients of HLA-matched related donor grafts, but reported poor outcomes for those of unrelated donor grafts [15, 16]. Of note, a previous report of allo-HSCT for patients with congenital amegakaryocytic thrombocytopenia from our center using T-cell depleted grafts from alternative donors reported survival without GVHD for all 3 patients [17]. There are only a few reports of patients with severe chronic neutropenia. A report on a cohort of 11 patients affected by severe chronic neutropenia and treated with allo-HSCT showed that patients who had an HLA-matched donor survived without major complications while 2 of 3 patients who had an unrelated or mismatched donor died [18]. In the CGD setting, positive reports using a donor other than a HLA-matched related one were reported with a 4-year OS of nearly 75%. Nonetheless, reduction of chronic GVHD rate is of paramount importance in patients with pre-existing lung or gastrointestinal fibrosis [19].

In light of previously published results, and our results in patients with FA,[11] our aims in this series were twofold. The first aim was to avoid the use of radiation in patients and especially children with non-malignant disorders as there was no need for its anti-leukemic effect, while using chemotherapeutic and immunosuppressive agents achieve the necessary myelosuppression and immunosuppression. We used two common chemotherapy regimens as stated above and previously described in other transplant series for malignant disorders [20, 21].

The choice of these regimens was based on the need for immunosuppression for the multiply transfused patients (using thiotepe, fludarabine and cyclophosphamide) and the increased need for myelosuppression for patients who had normal marrow function. In addition, prior organ dysfunction played a role in the use of the cytoreductive chemotherapy combination (i.e. cardiac dysfunction excluded the use of cyclophosphamide, liver dysfunction the combination of busulfan and cyclophosphamide and GI dysfunction the use of melphalan). In addition, for patients with dyskeratosis congenita, we used an approach similar to that used for patients with FA that included low dose busulfan, low dose cyclophosphamide and standard dose fludarabine.

The second aim of this transplant approach was the reduction in GVHD. Absent the need for graft-versus-leukemia effect, there is greater opportunity for sparing the organ dysfunction that chronic GVHD might add in patients with prior lung or hepatic dysfunction, and in patients with dyskeratosis congenita at risk for late complications involving these organs, as well as avoiding secondary malignancies. T-cell depletion is well established as the best approach for the prevention of GVHD as previously described for both malignant and non-malignant disorders [22, 17, 11]. In this present series, the T-cell depletion methods used were those available at the time of the treatment of the patients, as described in the methods section.

Our study using chemotherapy-only cytoreduction and T-cell depleted grafts showed acceptable organ toxicity, a low rate of GVHD and an overall good survival outcome, confirming a significant role for this transplant approach for patients with NMHD lacking an HLA-matched related donor.

The major issues related to T-cell depletion have been a potentially higher risk of graft rejection and a delayed immune recovery with a higher rate of infections. In our study population graft rejection was not observed, a result comparable to that of unmodified allo-HSCT and to that of our prior reports series of T-cell depleted transplants[23, 11, 24]. In terms of infections, CMV reactivation without progression to CMV disease was observed in 4 patients, EBV-LPD in 1 patient, and fungal infections in 1 patient. The patient with EBV-LPD was successfully treated. In the majority of cases adequate supportive care, antimicrobial therapy, and adoptive cellular therapy were sufficient to control these complications. Moreover, we were able to show that the immune recovery rate was similar to that previously reported by our center in pediatric recipients of T-cell depleted transplants [10]. It is to be noted that the delayed immune reconstitution can be associated an increased risk of opportunistic infections, requiring aggressive monitoring, prophylaxis and treatment.

Although we recognize the limitations imposed by the rarity and heterogeneity of the disorders affecting patients comprising our sample, several prognostic factors were analyzed in this patient series. We found that a younger age at allo-HSCT (< 6 years) was associated with a significantly better OS in this small patient population. This may correspond to a generally shorter time period from diagnosis to transplant in patients < 6 years old. Allo-HSCT earlier during the course of the disease is likely to be associated with fewer disease-associated comorbidities, fewer transfusions and fewer infectious complications. The approach of performing an allo-HSCT at a younger age and/or earlier during the course of the disease has been reported for allo-HSCT for thalassemia; in a recent multicenter analysis from the Center for International Blood and Marrow Transplant Research, patients younger than 7 years at allo-HSCT had a significantly better OS than older patients [25]. Similarly, better survival results were recently reported for patients with severe chronic neutropenia where patients who underwent allo-HSCT who were younger than 10 years old had a superior survival to older patients [26].

This is a retrospective study with a relatively small patient cohort. However, all patients in this cohort had non-malignant hematologic disorders, and were treated with a similar transplant approach. The disease spectrum of these patients is a heterogenous one due to rare incidences. Future studies will need to be planned similarly to those in pediatric oncology where multicenter studies with specific questions are conducted. A multi-center, prospective study of transplantation of patients with Fanconi anemia using a similar approach of chemotherapy only cytoreduction followed by T-cell depleted grafts is presently nearing completion.

CONCLUSIONS

Our chemotherapy-only cytoreduction and T-cell depleted grafts were able to secure the engraftment of transplants from alternative donors in multiply transfused patients with

NMHD, with acceptable toxicity, minimal risks of GVHD, no late effects of TBI, and a 5-year OS of 77%, albeit in a heterogeneous cohort of rare disorders. A decrease of GVHD and organ toxicity is an important aim, along with reduction of long term complications especially in the setting of the pediatric population. Our findings should next be confirmed in the context of a multicenter prospective study.

Acknowledgments

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748. We acknowledge the expert care provided to patients by staff of the Department of Pediatrics at MSK. We thank Joseph Olechnowicz for editorial assistance. A.M. received a philanthropic support from Associazione Italiana Contro le Leucemie-Linfomi e Mieloma ONLUS

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Figure 1. Overall Survival (A) Entire patient cohort N = 19, and (B) According to age: patients 6 years or younger, or patients older than 6 years at time of BMT

Patients characteristics

Table I

Patient #	Diagnosis	Age at SCT (years)	Gender	Prior Therapy	Prior transfusions	Prior infections	Severe prior infections	Other
1	AIHA	10.5	F	Steroids – CSA – MMF Rituximab – Azathioprine – Splenectomy-Plasmapheresis Alemtuzumab	YES	YES	CMV pneumonia	Progressed to AA prior to SCT Transfusion Dependent
2	AA	6.2	M	ATG + CSA	YES	YES	Pneumonia (unspecified)	Transfusion Dependent
3	AA	10.0	F	ATG + CSA	YES	YES	<i>Staphylococcus. Aureus</i> + <i>Streptococcus. Viridans</i> sepsis	Short stature – Microcephaly Negative genetic testing Transfusion Dependent
4	AA	10.6	M	ATG + CSA + steroids	YES	YES	Multiple febrile episodes	Obesity History of autoimmune hepatitis Negative genetic testing Transfusion Dependent
5	AA	5.4	M	ATG + CSA + steroids	YES	NO	Pneumonia	Transfusion Dependent
6	AA	15.3	M	ATG + CSA (3 courses) Steroids – G-CSF	YES	YES	Multiple febrile episodes	Transfusion Dependent
7	AA/PNH	5.2	M	CSA – Steroids	NO	NO	Multiple febrile episodes	
8	CGD	3.2	M	Antibiotic-Antifungal prophylaxis Steroids	NO	YES	CMV infection <i>Granulibacter bethesdensis</i> <i>adenitis</i>	
9	CGD	4.5	M	Antibiotic-Antifungal prophylaxis Steroids	NO	YES	<i>B. Cepacia</i> severe pneumonia, <i>Nocardia spp.</i> facial abscess	
10	CAMT	0.7	F	NA	YES	NO	NA	
11	CAMT	4.1	F	NA	YES	NO	NA	Progressed to AA prior to SCT Transfusion Dependent
12	DC	10.8	F	ATG+CSA ATG-steroids Erythropoietin – Androgens	YES	YES	<i>Klebsiella Pneumoniae</i> sepsis <i>Pseudomonas Putida</i> sepsis AFB positive myositis	Duration of AA of 6 years Transfusion Dependent
13	DC	9.0	F	NA	YES	YES	Pneumonia + colitis	Dandy-Walker syndrome Transfusion Dependent
14	DC	8.8	M	NA	YES	YES	<i>C. difficile</i> enterocolitis × 2	Transfusion Dependent
15	FHLH	1.1	M	Alemtuzumab CSA – Steroids	NO	YES	Multiple febrile episodes	

Patient #	Diagnosis	Age at SCT (years)	Gender	Prior Therapy	Prior transfusions	Prior infections	Severe prior infections	Other
16	SCN	3.8	M	High Dose G-CSF	NO	YES	Recurrent upper and lower respiratory tract infections, impetigo, <i>P. Aeruginosa</i> sepsis	Pulmonary bronchiectasis
17	SCN	4.8	F	High Dose G-CSF	YES	YES	Recurrent <i>P. Aeruginosa</i> ENT infections – Pneumonia	<i>P. Aeruginosa</i> Ecthyma gangrenosum with nasal gangrene
18	SDS	18.1	F	NA	YES	YES	Multiple infections Cellulitis, otitis, sinusitis	Progressed to hypoplastic anemia and 7q-associated MDS syndrome

AIHA, autoimmune hemolytic anemia; CSA, cyclosporine; MMF, mycophenolate; IVIG, intravenous immunoglobulin; CMV, cytomegalovirus; AA, aplastic anemia; ATG, anti thymocyte globulin; G-CSF granulocyte colony stimulating factor; CGD, chronic granulomatous disease; CAMT, congenital amegakaryocytic thrombocytopenia; DC, dyskeratosis congenita; FHLH, Familial Hemophagocytic Lymphohistiocytosis; SCN, Severe Congenital Neutropenia; SDS, Shwachman Diamond syndrome.

Table II

Donors, transplant characteristics and survival of the study cohort.

Patient #	Donor	HLA match	HLA mismatch rejection/GVHD	Graft source	Conditioning regimen			Outcome	Follow-up (post SCT)
1	Unrelated	8/10	A-C/A-C	PBSC	THIO	CY	FLU	Died – Infection	9 months
2	Unrelated	9/10	A/A	BM	THIO	MEL	FLU	Alive	33 months+
3	Unrelated	10/10	NONE	BM	THIO	CY	FLU	Died-TRM	2 months
4	Unrelated	10/10	NONE	PBSC	THIO	MEL	FLU	Died-TRM	1 day
5	Unrelated	9/10	A/A	PBSC	THIO	MEL	FLU	Alive	37 months
6	Unrelated	10/10	NONE	PBSC	THIO	MEL	FLU	Died – Infection	1 month
7	Unrelated	10/10	NONE	BM	THIO	MEL	FLU	Alive	36 months+
8	Related	10/10	NONE	PBSC	THIO	MEL	FLU	Alive	11 months+
9	Unrelated	8/10	B-DQ/B-DQ	PBSC	THIO	MEL	FLU	Alive	7 months+
10	Unrelated	10/10	NONE	BM	BU	MEL	FLU	Alive	72 months+
11	Unrelated	8/10	B/A-B	PBSC	THIO	MEL	FLU	Alive	90 months+
12	Unrelated	9/10	A/A	PBSC	BU	CY	FLU	Died DC-associated complications	66 months+
13	Unrelated	10/10	NONE	PBSC	BU	CY	FLU	Alive	61 months
14	Unrelated	10/10	NONE	PBSC	BU	CY	FLU	Alive	25 months +
15	Related	5/10	A-B-C-DR-DQ/A-B-C	PBSC	THIO	MEL	FLU	Alive	7 months +
16	Unrelated	8/10	DR-DQ/DR-DQ	PBSC	BU	MEL	FLU	Alive	61 months +
17	Related	7/10	A-B/A-B-C	PBSC	THIO	MEL	FLU	Alive	17 months +
18	Unrelated	8/10	DR-DQ/DR-DQ	BM	THIO	CY	FLU	Alive	42 months +

PBSC, peripheral blood stem cell; THIO, thiotepa; CY, cyclophosphamide; FLU, fludarabine; BM, bone marrow; MEL, melphalan; BU, busulphan; RIC, reduced intensity conditioning; DC dyskeratosis congenita