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Hematopoietic stem cell transplantation without in vivo T-cell depletion for pediatric aplastic anemia: A single-center experience

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Abstract

For young patients, HLA-MRD HSCT is the first-line treatment of SAA. However, due to China's birth control policy, few patients could find suitable sibling donors and HLA-MUD. More and more transplantation centers have used Haplo-D as the donor source for young adult and pediatric patients. However, studies with larger amount of pediatric patients are rare. We retrospectively analyzed the data of children with AA who were treated with allogeneic HSCT and compared the therapeutic efficacy of Haplo-HSCT and MRD/MUD group. A total of 62 patients were enrolled. Implantation was successfully performed in 58 patients. There was no significant difference in the time for reconstruction of hematopoietic function between patients in the two groups. Thirty-two had grade I-IV aGVHD with incidence of 51.61%. The incidence of aGVHD was 79.41% for patients in the Haplo-HSCT, significantly higher than that of 17.86% for patients in the MRD/MUD group ($P < .01$). However, the incidence of cGVHD was not significantly different between patients in the two groups (26.47% vs 10.71%, $P = .09$), the incidence of CMV infection was 28.57% and 52.94% for patients in the MRD/MUD and Haplo group, respectively, showing no significant difference ($P = .053$). The incidence of EBV infection was 47.06% for patients in the Haplo group and 28.57% for patients in the MRD/MUD group, showing no significant difference ($P = .11$). However, the 3- and 5-year cumulative OS and FFS rates showed statistically significant difference in the two groups, $P = .012$ and .045, respectively. Compared to Haplo-HSCT, MRD/MUD is more economic. In this study, we achieved good Haplo transplantation results. The incidences

Abbreviations: aGVHD, acute graft-vs-host disease; ALG, antilymphocyte globulin; ANC, absolute neutrophil count; ATG, antithymocyte globulin; Bu, busulfan; cGVHD, chronic graft-vs-host disease; CMV, cytomegalovirus; CsA, cyclosporine; EBV, Epstein-Barr virus; FFS, failure-free survival; Flu, fludarabine; GVHD, graft-vs-host disease; Haplo-D, haploidentical-related donor; HSCT, hematopoietic stem cell transplantation; IST, immunosuppressive therapy; MMF, mycophenolate mofetil; MRD, matched-related donor; MTX, methotrexate; MUD, matched unrelated donor; OS, overall survival; PBSC, peripheral blood hematopoietic stem cells; PCR-SSP, sequence-specific primer polymerase chain reaction; PNH, paroxysmal hemoglobinuria; SAA, severe aplastic anemia; TBI, total body irradiation; TMA, thrombotic microvascular disease; VOD, vein occlusion syndrome.

Li and Wang contributed equally to this work and should be considered cofirst authors.

of cGVHD and CMV/EBV were not significantly different between Haplo group and MRD/MUD group. Although OS and FFS of the Haplo group were not as good as those of the MRD/MUD group, it is still acceptable as an alternative treatment under emergency.

KEYWORDS
aplastic anemia, haploidentical donor, hematopoietic stem cell transplantation, pediatric

1 | INTRODUCTION

SAA is a bone marrow failure disease threatening the lives of pediatric patients. Allogeneic HSCT is an effective modality in treatment of SAA.[1] For pediatric, adolescent, and young patients, HLA-MRD HSCT is the most commonly accepted first-line treatment modality.[1,2] Studies from multiple centers showed that the success rate of HLA-MRD-HSCT was as high as 100% and the 5-year OS rate was 86.4%-91.0%.[1,3-5] However, because of China's birth control policy, less than 30% of pediatric patients could find suitable sibling donors.[6] For pediatric patients without suitable MRD, IST is recommended. If this therapy fails, HLA-MUD HSCT should be conducted consecutively.[1] Currently, China's unrelated donor bank is constantly increasing, and bone marrow bank has over 1.99 million donors. Although the outcome of using MUD-HSCT to cure pediatric patients with SAA is similar to that of using MRD-HSCT,[7] only limited pediatric patients could have MUD. In addition, searching and preparing donor takes several months and some SAA patients are in urgent condition or have infection. Therefore, patients have no time to wait for or seek suitable MUD from China's bone marrow bank. Multiple repeated ISTs are difficult to be an effective alternative to treat pediatric patients with SAA due to clonal diseases and its low responsive rate.[2,8,9]

Searching and preparing Haplo-D are relatively easy and can be finished in a short period. More and more transplantation centers around the world have used Haplo-D as the donor source for young adult and pediatric patients.[10-13] Recent reports showed that although OS and FFS have made significant advances,[13] Haplo-HSCT still has its shortcomings compared with MRD and MUD-HSCT.[13] Most previous studies included both adult and pediatric patients in small size and had significantly different enrollment clinical characteristics therefore are not very comparable. Moreover, studies with larger amount of pediatric patients are rare. Thus, we retrospectively analyzed the data of children with aplastic anemia who were subjected to allogeneic HSCT in our hospital and compared the therapeutic efficacy of Haplo-HSCT and MRD/MUD.

2 | PATIENTS AND METHODS

2.1 | Patients' information

A total of 62 patients who were diagnosed aplastic anemia in our hospital from January 2006 to December 2016 and treated with HSCT were enrolled in the study. The diagnosis and classification of aplastic anemia were based on the International Standardized Diagnosis and Treatment Guidelines.[1] All enrolled patients had negative chromosome breakage test results, and none had any characteristic of dyskeratosis congenita. Patients with clonal evolution were excluded from this study. None had any evidence of dyshematopoiesis or chromosomal abnormalities. All guardians have signed the informed consent form. All medical treatments have been approved by the Ethics Committee of our hospital. Among these patients, 26 were male, and 36 were female. They were aged at 1 years 2 months to 16 years 9 months with median age of 7 years 1 month. The period from diagnosis to HSCT was 0.5 to 84 months with median of 3 months. Most patients received multiple blood product infusion. Among them, 4 patients had been treated with ATG (Sanofi, France)/ALG (Wuhan Institute of Biological Products) combined with CsA but did not achieve hematologic remission until 6 months after IST. One patient had PNH clonal positive.

Prior to transplantation, donors and recipients were examined using PCR-SSP for HLA genotyping techniques. Among them, 33 patients were subjected to matching for sites A, B, and DRB1, and 29 patients were subjected to high-resolution HLA matching. All donors were selected from Chinese bone marrow bank or Taiwan bone marrow bank ≥9/10 MUD (one was 9/10, others are 10/10). If no suitable donor was available in the above two banks, Haplo-HSCT was selected among the relatives. The selection criteria for Haplo-D included age (preferring younger donor), gender (preferring male), and physical condition. Table 1 shows the general clinical characteristics of patients.

2.2 | Pretreatment modalities

The basic pretreatment included giving 50 mg/kg/d cyclophosphamide together with either 3 mg/kg ATG or 5 mg/kg ALG at −5 to −2 days prior to transplantation (CA). Besides the basic treatment, 43 patients were given 25 mg/m^2/d Flu at −6 to −2 days prior to transplantation (FCA), one patient with PNH-aplastic anemia was given 0.8 mg/kg Bu every 6 hour at −7 and −6 days prior to transplantation, one patient who failed ATG treatment and 6 patients with blood transfusion-dependent non-SAA were treated with 200 cGy of TBI at −6 days prior to transplantation. See Table 1.

TABLE 1 Patient and graft characteristics

Variables	Haplo (N = 34)	MRD/MUD (N = 28)	*P*
Age (mo), median (range)	63.5 (14-201)	95 (14-182)	.09
Male/female, no.	16/18	10/18	.44
NSAA/SAA, no.	6/28	5/23	.13
Neutrophil count ($\times 10^9$/L, mean ± SD)	0.36 ± 0.04	0.45 ± 0.06	.10
Platelet count ($\times 10^9$/L, mean ± SD)	9.79 ± 1.32	13.75 ± 1.97	.13
Interval from AA diagnosis to SCT	12.09 ± 3.65	15.08 ± 4.23	.47
ABO matched, no. (%)	19 (55.88%)	15 (53.57%)	.52
Donor-patient sex match, no. (%)	18 (52.94%)	13 (46.43%)	.79
Graft type, no. (BM+PB/PB)	32/2	2/26	<.01
MNCs count ($\times 10^8$/kg, mean ± SD)	21.31 ± 1.53	13.59 ± 1.29	.01
CD34+ count ($\times 10^6$/kg mean ± SD)	18.94 ± 1.74	10.17 ± 1.28	.01
Preconditioning regimen (FCA/CA)	31/3	11/17	<.01

2.3 | Donor mobilization and sample collection

The donor bone marrow was mobilized for consecutive 5 days using 5-10 μg/kg G-CSF. Bone marrow and PBSC were collected on the 4th and 5th day, respectively, from MRD/Haplo-D. Similarly, PBSC were also collected on the 5th day from MUD or the 6th day if the total amount of mononuclear cells and CD34+ cells collected on the 5th day did not reach the need for transplantation. MRD/Haplo-D HSCT was performed using bone marrow plus PBSC and MUD-HSCT was performed using PBSC only. The median amount of infused mononuclear cells, and CD34+ cells was 17.58 (5.47~51.23) × 10^8/kg and 13.06 (1.22~24.32) × 10^6/kg, respectively. Red blood cells were removed using hydroxyethyl starch if the donor and recipient had incompatible main ABO blood type, and plasma was removed using density gradient centrifugation if the donor and recipient had incompatible minor ABO blood type.

2.4 | Prevention and treatment of GVHD

CsA or tacrolimus (FK506) plus MMF and short-range MTX were used to prevent GVHD. Patients with grade II-IV aGVHD were treated with a total of 1-2 mg/kg methylprednisolone or anti-CD25 monoclonal antibody. At 9 months after transplantation, if patients had normal blood indexes, donor-type chimera and insignificant GVHD, the use of CsA or FK506 was reduced monthly and eventually stopped.

2.5 | Definition and post-transplantation evaluation

Successful neutrophil transplantation was defined as ANC ≥0.5 × 10^9/L for 3 consecutive days. Successful platelet transplantation was defined as PLT ≥20 × 10^9/L for 7 consecutive days without platelet transplantation.[1] Primary transplantation failure was defined as neutrophils ≤0.5 × 10^9/L for 28 consecutive days. Secondary transplantation failure was defined as reappearance of ANC <0.5 × 10^9/L after transplantation.[3] DNA sequencing of short tandem repeat locus and locus AMEL in sex chromosome were used to examine the donor/recipient chimeric state after hematopoietic reconstitution. After transplantation, patients were followed up once a month for the first 3 months, and once every 2-3 months afterward if they had normal blood routine or once per 0.5-1 month if they had abnormal blood routine. A complete donor chimera was achieved if the donor component was >95.0%. A mixed chimera is achieved if the donor component was 2.5%-95.0%. A complete recipient type was defined as the donor component <2.5%, indicating that primary HSCT failed.[1] The OS was defined as the time from HSCT to death or the last follow-up, and FFS was defined as the time from HSCT to complete remission. Follow-up included hematopoietic reconstruction status, occurrence of GVHD, OS, FFS, and other indicators and ended on May 1, 2017.

2.6 | Statistical analysis

SPSS20.0 software was used for statistical analysis. Differences in means, sample rate, and rate were compared using nonparametric rank sum test, chi-square test, and log-rank test, respectively. Survival rate was analyzed using Kaplan-Meier method. A $P < .05$ was considered as statistically significant difference.

3 | RESULTS

3.1 | Cases and characteristics of pediatric patients subjected to transplantation

The pediatric patients were divided into either MRD/MUD group (n = 28) or Haplo group (n = 34) according to the type of transplantation. Of patients in this study who had not received IST, some of them were in very SAA and had serious infections (eg, multiple skin abscesses, pneumonia, serious intestinal infection, and liver abscess) at the time of transfer to our hospital. For the remaining patients, the parents refused to consent to IST because rabbit ATG is known to be much less effective than horse ATG, which is not available in China. Table 1 shows the characteristics of patients in the two groups. It is clear that these patients were significantly different in type of

TABLE 2 Clinical outcomes after HSCT

	Haplo (N = 34)	MRD/MUD (N = 28)	*P*
Neutrophil engraftment, median (mo, range)	13 (10-20)	13 (10-18)	.41
Platelet engraftment, median (mo, range)	16.5 (7-30)	17.5 (8-120)	.13
aGVHD, no. (%)	27 (79.41%)	5 (17.86%)	<.01
III-IV°, no. (%)	4 (14.81%)	0	<.01
cGVHD, no. (%)	9 (26.47%)	3 (10.71%)	.09
CMV, no. (%)	18 (52.94%)	8 (28.57%)	.053
EBV, no. (%)	16 (47.58%)	8 (28.57%)	.11

transplantation, number of back-transfused MNCs, number of back-transfused CD34+ cells, and pretreatment modality. Patients in the Haplo group had significantly higher numbers of back-transfused MNC- and CD34-positive cells and most of them adopted combined Flu pretreatment.

3.2 | Reconstruction of hematopoietic functions

Implantation was successfully performed in 58 patients. The median implantation time was 13 days (10~20) days for ANC and 17 days (7~120) days for platelet. There was no significant difference in the time for reconstruction of hematopoietic function between patients in the two groups (Table 2). Two patients had primary implant failure, all in the Haplo group. Two patients had secondary implant failure, of whom, one was in the Haplo group and the other one was patient with MUD.

3.3 | GVHD

Among the 62 patients, 32 had grade I-IV aGVHD with incidence of 51.61%. The incidence of aGVHD was 79.41% for patients in the Haplo-HSCT, significantly higher than that of 17.86% for patients in the MRD/MUD group ($P < .01$). However, for aGVHD in Haplo-HSCT, 85.19% of them was grade I-II aGVHD. In addition, the incidence of cGVHD was not significantly different between patients in the two groups (26.47% vs 10.71%, $P = .09$). See Table 2.

3.4 | Post-transplantation infection

A total of 26 patients had post-transplantation CMV infection. The incidence of CMV infection was 52.94% for patients in the Haplo group and 28.57% for patients in the MRD/MUD group, showing no significant difference ($P = .053$). A total of 24 patients had post-transplantation EBV infection. The incidence of EBV infection was 47.06% for patients in the Haplo group and 28.57% for patients in the MRD/MUD group, showing no significant difference ($P = .11$). Among the 24 patients with post-transplantation EBV infection, 1 developed into lymphoid tissue proliferative disease and 3 developed into EBV pneumonia, as shown in Table 2.

3.5 | Survival analysis

The median follow-up time was 32.5 months (0.5~132) months, and the OS rate was 88.7%, as shown in Figure 1. Based on the transplantation grouping, the 3- and 5-year cumulative OS rates were 79.4% and 79.4% for patients in the Haplo group, and 100% and 100% for patients in the MRD/MUD group, respectively, showing statistically significant difference ($P = .012$, Figure 2). The overall FFS rate was 95.6%, as shown in Figure 3. The 3- and 5-year cumulative FFS rates were 93.3% and 93.3% for patients in the Haplo group, respectively, and 100% and 100% for patients in the MRD/MUD group, respectively, showing statistically significant difference ($P = .045$, Figure 4). A total of 7 patients died, all in the Haplo group. Among them, 4 patients died of post-transplantation sepsis and severe infection, 2 died of post-transplantation TMA, and 1 died of autoimmune multiple gland disease.

3.6 | Health economics

The total cost of patients in the MRD/MUD-HSCT and Haplo-HSCT groups at admission and discharge was compared. The results showed that the total cost was $43 293.50 ± 3849.49 for patients in the Haplo group and $32 330.19 ± 2016.66 for patients in the MRD/MUD group, showing significant difference between the two groups ($P = .01$).

4 | DISCUSSION

With the improvement of high-resolution HLA matching technology and pretreatment modality and the strengthening of supportive therapy, MUD-HSCT treatment of SAA patients has achieved similar efficacy with MRD-HSCT.[5] MUD-HSCT is the first recommendation for SAA patients without MRD but failed in IST.[1] However, only limited patients had access to unrelated donors. In addition, as the first-line treatment modality, the efficacy of r-ATG is worse than h-ATG. Furthermore, h-ATG is not supplied for developing countries such as China. Because of the easiness to find donor and its economy, Haplo-HSCT gradually draws more attention. In recent years, using Haplo-HSCT to treat SAA patients is widely applied in many

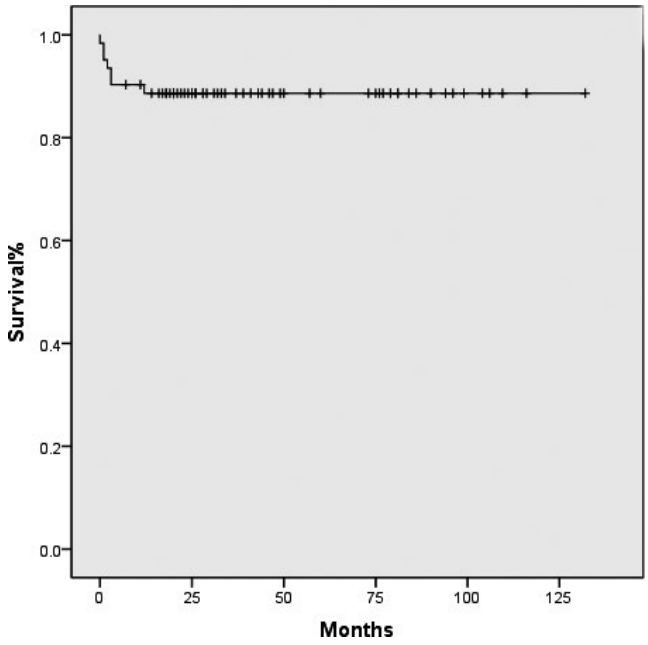

FIGURE 1 OS of all patients

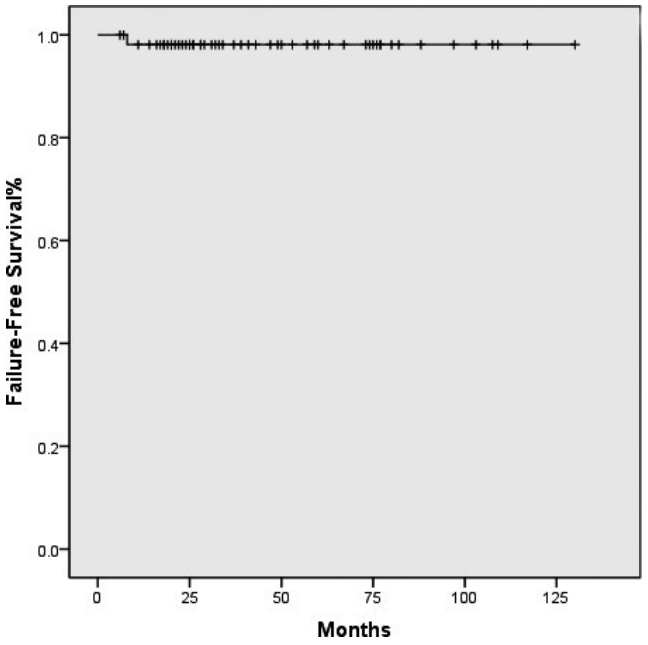

FIGURE 3 FFS of all patients

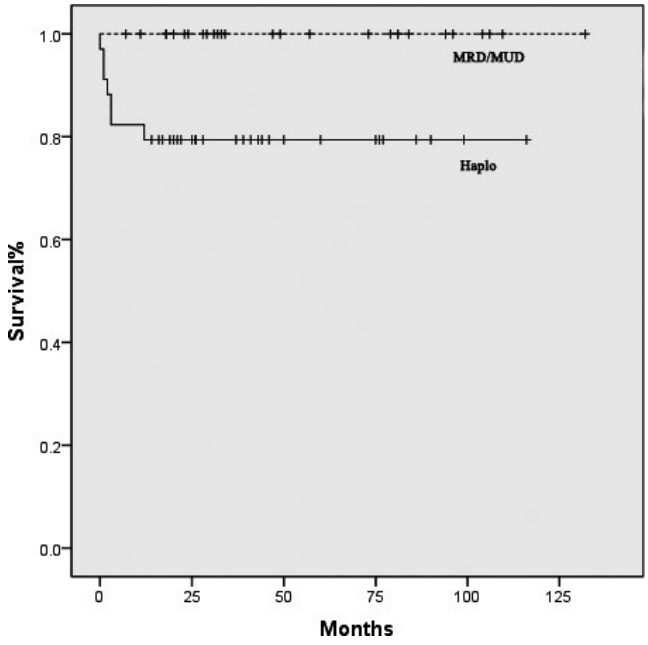

FIGURE 2 OS of the two groups

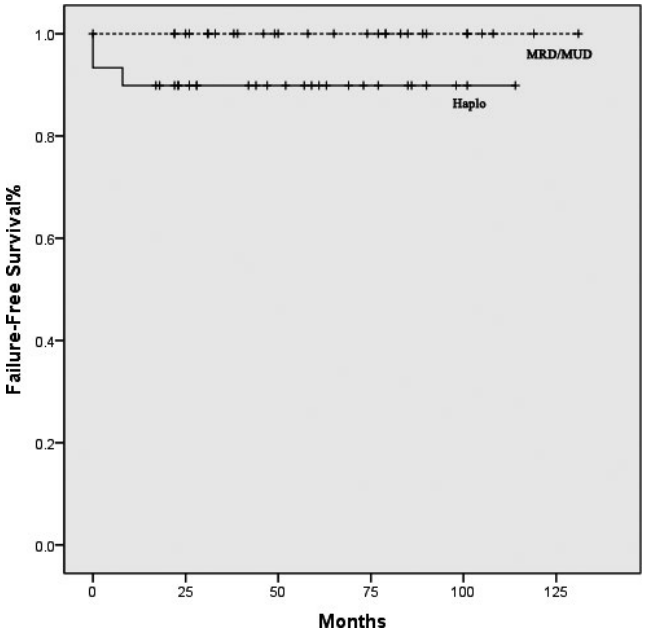

FIGURE 4 FFS of the two groups

transplantation centers. However, there is no uniformed pretreatment modality, and its efficacy needs to be further improved.

Passweg et al from Switzerland have reported the early study results of the International Blood and Bone Marrow Transplantation Research Center (CIBMTR). Among the 86 cases of HSCT with HLA-unmatched-related donors, the transplantation failure rate was 21%-25% at 100 days and 25%-26% at 1 year, and the 5-year OS rate was only 35%-49%.[14] In recent years, a number of hospitals in China have carried out Haplo-HSCT to treat patients with SAA. In 2014, Wang et al reported Haplo-HSCT salvage treatment for 17 children with SAA. They found that transplantation was successful in all patients. Among them, 1 case experienced rejection and self-recovered. The incidence of grade II-IV aGVHD was 30.5% and that of cGVHD was 21.3%. The OS rate was 71.25%.[15] Wu et al reported 21 cases of young SAA patients treated with G-CSF mobilization of bone marrow combined with transplantation of peripheral blood stem cells plus third-party umbilical cord blood mesenchymal stem cells and found that (i) the median transplantation time for neutrophils and platelets was 12 (8-21) days and 14 (10-23) days, respectively; (ii) all 21 patients were complete donor chimeric; (iii) the incidence of grade

II-IV aGVHD was 42.8%, that of grade III-IV aGVHD was 23.8%, and that of cGVHD was 50.0%; (iv) the survival rate was 80.9%, and the 2-year disease-free/progression-free survival rate was 74.1%.[16]

Different from previous in vitro T-cell removal and pretreatment modalities with TBI and high-dose CD34-positive screening for HSCT,[17,18] in this study, we comprehensively improved the modality by including non-radiotherapy in the pretreatment, eliminating in vitro T-cell removal, adopting combined transplantation of bone marrow and peripheral hematopoietic stem cells with or without mesenchymal stem cells and achieved good Haplo transplantation results. The incidences of cGVHD and CMV/EBV were not significantly different between Haplo group and MRD/MUD group. Although OS and FFS of the Haplo group were not as good as those of the MRD/MUD group, it is still acceptable as an alternative treatment under emergency.

In this study, the higher successful transplantation rate is achieved due to many reasons, including utilization of G-CSF mobilized bone marrow plus peripheral blood, sufficient stem cells as well as back infusion of third-party mesenchymal stem cells. As we all know, aplastic anemia is a benign disease. Therefore, it is necessary to avoid the occurrence of serious GVHD. Our study showed that the incidence of severe GVHD in the Haplo group was not higher than that in the MRD/MUD group, and the post-transplantation use of cyclophosphamide and pretreatment with other new drugs would be the future study direction. Another challenge for Haplo-HSCT is the occurrence of viral infection after transplantation. Our study suggests that the incidences of CMV and EBV infection were not significantly different between the two groups. This low incidence of infection may benefit from an active prophylactic use of antiviral drugs after transplantation. In addition, Haplo donors can provide lymphocytes for targeted antivirus therapy after transplantation, making antiretroviral therapy more effective.

This study showed that the OS rate and FFS rate were lower in Haplo group than MRD/MUD group. This may be caused by higher bacterial and fungal infection due to more intensive pretreatment. In this study, 4 children died of post-transplantation sepsis and severe infection. In addition, the complications after Haplo transplantation have their own particularities. For example, post-transplantation TMA and hepatic VOD need special treatment, which requires accumulation of more relevant experiences. Even though, convenient and rapid finding of transplant donors shortened the time from diagnosis to transplantation and reduced the risk of infection, thus greatly improving the OS and FFS rates of patients. With the improvement of medical technology, more accurate matching technology will make the search for a more appropriate donor possible. Improvement in treatment of post-transplantation complications and supportive means will significantly extend the OS and FFS of such patients. However, our study still has deficiencies such as relatively small sample size and needs to be verified by multicenter research with more persuasive large sample size.

5 | SUMMARY

Finding the biological indicators that affect the therapeutic effect of IST and the clinical features that affect the efficacy of HSCT, and further realizing active selection of timing for Haplo-HSCT is the future research directions. To achieve these goals, it is necessary to initiate registration of SAA patients, obtain the results of a variety of biological indicators prior to treatment, and design prospective study based on the treatment efficacy and analysis results of biological indicators.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

Sidan Li and Bin Wang: involved in data collection, drafting article, data analysis/interpretation, and statistics; Lingling Fu, Yilin Pang, Guanghua Zhu, Xuan Zhou, Jie Ma, Yan Su: performed concept/design, critical revision of article and data collection; Maoquan Qin and Runhui Wu: performed concept/design, drafting article, data analysis/interpretation, statistics, and critical revision of article.

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