



Full Length Article

Pediatric

Haploidentical Hematopoietic Stem Cell Transplantation in Pediatric Patients with Acquired Hypocellular Bone Marrow Failure



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Children with acquired hypocellular bone marrow failure of unknown cause (AHBMF) are usually diagnosed either with severe aplastic anemia (SAA) or refractory cytopenia of childhood (RCC). Patients with AHBMF who lack a matched donor and who failed or relapsed after immunosuppressive therapy (IST) need alternative therapies. Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) offers a curative treatment for these patients. We report a multicenter Spanish experience with haplo-HSCT in pediatric patients with AHBMF. Eleven pediatric patients (SAA, n = 9; RCC, n = 2) underwent haplo-HSCT with different lymphodepletion strategies. Most patients (10 of 11) had previously failed to respond or relapsed after IST. The conditioning regimen was reduced intensity in SAA and myeloablative in RCC. Patients with SAA received low-dose radiotherapy as part of their conditioning regimen. All patients engrafted. Viral reactivation was common (8 of 11). Acute GVHD grade \geq II was seen in 5 patients. Chronic GVHD was diagnosed in 4 of the long-term survivors. Transplantation-associated microangiopathy was a frequent complication in SAA patients and was related to worse outcome. Two patients died of transplantation-related complications. Overall survival was 81%, with a median follow-up of 36 months. Haplo-HSCT can be a successful salvage curative treatment for pediatric patients with AHBMF, but with significant toxicities that must be addressed. Transplantation-associated microangiopathy was the most critical complication.

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INTRODUCTION

Acquired hypocellular bone marrow failure without underlying genetic cause (AHBMF) during childhood is usually diagnosed as either severe acquired aplastic anemia (SAA) or refractory cytopenia of childhood (RCC). SAA and RCC are

considered separate entities, but differentiating them can be challenging. Although SAA and RCC can be treated with relative success with immunosuppressive therapy (IST) with antithymocyte globulin and cyclosporine, matched donor hematopoietic stem cell transplantation (HSCT) is the treatment of choice [1–3]. Patients with SAA/RCC who lack a matched stem cell donor and fail to respond or relapse after IST therapy urgently need novel curative therapies [2,4].

In the last few years, haploidentical hematopoietic stem cell transplantation (haplo-HSCT) is being increasingly used as an effective alternative treatment for patients who need HSCT and do not have a fully matched stem cell donor. The

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experience with haplo-HSCT as a treatment for SAA/RCC is appealing but limited, particularly in pediatric patients [5–11]. We assessed the Spanish experience with haplo-HSCT in the treatment of pediatric patients with SAA/RCC.

METHODS

We performed a retrospective multicenter review of pediatric patients with AHBMF diagnosed with either SAA or RCC and treated with haplo-HSCT at any time during their disease course. All patients were treated in 6 hospitals in Spain affiliated with Grupo Español de Trasplante de Médula en Niños (GETMON) within the last 6 years.

A regulatory ethics committee approved this study, and informed consent was requested before data gathering. This study followed the principles outlined in the Declaration of Helsinki and Good Clinical Practice.

This review was limited to pediatric patients (age <18 years at the time of cell infusion) with hypocellular acquired bone marrow failure. The diagnostic criteria for SAA and RCC were those accepted by the European Working Group of MDS and SAA in Children (EWOG-MDS/SAA) [12,13]. All patients were studied to rule out Fanconi anemia. Different haplo-HSCT platforms were accepted for inclusion in the study, including post-transplantation cyclophosphamide and ex vivo lymphodepletion, TCR- $\alpha\beta^+$ /CD19⁺ depletion, and CD45RA depletion. Different conditioning and graft-versus-host disease (GVHD) prophylaxis regimens were permitted as well. Local physicians collected the data at the corresponding hospital where the haplo-HSCT was performed. The data were centrally analyzed.

Definitions

Diagnosis of SAA and RCC was based on the criteria endorsed by the EWOG-MDS/SAA. Neutrophil engraftment was defined as the first day of 3 consecutive days of a total neutrophil count >500/mm³. Platelet engraftment was defined as a platelet count >20,000/mm³ for 3 consecutive days, without the need for platelet transfusion for 1 week.

Graft failure was defined as the lack of graft or donor chimerism. Primary graft failure was diagnosed if no signs of engraftment/chimerism were noticed in the first 30 days post-infusion, and secondary graft failure was diagnosed if the event occurred after previous engraftment. Persistent non-autoimmune cytopenia without another feasible explanation was considered a poor graft if associated with full donor chimerism.

Diagnosis and grading of acute GVHD were done according to the Mount Sinai criteria [14], and diagnosis and grading of chronic GVHD were based on National Institutes of Health consensus criteria [15].

Viral surveillance and infection prophylaxis were performed according to institutional policies. Viral reactivation was diagnosed if a positive specific PCR test prompted a directed treatment against the detected virus.

Statistical Methods

Statistical analyses were performed with the SSPS version 21 informatics package (IBM, Armonk, NY). Patient and transplantation data are presented as median, mean, or percentage as appropriate. Event-free survival and overall survival (OS) were estimated using the Kaplan-Meier method. An event was defined as relapse, graft failure, or death and was calculated from day 0 to the day of the occurrence. Transplantation-related mortality (TRM) was defined as death directly related to a procedural complication, even if occurring beyond the first 100 days post-transplantation.

RESULTS

Patient Characteristics

Between 2016 and 2021, 11 patients (5 girls and 6 boys) with refractory SAA (n = 9) or RCC (n = 2) were treated with haplo-HSCT at 6 centers. Most patients had been heavily pre-treated, refractory to IST (10 of 11) and eltrombopag (8 of 9). All 11 patients were transfusion-dependent. One patient with RCC underwent haplo-HSCT without previous IST because of social and familial preferences. Iron overload was frequent; most patients had a serum ferritin concentration >1500 ng/mL. All patients had a hypocellular acquired marrow failure without significant increases in blast number. None of the patients had a cytogenetic anomaly. Germline *GATA2* mutation was evaluated in only 5 patients, all with negative results. The median age at haplo-HSCT was 11.2 years (range, 8.99 to 16.95 years). None of the patients underwent haplo-HSCT after an advanced myelodysplastic syndrome or leukemia. All patients had good performance status, with a Lansky score >70. The median time from diagnosis to haplo-HSCT was 7.35 months (range, 23 to 56.61 months). Patient characteristics are summarized in Table 1.

Transplantation Characteristics

Lymphodepletion strategies included post-transplantation cyclophosphamide (n = 5), α/β CD19 depletion (n = 2), and CD45RA depletion (n = 4). The hematopoietic stem cell source was peripheral blood in all cases. Nine donors were mobilized with G-CSF and 2 were mobilized with G-CSF and plerixafor. The median donor age was 45 years (range, 13 to 59 years). Conditioning was based on fludarabine and cyclophosphamide in combination with reduced-dose total body irradiation (TBI) or nodal irradiation with or without antithymocyte globulin in all SAA patients and was myeloablative with busulfan/treosulfan, fludarabine, and thiopeta in the RCC patients. GVHD prophylaxis varied across the centers. The mean infused CD34⁺ cell dose was $5.39 \pm 2.29 \times 10^6$ /kg. Transplantation characteristics are summarized in Table 2.

Engraftment and Post-Transplantation Chimerism

All 11 patients engrafted. The median time to neutrophil engraftment was 13 days (range, 9 to 26 days), and the median time to platelet engraftment was 11 days (range, 10 to 37 days). All engrafted survivors achieved transfusion independence (median 16 days, range, 10 to 80 days). Ten of the 11 patients achieved sustained complete donor chimerism. One patient with SAA (patient 3) had mixed chimerism of total nucleated cells (82%) and CD3⁺ cells (13%) cells at initial evaluation. On day +57, mononuclear cell chimerism was 89% donor, but 0% donor on CD3⁺ cells. This situation was reverted with donor lymphocyte infusion (DLI). The patient developed severe autoimmune cytopenia after DLI, and required intensive IST.

GVHD and Post-Transplantation Complications

Five of the 11 patients developed acute GVHD \geq II (3 were grade IV), requiring corticosteroid and other immunosuppressive treatments in some cases. Four patients developed chronic GVHD, which was severe in two cases. Viral reactivation was common (8 of 11; cytomegalovirus, n = 5; adenovirus, n = 2; BK virus, n = 3), but neither Epstein-Barr virus reactivation nor human herpesvirus 6-related disease was observed. Patients with cytomegalovirus and adenovirus did not develop disease but received preemptive treatment with either ganciclovir or cidofovir. Patients with BK virus had hemorrhagic cystitis and received symptomatic treatment. Three patients developed transplantation-associated microangiopathy (TAM), but none

Table 1
Patient Characteristics

| ID | Sex | Age, yr | Diagnosis | Cytogenetics | Chromosomal Fragility Induced by Diepoxybutane | Telomere Length | GAFA 2 | Previous Treatment | Pretransplantation Ferritin, ng/mL | Pretransplantation Lansky Score, % | Pretransplantation Disease Status |
|----|-----|---------|-----------|--------------|--|-----------------|----------|--------------------------------|------------------------------------|------------------------------------|-----------------------------------|
| 1 | M | 8.4 | SAA | Normal | Negative | Normal | Not done | IST for 2 cycles + eltrombopag | 2194 | 100 | Refractory |
| 2 | F | 11.4 | SAA | Normal | Negative | Not done | Negative | IST for 1 cycle | 1661 | 100 | Refractory |
| 3 | M | 10.8 | SAA | Normal | Negative | Not done | Not done | IST for 2 cycles + eltrombopag | 3685 | 80 | Refractory |
| 4 | M | 9.4 | RCC | Normal | Negative | Normal | Negative | IST for 2 cycles + eltrombopag | 350 | 100 | Refractory |
| 5 | F | 16.3 | SAA | Normal | Negative | Normal | Not done | IST for 1 cycle + eltrombopag | 1732 | 70 | Refractory |
| 6 | F | 10.9 | RCC | Normal | Negative | Normal | Not done | None | 1732 | 80 | Active |
| 7 | M | 6.5 | SAA | Normal | Negative | Normal | Negative | IST for 2 cycles + eltrombopag | 223 | 90 | Refractory |
| 8 | M | 8.52 | SAA | Normal | Negative | Not done | Not done | IST for 2 cycles + eltrombopag | 1561 | 100 | Refractory |
| 9 | F | 9.9 | SAA | Normal | Negative | Not done | Not done | IST for 2 cycles + eltrombopag | 3715 | 90 | Refractory |
| 10 | F | 14.6 | SAA | Normal | Negative | Normal | Negative | IST for 1 cycle + eltrombopag | 300 | 100 | Refractory |
| 11 | M | 13.6 | SAA | Normal | Negative | Not done | Not done | IST for 1 cycle | 1990 | 100 | Refractory |

had veno-occlusive disease necessitating pharmacologic treatment. All patients with severe TAM had significant renal impairment, effusions, and hematologic alterations; These two patients weretreated with eculizumab. Eight of the 9 long-term survivors stopped IST at a median of 14 months (range.46 to 32 months).

Survival

The mean OS for the whole cohort was 81.8 ± 11.6%, with a median follow-up of 36 months (range, 9.2 to 75.4) months (Figure 1A). We observed 100% survival for the RCC patients and 77.8% for the SAA patients (P = .49) (Figure 1B). Mean immunosuppressor-free, relapse-free survival was 60 ± 19.7% (Figure 1C). There was no secondary graft failure. Two patients died of transplantation-related complications on days +218 and +324; causes of death were GVHD, TAM, and respiratory failure. TAM significantly impacted OS (100% versus 33 ± 27.3%; P = .01) (Figure 1D).

DISCUSSION

Haplo-HSCT was an excellent curative option in our pediatric patients with AHBMF, with an OS of 81.8 ± 11.6% at 36 months post-transplantation. Our data from an exclusively pediatric setting support the recent meta-analysis from the European Society for Blood and Marrow Transplantation concluding that haplo-HSCT is a suitable alternative for patients with SAA refractory to IST or with a high risk of clonal evolution [9]. These results corroborate previous experience reported by other groups demonstrating the curative potential of haplo-HSCT in refractory aplastic anemia [5–9]. We saw good outcomes in our 2 patients with RCC, an entity with little published experience with haplo-HSCT [10]. One of the patients with RCC underwent successful haplo-HSCT without previous treatments, illustrating the possibility of considering haplo-HSCT as a front-line treatment in certain high-risk cases, as is currently being done successfully in some centers with limited resources [16].

In most cases, we observed an excellent engraftment rate with sustained complete chimerism, remarkable results for patients with SAA. These results may be related to the intense receptor immunosuppression, the systematic use of low-dose radiotherapy, and the adequate cellular dose. In a previous report, Im et al. [11] described significant graft issues when omitting radiotherapy in ex vivo depleted haplo-HSCT [11]. The impact of radiotherapy and its dosing during conditioning in haplo-HSCT for SAA also has been pointed out by Arcuri et al. [8] and DeZern et al. [17] in a post-transplantation cyclophosphamide platform. We believe that low-dose radiotherapy (TBI or total nodal irradiation) should be considered part of the conditioning regimen in haplo-HSCT for SAA, to avoid problems with engraftment and chimerism. For patients with RCC, our data suggest no apparent need for radiotherapy in a haplo-HSCT setting if myeloablative conditioning is provided.

In our series, TRM was acceptable although significant. TRM was related to GVHD, respiratory failure and TAM. Two deaths were observed, both occurring beyond the first 100 days, and severe TAM was involved in both cases.

It is notable that 3 out of our 9 patients with SAA developed TAM. These patients had significantly worse outcomes. SAA is considered a high-risk factor for TAM [18], possibly related to previous prolonged exposure to calcineurin inhibitors. In fact, TAM was not a significant complication in a cohort of therapy-naive SAA patients treated with a haplo-HSCT and post-transplantation cyclophosphamide scheme with low-dose radiotherapy [17]. Nonetheless, we cannot entirely rule out

Table 2
Transplantation Characteristics

| ID | Sex | Age, yr | Diagnosis | Time from Diagnosis to Haplo-HSCT, mo | Donor Sex/ Age (yr)/ Relation | Recipient/ Donor CMV Serostatus | Lympho-depletion Platform | Conditioning | GVHD Prophylaxis | CD34 ⁺ Cell Dose, × 10 ⁶ /kg | Neutrophil/ Platelet Engraftment Day | Acute GVHD Grade (Treatment) | Chronic GVHD Severity | Viral Infection | Other Complications | Status, Day and Cause of Death |
|----|-----|---------|-----------|---------------------------------------|-------------------------------|---------------------------------|---------------------------|---|------------------|--|--------------------------------------|---|-----------------------|-------------------------------|---|--|
| 1 | M | 8.9 | SAA | 7.36 | M/43/father | +/- | CD45RA depletion | Flu 150 mg/m ² + Cy 200 mg/kg + nodal irradiation 8 Gy | CsA | 5.0 | +11/+15 | Grade II (corticosteroids) | None | Adenovirus | | Alive, no disease |
| 2 | F | 12.1 | SAA | 8.08 | F/45/mother | +/+ | PTCy | Flu 120 mg/m ² + Cy 29 mg/kg + TBI 2 Gy + ATG (G) 4.5 mg/kg (day -7) | MMF + TK | 2.03 (bone marrow) | +26/+35 | None | None | BK virus cystitis | | Alive, no disease |
| 3 | M | 11.1 | SAA | 2.76 | F/45/mother | +/+ | α/β CD19 depletion | Flu 140 mg/m ² + Cy 100 mg/kg + TBI 2 Gy + ATG (G) 7.5 mg/kg (day -3) | Other | 5.93 | +13/+11 | None | None | Adenovirus, BK virus cystitis | Mixed chimerism, DLI, severe autoimmune cytopenia | Alive, no disease |
| 4 | M | 9.3 | RCC | .23 | M/52/father | +/+ | α/β CD19 depletion | Flu 140 mg/m ² + Bu 16 mg/kg + thiotepa 15 mg/m ² | CsA | 8.49 | +13/+10 | None | None | None | <i>Clostridium difficile</i> diarrhea | Alive, no disease |
| 5 | F | 16.9 | SAA | 7.29 | M/26/brother | -/- | PTCy | Flu 150 mg/m ² + Cy 29 mg/kg + TBI 2 Gy + ATG (G) 4.5 mg/kg (day -7) | MMF + TK | 3.3 | +17/+37 | None | Mild | None | | Alive, no disease |
| 6 | F | 11.1 | RCC | 2.14 | F/39/mother | +/+ | PTCy | Flu 160 mg/m ² + treosulfan 42 g/m ² + thiotepa 8 mg/m ² | MMF + TK | 5.5 | +15/+11 | Grade IV (corticosteroids and ECP) | Severe | CMV | | Alive, no disease |
| 7 | M | 11.2 | SAA | 56.1 | M/13/brother | +/+ | CD45RA depletion | Flu 150 mg/m ² + Cy 200 mg/kg + nodal irradiation 8 Gy | Other, then CsA | 6.41 | +9/+11 | Grade IV (corticosteroids, ECP, and MMF) | None | CMV | TAM, <i>Escherichia coli</i> sepsis, Enterobacter infection | Alive, no disease |
| 8 | M | 9.4 | SAA | 10.64 | F/41/mother | +/+ | CD45RA depletion | Flu 150 mg/m ² + Cy 200 mg/kg + nodal irradiation 8 Gy | Other | 6.29 | +11/+12 | Grade IV (corticosteroids, ECP, MSCs, and 3 other immune suppressors) | Severe | CMV | TAM, respiratory failure, pneumonia | Late TRM, day +218 (TAM and respiratory failure) |
| 9 | F | 12.1 | SAA | 26.45 | F/46/mother | +/+ | CD45RA depletion | Flu 150 mg/m ² + Cy 200 mg/kg + nodal irradiation 8 Gy | CsA | 7.73 | +10/+10 | Grade II (corticosteroids) | None | CMV, BK virus cystitis | Sepsis, PRES, TAM, respiratory failure, invasive fungal infection | Late TRM, day +324 (TAM and respiratory failure) |
| 10 | F | 14.7 | SAA | 2.27 | F/48/mother | +/- | PTCy | Flu 150 mg/m ² + Cy 29 mg/kg + TBI 4 Gy + ATG (G) 4.5 mg/kg (day -7) | MMF + TK | 1.4 | +20/+11 | None | Mild | None | | Alive, no disease |
| 11 | M | 16.9 | SAA | 40.15 | F/59/mother | +/- | PTCy | Flu 150 mg/m ² + Cy 29 mg/kg + TBI 2 Gy | MMF + TK | 7.27 | +19/+22 | None | None | CMV | | Alive, no disease |

CMV indicates cytomegalovirus; PTCy, post-transplantation cyclophosphamide; DLI, donor lymphocyte infusion; Flu, fludarabine; Cy, cyclophosphamide; CsA, cyclosporine; MMF, mycophenolate mofetil; TK, tacrolimus; ECP, extracorporeal photopheresis; MSCs, mesenchymal stem cells; ATG, antithymocyte globulin; (G), Genzyme; (F), Fresenius; PRES, posterior reversible encephalopathy.

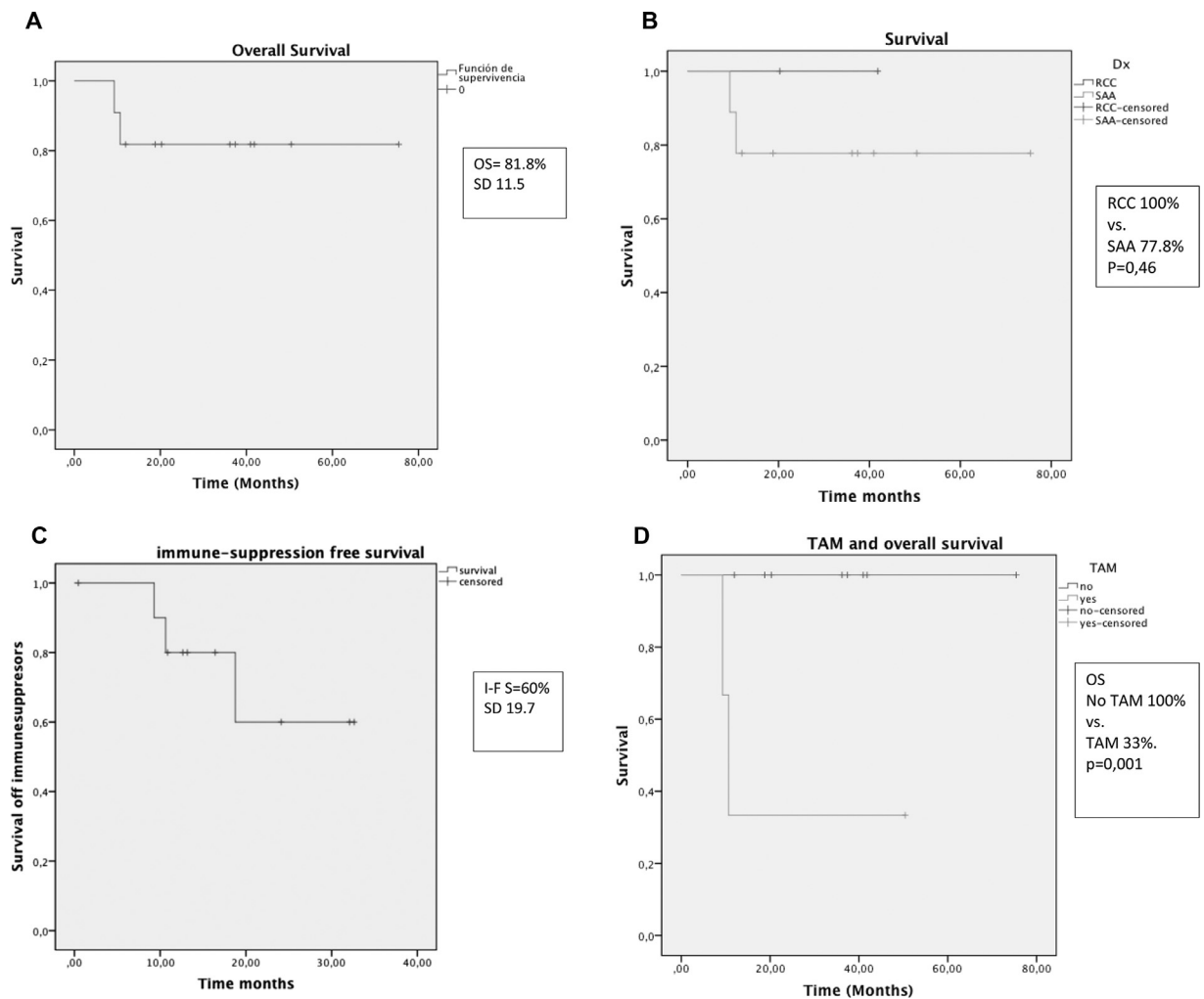


Figure 1. (A) OS of patients with SAA/RCC treated with haplo-HSCT. (B) Survival according to diagnosis. (C) Immunosuppressor-free survival. (D) Impact of TAM on OS in patients with SAA/RCC treated with haplo-HSCT.

other conditioning-related issues, as all patients with TAM in our series had undergone CD45RA-depleted haplo-HSCT with nodal irradiation and had received a higher dose of cyclophosphamide. We propose active surveillance for TAM during haplo-HSCT for SAA, because prompt treatment could impact survival. In the future, prophylactic treatment should be considered when available.

We also faced considerable rates of severe acute and chronic GVHD that, although it did not directly impact survival, need to be improved. Research into novel strategies and agents to prevent and treat GVHD should be incorporated into clinical practice in the haplo-HSCT setting.

In our series, the median donor age was 45 years, which also might have contributed to higher rates of toxicity and GVHD. The negative impact of donor age in haplo-HSCT has been described in previous reports [19,20]. Choosing the youngest suitable donor could help improve outcomes.

The limited number of cases in our series precludes us from assessing which haplo-HSCT platform is best suited for SAA/RCC patients. Although the 2 deaths occurred in patients with CD45RA-depleted haplo-HSCT, this association was not statistically significant. Given that more than one-half of our patients underwent a successful haplo-HSCT with ex vivo lymphodepletion, we believe that these procedures may be as safe

as the more widely used post-transplantation cyclophosphamide strategy.

Our experience shows that haplo-HSCT offers successful curative therapy for pediatric patients with refractory SAA/RCC. Direct research on reducing toxicity and obtaining better GVHD control in haplo-HSCT for these conditions is needed.

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