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ORIGINAL ARTICLE

Efficacy and safety of autologous hematopoietic stem-cell transplantation in multiple sclerosis: a systematic review and meta-analysis

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Abstract

Background Autologous hematopoietic stem-cell transplantation (AHSCT) has been utilized as a treatment option for multiple sclerosis (MS) since 1995. However, this procedure has not been widely implemented in clinical practice owing to its mortality risk. Here, we conduct a meta-analysis to evaluate the long-term efficacy and safety of AHSCT in MS treatment, aiming to optimize the benefit/risk ratio of this therapeutic strategy.

Methods We searched the PubMed Web site and clinicaltrials.gov databases. The efficacy endpoints were progression-free survival (PFS) and disease activity-free survival. The safety outcomes were transplant-related mortality (TRM) and overall deaths.

Results Eighteen eligible studies with a total of 732 participants were enrolled. The PFS was 75% (95% CI, 0.69–0.81), and the estimate of disease activity-free survival was 61% with 48-month follow-up. Subgroups analysis showed that low- and intermediate-intensity regimens were associated with higher PFS 80%. Relapsing remitting MS (RRMS) benefited more from AHSCT than other MS subtypes with PFS 85%. Patients with Gd+ lesions at baseline MRI responded better to AHSCT with PFS 77%. The estimate of TRM was 1.34% (95% CI, 0.39–2.30), and the overall mortality was 3.58%. TRM was significantly higher in high-intensity regimen studies (3.13%) and in older studies (1.93%) performed before 2006.

Conclusions This meta-analysis provides evidences that AHSCT can induce long-term remissions for MS patients with a high degree of safety. We indicate low- and intermediate-intensity regimens and RRMS patients with the presence of Gd+ lesions at baseline MRI can obtain the optimal benefit/risk ratio from AHSCT.

Keywords Multiple sclerosis · Autologous hematopoietic stem-cell transplantation · Meta-analysis · Systematic review · Progressive

Introduction

Multiple sclerosis (MS) is an immune-mediated and CNS demyelinating disease affecting more than two million people worldwide especially manifests in young adults. This disorder can give rise to permanent disability, impair quality of life, and shorten life expectancy. During the past two decades, disease-modifying treatments (DMTs) have become available and shown to reduce clinical relapse, suppress disease activity in patients with relapsing remitting MS (RRMS). However, DMTs showed little benefit in disability progression and could not effectively treat other subgroups of MS: progressive and treatment-refractory MS [1, 2]. Given B cells and humoral immunity play a key role in MS pathogenesis, recently B cell depletion strategy has been an option for MS treatment [3, 4]. Promising results from B cell depletion by three therapeutic monoclonal antibodies (rituximab, ocrelizumab, and ofatumumab) in clinical phase II and III trials have confirmed the efficacy and safety of such therapy in MS, including progressive forms [5, 6]. However, outcome assessments in most

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studies are limited to a short follow-up and the long-term outcomes of B cell depletion are still uncertain.

Autologous hematopoietic stem-cell transplantation (AHSCT), traditionally used for the treatment of hematological tumors, has been utilized as a treatment option for severe autoimmune diseases (ADs) since 1995 [7, 8]. It has been shown that AHSCT can induce long-term remissions compared with conventional immunosuppressive therapy. The results of retrospective analysis and prospective randomized phase II/III studies identified its feasibility, efficacy, and safety in the major ADs particularly for MS [9, 10]. A series of retrospective reports from the European Group for Blood and Marrow Transplantation (EBMT) [11–13], which owned largest cohort of MS patients underwent AHSCT, showed a progression-free survival at 3 and 5 years of 74% and 45%, respectively. Meanwhile, transplant-related mortality has dropped dramatically from 7.3% in 1995–2000 to 1.3% in 2001–2007, and further decreasing to 0.7% during 2008–2016 and down to 0.2% in the past 5 years (2012–2016) over the years [14].

Considering the limitation of retrospective reports, recently, the results of phase II clinical trial (ASTIMS) have been published, comparing mitoxantrone (MTX) with AHSCT for the treatment of aggressive forms of MS [15]. This was the first multicenter, randomized trial to assess the effects of AHSCT vs conventional therapies for MS. The data of ASTIMS demonstrated AHSCT was significantly superior to MTX in reducing MRI activity and clinical relapse in severe cases of MS. However, this procedure has not been widely implemented in clinical practice and only been a rescue treatment when other therapy failed; the most important reasons were its mortality risk and uncertainty about optimal patients/transplant regimen choice.

In this situation, we performed a systematic review and meta-analysis to evaluate the long-term efficacy and safety of AHSCT in MS treatment, with aim to select proper participants/methodology and optimize the benefit/risk ratio of this therapeutic strategy.

Methods

All analyses were based on previous published studies, and ethical approval and patient consent had been stated in all included studies.

Search strategy

We searched the PubMed Web site and clinicaltrials.gov databases (published until December 31, 2017) using the keywords "multiple sclerosis" and "autologous hematopoietic stem-cell transplantation." The search was restricted to English language and published articles.

Study selection

Two authors screened the search results, excluded irrelevant publications based on the title and abstract, then obtained full-texts of potentially relevant articles. Eligible studies were selected according to the following criteria: (1) only uncontrolled observational studies were included; (2) English language and published articles included; and (3) the efficacy outcome was progression-free survival reported. In addition, we excluded trials based on the following criteria: (1) case reports and studies that included fewer than ten patients; (2) published only as abstract. The other two neurologists independently extracted the following messages: numbers of enrolled patients, age, length of follow-up, interval from diagnosis to transplantation, types of MS, numbers of Gd+ at baseline MRI scan, Expanded Disability Status Scale (EDSS) score at baseline, conditioning regimen intensity, efficacy, and safety outcomes.

Efficacy and safety measures

In this systematic review and meta-analysis, the primary efficacy endpoint is progression-free survival, which is defined as the probability of being alive without confirmed disability progression (increase in EDSS > 1 if initial EDSS < 5.0 or > 0.5 if initial score > 5.5 after transplantation). The secondary efficacy endpoint is disease activity-free survival (no acute clinical relapse, no sustained progression of EDSS score, and no gadolinium-enhanced or new T2 lesions on MRI scan). The safety outcome is transplant-related mortality and overall mortality. Transplant-related mortality is defined as deaths within 100 days of AHSCT treatment.

Data synthesis and analysis

Data was entered into and analyzed using the Stata12. The efficacy outcome measures were pooled using the method of inverse variance, with random effects; the combined estimates were reported with 95% CIs. The I^2 test was used to assess the presence of between-study heterogeneity. I^2 with significance was set at $P < 0.10$ statistically. Fixed-effect model was used to assess low heterogeneity ($P > 0.10$), and random-effect model was used to assess high heterogeneity. Publication bias was assessed by visual examination of funnel plots. A stratified analysis was performed to explain the heterogeneity.

Results

Study characteristics

Eighteen RCTs were included in our meta-analysis with a total of 732 participants enrolled [16–33]. The search procedure is listed in Fig. 1. The mean onset age of all patients was ranged from 9 to 64 years. The mean MS duration ranged from 4 to 336 months, and the mean follow-up after AHSCT therapy ranged from 19 months to 6.7 years. Numbers of participants ranged from 14 to 145, detailed features are summarized in Table 1, and all trials reported progression-free survival assessed by EDSS scores, TRM, and overall mortality. According to EBMT classification, a combination of total body irradiation (TBI) plus anti-thymocyte globulin (ATG) (TBI/ATG) is considered a high-intensity conditioning regimen, and intermediate-intensity regimen used mostly is the BEAM plus ATG (BEAM/ATG). BEAM is a combination of etoposide, melphalan, carmustine, and cytosine arabinoside. Four studies utilized a high-intensity regimen, and three trials analyzed the subgroup of Gd+ lesion at baseline MRI. There were 329 RRMS, 307 SPMS, 51 PPMS, and 44 progressive relapsing MS (PRMS) patients.

Efficacy endpoints assessment

In the pooled cohort of 708 patients with a median follow-up of 48 months after transplantation, the pooled estimate of PFS was 75% (95% CI, 0.69–0.81; $I^2 = 74.7\%$, $P < 0.0001$), suggesting substantial heterogeneity among studies (Fig. 2). The difference in onset age, MS subtypes, intensity of conditioning regimens, and baseline MR characteristics among studies can contribute to the heterogeneity of consequence. Therefore, we analyzed the associations of subgroups with PFS separately for this outcome (Fig. 3). Onset age appeared to have no significant association with PFS, and there was slight difference between under 40 years and beyond 40 years with PFS 53% (95% CI, 0.29–0.78) vs 51% (95% CI, 0.30–0.72). However, other factors were significantly associated with PFS. Low- and intermediate-intensity regimen resulted in higher PFS than do high-intensity regimen 80% (95% CI, 0.75–0.85) vs 58% (95% CI, 0.40–0.75). RRMS patients benefited more from AHSCT than other MS subtypes with PFS 85% (95% CI, 0.77–0.92). Patients with Gd+ lesions at baseline MRI responded better to AHSCT than Gd− patients with PFS 77% (95% CI, 0.61–0.94) vs 47% (95% CI, 0.33–0.62). The pooled proportion of patients who were disease activity-free survival was 61% (95% CI, 0.53–0.69; $I^2 = 49\%$, $P = 0.056$) at a median follow-up of 48 months (Fig. A1).

Mortality

In the pooled cohort of 731 transplanted patients, 9 transplant-related deaths occurred. As show in Fig. 4, the estimate of TRM was 1.34% (95% CI, 0.39–2.30, $I^2 = 37\%$, $P = 0.058$).

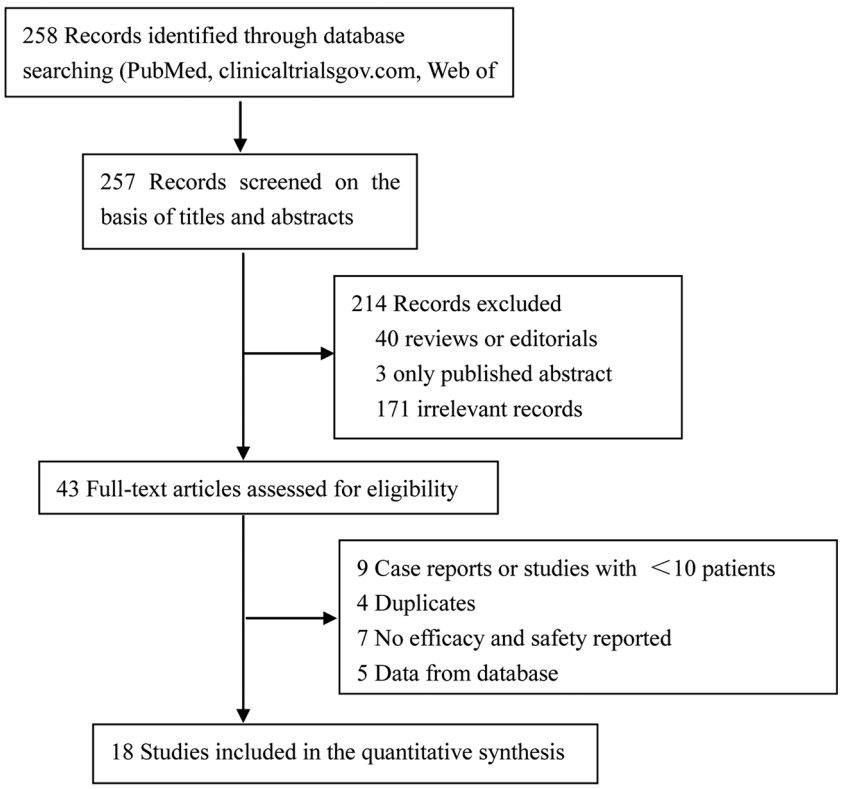

Fig. 1 Flowchart of included/excluded studies

Table 1 Characteristics of studies included in the meta-analysis

Authors	Sample size, *n*	Age (years), median (range)	Regimen intensity	MS duration, median (range)	Types of MS	MRI active	MRI inactive	EDSS, median (range)	Follow-up, median (range)
Fassas et al.[22]	24	40 (22–54)	Intermediate	10.5 (2–28) years	13SP.3PR.8PP	6	18	6.0 (4.5–8.0)	40 (21–51) months
Burt et al.[33]	21	NA (21–52)	High	NA (9 months–15 years)	14SP.6PR.1RR	9	12	7.0 (3.0–8.5)	NA (1–5) years
Nash et al.[26]	26	41 (27–60)	High	84 (10–277) months	8PP.17SP.1RR	NA	NA	7.0 (5.0–8.0)	24 (3–36) months
Saiz et al.[29]	14	30 (22–45)	Intermediate	8.0 (1–19) years	5RR.9SP	5	9	6.0 (4.5–6.5)	3 years
Saccardi et al.[28]	19	36 (26–52)	Intermediate	12 (4–19) years	15SP.4RR.	NA	NA	6.6 (5.5–8.0)	36 (12–72)
Ni XS et al.[27]	21	37 (15–58)	Intermediate	46 (6–144) months	16SP.2PP.2PR. 1Malignant	8	13	7.5 (5.0–9.5)	42 (6–65) months
Hamerschlak et al.[23]	41	42 (27–53)	Intermediate	8.0 (2–22) years	4PP.33SP.4RR	8	27	6.0 (4.0–7.0)	3 years
Juan Xu et al.[31]	36	35 (20–51)	Intermediate	72.39 (7–336) months	36SP	NA	NA	6.58 (4.5–9.0)	48.92 (10–91) months
Krasulova'et al.[24]	26	33 (19–44)	Intermediate	7.0 (2–19) years	11RR 15SP	NA	NA	6.0 (2.5–7.5)	66 (11–132) months
Bing Chen et al.[32]	25	37.3 (15–64)	Intermediate	48 (7–147) months	19SP.1PP.2PR.3RR	14	11	8.0 (3.0–9.5)	59.6 (4.5–111) months
Bowen et al.[19]	26	41 (27–60)	High	84 (10–277) months	17SP.8PP.1RR	7	16	7.0 (5.0–8.0)	48 (3–72) months
Mancardi et al.[25]	74	35.7(16–53)	Intermediate	11.2 (1–28) years	41SP.33RR	32	13	6.5 (3.5–9.0)	48.3 (0.8–126) months
Burman et al.[21]	48	31 (9–52)	Intermediate	75 (4–300) months	40RR.5SP.2PP.1PR	32	16	6.0 (1.0–8.5)	47.4 (12–108) months
Burt et al.[18]	145	37 (18–60)	Low	61 (9–264) months	118RR.27PR	84	61	4.0 (3.0–5.5)	5 years
Shevchenko et al.[30]	99	34.6(18–54)	Intermediate	5.0 (0.5–24) years	43RR.35SP.18PP.3PR	40	59	3.5 (1.5–8.5)	48.9 months
Atkins et al.[20]	24	34 (24–45)	High	5.8 (1.3–11.2) years	12RR.12SP	NA	NA	5.0 (3.0–6.0)	6.7 (3.9–12.7) years
Nash et al.[17]	25	37 (31–42)	Intermediate	4.9 (2.5–7.3) years	25RR	NA	NA	4.5 (4–5.0)	62 (12–72) months
Casanova[16]	38	36.7 (9.1)	Intermediate	9.5 (7.6) years	22RR.10SP	20	18	5.3 (1.2)	8.4(2–16) years

EDSS Expanded Disability Status Scale, *NA* not available, *RR* relapsing remitting, *SP* secondary progressive, *PP* primary progressive, *PR* progressive relapsing, *malignant* malignant multiple sclerosis, *MRI active* no. of patients with gadolinium-enhanced lesions on baseline MRI, *MRI inactive* no. of patients without gadolinium-enhanced lesions on baseline MRI

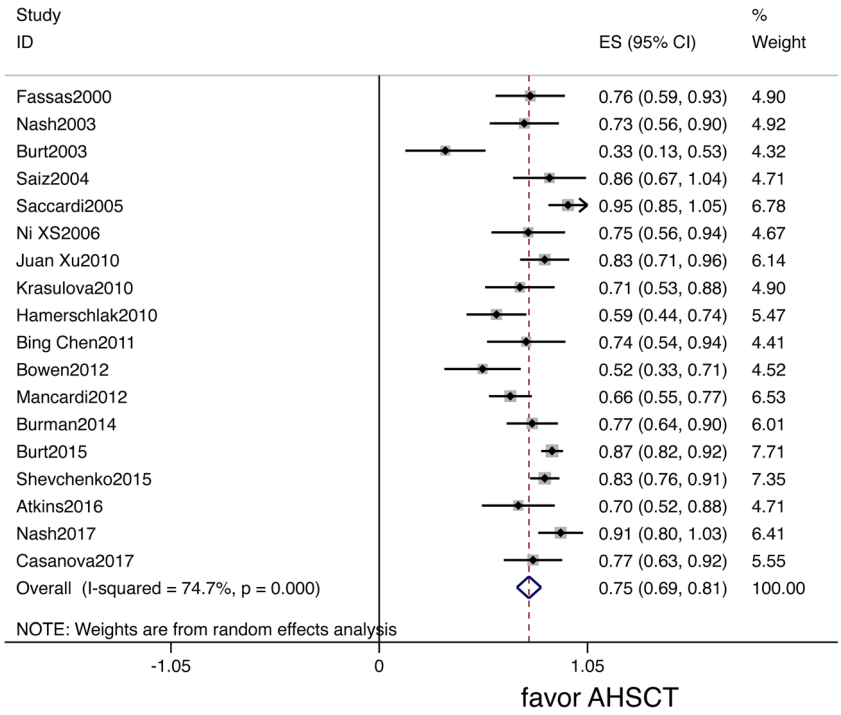

Fig. 2 Forest plot for progression-free survival in each study and pooled estimates

TRM was significantly higher in high-intensity regimen studies (3.13%, 95% CI, 1.18–5.08) when compared with low- and intermediate-intensity regimen (0.97%, 95% CI, − 0.05–1.98) and in older studies performed before 2006 (1.93%, 95% CI, 0.13–3.72) (Fig. 5). A total of 27 patients died during the follow-up, with the pooled estimate of overall mortality was 3.58% (95% CI, 2.30–4.86, $I^2 = 64.7\%$, $P = 0.000$) (Fig. A2). The leading cause of overall mortality was infection (14cases) and pneumonia (6 cases). Of these 25 cases, six cases were associated with disease progression. The major cause of non-treatment-related deaths was disease progression.

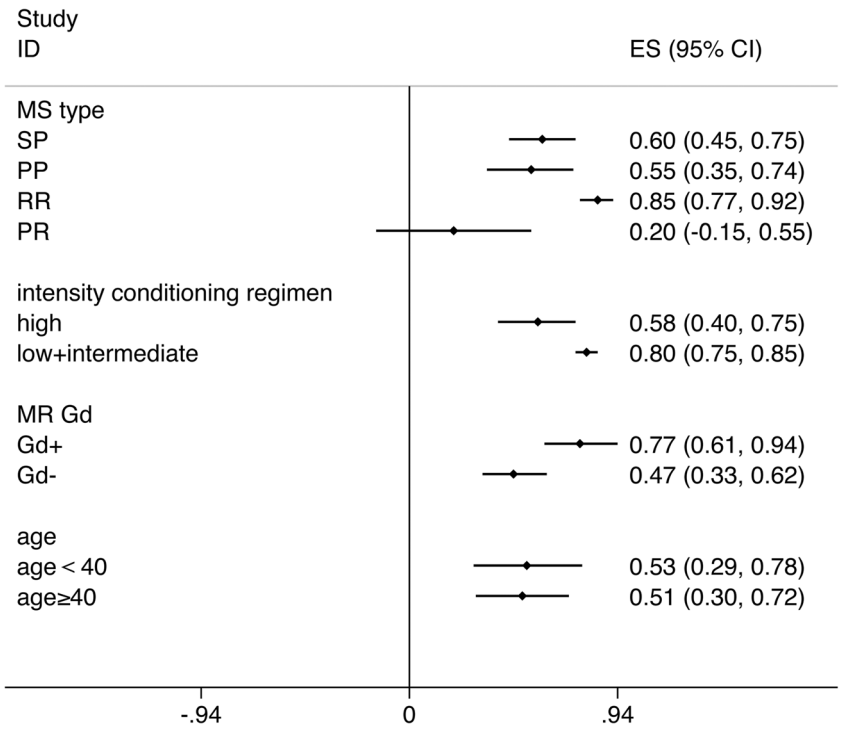

Fig. 3 Forest plot for progression-free survival in studies with different subgroups

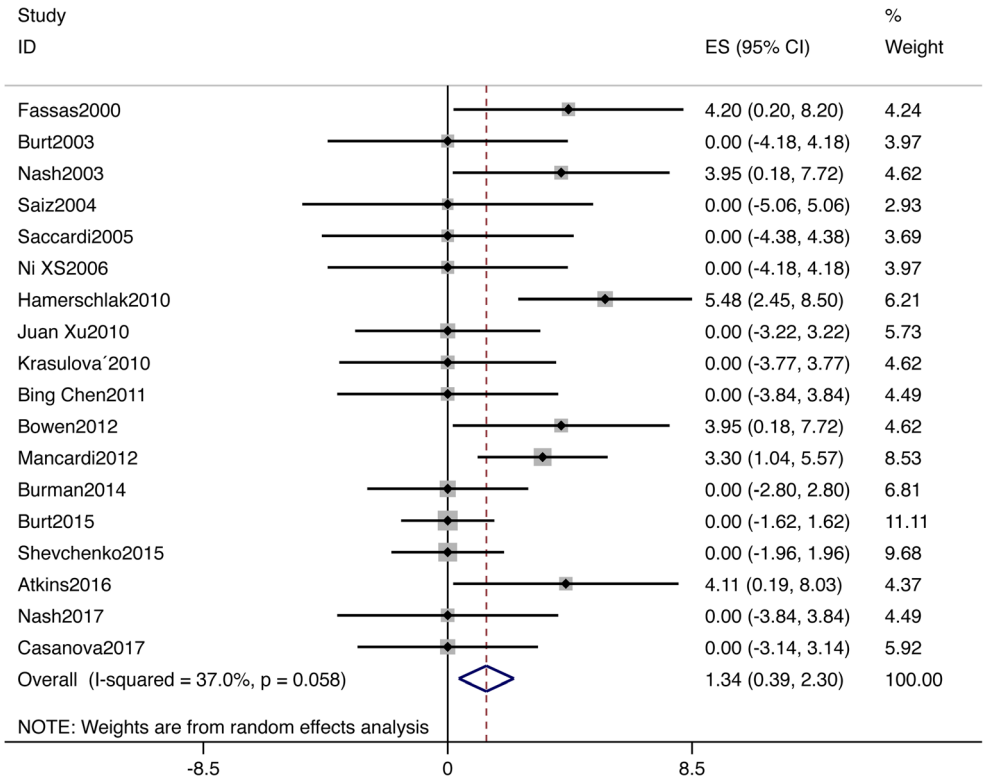

Fig. 4 Forest plot for transplant-related mortality in each study and pooled estimates

Discussion

AHSCT, as a one-time treatment option for MS patients, has attracted eyeballs of neurologists recently. Compared with DMTs and B cell depletion treatments, AHSCT induced long-term sustained remissions for MS patients. However, this procedure is not uniform across studies referring to recruitment of patients with MS subtypes and the selection of intensity regimen, which could lead to the heterogeneity of consequence. Owing to the mortality risk and the lack of large randomized controlled trial, the application of AHSCT in clinical practice is still limited. Therefore, this meta-analysis will provide more useful evidences about the long-term efficacy outcomes of AHSCT including demographic/disease-related and treatment-related variables as well as safety, with aim to optimize benefit/risk ratio of this procedure.

In this analysis, we chose to use progression-free survival as main efficacy endpoint. Seventy-five percent of patients remained free from EDSS score deterioration after AHSCT with a median follow-up of 48 months; the efficacy outcome

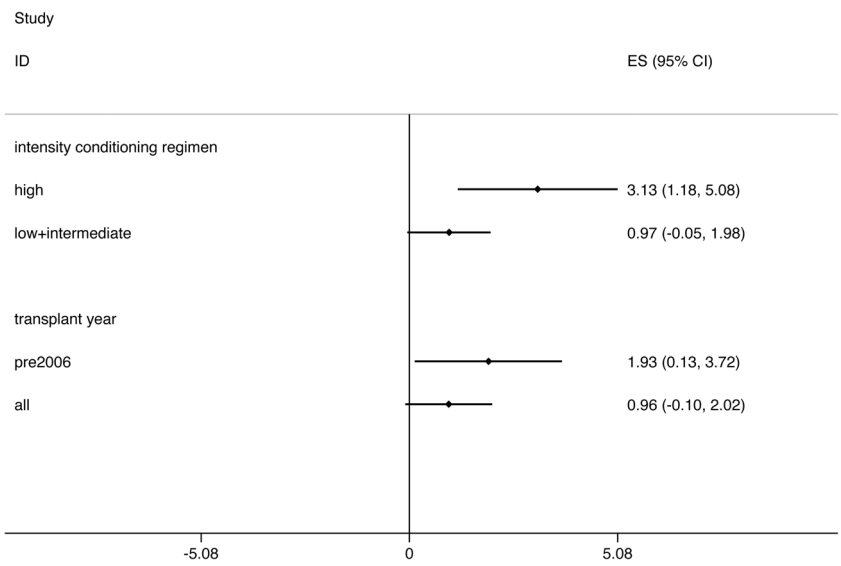

Fig. 5 Forest plot for transplant-related mortality in studies with different subgroups

was the same as those reported in previous and contemporary meta-analysis [34, 35]. In the present meta-analysis, 63% of patients had no new MRI lesions, no clinical relapse, and no EDSS progression post-AHSCT at 48 months, which suggested that AHSCT could induce sustained remissions for MS. Given substantial heterogeneity among studies in primary efficacy endpoint ($I^2 = 74.7\%$, $P < 0.0001$), we analyzed the associations of different subgroups including onset age, MS subtypes, intensity of conditioning regimens, and baseline MR characteristics with PFS separately.

Different subtypes of MS were included in our analysis. The proportion of RRMS was 40%, and PFS was estimated to be 85% (95% CI, 0.77–0.92); by contrast, the PFS was estimated to be 52% in progressive MS (60%) after AHSCT treatment, indicating that RRMS respond better to AHSCT than other MS subtypes. This outcome was consistent with recent evidence of good efficacy in RRMS [36]. Other original studies proved the best candidates for transplantation seem to be patients with RRMS through long-term follow-up [16–18]. A possible explanation for this finding was RRMS patients had lower EDSS score prior to transplantation and were in the early stage of disorder. Muraro et al.'s report found lower baseline EDSS scores were the factors associated with better outcomes.

Progressive forms of MS are classified as aggressive forms that can lead rapidly to a high burden of disability and, at times, even to death in a short period of time. Currently available DMTs proven to be effective for RRMS have little or no efficacy in progressive multiple sclerosis. Thus, effective treatments for progressive forms of MS remain a challenge in MS management. Although the pathogenic mechanism underlying progression is incompletely understood, axonal injury is a major contributor to irreversible disability [37]. Accordingly, AHSCT, acting on the immune system, likely has little benefit in progressive MS [16, 18]. These findings suggests that other therapeutic approaches, such as neuroprotective strategies, will be necessary in treatment of progressive multiple sclerosis. AHSCT should not be used as a rescue treatment after failure of all available treatments and the ideal candidate for AHSCT should be refined.

In our analysis, the treatment response was most notable in the group of patients with low- and intermediate-intensity regimens than do high-intensity schemes with PFS 80% (95% CI, 0.75–0.85) vs 58% (95% CI, 0.40–0.75). The similar outcomes were observed in previous meta-analysis. Reston et al. reported 79.4% PFS in patients receiving intermediate-intensity conditioning regimens, while 44.6% PFS in patients receiving high-intensity regimens [35]. Since higher treatment intensity was associated with higher mortality risk, recently, BEAM, as an intermediate-intensity conditioning regimen, has been most frequently used. BEAM showed better outcome and less toxicity when compared with the high-intensity regimens [11, 30, 38]. We also demonstrated TRM was significantly associated with regimen intensity: studies using high-intensity schemes had a TRM of 3.13% (95% CI, 1.18–5.08), while those using low- and intermediate-intensity regimens had a TRM of 0.97% (95% CI, − 0.05–1.98). These results in favor of low- and intermediate-intensity conditioning regimen are the best choice.

In subgroup analysis, we found patients with Gd+ lesions prior to AHSCT were associated with a favorable outcome when compared to patients with Gd− lesions (PFS 77% vs 47%). The similar conclusions were drawn from previous published reports [21, 35]. Three trials analyzed the effects of Gd+ lesions at baseline MRI scan on PFS [19, 21, 25], and they found that the treatment response was most notable in the group of patients with the presence of Gd+ lesions at baseline. This phenomenon can be explained that patients with Gd+ lesions are more likely to have an inflammatory disease. This information might suggest the optimal therapeutic window for this procedure was in the inflammatory stages of MS.

The main problems of AHSCT are the safety issues, and TRM is the main concern that has limited the use of this procedure. With better selection of patients and decreased use of high-intensity conditioning regimen, TRM has dropped over the years [14]. In our meta-analysis, the estimate of TRM (1.34%) was the same as previous reports. A marked reduction of TRM was closely related to the recruitment of RRMS patients and to use of low- and intermediate-intensity conditioning regimens. In view of previous studies, we found that no TRM occurred in those studies which enrolled RRMS patients, suggesting MS subtype may be an important factor associated with higher deaths. In the latest meta-analysis, Maria Pia Sormani et al. also reported higher baseline EDSS scores and a lower proportion of patients with RRMS were significantly associated with a higher TRM [34]. Now, at least in north of Europe, the low-intensity protocol of 200 mg of cyclophosphamide for kg is the most utilized type of conditioning regimen, and Burt and colleagues reported 0% of TRM in their cohort of MS patients who received AHSCT with use of low-intensity conditioning therapy [18]. We observed 0.97% TRM in low and intermediate conditioning regimens from our subgroup analysis compared with higher TRM (3.13%) in high-intensity conditioning therapy. In combination, these data indicate that AHSCT is safe as a therapy option in MS treatment if RRMS patients with lower EDSS scores were enrolled and low- and intermediate-intensity conditioning regimens were used. Meanwhile, we analyzed the overall mortality (3.31%) and found disease progression and high-intensity conditioning regimen were the main cause.

Our meta-analysis is limited in many aspects. Firstly, only published data were included, which might cause potential publication bias. Secondly, this analysis lacked randomized control trials due to the published evidence mainly consisted of case series and retrospective database studies. Thirdly, the

differences in AHSCT procedure, characteristics of MS patients, and the duration of follow-up across studies could lead to potential heterogeneity. Subgroup data were not always available in the included trials, and different subgroup analyses were affected by many factors. Finally, it is well known that EDSS has a number of shortcomings as a measurement of disability. It is difficult to compare EDSS progression in different studies due to its poor reproducibility and low inter-rater agreement.

This meta-analysis provides evidences that AHSCT can induce long-term remissions for MS patients with a high degree of safety. We indicate low- and intermediate-intensity regimens and RRMS patients with the presence of Gd+ lesions at baseline MRI can obtain the optimal benefit/risk ratio from AHSCT.

Author contributions C.T and G.F.F performed the study selection, data extraction, statistical analysis, and drafted the manuscript. All authors participated in study design, revised the protocol, contributed to interpretation of the results, critically revised the manuscript for important intellectual content, and read and approved the final version of this manuscript.

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Compliance with ethical standards

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

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