



Haploidentical transplantation and posttransplant cyclophosphamide for treating aplastic anemia patients: a report from the EBMT Severe Aplastic Anemia Working Party

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Abstract

In the absence of an HLA-matched donor, the best treatment for acquired aplastic anemia patients refractory to immunosuppression is unclear. We collected and analyzed data from all acquired aplastic anemia patients who underwent a haploidentical transplantation with posttransplant cyclophosphamide in Europe from 2011 to 2017 ($n = 33$). The cumulative incidence of neutrophil engraftment was 67% (CI_{95%}: 51–83%) at D +28 and was unaffected by age group, stem cell source, ATG use, or Baltimore conditioning regimen. The cumulative incidence of grades II–III acute GvHD was 23% at D +100, and limited chronic GvHD was 10% (0–20) at 2 years, without cases of grade IV acute or extensive chronic GvHD. Two-year overall survival was 78% (64–93), and 2-year graft-versus-host disease-free survival was 63% (46–81). In univariate analysis, the 2-year OS was higher among patients who received the Baltimore conditioning regimen (93% (81–100) versus 64% (41–87), $p = 0.03$), whereas age group, stem cell source, and ATG use had no effect. Our results using unmanipulated haploidentical transplantation and posttransplant cyclophosphamide for treating refractory AA patients are encouraging, but warrant confirmation in a prospective study with a larger number of patients and longer follow-up.

Introduction

About 30% of patients with severe aplastic anemia (SAA) treated with standard immunosuppressive treatment (IST) who lack a human leukocyte antigen (HLA)-matched sibling donor might be refractory [1, 2], and 30 to 60% may eventually relapse [2]. Allogeneic hematopoietic stem cell transplantation (HSCT) is the sole curative option; however, this choice depends on the patient's eligibility to undergo HSCT and the availability of an HLA-matched unrelated

donor (MUD) [3]. Strategies for transplant-eligible patients without an HLA-matched donor remain unsatisfactory.

Most refractory patients will remain unresponsive to second-line treatments and are at risk of life-threatening complications [4]. Eltrombopag provides hematological improvement to nearly 40% of refractory patients [5–7], and less than 30% respond to another cycle of IST [8, 9]. Furthermore, clonal evolution to myelodysplastic syndromes and acute myeloid leukemia are more frequent among refractory patients [10, 11] and are associated with a dismal prognosis.

HSCT using alternative sources (mismatched unrelated, cord blood, or haploidentical) may be curative and reduce the risk of clonal evolution. However, the risks of graft failure, severe infectious complications, and graft-versus-host disease (GvHD) might be higher than in transplantations using HLA-matched donors [3].

Nevertheless, the number of HSCTs using alternative donors for treating SAA patients has increased in Europe. In particular, the use of haploidentical donors leaped from six

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in 2007 to 58 in 2016 [12], especially with posttransplant cyclophosphamide (PTCy) as GvHD prophylaxis. Cyclophosphamide seems to deplete donor's expanding alloreactive T cells between day +3 and day +4, reducing GvHD incidence and improving engraftment [13]. Yet few studies addressed this strategy in aplastic anemia (AA), and most are pediatric.

Here, we report the outcomes of SAA patients who underwent an unmanipulated haploidentical transplantation with PTCy in European Society for Blood and Bone Marrow Transplantation (EBMT) centers.

Methods

Study population and definitions

We extracted patient information from the EBMT ProMise database. We included all consecutive patients from 2010 to 2017 that fulfilled the three inclusion criteria: (a) diagnosis of acquired AA; (b) who received a mismatched-related donor transplantation; and (c) PTCy. Informed consent for transplantation was obtained according to European regulations and the Helsinki Declaration. The Severe Aplastic Anemia Working Party (SAA WP) scientific council approved this study. By EBMT guidelines, the SAA WP Data Office collected and analyzed data.

Definitions

The definitions used for data entry in the EBMT database are described elsewhere [14]. We classified patients younger than 18 years as pediatrics. Full donor chimaerism consisted in 95% cells of donor's origin; mixed chimaerism consisted in cells from both donor and recipient's origin; autologous reconstitution consisted in cells of recipient's origin; aplasia consisted in insufficient cells to measure chimaerism. The source of cells for chimaerism measurement was not available for this cohort. GvHD-free/relapse-free survival (GRFS) was defined as being alive without AA, acute GvHD (aGvHD) III/IV, extensive chronic GvHD (cGvHD) and graft loss [15]. GvHD-free survival (GFS) was defined as being alive without aGvHD grades III and IV, and no limited or extensive cGvHD. Neutrophil engraftment was defined as the time by which the absolute neutrophil count was $>0.5 \times 10^9/\text{L}$ for 3 consecutive days, and platelet engraftment as a platelet count $>20 \times 10^9/\text{L}$ or $>50 \times 10^9/\text{L}$ for seven consecutive days without transfusion support. The Baltimore conditioning regimen consisted of fludarabine 30 mg/m^2 IV daily from day -6 to day -2 (total dose: 150 mg/m^2), cyclophosphamide 14.5 mg/kg IV daily from day -6 to day -5 (total dose: 29 mg/kg) and total body irradiation (TBI) of 200 cGy on day -1 [13]. Cyclophosphamide was given at a dose of 50 mg/kg

at D +3 and +4. We were unable to collect information regarding donor-specific antibodies. We did not evaluate the effect of graft cellularity on outcome variables due to insufficient data for 11 patients. Information about ABO matching was unavailable for the majority of patients and was therefore not included. We did not include patients who received combined peripheral blood (PB) and bone marrow grafts in comparisons of outcome variables stratified by stem cell source.

Statistics

We presented continuous variables as medians and range, and categorical variables as counts and percentages, and used the Fisher exact test for comparisons. Overall survival (OS), GFS and GRFS were calculated using the Kaplan–Meier product limit estimation method, and differences in subgroups were assessed by the log-rank test.

Median follow-up was determined using the reverse Kaplan–Meier method. Competing risks analyses were separately applied to estimate the incidences of aGvHD, cGvHD, neutrophil, and platelet engraftment. For each of the outcomes, the competing events were no engraftment, graft loss, relapse, second transplant, and death. Events for GRFS calculation were grade III–IV aGvHD, extensive cGvHD, no engraftment, graft loss, relapse, second transplant, and, death. Subgroup differences in competing risks analyses were assessed using the Gray's test. OS, GFS, GRFS and cGvHD were evaluated at 2 years. Two-year outcomes were of specific interest; after 2 years, 17 patients were lost to follow-up. Estimates were provided at 12 months if the number of patients at risk in any of the subgroups being compared dropped below five by 24 months. Acute GvHD, platelet, and neutrophil engraftment endpoints were evaluated by day +100. All estimates were reported with 95% confidence intervals (CI_{95%}). We did not include patients who received combined PB and bone marrow grafts in comparisons of outcome variables stratified by stem cell source. All *p*-values were two-sided and *p* < 0.05 was considered significant. Statistical results were reported following the EBMT statistical guidelines [16]. Statistical analyses were performed using the SPSS software, version 22 (SPSS Inc., Chicago, IL) and R statistical platform, version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) using packages 'prodlm', 'survival', and 'cmprsk'.

Results

Patient, disease, and transplant characteristics

We identified and analyzed the total of 33 patients that fulfilled the inclusion criteria. Data were complete on all

Table 1 Patients characteristics.

Characteristics	Total cohort
Number of patients	33
Age at transplantation, median (range)	20.4 (2.5–45.4)
Pediatric, <i>n</i> (%)	13 (39.4)
Adult, <i>n</i> (%)	20 (60.6)
Male (%)	24 (72.7)
Disease classification at diagnosis (%)	
Nonsevere	2 (6.7)
Severe	16 (53.3)
Very severe	12 (40.0)
Missing	3
Previous ATG-based immunosuppression	22 (96)
Upfront transplant	1 (4)
Missing	10
Previous transplantation	5 (15.2)
Previous transfusions (%)	
<20 units	9 (45.0)
20–50 units	7 (35.0)
>50 units	4 (20.0)
Missing	13
Clonal evolution (%)	2 (6)
MDS	1 (3.0)
PNH	1 (3.0)

MDS myelodysplastic syndromes, *PNH* paroxysmal nocturnal hemoglobinuria

variables of interest for 26 individuals (78.7%). Thirty-two patients (97%) underwent at least one previous line of treatment (Table 1). Three patients received the haploidentical transplantation following a relapse after a previous transplant, and two patients after two transplantations. Four of these five previously transplanted patients had received transplants from a MUD. One patient had undergone two transplantations with a same haploidentical donor, but without PTCy (therefore not included in this study); a different haploidentical donor and PTCy were used for the third transplantation.

The median interval from diagnosis to transplant was 9.3 (1.9–201.2) months. One patient, diagnosed in 1998 with nonsevere AA, was treated with IST in 2013 because of disease progression, and subsequently transplanted the following year.

Donor and transplant characteristics are presented in Table 2. Two patients received a combined PB and bone marrow (BM) graft, but there is not enough information to specify whether it was part of a protocol. Five of the 12 patients transplanted with BM grafts for whom this information was available received less than 3×10^8 TNC/kg. Seven patients (21.2%) received a myeloablative conditioning

Table 2 Transplant characteristics.

Characteristics	Total cohort (%)
Mismatched-related donor	33 (100)
Father	12 (37.5)
Mother	11 (34.4)
Brother	5 (15.6)
Sister	3 (9.4)
Cousin	1 (3.1)
Missing	1
Donor age, median (range)	39 (14.2–69.3)
Donor/recipient gender	
Match	17 (51.5)
Male to female	5 (15.2)
Female to male	11 (33.3)
Donor/recipient CMV status	
neg/neg	5 (16.7)
neg/pos	3 (10.0)
pos/pos	15 (50.0)
pos/neg	7 (23.3)
missing	3
Stem cell source	
BM	17 (51.5)
PB	14 (42.5)
BM and PB	2 (6.0)
Graft cellularity per recipient kg, median (range)	
BM ($TNC \times 10^8$)	3.5 (0.8–240)
PB ($CD34^+ \times 10^6$)	7.1 (4.5–619)
Conditioning regimen (%)	
Baltimore	16 (48.5)
other	17 (51.5)
TBI	20 (60.6)
ATG	10 (30.3)
GvHD prophylaxis, besides PTCy	
Calcineurin inhibitor	31 (93.9)
MMF	29 (87.9)
Year of transplantation, median (range)	2015 (2010–2017)

We did not evaluate the effect of graft cellularity on outcome variables due to insufficient data

BM bone marrow, *PB* peripheral blood, *TNC* total nucleated cells, *TBI* total body irradiation, *ATG* antithymoglobulin, *GvHD* graft-versus-host disease, *PTCy* posttransplant cyclophosphamide, *MMF* mycophenolate mofetil

and Baltimore was the most frequently used reduced-intensity conditioning regimen. Ten patients received in vivo T-cell depletion with antihuman thymocyte immunoglobulin (ATG) and none with alemtuzumab.

One 21-year-old man with very severe AA received an upfront haploidentical transplantation in 2016. He was transplanted from his 24-year-old brother 1.9 months after

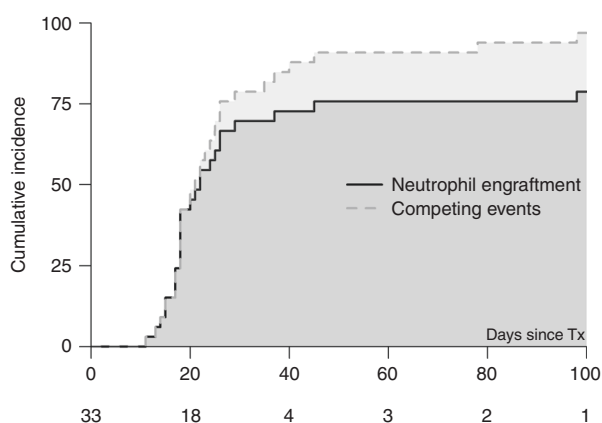


Fig. 1 Stacked cumulative incidence of neutrophil engraftment. The area between the curves indicates the probability of having one of the corresponding events; the dark gray area indicates neutrophil engraftment and the light gray area the competing events: no engraftment, graft loss, relapse, second transplant and death.

diagnosis, with a T-replete PB graft, and received Baltimore conditioning, PTCy, cyclosporin, and mycophenolate mofetil (MMF) as GvHD prophylaxis. He engrafted with full donor chimaerism, and was alive and GvHD-free at last follow-up (15.9 months).

Hematological recovery and engraftment

The cumulative incidence of neutrophil engraftment was 67% (CI_{95%}: 51–83) at D +28 and 79% (65–93) at D +100 (Fig. 1). The median time for neutrophil engraftment was 22 days (CI_{95%}: 18–26, range 11–98). Age group, stem cell source, conditioning regimen, and ATG use did not affect engraftment by day +28 (Table 3).

The cumulative incidences of platelet engraftment $20 \times 10^9/L$ (Fig. 2a) and $50 \times 10^9/L$ were 42% (26–59) and 14% (1–26) at D +28, 64% (47–80%) and 45% (27–63) at D +100, respectively. In univariate analysis, PB grafts yielded a higher $50 \times 10^9/L$ engraftment (75% (51–99)) than BM grafts (25% (4–46%)) $p = 0.011$ by D +100 (Fig. 2b), but no significant difference was seen for $20 \times 10^9/L$. Five patients were excluded from the former comparison: two because of combined marrow and PB grafts and three because of missing data on platelet $50 \times 10^9/L$ engraftment.

Information about chimaerism was available for 24 patients: 15 full donor, four mixed, two graft losses after successful engraftment, two autologous reconstitutions without significant hematological improvement, and one aplasia. From the entire cohort, seven patients failed to engraft (Table 3); four died and three were salvaged with another transplant. Four patients lost the graft—all before 5 months after transplantation—and one subsequently died.

Table 3 Transplant outcomes ($n = 33$).

Characteristics	<i>n</i>	Neutrophil engraftment % (CI _{95%})	<i>p</i>	Failure (<i>n</i>)	Loss (<i>n</i>)	2-year GFS % (CI _{95%})	<i>p</i>	2-year GRFS % (CI _{95%})	<i>p</i>	2-year OS % (CI _{95%})	<i>p</i>
Age group											
Pediatric	13	69 (44–94)	0.94	4	2	66 (38–94)	0.34	55 (25–84)	0.49	92 (78–100)	0.12
Adult	20	65 (44–86)		3	2	52 (29–75)		68 (48–89)		69 (49–90)	
Stem cell source											
Bone marrow	17	65 (42–87)	0.34	4	3	48 (22–74)	0.32	57 (31–83)	0.22	82 (63–100)	0.75
Peripheral blood	14	79 (57–100)		1	1	70 (46–95)		79 (57–100)		79 (57–100)	
T-depletion ^a											
ATG	10	50 (19–81)	0.10	4	2	^a		^a		70 (42–98)	0.40
No ATG	23	74 (56–92)		3	2					82 (66–98)	
Conditioning											
Baltimore	16	69 (46–91)	0.64	2	3	68 (44–91)	0.13	73 (51–96)	0.23	93 (81–100)	0.03
Non-Baltimore	17	65 (42–87)		5	1	50 (25–75)		53 (31–76)		64 (41–87)	

GFS graft-versus-host disease-free survival, GRFS graft-versus-host disease relapse-free survival, OS overall survival

^aEstimates for 2-year GFS and GRFS related to ATG were provided at 12 months because the number of patients at risk in ATG subgroup was inferior to five by 24 months (see text) Among the studied characteristics, only conditioning regimen affected outcome in univariate analysis (highlighted in bold)

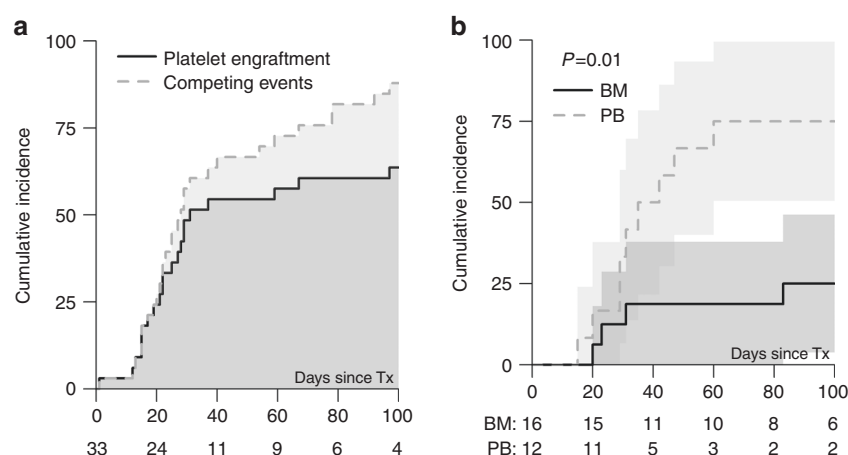


Fig. 2 Cumulative incidence of platelet engraftment. **a** Stacked cumulative incidence of platelet engraftment $20 \times 10^9/L$. The area between the curves indicates the probability of having one of the corresponding events; the dark gray area indicates platelet engraftment and the light gray area the competing events. **b** The cumulative

incidence of platelet engraftment $50 \times 10^9/L$ stratified by stem cell source. The shaded areas indicate the corresponding 95% confidence intervals. The competing events were no engraftment, graft loss, relapse, second transplant, and death.

Graft-versus-host disease

The cumulative incidence of aGvHD grades II–III was 23% at D +100 (Fig. 3); there were no reported cases of grade IV and grading was missing for two patients. The two-year cumulative incidence of limited cGvHD was 10% (0–20); there were no reported cases of extensive cGvHD. All cGvHD events reported here occurred before 2 years.

One- and 2-year GFS were 62% (45–79) and 58% (40–76), respectively. In univariate analysis, age group, stem cell source, or Baltimore conditioning results were comparable by 2 years (Table 3). By 1 year, ATG use also had no significant effect on GFS: ATG 40% (10–70), no ATG, 73% (54–92), $p = 0.09$.

GRFS was 63% (46–81) at 1 and 2 years. In univariate analysis, age group, stem cell source, or Baltimore conditioning regimen did not affect GRFS (Table 3). By 1 year, ATG use had no effect on GRFS: ATG 57% (20–94), no ATG 65% (46–85), $p = 0.75$.

OS and mortality

With a median follow-up of 35.9 (24.6–43.0) months, 1 and 2-year OS were 82% (68–95) and 78% (64–93), respectively (Fig. 4a). When stratified by conditioning regimen, Baltimore yielded a higher 2-year OS (93% (81–100)) when compared with nonBaltimore regimens (64% (41–87), $p = 0.03$) in univariate analysis (Fig. 4b). Age group, stem cell source, or ATG use did not affect 2-year OS (Table 3). In total, seven patients died within the first 2 years after haploidentical transplantation: five of infection, one of PTLT,

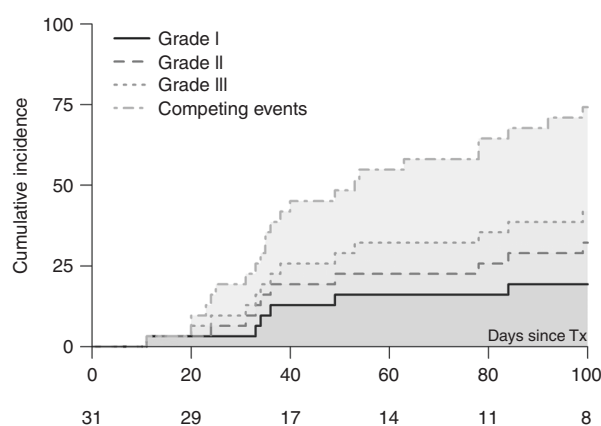


Fig. 3 Cumulative incidence of separate aGvHD grades. The probabilities correspond to the area under the curve between two different lines: at day +100, CI of grade I: 19% (CI_{95%}: 5–33), grade II: 13% (1–25), and grade III: 10% (0–20%). Competing events are no engraftment, death, relapse/graft loss, and second transplant and reached 32% (16–49).

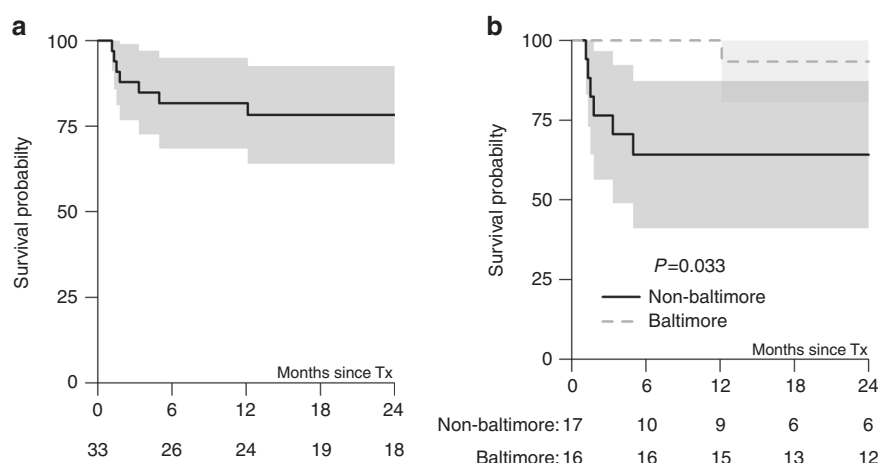
and the other of transplant-related toxicity. Another patient died of infection 39 months after transplantation.

Discussion

This is the largest multicentric cohort reporting the outcomes of haploidentical transplantation using unmanipulated graft and PTCy for refractory SAA patients. We report good neutrophil engraftment and survival, low incidence of acute and cGvHD without any severe cases, and an acceptable GRFS.

Fig. 4 Overall survival.

a Kaplan–Meier survival curves of the overall survival of the entire cohort and **b** OS stratified by Baltimore or nonBaltimore conditioning regimen. The shaded regions indicate the 95% confidence intervals.



The prognosis of refractory SAA patients has improved in the last decades. Five-year OS increased from 23% in the 90 s to 57% ($p < 0.001$) in 2000. This improvement is due to the progress in antifungal therapy [17], and better HLA matching for transplantation from MUD [18, 19]. The best treatment for transplant-eligible refractory patients aged 30 years or less for whom a MUD is available is transplantation [2, 3, 18]. In the absence of a MUD, the best option is not consensual [2]. Still, patients receiving nontransplant treatments face the risks of clonal evolution and chronic transfusions [10, 20]. Alternative donor transplantation might cure and provide a good quality of life; however, nonengraftment, GvHD and infections are concerns.

We report a 2-year OS of 78% in a population with a median age of 20.4 years. By 2 years, pediatric patients presented a 92% OS compared with 69% for adults, but this difference was not significant ($p = 0.12$). Our results compare favorably with the best supportive care and previous retrospective studies using cord blood, mismatched unrelated donors, or haploidentical donors. Unrelated cord blood transplantation provided a 3-year OS of 38% [21]. Using the best predictive factors of the previous report, a phase 2 study found a 1-year OS of 88.5% but nonnegligible GvHD in young patients [22], emphasizing the need of prospective studies. One-antigen mismatched unrelated donors provided a 5-year OS of 57% to 72.7% in retrospective studies [23, 24], and prognosis was worse if more than one mismatch were present [25]; the CI of cGvHD was about 25% in these cohorts. Haploidentical donors seems an acceptable strategy according to other retrospective studies: ex-vivo T-cell depletion provided excellent OS and low GvHD incidence in refractory SAA of pediatric patients, but at the expense of delayed immune reconstitution and considerable viral reactivation [26, 27]; ATG, posttransplant intensified immunosuppression and combined PB and BM grafts provided adequate engraftment and survival [28–34], but nonnegligible GvHD. One multicentric prospective study using the GIAC

strategy found a 3-year OS of 89% with a CI of extensive cGvHD of 10% [35].

We do not report any cases of acute grade IV or extensive cGvHD, nor any deaths related to GvHD. Our results are in alignment with previous reports of unmanipulated haploidentical transplantation with PTCy: one study with 16 patients reported a 1-year OS of 67.1% with three patients presenting grade II–IV aGvHD [36]; another study with eight patients reported six engraftments and no severe aGvHD [37]. In both, all patients received the Baltimore conditioning regimen. Adding ATG to this regimen, a phase 2 study reported all 16 patients receiving alternative transplantation—13 haploidentical—alive and off immunosuppression by 21 months [38].

In our study, patients conditioned with the Baltimore regimen presented a better OS than the heterogeneous group of nonBaltimore regimens (2-year OS of 93% vs. 64%, respectively, $p = 0.03$) that comprised 41% of myeloablative conditioning. Deaths occurred mostly early after transplantation in the nonBaltimore group, likely because of toxicity. The combination of fludarabine and cyclophosphamide is currently the backbone for conditioning alternative donor transplantations in SAA patients [22, 39]. The inclusion of low-dose TBI seems to reduce the risk of rejection without prohibitive toxicity [40, 41].

We did not identify the benefit of ATG in reducing GvHD and improving survival reported in sibling or unrelated donor transplants [41, 42]. We saw less engraftment among patients treated with ATG; although suggestive, this difference was not significant.

We did not confirm the expected lower incidence of GvHD with BM grafts in SAA patients [43, 44]; we found no stem cell source effect on GvHD or survival. The use of PB grafts was associated with better platelet engraftment. Though missing data on cellularity precludes firm conclusions, we speculate that the number of infused cells might have influenced. No patients transplanted with a PB graft

received a dose inferior to recommendations, whereas about 30% (5/17) of BM did [45, 46].

We acknowledge that the sample size precluded multivariate analyses and reduced power. Other limitations were the lack of data concerning donor-specific antibodies, ABO matching, and chimaerism, and the retrospective nature of this study.

In conclusion, we confirm the encouraging initial results of unmanipulated haploidentical transplantation using the Baltimore conditioning regimen and PTCy for refractory SAA patients. We found that 63% of the overall patients and 73% of those treated with the Baltimore regimen were alive, transfusion-independent, and without severe GvHD 2 years later. We could not find any stem cell source effect on survival in this cohort; the impact of ATG and patient's age in haploidentical transplantation with PTCy for SAA needs to be measured in a larger population. We plan to conduct a prospective phase two trial using the Baltimore conditioning to confirm the safety and efficacy of haploidentical transplantation with PTCy for treating relapsed or refractory SAA patients.

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Author contributions PHP, RPL, CD and AR planned this study. PHP, DJE and RPL wrote the paper with support of GS. PB was responsible for data collection and processing. DJE performed statistical analyses. All authors provided critical feedback and helped shape the research, analyses, and paper.

Compliance with ethical standards

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

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