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ARTICLE

Immunosuppressive therapy versus haploidentical transplantation in adults with acquired severe aplastic anemia

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Abstract

Our study aimed to compare treatment outcomes between hematopoietic stem cell transplantation (HSCT) from haploidentical donors (HID) and immunosuppressive therapy (IST) in adults with acquired severe aplastic anemia (SAA). The medical records of 113 SAA adults who received IST, including rabbit ATG and cyclosporin ($N = 37$), or HID HSCT ($N = 76$) within 6 months of diagnosis at two institutions were retrospectively reviewed. Estimated 8-year overall survival (OS) was comparable between the IST and HID HSCT groups (75.6 vs. 83.7%, respectively, $P = 0.328$), but failure free survival (FFS) was significantly lower in IST group than HID HSCT group (38.5 vs. 83.7%, respectively, $P = 0.001$). Furthermore, a significant improvement in FFS was observed with HSCT over IST in patients under 40 years old. At the last follow-up, patients in HSCT group achieved better Karnofsky Performance Status (KPS) than those in IST group (100 [20–100] vs. 90 [20–100], $P = 0.002$). In terms of blood count, 83.1% (54/65) of patients in HSCT group showed complete recovery compared to only 38.2% (13/34) in IST group ($P < 0.001$). These data suggest that HID HSCT could be an effective alternative treatment option for SAA adults, and additional prospective studies are necessary.

Introduction

Immunosuppressive therapy (IST) and hematopoietic stem cell transplantation (HSCT) are two effective treatment choices in severe aplastic anemia (SAA) [1, 2]. The recommended standard first-line therapy for younger adults with SAA is matched related donor (MRD) HSCT [1, 3]. For younger adults without a matched sibling donor and older adults, IST, including antithymocyte globulin (ATG) and cyclosporin (CsA), is considered to be the first-line option [1, 3].

As demonstrated in several large studies, the standard regimen for first-line IST with ATG and CsA produces hematological recovery in 50–70% of patients [4, 5]. Although the survival of patients treated with IST improved from 57 to 73% in the last decade [6], relapse occurs in up to one third of cases, and the respective risk of later clonal evolution to myelodysplastic syndrome/acute myeloid leukemia and hemolytic PNH is 15 and 10%, respectively, during long-term follow up [7, 8]. Additionally, horse ATG, which is proven superior to rabbit ATG, is unavailable in China [9, 10].

In comparison to IST, HSCT shows faster restoration of hematopoiesis and lower risk of clonal diseases [11]. With the evolution of conditioning regimens and progression of transplantation technology, the outcomes of haploidentical donor HSCT (HID-HSCT) have also improved dramatically. Recent reports have suggested that haploidentical transplantation with the application of various regimens is feasible in treating SAA [12–16]. Encouragingly, the results of haploidentical transplantation conditioning with a unified regimen, as an upfront or salvage choice, are comparable to those of MRD HSCT for SAA in two multicenter studies [17, 18].

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Since age is regarded as an influencing factor in SAA, different algorithms are recommended in each age group [1, 3, 19]. Recently, an increasing number of studies have reported outcomes of IST versus HSCT, especially from alternative donors [20–23]. However, the patients included in these studies were mainly children. Furthermore, HID HSCT could be conducted at an early stage without the overuse of transfusions, any IST or a long disease course, all of which have been identified as adverse factors for survival following HSCT [24, 25]. To determine whether early HID HSCT or IST is a better choice for adults with SAA when a matched sibling is not available, we conducted the current analysis.

Methods

Patients

This was a retrospective study at two of the largest and most experienced centers for SAA in China. From August 2009 through October 2017, all eligible adult patients (age ≥ 18 years) were consecutively enrolled. Patients with congenital bone marrow disorders (Fanconi anemia, Diamond-Blackfan anemia, and dyskeratosis congenital (DKC)) and classic paroxysmal nocturnal hemoglobinuria (PNH) were excluded. In detail, chromosome breakage and gene test was used to exclude Fanconi anemia. Telomerase RNA component mutation analysis was performed to detect hidden forms of DKC when congenital forms were suspected. All patients were newly diagnosed with acquired SAA, had no available MRD or matched unrelated donor (MUD), were administered with standard immunosuppressive therapy (IST) or HID HSCT within 6 months after definite diagnosis, and had no prior treatments with ATG. The analysis was completed as of 30 April 2018. Patients with SAA were informed of advantages and disadvantages of the two treatment options, from which individual decisions were made. All patients provided signed Institutional Review Board-approved informed consent, in accordance with the Declaration of Helsinki. Fifteen HID HSCT recipients reported here were included in two previous reports [17, 18].

Immunosuppressive therapy (IST)

IST consisted of rabbit ATG and CsA. Rabbit ATG (Sangstat, Lyon, France) was administered intravenously at a dose of 3–4 mg/kg/d for five consecutive days. Oral CsA (5 mg/kg/d) was started on day six in divided doses and continued for at least one year, with dosing adjusted to maintain a whole blood concentration of 150–250 ng/mL. For prevention of allergic reactions, methylprednisolone (1 mg/kg/d) was administered intravenously from day 1, 0.5 mg/kg/d orally on day 14, then tapering the dose until discontinuation on day 28.

Haploidentical transplantation

Patients with HID HSCT were conditioned as described previously [17] with busulfan (Bu, 0.8 mg/kg four times i.v. daily on days—7 and —6), cyclophosphamide (Cy, 50 mg/kg once i.v. daily on days—5to –2), and rabbit ATG (2.5 mg/kg once i.v. daily on days—5to–2). Hematopoietic stem cell sources included granulocyte colony-stimulating factor-primed bone marrow combined with peripheral blood samples. Details of graft versus host disease (GvHD) prophylaxis and other supportive care are consistent with our previous experience [12, 17].

Definitions and evaluations

Patients in the IST cohort were evaluated at three and six months post-therapy. A complete response (CR) was defined as an absolute neutrophil count (ANC) of more than 1.0×10^9/L, a hemoglobin level of more than 100 g/L, and a platelet count of more than 100×10^9/L (all three criteria had to be met). A partial response (PR) was defined as transfusion independence and no longer meeting the criteria for severe disease, and no response (NR) was defined as blood counts that continued to meet the criteria for SAA. Overall response included both CR and PR [22, 26].

In the HSCT group, neutrophil and platelet engraftment was defined as previous report [17]. Primary graft failure (GF) was defined as failure of myeloid engraftment until day + 28. Secondary GF was defined as absence of graft function after full engraftment [27]. Acute and chronic GvHD (aGvHD and cGvHD) were scored using standard criteria [28, 29].

The main objective was to compare survival outcomes between the two groups. FFS was defined as survival with response. IST treatment failure included death, no response by 6 months and beyond, disease progression requiring intervention, relapse, and clonal evolution [2]. Failures after HSCT was defined as death, primary and secondary graft failure and relapse, whichever occurred first. GvHD-free, failure-free survival (GFFS) was defined as grade 3-4 acute GvHD, extensive chronic GvHD, and treatment failures [18]. Overall survival (OS) was defined as time from treatment to death. Performance status pre-transplantation and at the last follow-up was graded by the Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Status (KPS) score.

Statistical analysis

Patient characteristics were compared using chi-square or Fisher's exact tests for binary variables, and the Mann–Whitney *U*-test for continuous variables. The survival probabilities were assessed according to Kaplan-Meier method and the groups were compared using the log-rank test. Multivariate models were built using a backward selection method with a threshold *P* value of <0.05. Cumulative incidences of GvHD were estimated in the competing risk model, with death as the competing event. Statistical analysis was carried out using SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA) and the R software package (version 2.6.1; http://www.r-project.org).

Results

Basic characteristics

The characteristics of subjects in the IST and HSCT cohorts are summarized in Table 1. The IST ($n = 37$) and HSCT ($n = 76$) groups were similar in terms of age at treatment, sex ratio, and severity of disease. However, the median time interval from SAA diagnosis to treatment was longer in the HSCT group than in the IST group (3 [1–6] months vs. 2 [1–6] months respectively, $P < 0.001$). Twenty-seven percent of IST and 9.2% of HSCT was performed in the first 4 years ($P = 0.013$).

Table 1 Patient characteristics

	IST group $N = 37$	HSCT group $N = 76$	*P*
Age, year, median (range)	32 (18–62)	28 (18–49)	0.055
Gender			
Male	24 (64.9%)	46 (60.5%)	0.656
Female	13 (35.1%)	30 (39.5%)	
Severity, No. of patients (%)			
VSAA	7 (18.9%)	24 (31.6%)	0.157
SAA	30 (81.1%)	52 (68.4%)	
Disease course before ATG/SCT, month, range			
AA course	2 (1–48)	6 (1–216)	<0.001*
SAA course	2 (1–6)	3 (1–6)	<0.001*
Treatment year			0.013*
2009–2012	10 (27.0%)	7 (9.2%)	
2013–2017	27 (73.0%)	69 (90.8%)	
For alive patients at last follow-up			
No. (%)	34 (91.9%)	65 (85.5%)	0.510
Follow-up, month, median (range)	20.2 (3.2–96.0)	24.7 (6.1–103.0)	0.565
Patients with normal blood routine, No. (%)	13 (38.2%)	54 (83.1%)	<0.001*
KPS	90 (20-100)	100 (20-100)	0.002*

P value < 0.05

Outcomes of IST

All 37 cases were evaluated at three months after initiation of IST. A total of 14 cases (37.8%) achieved PR. Only one subject (2.7%) had CR at this point. By six months, two patients died, one was lost to follow-up, and two transferred to transplantation. Overall, of 32 evaluable patients receiving an initial course of IST, six patients (18.7%) had evidence of a CR and 15 patients (46.9%) showed a PR.

Eleven patients (34.4%) experienced NR at 6 months, and two had disease relapse at 5.7 and 5.0 years post-IST. During follow-up there were seven cases receiving salvage HSCT from six HIDs and one MUD. In detail, two cases had salvage HID HSCT at 4 months because of non-response and personal choice prior to the 6 month evaluation, two cases had HID HSCT as a result of relapse, and the remaining cases underwent one MUD and two HID HSCTs because of NR at 6 months.

The median follow up were 20.2 (3.2–96.0) months among alive patients in the IST group. Causes of death included one cerebral hemorrhage on day 133, one massive cerebral infarction on day 126 and a cytomegalovirus infection after salvage transplantation on day 2328 after initial IST treatment.

Outcomes of HID HSCT

Descriptions of patients and grafts in the HSCT group are provided in Table 2. Seventy-five patients survived for more than 28 days, and all achieved myeloid engraftment. Neutrophil and platelet engraftment took a median time of 12 (9–21) days and 14 (7–101) days, respectively. Seventy-three of 75 cases had stable full-donor chimerism. There were two secondary graft failures. One patient who had developed secondary GF received secondary transplantation from another haploidentical donor but died in spite of achieving successful engraftment. The other case abandoned further intervention.

Acute GvHD (aGvHD) developed in 42/75 patients (56.0%); 23 patients (30.7%) were grade I, 11 patients (14.7%) were grade II, seven patients (9.3%) were grade III and 1 (1.3%) was grade IV. The cumulative incidence (CI) of grade II–IV acute GVHD in all patients was 25.00 ± 0.25%. The overall incidence of grade III-IV acute GVHD was 10.53 ± 0.13%.

A total of 73 patients survived for more than 100 days and were evaluable for chronic GvHD (cGvHD). Limited

Table 2 Patient and graft characteristics in HSCT group

Variable	No. (%)
HLA mismatched locus	
0	1 (1.3%)
1	3 (3.9%)
2	14 (18.5%)
3	58 (76.3%)
ECOG pre-SCT	
0	19 (25.0%)
1	44 (57.9%)
2	13 (17.1%)
Donor selection	
Parent	40 (52.6%)
Sibling	25 (32.9%)
Child	11 (14.5%)
Donor-patient sex match, no. (%)	
Male–male	38 (50.0%)
Male–female	24 (31.6%)
Female–male	6 (7.9%)
Female–female	8 (10.5%)
ABO match, no. (%)	
Matched	43 (56.6%)
Minor mismatched	13 (17.1%)
Major mismatched	11 (14.5%)
Different	9 (11.8%)
Median MNCs, $\times 10^8$/kg (range)	10.11 (3.64–25.13)
Median CD34 + cells, $\times 10^6$/kg (range)	3.75(0.67–10.31)
Neutrophil engraftment, days, median (range)	12 (9–21)
Platelet engraftment, days, median (range)	14 (7–101)

cGvHD developed in nine patients (12.3%), and five patients (6.8%) had extensive cGvHD. The cumulative incidences of cGvHD and extensive cGvHD were 21.25 ± 0.28 and 8.04 ± 0.13%, respectively.

At a median follow-up of 24.7 months (range, 6.1–103.0 months), 65 of the 76 patients (85.5%) had survived. Attributable causes of death included severe GvHD (two patients), severe pneumonia (two patients), post-transplant lymphoproliferative disease (PTLD, three patients), secondary graft failure (two patients), invasive fungal infections (1 patient), and suicide (1 patient).

Survival outcomes

The estimated FFS at eight years from the beginning of therapy was 83.7 ± 4.8% in the HSCT group compared with 38.5 ± 13.2% in the IST group ($P = 0.001$) (Fig. 1). Overall survival was not significantly different between the IST group (75.6 ± 17.2%) and HSCT group (83.7 ± 4.8%)

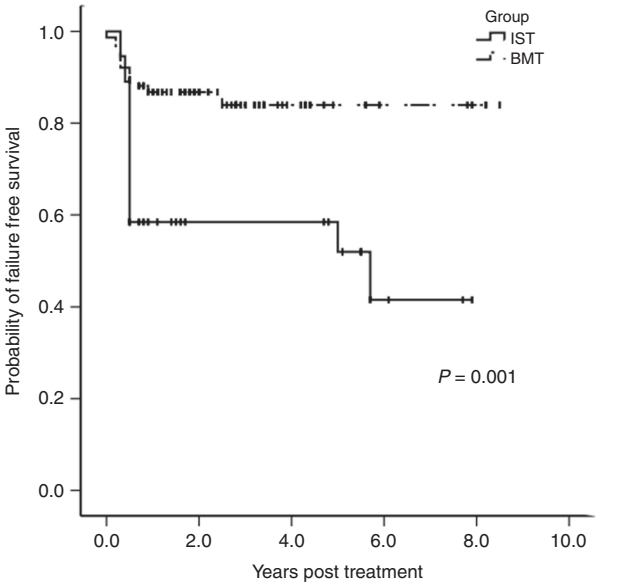

Fig. 1 Failure free survival of IST vs. HID HSCT in the whole cohort ($P = 0.001$)

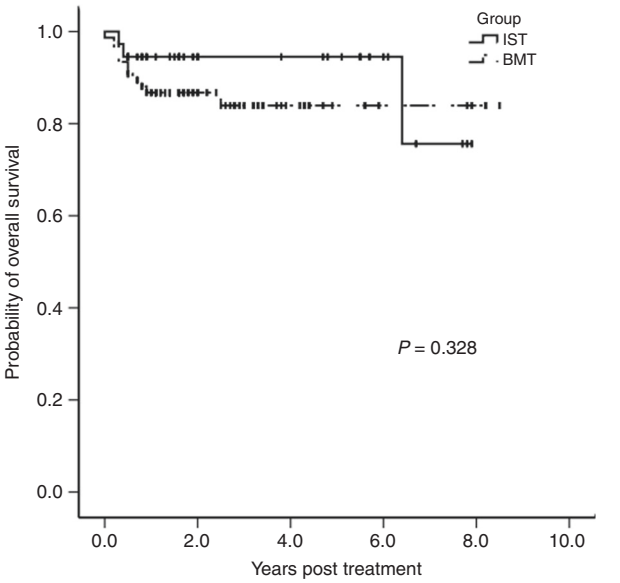

Fig. 2 Overall survival of IST vs. HID HSCT in the whole cohort ($P = 0.328$)

(Fig. 2). The composite end point GFFS was also calculated in the HSCT group, with an estimated probability of 72.4 ± 5.7% during follow-up.

All probable factors affecting outcomes were analyzed by univariate analysis, as indicated in Table 3. Our multivariate analysis for the whole cohort included the above factors. In the whole cohort, the choice of IST was the only factor associated with decreased FFS (Table 4). None of the factors were identified as affecting overall survival.

Table 3 Factors associated with outcomes in univariate analysis

Variable	No.	OS		FFS	
		8-year OS rate (%)	*P*	8-year FFS rate (%)	*P*
Sex			0.886		0.358
Male	70	69.1 (15.9)		55.0 (12.1)	
Female	43	87.9 (5.1)		80.8 (6.1)	
Age			0.310		0.624
18–39	91	75.8 (9.7)		65.2 (8.8)	
≥ 40	22	95.2 (4.6)		85.7 (7.6)	
Severity of disease			0.706		0.715
SAA	82	75.1 (10.7)		65.6 (9.9)	
VSAA	31	90.3 (5.3)		38.7 (27.6)	
SAA course (m)			0.396		0.949
≤2 m	51	73.5 (16.7)		58.5 (13.1)	
>2 m	62	81.6 (6.4)		72.2 (6.9)	
Treatment method			0.328		0.001*
IST	37	75.6 (17.2)		38.5 (13.2)	
HSCT	76	83.7 (4.8)		83.7 (4.8)	
Treatment year			0.085		0.218
2009–2012	17	88.9 (10.5)		72.8 (12.0)	
2013–2017	96	83.6 (4.7)		72.5 (5.2)	

SAA Severe aplastic anemia, *VSAA* Very severe aplastic anemia, *IST* Immunosppressive therapy, *HSCT* Hematopoietic stem cell transplantation

P value < 0.05

Table 4 Multivariate analysis of adverse factors associated with survival outcomes

Outcome	Hazard ratio (95%Confidence interval)	*P* value
Overall survival		
Treatment of IST	1.269 (0.320–5.040)	0.735
Failure free survival		
Treatment of IST	4.275 (1.957–9.338)	<0.001*
Treatment year before 2013	3.525 (0.937–13.257)	0.062

P value < 0.05

Analysis of subgroup

We further analyzed survival outcomes for each age group (18–39 and ≥40) as age was regarded as a vital factor in deciding on a treatment option. For younger adults (under 40 years old), OS at eight years was not statistically significantly different between the two groups (76.8 ± 17.5% for IST and 81.1 ± 5.5% for HID-HSCT recipients; $P = 0.231$), however, FFS was obviously improved in the HSCT group (81.2 ± 5.5% vs. 39.0 ± 13.5%; $P = 0.002$). In adults 40 years or older (12 cases in the IST group and 10 cases in the HSCT group), no significant difference was observed in either OS or FFS between the two treatment groups. However, four patients (30%) suffered from treatment failures in the IST group and none in HSCT group. A trend of improved FFS in older patients was also observed in Fig. 3 ($P = 0.082$).

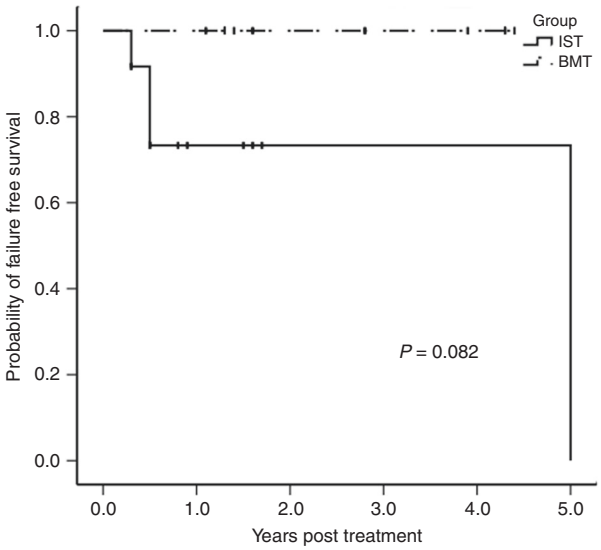

Fig. 3 Failure free survival of IST vs. HID HSCT in adults 40 years or older ($P = 0.082$)

In the HSCT group, no statistically significant difference was seen in GFFS at eight years (100.0% in 40 years or older vs. 68.2 ± 6.5% in younger group, $P = 0.066$). Patients 40 years or older had younger donors than other

patients (median donor age [range] of 23 [16–53] versus 46 [10–63], $P = 0.007$). The proportion of donors less than 30 years old for adults ≥ 40 years was also significantly higher (70.0 vs. 25.8%, $P = 0.005$).

Evaluations in live patients

At the last follow up, 54 patients (83.1%) who received HID HSCT had a complete recovery of blood counts to within the normal range, and only 13 cases (38.2%) in the IST cohort had normal blood counts ($P < 0.001$). Patients in the HSCT group also achieved a higher KPS score than those in the IST group (100 [20–100] vs. 90 [20–100], $P = 0.002$).

Discussion

Recent efforts to optimize conditioning regimens and graft manipulation have greatly improved HID-HSCT for SAA [12–18]. Economic conditions allowing either IST or HID HSCT and unavailability of horse ATG for patients in China were also weighed. To the best of our knowledge, this is the first study to compare the outcomes of SAA adults treated with IST or HID HSCT.

Consistent with our previous experience [30], SAA adults showed stable engraftment and satisfactory survival after HID HSCT. Our retrospective study focusing on adults presented a CI of neutrophil engraftment of 98% and a 3-year FFS of 83.5% [30]. Various conditioning regimens have been applied in SAA patients in recent years [12–15, 31, 32]. Gao *et al*. reported on a multicenter cohort of SAA HID-HSCT recipients showing a primary GF rate of 3.8% and an OS rate of 84.6% in adults using fludarabine (Flu), Cy and ATG [14]. Haploidentical transplantation using post-graft Cy after conditioning with Flu, Cy and TBI also produced sustainable engraftment in 75% (6/8) and survival in 62.5% (5/8) of adults [15]. Another study on adult SAA by Kim *et al*. indicated a survival rate of 48.2% following HID HSCT with Bu/Flu/ATG [31]. As stated previously, stable engraftment in our data is attributed to an intensive regimen adding Bu, a combined graft of BM and PB, and potent GvHD prophylaxis [12].

Another area of concern in haploidentical transplantation is the incidence of GvHD. Previous studies on SAA adults following HID HSCT described incidences of II–IV aGvHD and III–IV aGvHD ranging from 12.0 to 38.5 and 0 to 15.4%, respectively [14, 15, 31]. Similarly, the incidences of II-IV and III-IV aGvHD in our current cohort were 25.0 and 10.5%. Our unpublished analysis also revealed a trend of lower acute GvHD among adults in comparison with children. We found that donors for adult patients were younger and verified that younger donors might be associated with lower incidence of GvHD [33]. GFFS, a composite indicator, remains promising with a probability of 72.4% in the BMT cohort. Additionally, most GvHD was controlled and sublethal.

For IST, horse ATG was proven superior to rabbit ATG [9]. However, standard IST including horse ATG was unavailable in China. Currently, the response rate to initial IST was only 40.5% (15/37) at 3 months, which increased to 65.6% (21/32) at 6 months, similar with results reported by others. The overall response was described as 50–70% by Bacigalupo *et al*. in a large-size cohort [6]. In a recent study on eltrombopag added to standard immunosuppression, the overall response rate was more than 80% at 6 months and the survival rate reached 97% at a median follow up of 2 years [26]. However, outcomes of survival with response (FFS) were not shown in this study. Several published studies have reported FFS to be much more comprehensive, since long-term complications in IST, graft failure and secondary malignancy in HSCT must be considered [2, 34, 35]. The FFS was unsatisfactory in our IST cohort, with an estimated 8-year FFS of 38.5%. Although CR criteria was slightly different in various studies [2, 22, 26], this did not affect overall response evaluation and FFS.

Recommendations vary based on age category [1, 3] as mortality post-transplantation increased with age, especially for those older than 40 years [35, 36]. In the current comparison, we demonstrate a better FFS of haploidentical transplantations compared to IST in adult SAA patients under 40 years of age. Unlike the results of previous studies showing a disadvantage of HSCT over IST in patients older than 40 years [35], a trend of higher FFS was also observed in older adults in our study. The possible reasons are as follows: first, older adults undergoing HSCT in our cohort had good performance status with a median ECOG of one; second, early HSCT avoided multiple transfusions and preserved organ function; third, older adults in our report had younger donors, and younger donors were associated with improved outcomes because of better hematopoiesis and immunity [33]. Lastly, our regimen might be well-tolerated in older patients and overcome negative effect of age.

In addition to superior FFS, complete recovery of hematopoiesis and performance status are also obvious advantages of transplantation. It is well known that IST often results in amelioration of cytopenia rather than a cure [2, 34]. In our data, the majority of patients (83.1%) receiving transplantation achieved normal blood counts with stable full-donor chimerism. In contrast, poor performance status was found in IST cases, probably associated with prolonged cytopenias and only partial remissions.

Although 15 subjects were reported previously, the follow-up was updated in the present study, with a distinct study objective. Our retrospective study does have characteristic limitations. First, there may be a selection bias

between the two groups. Second, it is difficult to fully interpret the overall conclusions due to practice differences among treatment groups in the two different transplantation centers. Third, the number of older adults in the two groups was low for a definite conclusion and further prognostic analysis. Finally, yet importantly, results might have been different in non-Asian populations.

In summary, we show that adults with SAA undergoing early HID HSCT have better FFS than those who underwent IST using rabbit ATG. Our unified HID HSCT regimen has proven to have excellent survival and engraftment along with low incidence of GvHD. Hence, we believe that the role of the haploidentical donor for SAA adults should be re-evaluated as an appropriate treatment option. Further prospective multicenter research is required to confirm this.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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