Biol Blood Marrow Transplant 25 (2019) 975–980

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Comparison of Outcomes of Frontline Immunosuppressive Therapy and Frontline Haploidentical Hematopoietic Stem Cell Transplantation for Children with Severe Aplastic Anemia Who Lack an HLA-Matched Sibling Donor

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Article history:
Received 10 October 2018
Accepted 9 January 2019

Key Words:
Severe aplastic anemia
Haploidentical transplantation
IST
Hematopoietic stem cell

A B S T R A C T

We compared the outcomes of immunosuppressive therapy (IST) with those of T cell-replete haploidentical donor hematopoietic stem cell transplantation (haplo-HSCT) in children and adolescents with severe aplastic anemia (SAA). The medical records of 49 patients with SAA who received frontline IST (n = 29) or frontline haplo-HSCT (n = 20) between 2012 and 2016 were analyzed retrospectively. Fourteen patients responded after the first IST, and 1 patient responded after the second IST in the frontline IST group; 12 patients underwent salvage HSCT after IST failure. Sixteen of the 20 patients who underwent frontline haplo-HSCT survived without treatment failure. The 3-year overall survival of the frontline IST group was comparable to that of the frontline haplo-HSCT group (79.3 ± 7.5% versus 85.0 ± 8.0%; $\chi^2 = 0.110$; $P = .740$). The 3-year failure-free survival was lower in the frontline IST group compared with the frontline haplo-HSCT group (35.9 ± 10.9% versus 80.0 ± 8.9%; $\chi^2 = 4.089$; $P = .043$). Five patients of the IST group who underwent salvage HSCT achieved long survival without event. The event-free survival was lower in the salvage HSCT group compared with the haplo-HSCT group (41.7 ± 14.2% versus 80.0 ± 8.9%; $\chi^2 = 3.992$; $P = .046$), and the incidences of acute GVHD, grade II-IV acute GVHD, chronic GVHD, and severe infection were comparable between the 2 groups. Our results suggest that frontline haplo-HSCT may be a better treatment than IST for children and adolescents with SAA who lack an HLA age-matched familial donor.

INTRODUCTION

Severe aplastic anemia (SAA) is a hematopoietic failure disorder caused by the destruction of hematopoietic stem cell cloning owing to immune abnormalities, with severe bleeding and infection the main causes of death. Traditionally, SAA has been treated by reducing stem cell damage and restoring hematopoiesis. Matched sibling donor (MSD) hematopoietic stem cell transplantation (HSCT) is the preferred option for children and adolescents with SAA [1,2]. In the absence of an MSD, immunosuppressive therapy (IST) and 9/10 or 10/10 HLA-matched unrelated donor (URD) HSCT can be selected [3]. There are many disadvantages of IST, including a slower effect, serum disease, and recurrence, and it is difficult to obtain a URD, with an opportunity of <30% in China's Henan Province. Haploidentical-HSCT (haplo-HSCT) donors are more accessible and have shorter waiting times.

With the improvements in transplantation technology and an acceptable incidence of graft-versus-host disease (GVHD), haplo-HSCT has become a viable alternative treatment for patients who lack an MSD or a salvage treatment for IST failure. According to the latest recommendations from the Chinese Society of Hematology, haplo-HSCT can be considered a frontline treatment for young patients without a suitable MSD or URD [4]. To compare the safety and efficacy of T cell-replete haplo-HSCT with that of IST as a frontline treatment for SAA in young patients, we analyzed the clinical data of 49 children and adolescents with SAA seen at Henan Provincial People's Hospital.

METHODS

Patients

We retrospectively reviewed the clinical data of 49 consecutive patients with acquired SAA who lacked an HLA-matched sibling donor seen at Henan Provincial People's Hospital between January 2012 and December 2016.

Financial disclosure: See Acknowledgments on page 980.

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https://doi.org/10.1016/j.bbmt.2019.01.017

Twenty-nine patients were treated with initial IST, and 20 patients received haplo-HSCT as frontline treatment. All patients were age <18 years, were newly diagnosed with SAA, and had not received any previous IST. SAA was diagnosed according to standard criteria [1]; patients with an absolute neutrophil count (ANC) $<.2 \times 10^9$/L and meeting the criteria for SAA were classified with very severe aplastic anemia (VSAA). Patients who were age >18 years, had inherited bone marrow failure syndrome, or had undergone matched-sibling/unrelated donor HSCT were excluded from this study. The protocol of this clinical observation study followed the Declaration of Helsinki and was approved by the Ethics Committee of Henan Provincial People's Hospital and by the Institutional Review Board and Ethics Committee of Zhengzhou University. The choice of frontline treatment with IST or haplo-HSCT was made by the patients and their guardians, from whom informed consent was obtained according to the Declaration of Helsinki.

IST

According to standard therapy in Henan Province, the IST consisted of rabbit anti-human thymocyte globulin (rATG; 3.5 mg/kg/day for 5 days via i.v. drip) and cyclosporin A (CsA) (5 mg/kg/day orally, consecutive administration twice daily for more than 12 months). rATG (Sanofi, Paris, France) was administered for the first IST treatment but was replaced with an anti-human T lymphocyte rabbit immunoglobulin (rALG; 5 mg/kg/day for 5 days via i.v. drip) (Fresenius, Bad Homburg, Germany) for the second IST. The CsA concentration was measured regularly, and the dose was adjusted to maintain the CsA trough concentration at 150 to 200 ng/mL. Acyclovir for viral prophylaxis, fluconazole/voriconazole for fungal prophylaxis, and methylprednisolone were administered during ATG treatment.

Conditioning Regimens

Conditioning regimens in the haplo-HSCT group included (1) cyclophosphamide (CY) + rATG (CY 50 mg·kg^{-1}·d^{-1} for 4 days, rATG 2.5 mg·kg^{-1}·d^{-1} for 4 days); (2) CY + rATG + fludarabine (Flu) (CY 50 mg·kg^{-1}·d^{-1} for 4 days, rATG 2.5 mg·kg^{-1}·d^{-1} for 4 days, Flu 30 mg·m^{-2}·d^{-1} for 3 days); and (3) CY + rATG + Flu + busulfan (Bu) (CY 50 mg·kg^{-1}·d^{-1} for 2 days, rATG 2.5 mg·kg^{-1}·d^{-1} for 4 days, Flu 30 mg·m^{-2}·d^{-1} for 3 days, Bu 3.2 mg·kg^{-1}·d^{-1} for 2 days).

Conditioning regimens in the salvage HSCT (either a matched unrelated donor [MUD] or haploidentical donor) after first or second IST failure group included (1) CY + rALG + Flu (CY 50 mg·kg^{-1}·d^{-1} for 4 days, rALG 2.5 mg·kg^{-1}·d^{-1} for 4 days, Flu 30 mg·m^{-2}·d^{-1} for 3 days) and (2) CY + rALG + Flu + Bu (CY 50 mg·kg^{-1}·d^{-1} for 2 days, rALG 3.5 mg·kg^{-1}·d^{-1} for 4 days, Flu 30 mg·m^{-2}·d^{-1} for 5 days, Bu 3.2 mg·kg^{-1}·d^{-1} for 2 days).

Stem Cell Mobilization and Collection

The donor was continuously injected s.c. with 5∼10 μg/(kg·d) rhG-CSF for 4∼5 days. In the haplo-HSCT group, 8 patients received bone marrow (BM), 2 received peripheral blood stem cells (PBSCs), and 10 received both BM and PBSCs. In the salvage HSCT group, 8 patients received BM, 1 patient received PBSCs, and 3 patients received both BM and PBSCs. The total target mononuclear cell count was $\geq 3 \times 10^8$/kg, and CD34$^+$ cells were $\geq 3 \times 10^6$/kg of the recipient's weight [3].

GVHD Prophylaxis, Diagnosis, and Management

Prophylaxis against GVHD consisted of CsA, mycophenolate mofetil, and short-course methotrexate, as described previously [5]. The CsA dose was adjusted to achieve a drug trough level of 100 to 300 ng/mL. The diagnosis and classification of acute GVHD (aGVHD) and chronic GVHD (cGVHD) were based on international criteria [6,7]. For aGVHD, methylprednisolone, basiliximab (CD25 monoclonal antibody), or infusion of BM mesenchymal stem cells was administered.

Efficacy Evaluation and Follow-Up

To evaluate efficacy, 3-year overall survival (OS), failure-free survival (FFS), and event-free survival (EFS) were estimated. OS was defined as the time from the start of IST or transplantation to the date of the last follow-up or death. FFS was defined as survival with response. The last follow-up date for all surviving patients was September 1, 2018. Death, no response within 6 months, relapse, disease progression requiring a second course of IST or salvage HSCT, clonal evolution, or evolution to paroxysmal nocturnal hemoglobinuria were considered to indicate IST treatment failure. Hemoglobin at normal level for age, an ANC $>1.5 \times 10^9$/L, and platelet (PLT) count $>150 \times 10^9$/L were defined as complete response. Deviation from transfusion dependence and failure to meet SAA diagnostic criteria were defined as partial response. Both complete response and partial response are considered effective. Relapse was defined as blood transfusion dependence or an ANC $<.5 \times 10^9$/L after response. Treatment failure or an event after HSCT included death, engraftment failure, delayed rejection, relapse, and secondary malignancy. Delayed rejection was defined as primary engraftment followed by at least 2 cell lines of cytopenia with obviously hypocellular BM and without moderate to severe aGVHD. The day of myeloid engraftment was defined as the first day with ANC $\geq .5 \times 10^9$/L for 3 consecutive days; the day of PLT engraftment was defined as the first day with PLT $\geq 20 \times 10^9$/L for 7 consecutive days without PLT transfusion. After transplantation, BM morphology was reviewed regularly, and the chimeric rate was monitored.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM, Armonk, NY). Sample rates were compared using the chi-square test (Fisher's test), and median values were determined using a nonparametric test. Analysis for OS, FFS, and EFS was performed using the Kaplan-Meier method, and differences were compared using the log-rank test. Univariate and multivariate analyses were performed in the Cox regression model with a forward log-rank approach. $P < .05$ was considered to indicate statistical significance.

RESULTS

Patient Characteristics

Figure 1 shows the overall treatment flow and outcomes for all the patients in this study. Twenty of the 49 patients underwent frontline haplo-HSCT, and the remaining 29 patients received frontline IST. Twenty of the 27 patients (2 patients died early) who received frontline IST underwent salvage HSCT after IST failure. The clinical characteristics of the 49 young patients at the time of treatment are summarized in Table 1. No significant differences in age, sex, or median time from diagnosis to treatment was observed between the frontline IST group and the frontline haplo-HSCT group; however, disease status at the time of treatment differed significantly between the 2 groups ($P = .005$). Twelve of the 49 patients were diagnosed with VSAA, of whom 10 underwent haplo-HSCT as frontline treatment. The clinical features and outcomes of the salvage HSCT group after the first/second IST failure and those of the frontline haplo-HSCT group are shown in Table 2. The pretransplantation course was significantly shorter in the frontline haplo-HSCT group (median, 119 days [range, 32∼803 days] versus 495 days [range, 252∼1962 days]; $P = .001$).

Effectiveness of IST

In the frontline IST group, efficacy was not evaluated in 2 patients who died early, 1 on day +14 due to cerebral hemorrhage and the other on day +49 due to severe infection complicated by multiple organ dysfunction syndrome. No patient experienced a lethal allergic reaction during IST. At 6 months after initiation of the first course of IST, the treatment was effective in 14 patients (6 in complete remission, 8 in partial remission) and ineffective in 13 patients (9 who underwent salvage HSCT, and 4 who received a second course of IST. One of the 4 patients who received a second course of IST achieved complete remission, 1 patient relapsed after partial remission, and the treatment was ineffective in 2 patients. A total of 12 patients underwent salvage HSCT (24.5%), including 8 patients with a URD-HSCT and 4 patients with haplo-HSCT. The total effective rate of the first and second courses of IST was 55.6%. The 3-line hematopoietic recovery rate was significantly lower of the frontline IST group than in the frontline haplo-HSCT group (73.9% versus 100.0%; $P = .03$).

Transplantation Effectiveness

The clinical characteristics and outcomes of the patients with SAA who underwent HSCT, including the frontline haplo-HSCT group and the salvage HSCT after IST failure group, are summarized in Table 2.

Engraftment

In the frontline haplo-HSCT group, 1 patient died of a severe infection with cerebral hemorrhage at day +16, and the remaining 19 patients achieved hematopoietic reconstitution. The chimeric rate was detected at 1 month after transplantation. One

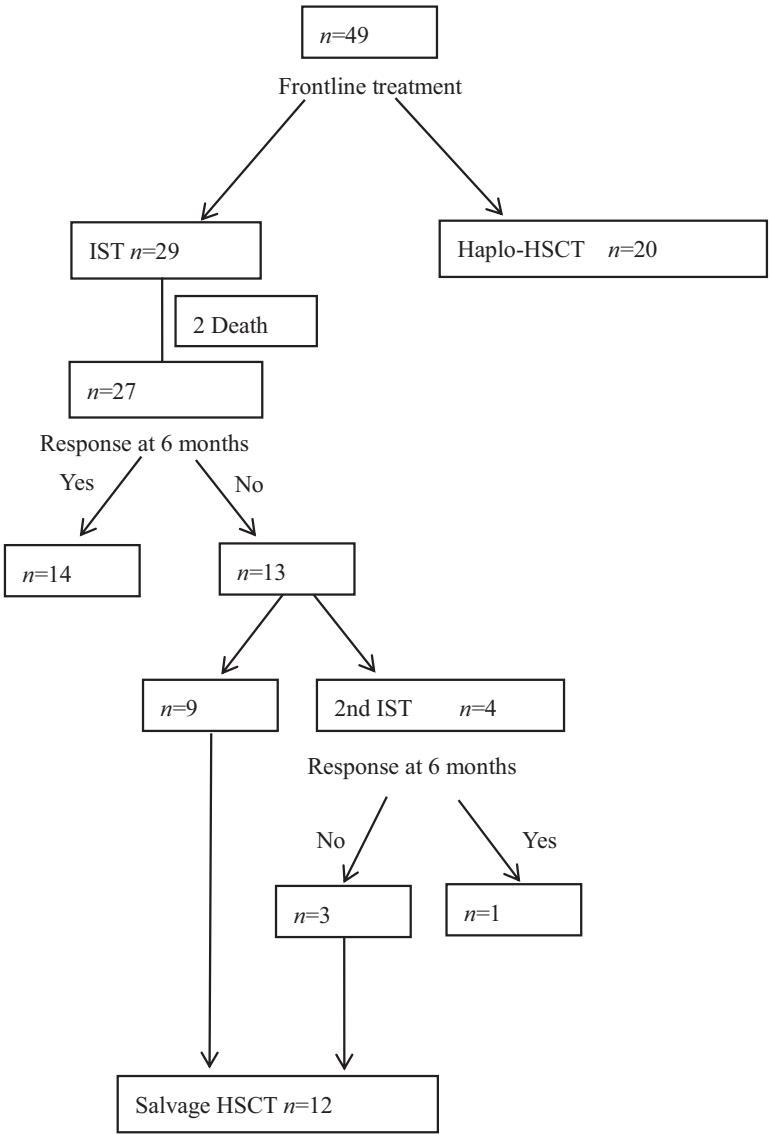

Figure 1. Treatment algorithm for 49 patients with SAA who lacked an HLA-matched sibling donor.

patient experienced delayed rejection with a 25.0% donor chimerism rate after achieving hematopoietic reconstitution with an 85.7% donor chimerism rate but finally achieved full-donor chimerism after the immunosuppressive agent was reduced. The remaining 18 patients were all fully chimeric. The median times to ANC and PLT engraftment were 16 days (range, 11∼26 days) and 19 days (range, 10∼34 days), respectively. In the salvage HSCT group, 11 of the 12 patients (91.7%) achieved

Table 1
Clinical Characteristics of 49 Children and Adolescents with SAA/VSAA

Characteristics	IST group (n = 29)	Haplo-HSCT group (n = 20)	*P* Value
Sex, male/female, n	16/13	14/6	.295
Age, yr, median (range)	12 (4∼17)	13 (4∼18)	.173
Status at therapy, n (%)			**.005**
SAA	27	11	
VSAA	2	9	
Time from diagnosis to treatment, d, median (range)	228 (16∼972)	119 (32∼803)	.360
Blood routine at diagnosis, median (range)			
Hemoglobin, g/L	73 (43∼125)	60 (39∼103)	.173
PLT, $\times 10^9$/L	33 (9∼88)	13 (0∼61)	<**.001**
ANC, $\times 10^9$/L	0.66 (0.10∼1.36)	0.215 (0∼.06)	.064
Salvage HSCT, n (%)	12 (41.4)	0 (0)	
For surviving patients			
Number (%)	23 (79.3)	17 (85.0)	.896
Follow-up, d, median (range)	1554 (14∼2454)	869.5 (16∼1414)	<**.001**
Patients with normal blood routine, n (%)	17 (73.9)	17 (100.0)	**.03**

Significant *P* values are in bold type.

Table 2
Features and Outcomes of the Haplo-HSCT and Salvage HSCT Groups after IST Failure

Variable	Haplo-HSCT Group (n = 20)	Salvage HSCT Group (n = 12)	*P* Value
Sex, male/female, n	14/6	7/5	.703
Age, yr, median (range)	13 (4∼18)	12 (4∼17)	.367
Stem cell source, BM/PBSC/BM + PBSC, n	8/2/10	8/1/3	.317
ABO match of donor to recipient, n (%)			.900
Match	9 (45.0)	4 (33.3)	
Major mismatch	6 (30.0)	5 (41.7)	
Minor mismatch	3 (15.0)	2 (16.7)	
Major and minor mismatch	2 (10.0)	1 (8.3)	
Donor-recipient sex match, n (%)			.445
Male-male	4 (20.0)	5 (41.7)	
Male-female	10 (50.0)	4 (33.3)	
Female-male	2 (10.0)	2 (16.7)	
Female-female	4 (20.0)	1 (8.3)	
Donor-recipient relationship, n (%)			
Parent-child	20 (100.0)	8 (66.7)	
Unrelated	0 (0.0)	4 (33.3)	
HLA-match, n (%)			
5/10	9 (45.0)	4 (33.3)	
6/10	6 (30.0)	2 (16.7)	
7/10	4 (20.0)	2 (16.7)	
8/10	1 (5.0)		
9/10		1 (8.3)	
10/10		3 (25.0)	
Time from diagnosis to transplantation, d, median (range)	119 (32 ∼ 803)	495 (252∼1962)	**.001**
Conditioning regimen, n (%)			<**.001**
Cy + ATG	16 (80.0)	1 (8.3)	
Cy + ATG + Flu + Bu	1 (5.0)	4 (33.3)	
Cy + ATG + Flu	3 (15.0)	7 (58.3)	
Infection post-transplantation, n (%)	16 (80.0)	7 (58.3)	.240
aGVHD, n (%)	11 (55.5)	8 (66.7)	.713
Grade II-IV aGVHD, n (%)	8 (40.0)	3 (25.0)	.465
cGVHD, n (%)	3 (15.0)	5 (33.3)	.379
PTLD, n (%)	1 (0.05)	2 (0.167)	.540
Mononuclear cells, × 10^8/kg, median (range)	6.305 (2.85∼17.48)	8.405 (3.84∼18.97)	.167
$CD34^+$ cells, × 10^6/kg, median (range)	6.35 (1.6∼20.1)	6.615 (3.2∼12.6)	.483
Day +28 myeloid engraftment , n (%)	19/19 (100)	11/12 (91.7)	.375
Median myeloid engraftment, d, median (range)	16 (11∼26)	15 (12 ∼25)	.914
Day +28 PLT engraftment, n (%)	19/19 (100)	11/12 (91.7)	.375
Median PLT engraftment, d, median (range)	19 (10∼34)	17 (10∼32)	.425

Significant *P* values are in bold type.

hematopoietic reconstitution, and 1 patient experienced primary engraftment failure and died of a severe infection on day +52. One patient experienced delayed rejection with a 15.0% donor chimerism rate after hematopoietic reconstitution (donor chimerism rate, 85.5%), was dependent on blood transfusion, and died of a severe pulmonary infection after stopping treatment due to economic reasons. In this group, the median times to ANC and PLT engraftment were 15 days (range, 12∼25 days) and 17 days (range, 10∼32 days), respectively.

Complications

aGVHD occurred in 19 of the 32 patients who underwent HSCT, including 12 patients with grade 0-I (60.0%) and 8 with grade II-IV (40.0%). Three patients experienced cGVHD (cumulative incidence, 15.0%), 1 with extensive cGVHD. There were no significant differences in the incidences of aGVHD, grade II-IV aGVHD, or cGVHD between the haplo-HSCT and salvage HSCT groups.

Twenty-three patients experienced a bacterial and/or fungal and/or virus infection within 100 days after transplantation, including 16 patients (80.0%) in the haplo-HSCT group and 7 patients (58.3%) in the salvage HSCT group ($P = .240$). The most common infections in the patients who underwent HSCT were reactivation of cytomegalovirus (CMV; 62.5%) and Epstein-Barr virus (EBV; 18.75%). CMV reactivation occurred in 13 patients (65.0%) in the haplo-HSCT group and 7 patients (58.3%) in the salvage HSCT group ($P = .724$). EBV viremia occurred in 3 patients (15.0%) in the haplo-HSCT group and in 3 patients (25.0%) in the salvage HSCT group ($P = .647$). Three patients (1 in the frontline haplo-HSCT group and 2 in the salvage HSCT group) developed EBV-associated post-transplantation lymphoproliferative disease (PTLD). The patient in the frontline haplo-HSCT group, died, whereas the 2 patients in the salvage HSCT group who developed PTLD were greatly improved after antivirus treatment and rituximab therapy, and the patients achieved long-term survival.

Survival

Frontline IST versus Frontline Haplo-HSCT

Three-year OS was comparable in the frontline IST and frontline haplo-HSCT groups (79.3 ± 7.5% versus 85.0 ± 8.0%; $\chi^2 = .110$; $P = .740$) (Figure 2A). However, FFS was significantly lower in the IST group compared with the haplo-HSCT group (35.9 ± 10.9% versus 80.0 ± 8.9%; $\chi^2 = 4.089$; $P = .043$) (Figure 2B). In univariate and multivariate analyses, factors related to OS outcomes were not identified; FFS outcomes were adversely associated with the choice of frontline IST ($P = .043$) but were not independent of the risk factors for FFS ($P = .054$).

Frontline Haplo-HSCT versus Salvage HSCT

Five of the 12 patients who received salvage HSCT achieved survival without an event. EFS was significantly lower in the salvage HSCT group compared with the frontline haplo-HSCT

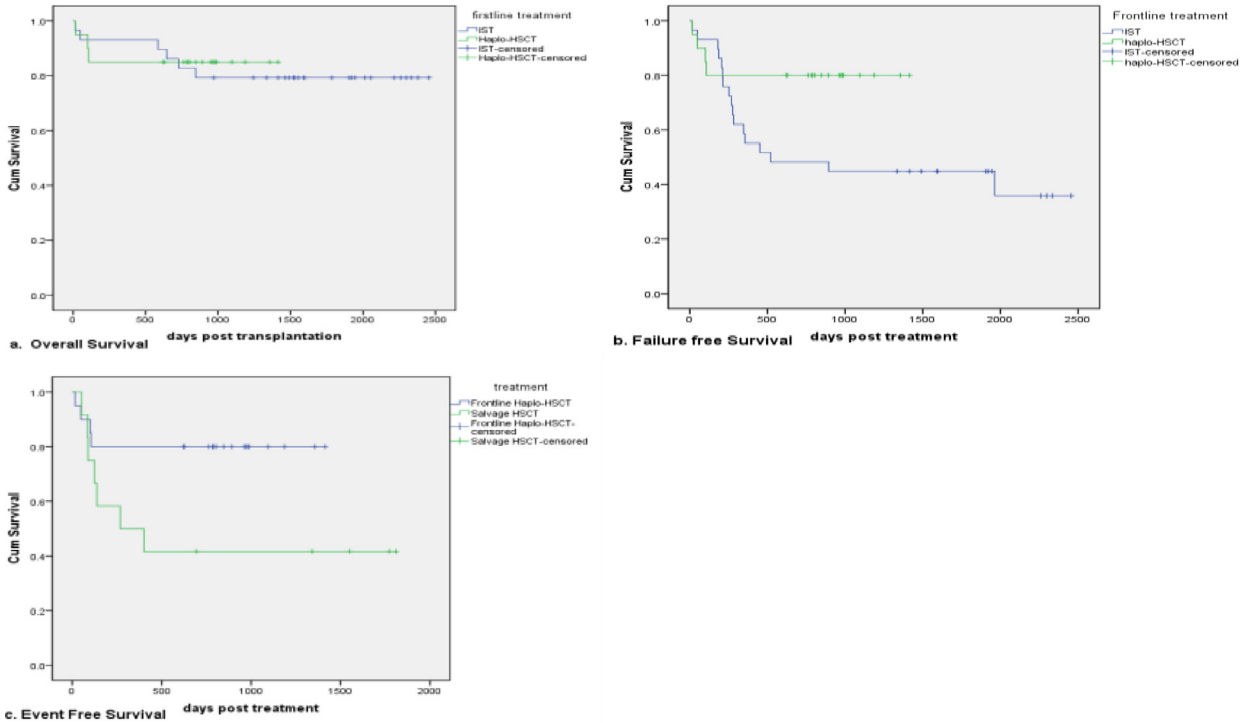

Figure 2. OS, FFS, and EFS according to the initial treatment modality. (A) No difference in 3-year OS rate was found between frontline IST and frontline haplo-HSCT groups (79.3 ± 7.5% versus 85.0 ± 8.0%; $\chi^2 = .110$; $P = .740$). (B) The 3-year FFS rate was significantly lower in the IST group compared with the haplo-HSCT group (35.9 ± 10.9% versus 80.0 ± 8.9%; $\chi^2 = 4.089$; $P = .043$). (C) EFS was significantly lower in the salvage HSCT after first or second IST failure compared with the frontline haplo-HSCT group (41.7 ±14.2% versus 80.0 ± 8.9%; $\chi^2 = 3.992$; $P = .046$).

group (41.7 ± 14.2% versus 80.0 ± 8.9%; $\chi^2 = 3.992$; $P = .046$) (Figure 2C). Nine of the 49 patients died, 4 due to severe infection, 3 due to severe GVHD complicated with infection, 1 due to sinusoidal obstructive syndrome, and 1 due to PTLD. In the frontline haplo-HSCT group, 3 patients died, including 1 due to severe infection, 1 due to severe GVHD complicated with infection, and 1 due to PTLD. In the salvage HSCT group, 4 patients died, 1 due to severe infection, 2 due to severe GVHD complicated with infection, and 1 due to sinusoidal obstructive syndrome.

DISCUSSION

Based on retaining residual hematopoietic function, IST can reconstitute autologous hematopoiesis by controlling immune abnormalities [8–10]. Allogeneic HSCT can reconstitute the blood and immune systems by implanting allogeneic hematopoietic stem cells based on removing hematopoiesis and suppressing immunity. Long-term OS in the children and adolescents with SAA in the MSD-HSCT frontline treatment group was >90%, similar to that in patients in the frontline IST treatment group [8,9]. Because frontline IST has many disadvantages, including treatment failure, recurrence, and clonal evolution, and because FFS was significantly higher in the MSD-HSCT group compared with the frontline IST treatment group (87% versus 33%; $P < .001$) [9], MSD is the frontline option for the diagnosis and treatment of children and adolescents with SAA/VSAA. However, in the absence of a suitable MSD, IST or MUD-HSCT may be a viable option. In the event of IST failure or in the absence of MUD, either a second course of IST or HSCT from a mismatched haploidentical donor or cord blood is recommended [2].

Given the current composition of the Chinese population, a child or adolescent with SAA is usually the only child of his or her family, and <30% have a suitable MSD. It takes longer to find a matched URD; thus, haplo-HSCT is a favorable option to access donors and shorten the waiting period. Haplo-HSCT also has been reported to achieve satisfactory efficacy as a frontline treatment for patients with SAA, especially children and adolescents [11–14]. According to the latest Chinese recommendations, haplo-HSCT can be used as frontline treatment for young patients without an appropriate MSD or URD [4].

Xu et al [11] compared the efficacy of frontline haplo-HSCT and frontline MSD-HSCT in the treatment of patients with SAA. There was no significant difference in engraftment rate between the 2 groups. Three-year OS was 86.1% in the haplo-HSCT group and 91.3% in the MSD-HSCT group ($P = .358$), and 3-year FFS was 85.0% and 89.8%, respectively ($P = .413$) [11]. Patients with SAA in the frontline haplo-HSCT group had 3-year OS of 85.0 ± 8.0% and FFS of 80.0 ± 8.9%, slightly lower rates than reported previously [11]. This may be because a larger proportion of patients with VSAA in the frontline haplo-HSCT group had an elevated risk of infection and bleeding, increasing the risk of early death.

Xu et al [11] also reported outcomes of 149 patients with SAA who underwent HSCT (haplo-HSCT, n = 101; MSD-HSCT, n = 48; MUD-HSCT, n = 27) after IST failure [15]. There was no significant differences in 3-year OS and FFS between the haplo-HSCT and MSD-HSCT groups (OS, 89.0% versus 91.0%, $P = .555$; FFS, 86.8%% versus 80.3%, $P = .659$) [15]. Although the salvage HSCT after IST failure group achieved acceptable OS and FFS, the rates of aGVHD and cGVHD were higher in the salvage HSCT group compared with the frontline MSD-HSCT group, the OS of patients age >12 years decreased with increasing age, and the risk of secondary tumors increased [9,16]. In a study of patients who received haplo-HSCT after IST failure, the engraftment rate was 96.15%; the rates of aGVHD,

grade III-IV aGVHD, and cGVHD were 61.52 ± 9.5%, 15.55 ± 8.48%, and 81.07 ± 11.51%, respectively; and 3-year OS and FFS were 76.30 ± 9.70% and 76.30 ± 9.70%, respectively [17]. In our study, 8 patients underwent haplo-HSCT and 4 patients underwent MUD-HSCT in the salvage HSCT group; the engraftment rate at day +30 was 91.7%; the rates of aGVHD, grade II-IV aGVHD, and cGVHD were 66.7%, 25.0%, and 33.3%, respectively; and EFS was 35.0 ± 15.4%. More samples are needed to further explore the efficacy of salvage haplo-HSCT after IST failure for children and adolescents with SAA.

In this study, we retrospectively evaluated the prognosis of children and adolescents with SAA/VSAA who received frontline haplo-HSCT or frontline IST. Our results show no significant difference in 3-year OS between the frontline IST and frontline haplo-HSCT groups (79.3 ± 7.5% versus 85.0 ± 8.0%; $\chi^2 = .110$; $P = .740$); however, FFS was significantly higher in the haplo-HSCT group compared with the IST group (80.0 ± 8.9% versus 35.9 ± 10.9%; $\chi^2 = 4.089$; $P = .043$) and EFS was significantly higher in the haplo-HSCT group compared with the salvage HSCT group (80.0 ± 8.9% versus 41.7 ± 14.2%; $\chi^2 = 3.992$; $P = .046$). Zhang et al [18] compared the prognosis of 28 children with SAA treated with haplo-HSCT and IST and found OS rates of 66.7% and 70.0%, respectively (P not significant). These results are similar to our present findings.

Choi et al [19] retrospectively analyzed the clinical data of 42 children and adolescents with SAA/VSAA, including 19 patients who received frontline IST, 23 who underwent frontline HSCT, and 11 patients in the IST group who underwent salvage HSCT after IST failure. No significant difference in 5-year OS was seen between the 2 groups, but the 5-year FFS was significantly higher in the HSCT group compared with the IST group (91.3% versus 30.7%; $P < .001$). Five-year EFS was higher in the HSCT group compared with the salvage HSCT group (91.3% versus 50.9%; $P = .015$). Although the frontline transplantation method of Choi et al is not the same as that used in the present study, many studies have shown no significant difference in hematopoietic reconstruction and overall prognosis among haplo-HSCT, MSD-HSCT, and URD-HSCT techniques [20,21]. In this study, there were no significant differences in rates of engraftment, aGVHD, grade II-IV aGVHD, and cGVHD between the frontline haplo-HSCT group and the salvage HSCT group, but EFS was significantly higher in the haplo-HSCT group. These findings suggest a higher overall efficacy of frontline haplo-HSCT compared with IST or salvage HSCT. In the absence of an MSD or a URD for children and adolescents with SAA/VSAA, haplo-HSCT has potential as a viable alternative frontline therapy.

This study has several limitations. Patient baseline conditions differ across the groups, and the proportion of patients VSAA is higher in the haplo-HSCT group. This is a retrospective study with a relatively small number of samples, and a prospective multicenter study should be performed in the future. The frontline treatment was selected by the guardian and patient after a thorough discussion. In addition, the choices of frontline and follow-up treatments were affected by the family's economic conditions and ability to understand information presented to them.

In conclusion, the efficacy of frontline haplo-HSCT is superior to that of either frontline IST or salvage HSCT after IST failure for children and adolescents with SAA who lack a suitable MSD. Haplo-HSCT may be considered the preferred choice for young (age <18 years) patients with SAA/VSAA who do not have an MSD; however, it is still necessary to expand the sample size for future studies.

ACKNOWLEDGMENTS

The authors thank all their colleagues who participated in this research, as well as the residents and nurses who cared for the study patients.

Financial disclosure: Nothing to report.

Conflict of interest statement: There are no conflicts of interest to report.

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