Haploidentical hematopoietic stem cell transplantation in aplastic anemia: a systematic review and meta-analysis of clinical outcome on behalf of the severe aplastic anemia working party of the European group for blood and marrow transplantation (SAAWP of EBMT)

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REVIEW ARTICLE

Haploidentical hematopoietic stem cell transplantation in aplastic anemia: a systematic review and meta-analysis of clinical outcome on behalf of the severe aplastic anemia working party of the European group for blood and marrow transplantation (SAAWP of EBMT)

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Abstract

Aplastic anemia (AA) is a serious hematological disorder, which is solely cured by hematopoietic stem cell transplantation (HSCT). Haploidentical HSCT is an emerging modality with encouraging outcomes in several blood conditions. The present study aims to comprehensively assess the feasibility and safety of haploidentical HSCT in patients with severe and very severe AA. It is a systematic review and meta-analysis of studies related to haploidentical stem cell transplantation in idiopathic AA investigating rates of successful engraftment, acute graft-versus-host disease (aGvHD), chronic GvHD (cGvHD), transplant-related mortality (TRM), and posttransplantation viral infections (including cytomegalovirus [CMV]) in patients with AA. The effects of reduced-intensity conditioning (RIC) and nonmyeloablative conditioning (NMA), as well as various GvHD prophylaxis regimens on these outcomes were evaluated. In total 15 studies were identified, (577 patients, 58.9% males), successful engraftment was observed in 97.3% of patients (95% CI, 95.9–98.7) while grades II–IV aGvHD and cGvHD were reported in 26.6% and 25.0%, respectively. The pooled incidence of TRM was 6.7% per year (95% CI, 4.0–9.4). RIC regimens were associated with higher proportions of successful engraftment (97.7% vs 91.7%, $P = 0.03$) and aGvHD (29.5% vs 18.7%, $P = 0.008$) when compared with NMA regimens with no differences in cGvHD or mortality incidence. When compared with methotrexate-containing regimens and other regimens, posttransplant cyclophosphamide-containing regimens reduced the rates of aGvHD (28.6%, 27.8%, and 12.8%, respectively, $P = 0.02$), CMV viremia (55.7%, 38.6%, and 10.4%, respectively, $P < 0.001$), and CMV disease in initially viremic patients (2.1%, 33.0%, and 0%, respectively, $P < 0.001$). We have concluded that Haploidentical HSCT was associated with promising outcomes in terms of successful engraftment and reduced complications. Future prospective trials are needed to identify the preferred conditioning regimen, GvHD prophylaxis, and graft source in the setting of haploidentical transplant for AA.

Introduction

Aplastic anemia (AA) is a rare, serious condition characterized by chronic primary hematopoietic (bone marrow (BM)) failure secondary to the absence of hematopoietic precursors. The first case was published in 1888 by Ehrlich [1] while the typical clinical features were identified later in the early twentieth century [2]. The incidence of AA ranges from 0.6 to 7 cases per million population/year and it occurs in all age groups with a slightly higher incidence in childhood as compared with other age groups [3, 4]. The

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presence of pancytopenia and hypocellular BM is a preliminary indication of AA, yet other mimicking conditions, such as infectious, inherited, lymphoproliferative, and toxin-related causes should be excluded prior to definitive diagnosis of acquired AA.

The frontline management of AA depends on the severity of the disease, donor availability, and patient's age. In children and young adults (≤40–50 years) who have a matched sibling donor (MSD) the preferable frontline approach is hematopoietic stem cell transplantation (HSCT). In patients aged >40–50 years or those without an MSD, combination immunosuppressive therapy (IST) using horse antithymocyte globulin (ATG) and cyclosporine A (CsA) is indicated. Besides, there is a growing body of evidence regarding the addition of eltrombopag to frontline IST in order to improve patients' outcomes (particularly in those with refractory severe aplastic anemia [SAA]) [5–7]. Alternate donor transplant is indicated in eligible young patients who fail IST (relapse or develop clonal disorders) [8, 9]. The preferred alternate donor source in the absence of an MSD is a matched unrelated donor (MUD). In the absence of an MUD, haploidentical family donors offer the advantage of immediate availability for almost any patient and an acceptable cell dose as compared with cord blood stem cells. The bidirectional alloreactivity in the setting of haploidentical HSCT (haploHSCT) can lead to graft-versus-host disease (GvHD) or graft rejection and represents a major drawback of haploHSCT [10]. Furthermore, several infectious complications have been reported, primarily due to delayed immune reconstitution [11]. However, over the past decade significant progress has been achieved by using haploHSCT to treat hematological malignancies [12, 13]. This achievement is attributable to the improvement in supportive care, and most importantly to the graft engineering using selective T-cell depletion in vivo and in vitro. With these advances, haploHSCT has become a viable alternative in the absence of MSD or MUD [14, 15]. However, the published literature about the use of haploHSCT for AA suffers from limited number of patients and heterogeneity of transplant strategy as far as conditioning, stem cell source and GvHD prophylaxis [16–19]. As such, we performed a systematic review and meta-analysis to achieve a comprehensive and analytical insight into the feasibility and safety of haploHSCT in patients with AA.

Methods

The recommendations of the Preferred Reporting Items for Systematic reviews and Meta-analyses statement [20] were used to formulate and outline the present systematic review and meta-analysis eligibility criteria.

All prospective or retrospective studies investigating AA patients who received haploidentical HCST treatment were eligible. Patients were diagnostically confirmed with SAA or very severe aplastic anemia [VSAA] based on the definition implied by the International Aplastic Anemia Study Group [21]. The authors of the included studies were required to provide a detailed description of the conditioning regimen used, GvHD prophylaxis, and the indication to undergo haploidentical HCST. Comparative investigations of haploidentical and other BM transplantation therapies were only considered for inclusion if they provided sufficient details about the outcomes of haploHSCT grafts. Studies were excluded if they recruited less than ten patients, were written in non-English language, or were not published in a peer-reviewed journal. In addition, systematic reviews, case reports, and letters to the editors were ineligible.

Types of outcomes measures

The primary outcomes were rates of successful engraftment, acute GvHD (aGvHD) grades II–IV, and chronic GvHD (cGvHD) as well as the incidence of transplant-related mortality (TRM) during the study period. Successful neutrophil engraftment was defined as an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L lasting for 3 consecutive days post transplantation. GvHD classification was based on the relevant international criteria [22, 23]. TRM was the incidence of death without disease progression.

Posttransplantation complications were deemed secondary outcomes in the current meta-analysis. These included regimen-related toxicity (RRT), as assessed using the Seattle Toxicity Criteria [24], posttransplant lymphoproliferative disease (PTLD), and hemorrhagic cystitis (HC). In addition, cytomegalovirus (CMV) viremia and Epstein–Barr virus viremia (EBV), which occurred in ≤100 days post transplantation, were considered.

Search strategy

The following databases were searched for eligible studies by two independent authors: PubMed, Scopus, Embase, and Google Scholar. The last access to these databases was on July 10, 2019, whilst eligible studies were not to be published earlier than 2010. The search process was implemented using specific keywords and combined using the Boolean operators "AND" and "OR." Additional studies were identified from the bibliographies of screened articles as appropriate.

Study selection and data collection

Initially, the authors screened the titles and abstracts of the obtained records, which were uploaded to a specific

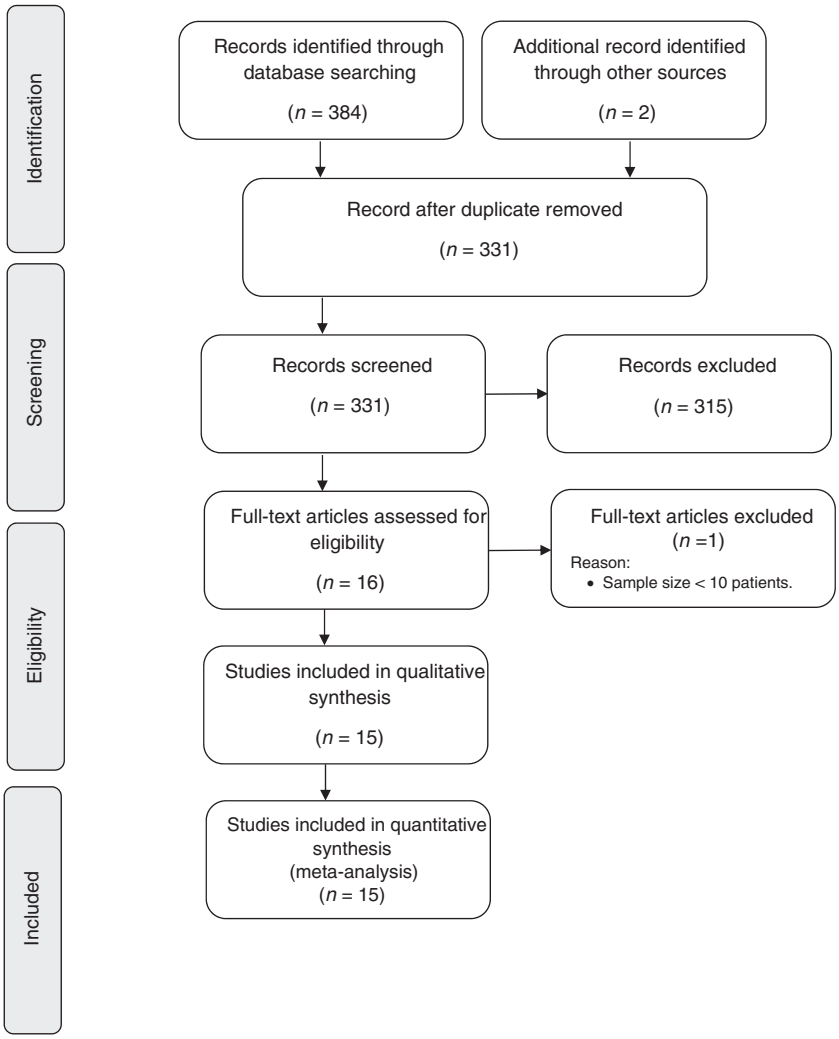

Fig. 1 A flow diagram depicting the search process used in this study.

reference-organizing software (Endnote v.X7) and duplicate records were omitted. Subsequently, the full-text versions of eligible studies were assessed for formal inclusion and any disagreement in the decisions about inclusion was resolved by consensus. Data extraction was performed in a predesigned Microsoft Excel Spreadsheet to collect the following data: (1) study data: last name of the first author, year of publication, country, and study duration (months); (2) patients' data: number of patients, median and range of age, and gender distribution; (3) graft source (BM, peripheral blood stem cells [PBSCs], or combined BM and PBSC); (4) conditioning regimens; (5) GvHD prophylaxis regimens; (6) primary outcomes: rates of successful engraftment, aGvHD II–IV, cGvHD (including frequency of patients with extensive and limited cGvHD), and TRM (incidence of mortality, causes of mortality, and median follow-up of patients); (7) secondary outcomes: rates of RRT, CMV viremia, EBV viremia, PTLD, and HC. Conditioning regimens were classified into reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) regimens as described previously [25].

Quality assessment

The methodological quality of the studies included was assessed using the Newcastle–Ottawa Scale (NOS) tool [26]. Using NOS criteria, quality assessment was performed by using eight items allocated to three main categories: selection (score 4), comparability (score 2), and outcomes assessment (score 4). However, the "comparability" category was omitted since the studies included did not contain comparative groups or at least haploHSCT group was solely considered. Therefore, each study was assigned a total score of 8, and a score ≥5 indicated a high-quality study.

Statistical analysis

All statistical tests were carried out using the RevMan 5.3 software. The incidence of TRM per year was computed from the incidence of mortality during the whole study period and the median follow-up time. Both TRM incidence and standard errors (SE) were calculated as described earlier

[27]. The rates of other primary and secondary outcomes were calculated using the formula: number of incident events/total sample size, whereas SE of sample proportions were computed using SE = sqrt $[p(1-p)/n]$, where "p" indicates proportion and "n" indicates sample size. Analysis was performed using the generic inverse variance method and a 95% confidence interval (CI) to yield pooled proportions. Statistical heterogeneity was assessed using the I^2 test, where the in-between study heterogeneity was considered significant at $I^2 > 50\%$. A fixed-effects model or a random-effects model was applied when there was a nonsignificant or significant heterogeneity, respectively. Subgroup analysis was performed based on conditioning and GvHD prophylaxis regimens. Statistical significance was considered at $P < 0.05$.

Results

Outcomes of the search process

The initial search yielded a total of 384 records across all databases, from which 55 duplicates were detected and deleted. In addition, two studies were identified from Google Scholar. Hence, 331 records were screened for eligibility. The full-text of 16 studies were thoroughly checked for inclusion. However, one study was excluded due to small sample size ($n = 6$) [28]. Ultimately, 15 studies were included in the qualitative and quantitative analysis (Fig. 1).

Characteristics of the included studies

Table 1 summarizes the characteristics of the included studies. In general, the included studies were published between 2013 and 2019 with a total durations of follow-up ranging from 36 to 136 months. ONE study was conducted in the United States [29], one in the United Kingdom [16], one in Brazil [19], two in Korea [17, 30], while others were conducted in China. Seven studies retrieved patients' data from registries/records [16, 19, 31–35], whereas the other studies employed a prospective follow-up design. NMA regimens were used in six (40%) studies [16, 19, 29, 36–38] and the remaining studies used RIC regimens. The authors added PTCy to GvHD prophylaxis regimens in three studies [16, 19, 29] and methotrexate (MTX) in eight studies [31, 32, 34–36, 38–40]. In a total of 577 patients (58.9% males, 20.1% with VSAA), BM-derived grafts were used in 93 patients (16.1%), PBSCs in 84 patients (14.6%), and combined BM and PBSC in 400 patients (69.3%).

Engraftment

The pooled rate of successful engraftment following haploHSCT was 97.3% (95% CI, 95.9–98.7) without heterogeneity among the included studies ($I^2 = 0\%$, Fig. 2). RIC regimens were associated with a significantly higher proportion of engraftment compared with NMA regimens (97.7% vs 91.7%, respectively, $P = 0.03$). There was no significant difference in the rates of engraftment between the different GvHD prophylaxis regimens ($P = 0.35$), though the addition of posttransplant Cy (PTCy) yielded a relatively lower engraftment rate (91.2%) when compared with MTX-containing (97.7%) or other regimens (97.3%, Fig. 2).

aGvHD II–IV and cGvHD

Among engrafted patients, the overall rate of aGvHD II–IV was 26.6% (95% CI, 23.0–30.1, $I^2 = 42\%$, Fig. 3). Interestingly, the incidence of aGvHD II–IV was lower when NMA conditioning regimens (18.7% vs 29.5% for RIC conditioning, $P = 0.008$) and PTCy-containing GvHD prophylaxis regimens were used (12.8% vs 28.6% for MTX-containing regimens and 27.8% for other regimens, $P = 0.02$).

The rate of cGvHD was 25.0% (95% CI, 18.9–31.1) with a significant heterogeneity between studies ($I^2 = 63\%$, Fig. 4). There was no difference in the incidence of cGvHD using different conditioning regimens and GvHD prophylaxis. Similarly, the incidence of extensive cGvHD (pooled rate was 5.6%, 95% CI, 3.1–8.1) was not affected by using different regimens.

Transplantation-related mortality

The pooled incidence of TRM per year after haploHSCT was 6.7% (95% CI, 4.0–9.4, $I^2 = 24\%$, Fig. 5). TRM was not affected by conditioning regimens (5.3% and 11.8% per year for RIC and NMA regimens, respectively, $P = 0.15$). Likewise, the impact of GvHD prophylaxis was not apparent although the use of PTCy led to a relative, but nonsignificant, increase in the incidence of mortality per year (27.9%) as compared with MTX addition (6.5%) and other regimens (5.6%, $P = 0.06$).

Post-transplantation complications

Table 2 summarizes the rates of posttransplantation complications after haploidentical HSCT. Using a random-effects model ($I^2 = 76\%$), the pooled proportion of RRT was 6.2% (95% CI, 1.0–11.3) following transplantation. However, RRT incidence was not impacted by conditioning or anti-GvHD regimens. Similarly, the rates of HC (21.6%, 95% CI, 8.3–34.8, $I^2 = 84\%$) were not different among patients who received different conditioning and GvHD prophylaxis regimens.

CMV viraemia was detected in 44.3% of patients (95% CI, 25.0–63.7, $I^2 = 97\%$). NMA conditioning regimens were

Table 1 Characteristics of the included studies.

Author	Country	Study duration (months)	Median age (range)	Sample size (% males, % with VSAA)	Conditioning regimen		GVHD prophylaxis regimen		Graft source (BM, PBSC, combined)	NOS
					Category	Details	Category	Details		
Clay et al. [16]	UK	40	32 (19–57)	8 (62.5, 50)	NMA	Cy: 14.5 mg/kg (for 2 days) Flu: 30 mg/m^2 (for 5 days) TBI (low dose, 200 cGy)	PTCy	Cy (high dose, 50 mg/kg for 2 days) CNIs (tacrolimus) MMF: 15 mg/kg (TID)	0, 8, 0	6
DeZern et al. [29]	USA	61	30 (11–69)	16 (62.5, 0)	NMA	Cy: 14.5 mg/kg i.v × 2 Flu: 30 mg/m^2 × 5 r-ATG: 0.5–2 mg/kg × 3 TBI: 200 cGy × 1	PTCy	Cy (high dose, 50 mg/kg i.v × 2) CNIs (tacrolimus) MMF	0, 16, 0	7
Esteves et al. [19]	Brazil	49	17 (5–39)	16 (68.75, 0)	NMA	Cy: 14.5 mg/kg (for 2 days) Flu: 30 mg/m^2 (for 5 days) TBI (low dose, 200–600 cGy)	PTCy	Cy (high dose, 50 mg/kg for 2 days) CNIs (CsA or tacrolimus) MMF: 15 mg/kg (TID)	13, 3, 0	5
Gao et al. [36]	China	42	25.4 (18–41)	26 (42.31, 38.46)	NMA	Cy: 45 mg/kg OD × 2 Flu: 30 mg/m^2 × 4 ATG: 2.5 mg/kg × 4	MTX	CNIs (CsA), MMF, MTX	0, 0, 26	7
Im et al. [17]	Korea	67	13.5 (3.8–21.7)	12 (75, 0)	RIC	Cy: 120 mg/kg + Flu: 150 mg/m^2 + ATG: 7.5 mg/kg Or TBI (low dose, 400 cGy) + Cy: 100 mg/kg + Flu: 150 mg/m^2 + ATG: 7.5 mg/kg	None	CNIs (CsA or tacrolimus) MMF: 15 mg/kg (TID)	0, 12, 0	6
Kim et al. [30]	Korea	108	12.7 (1.4–21.7)	32 (68.75, 37.5)	RIC	Cy: 120 mg/kg Flu: 150 mg/m^2 ATG: 2.5 mg/kg/day TBI (low dose, 400 cGy)	None	CNIs (CsA or tacrolimus) and MMF	0, 32, 0	7
Li et al. [37]	China	72	19 (4–29)	17 (58.82, 0)	NMA	Cy: 500 mg/day Flu: 30 mg/m^2 (for 4 days) ATG: 5 mg/kg/day	None	CD25 monoclonal antibody (20 mg) CNI (CsA): 3 mg/kg/day MMF: 50 mg/day	0, 0, 17	7
Lu et al. [34]	China	48	13 (4–42)	41 (60.98, 31.71)	RIC	Cy: 500 mg/m^2/day × 4 Flu: 30 mg/m^2/day × 4 r-ATG: 7.5 mg/kg/day × 4 BU: 3.2 mg/kg/day × 2	MTX	CNIs (CsA or tacrolimus), MMF, MTX	0, 0, 41	5
Wang et al. [39]	China	36	11.5 (3–18)	35 (48.57, 45.71)	RIC	Cy: 50 mg/kg × 4 r-ATG: 2.5 mg/kg/day × 4 BU: 0.8 mg/kg/6 h × 2	MTX	CNI (CsA): 2.5 mg/kg/day MMF: 25 mg/day MTX: 15 mg/m2	35, 0, 0	5
Xu et al. [40]	China	42	19 (2–45)	101 (65.35, 0)	RIC	Cy: 50 mg/kg × 4 r-ATG: 2.5 mg/kg/day × 4 BU: 0.8 mg/kg × 2	MTX	CNIs (CsA), MMF, MTX	1, 0, 100	7
Xu et al. [31]	China	39	22 (4–51)	89 (64.04, 22.47)	RIC	Cy: 50 mg/kg × 4 r-ATG: 2.5 mg/kg/day × 4 BU: 0.8 mg/kg/6 h × 2	MTX	CNIs (CsA), MMF, MTX	2, 9, 78	6
Xu et al. [35]	China	67	25 (18–45)	51 (62.75, 17.65)	RIC	Cy: 50 mg/kg × 4 r-ATG: 2.5 mg/kg/day × 4 BU: 0.8 mg/kg × 4	MTX	CNIs (CsA), MMF, MTX	0, 0, 51	5

Table 1 (continued)

Author	Country	Study duration (months)	Median age (range)	Sample size (% males, % with VSAA)	Conditioning regimen		GVHD prophylaxis regimen		Graft source (BM, PBSC, combined)	NOS
					Category	Details	Category	Details		
Yamei et al. [33]	China	66	8 (1–45)	77 (50.65, 6.49)	RIC	Cy: 25 mg/kg/day × 4 Flu: 35 mg/m^2 × 4 r-ATG: 2.5 mg/kg/day × 4 BU: 0.8 mg/kg/6 h × 2	None	CNIs (CsA: 3 mg/kg/day) MMF: 20 mg/kg/day Basiliximab: 0.5 mg/kg/day i.v	0, 0, 77	5
Yang et al. [32]	China	60	13 (4–18)	20 (70, 45)	RIC	Cy: 50 mg/day × 4 Flu: 30 mg/m^2 × 4 ATG: 2.5 mg/kg/day BU: 3.2 mg/kg × 2	MTX	CNIs (CsA), MMF, MTX	8, 2, 10	7
Zhu et al. [38]	China	136	5 (0.5–13.9)	36 (33.33, 22.22)	NMA	Cy: 120–200 mg/kg Flu: 150–200 mg/kg ATG: 10–12 mg/kg TBI: 2–5 Gy	MTX	CNI + MMF ± short-term MTX	34, 2, 0	6

ATG rabbit antithymocyte globulin, *BU* busulfan, *CNI* calcineurin inhibitor, *CsA* cyclosporin A, *Cy* cyclophosphamide, *Flu* fludarabine, *G-CSF* granulocyte colony-stimulating factor, *MMF* mycophenolate mofetil, *MTX* methotrexate, *NMA* nonmyeloablative, *NOS* Newcastle–Ottawa Score, *P* prospective, *R* retrospective, *rhG-CSF* recombinant human granulocyte colony-stimulating factor, *RIC* reduced-intensity conditioning, *TBI* total body irradiation, *PTCy* posttransplantation cyclophosphamide.

associated with low rates of CMV viremia (21.61%) in compared with RIC conditioning regimens (53.3%, $P = 0.04$). Furthermore, the addition of PTCy was associated with lower likelihood of CMV viremia (10.4%) compared with MTX-containing (55.7%) and other (38.6%, $P < 0.001$) regimens.

Notably, CMV disease despite preemptive treatment developed in 5.4% of patients who had initially experienced viremia (95% CI, 0.9–9.9, $I^2 = 56\%$) with no significant difference in the incidence of infection according to conditioning regimens. Importantly, PTCy- and MTX-containing regimens had a reduced incidence of CMV infections in susceptible patients in comparison to other GvHD prophylactic regimens (0% and 2.1% vs 33.0%, respectively, $P < 0.001$).

EBV viremia occurred in 23.8% of patients (95% CI, 13.5–34.1, $I^2 = 91\%$). PTLD was reported in 1.5% of patients (95% CI, 0.2–2.8, $I^2 = 0\%$). Different regimens had not impact the incidence of EBV viremia or PTLD.

Discussion

In the absence of an MSD or MUD, haploidentical HSCT is an attractive alternative approach especially with the quick and universal availability of such donors. The last decade has witnessed a sharp rise in the use of haploidentical transplant both for nonmalignant and malignant hematologic diseases [41]. In the present analysis addressing the use of haploHSCT for AA, the majority of patients (97.3%) achieved successful engraftment and had acceptable rates of RRT and TRM (6.2%, and 6.7%, respectively). Approximately one-quarter of patients experienced aGvHD II–IV (26.5%) or cGvHD (25.0%). The use of NMA conditioning regimens was associated with lower rates of aGvHD and CMV viremia, while higher engraftment was attained with the use of RIC regimens. The use of high dose PTCy (50 mg/kg for 2 days post transplantation) was associated with significant reductions in aGvHD and CMV viremia compared with regimens without PTCy, but at a price of nonstatistically significant reduction in engraftment and a higher mortality rate observed with PTCy use.

The outcomes of haploHSCT are promising, particularly when compared with other types of donors. In a recent Cochrane meta-analysis [42], TRM in MSD HSCT ranged between 20 and 42%, and GvHD was reported in 25–50% of patients. The chances of cure following allogenic BM transplantation have been estimated to range between 75–90% in patients aged <40 years receiving grafts from identical sibling donors [43], and these rates are comparable to older adults without significant comorbidities [44]. As for MUD, Peinemann et al. [45] have shown that the proportion of aGvHD II–IV was 8–86% and cGvHD was 0–26%, whereas the 5-year overall survival ranged from 28 to 94%.

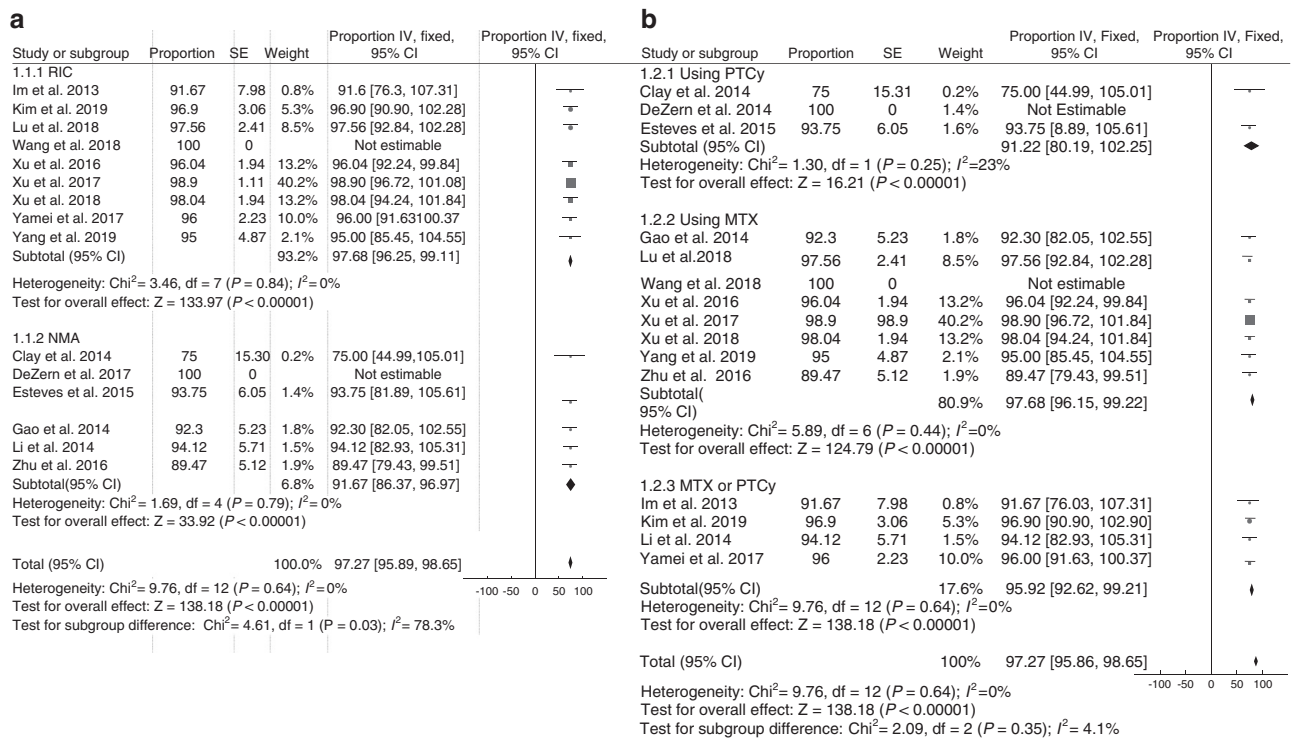

Fig. 2 Forest plot depicting the rates of successful engraftment following haploidentical HSCT based on the used conditioning regimens (**a**) and GvHD prophylaxis regimens (**b**).

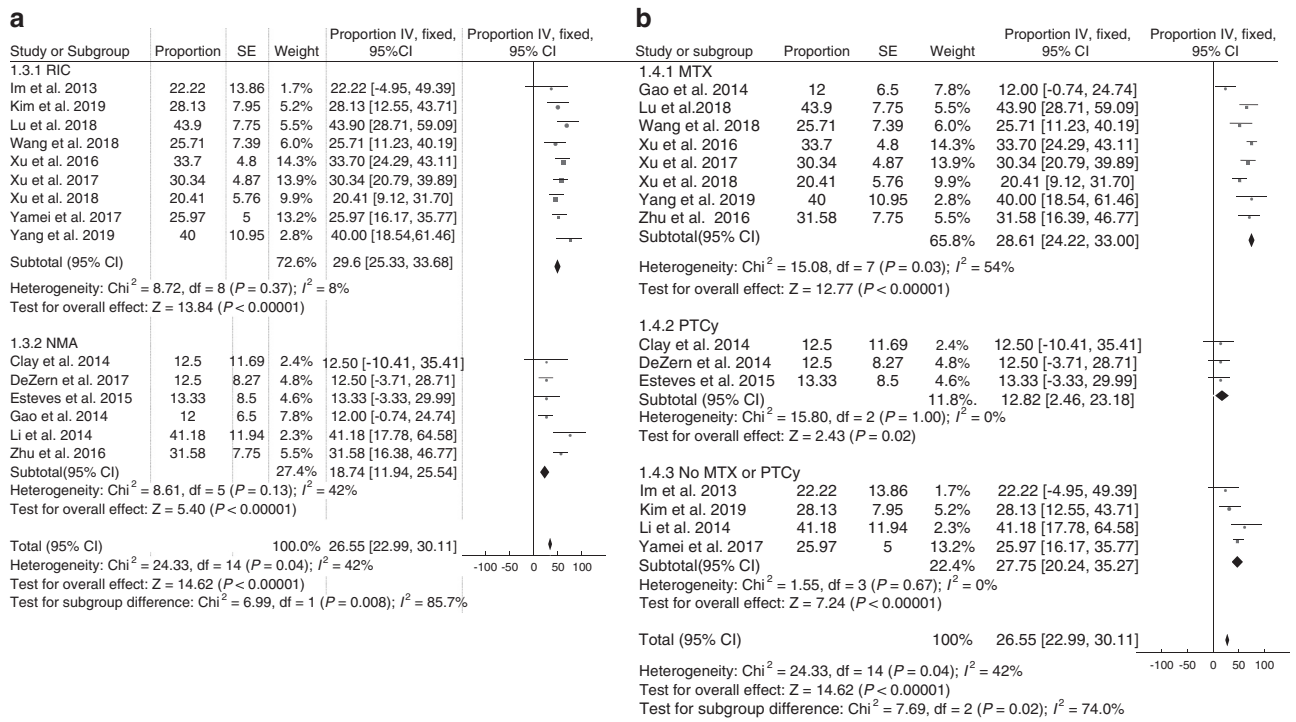

Fig. 3 Forest plot depicting the rates of aGvHD following haploidentical HSCT based on the used conditioning regimens (**a**) and GvHD prophylaxis regimens (**b**).

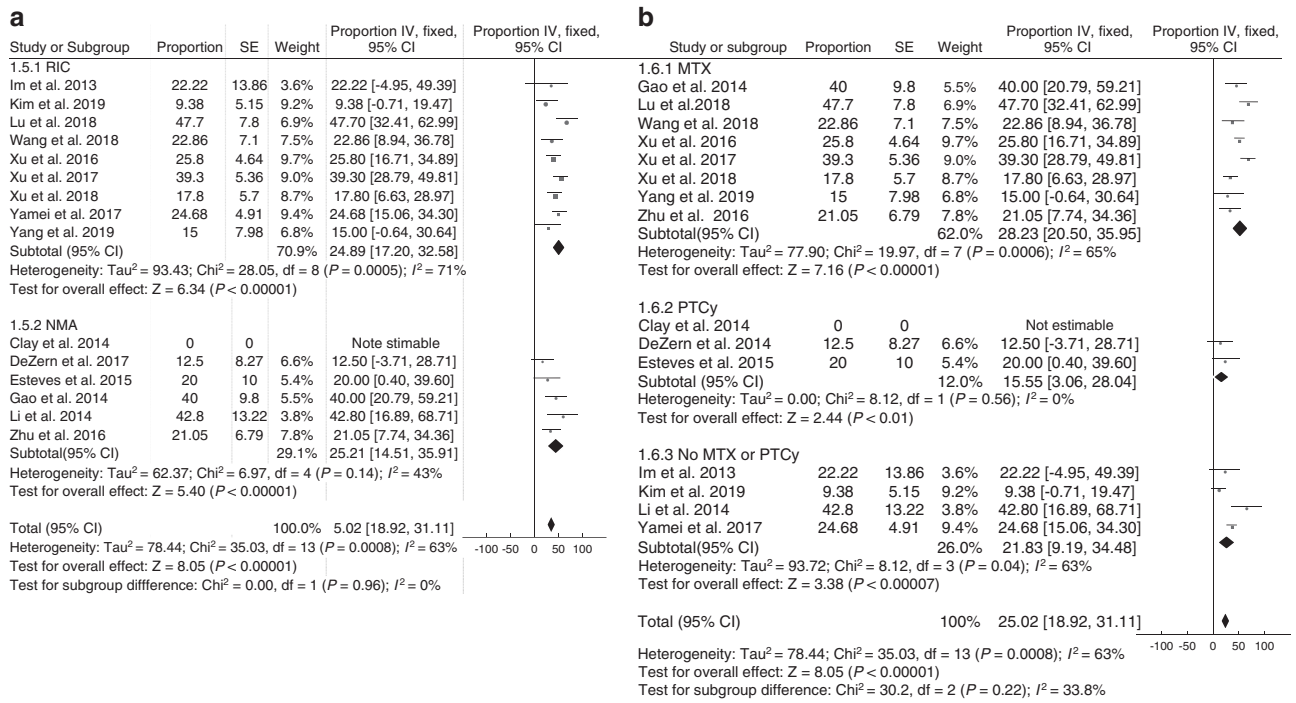

Fig. 4 Forest plot depicting the rates of cGvHD following haploidentical HSCT based on the used conditioning regimens (**a**) and GvHD prophylaxis regimens (**b**).

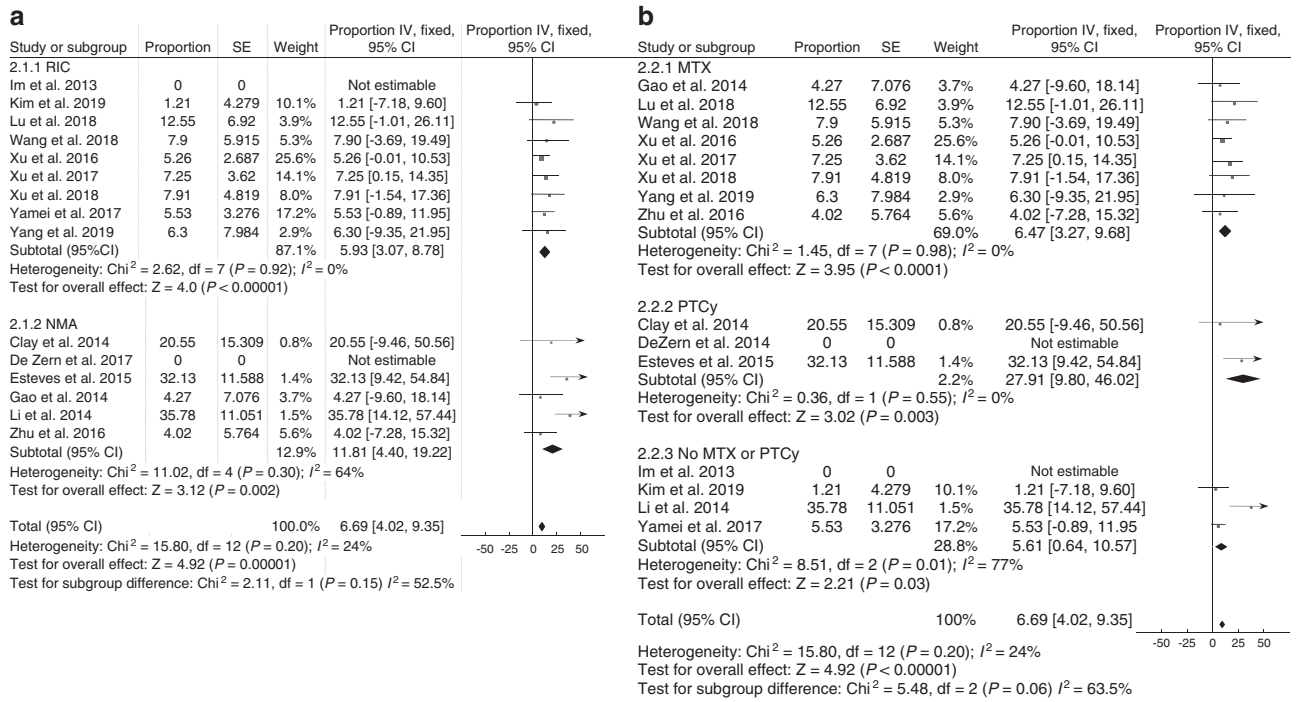

Fig. 5 Forest plot depicting the pooled incidence of transplantation-related mortality following haploidentical HSCT based on the used conditioning regimens (**a**) and GvHD prophylaxis regimens (**b**).

The rate of CMV viremia was low and the rate of CMV disease was zero with the use of PTCy as compared with other GvHD prophylaxis regimens. In a recent study using PTCy (included in this analysis [29]), CMV viremia was regularly monitored (on a weekly basis) and none of the patients had ≥500 copies of CMV/mL posttransplantation.

Table 2 Subgroup analysis of posttransplantation complications in patients undergoing haploidentical HSCT.

Parameters	RRT	CMV viremia	CMV disease	EBV viremia	PTLD	HC
Model (I^2, %)	*R* (76)	*R* (97)	*R* (56)	*R* (91)	*F* (0)	*R* (84)
No. of studies	5	13	13	13	9	6
Conditioning[a]						
RIC	6.18 [1.04, 11.32]	53.26 [28.05, 78.47]	4.07 [0.10, 8.04]	24.20 [12.07, 36.33]	1.53 [0.23, 2.84]	23.87 [7.85, 39.90]
NMA	NA	21.61 [6.12, 37.11]	27.50 [2.22, 52.78]	24.05 [−0.83, 48.93]	NA	11.76 [−3.55, 27.07]
P	NA	0.04	0.07	0.99	NA	0.28
GvHD prophylaxis[a]						
MTX	5.85 [0.35, 12.06]	55.74 [40.33, 71.14]	2.12 [0.09, 4.15]	24.86 [16.90, 32.83]	1.37 [−0.18, 2.92]	21.92 [−0.99, 44.82]
PTCy	NA	10.35 [−4.84, 25.54]	NA	32.10 [−22.85, 87.04]	NA	NA
Others	8.00 [1.94, 14.06]	38.60 [3.15, 74.05]	33.06 [17.76, 48.35]	19.98 [−6.48, 46.45]	1.93 [−0.49, 4.36]	20.08 [6.89, 33.27]
P	0.63	<0.001	<0.001	0.91	0.7	0.89

CMV cytomegalovirus, *EBV* Epstein–Barr virus, *F* fixed-effects model, *GvHD* graft-versus-host disease, *HC* hemorrhagic cystitis, *MTX* methotrexate, *NMA* nonmyeloablative regimen, *PTCy* posttransplantation cyclophosphamide, *PTLD* posttransplant lymphoproliferative disorder, *R* random-effects model, *RIC* reduced-intensity regimen, *RRT* regimen-related toxicity.
[a]Results are expressed as rates [95% confidence interval].

This is surprising as the use of PTCy is associated with a higher rate of CMV viremia and some studies have even proposed the use prophylactic anti-CMV antivirals when PTCy is used [46, 47]. This difference can be partially explained by the different definitions used to define CMV viremia in clinical practice and the nonavailability of data regarding the frequency of donor–recipient CMV status match or mismatch in this study. This issue could be better evaluated in a prospective trial.

In the present analysis, NMA regimens were associated with lower rates of aGvHD II–IV and CMV viremia at a price of lower engraftment in comparison to RIC regimens. This is in line with previous studies showing better engraftment with more intense regimens at a price of increased toxicity and TRM [25].

In general, haploidentical HSCT appears to be a safe alternative in the absence of a matched donor. Other innovative techniques such as co-infusion of regulatory and conventional T cells [48], α/β T-cell depletion [30, 49], CD45RA depletion [50], and the infusion of natural killer cells after haploHSCT [51] are under investigation to improve the outcomes of haploHSCT.

Conclusion

Haploidentical HSCT is an emerging transplant modality that provides promising outcomes. Engraftment success was notable in the majority of patients with severe and very severe AA, while RRT, TRM, and GvHD rates were

Table 3 Recommendations for future studies aiming to improve the outcomes of Haploidentical HSCT for SAA patients.

Future studies should consider
• Multicenter, multinational trials recruiting from different ethnic backgrounds.
• This will allow recruiting larger numbers of patients and will allow randomization to different arms to answer more questions.
• Analysis of donor subgroups effect on outcomes (i.e., father, mother, siblings).
• Analysis of donor and patient characteristics effect on outcomes while using different conditioning (NMA vs RIC) and different GvHD prophylaxis (PTCy vs others).
• Randomized phase II study to compare the outcomes of transplant for SAA using matched unrelated vs haploidentical donor.
• Head-to-head comparisons of RIC and NMA regimens in the setting of haploidentical transplant.
• Randomized phase II study to compare the outcomes of haploidentical transplant for SAA using peripheral blood vs bone marrow graft (mobilized and nonmobilized subgroups).
• Randomized phase II study to compare the outcomes of haploidentical transplant for SAA using PTCy vs other GvHD prophylaxis.

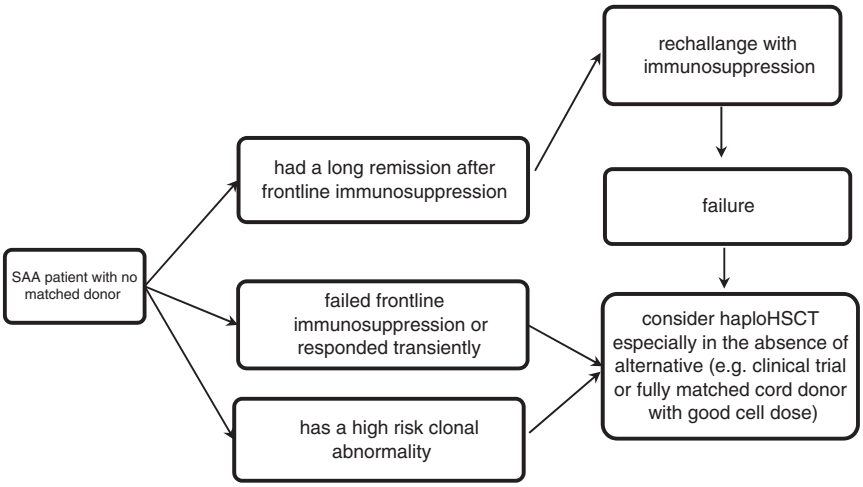

Fig. 6 Author's opinion regarding haploidentical transplant for SAA.

acceptable. NMA conditioning was better in terms of lower CMV viremia and acute GVHD but not in terms of RRT, mortality, and engraftment. The addition of PTCy showed lower GvHD and lower CMV incidence at a price of nonsignificant increase in the incidence of mortality per year. NMA vs RIC and PTCy vs others may be used depending on patient's and donor's profiles or the institution's setup and resources. To best answer these questions, prospective randomized trials are much needed. Table 3 is a summary of recommendations for future studies aiming to improve the outcomes of haploidentical HSCT for SAA patients. Obviously, this analysis has many limitations, most notable that the outcomes were mainly retrieved from nonrandomized and nonprospective studies, which are possibly subject to bias and lacking comparative analyses. In addition, 80% of studies in this meta-analysis were conducted in Eastern Asia where the platforms used for haploidentical transplantation (conditioning, graft source, GvHD prophylaxis, graft depletion, etc.) are different from the ones used in the other parts of the world, and also where the pharmacogenomics and drug metabolism are different. Therefore, haploidentical transplantation is an emerging therapeutic modality that needs additional prospective studies with adequate follow-up to validate its role in the management algorithm. Figure 6 is a summary of the author's opinion regarding haploidentical transplant for SAA.

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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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