Busulfan plus fludarabine compared with busulfan plus cyclophosphamide as a conditioning regimen prior to hematopoietic stem cell transplantation in patients with hematologic neoplasms: a meta-analysis

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Abstract: Objectives: The aim of the article is to critically appraise and synthesize available evidence regarding the efficacy and regimen-related toxicity (RRT) of Busulfan plus fludarabine (BuFlu) compared to busulfan plus cyclophosphamide (BuCy) as a conditioning regimen, prior to allogeneic hematopoietic stem cell transplantation (HSCT) in patients with hematologic neoplasms. Methods: A meta-analysis was attempted on clinical controlled trials (CCTs), randomized or non-randomized controlled trials (RCTs or non-RCTs), comparing BuCy with BuFlu. We did a systematic search of the indexed medical literature using appropriate keywords to identify potentially relevant articles. The primary outcome of interest was efficacy measured by overall survival (OS) and event-free survival (EFS), acute graft-versus-host-disease (aGVHD). Chronic GVHD (extensive) and other toxicity were secondary endpoints. A relative risk or risk ratio (RR) and 95% confidence interval (CI) was calculated for each outcome in the meta-analysis. Results: Nine clinical controlled trials were included, of which 4 tries were RCTs involving 584 patients and the other 5 were non-RCTs involving 571 patients. The cumulative incidences of OS, EFS, acute graft-versus-host disease (aGVHD) were not significantly different between the two regimens. The non-relapse mortality was higher in BuCy but non-significant increment (RR=1.48, 95% CI: [0.97-2.26]). Liver related toxicity was significantly higher with BuCy compared to BuFlu (RR=1.90, 95% CI: [1.00-3.61]). Conclusion: Liver related toxicity is significantly lesser with BuFlu, but BuFlu regimen has no significant benefits compared with BuCy in OS, EFS, aGVHD. For all this, the weight of evidence favors BuFlu over BuCy as a first choice-conditioning regimen for patients with hematologic neoplasms, especially for people who have poor liver function.

Keywords: Busulfan, fludarabine, cyclophosphamide, myeloablative conditioning regimen, allogeneic hematopoietic stem cell transplantation

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the effective methods to improve survival and to reduce recurrence of malignant hematological disease. While increasing the dose of radiation (chemotherapy) among allo-HSCT can eliminate tumor cells more thoroughly, it also increases toxicity, resulting in high transplantation related mortality (TRM) and impacting on long-term survival [1]. The classical solution in the process of pre-treatment of allo-HSCT is busulfan plus cyclophosphamide (BuCy) [2]. It also, however, has the higher regimen-related toxicity (RRT). In recent years, fludarabine (Flu) was introduced in pre-transplant conditioning regimen due to its strong antitumor and weak immunosuppressive and toxic side effects. Slavin [3] confirmed that program of low doses of busulfan (Bu, oral 8 mg/kg) and Flu combined anti-thymocyte globulin (ATG) regimen, carried out with type-identical sibling transplants, is well tolerated and implanted properly. Kroger [4] also confirmed that the regimen was well tolerated, but high recurrence rate (32% in one year) was still one of the main reasons for the failure of transplantation. There is no conclusive evidence on the superiority of one regimen over the other in terms of efficacy as well as toxicity. Retrospective
comparative studies including reports from international transplant registries, as well as prospective randomized controlled trials (RCTs) have yielded conflicting results and it remains to be defined for the most optimal conditioning regimen prior to transplantation in hematologic neoplasms. This study was to critically appraise all the available evidence and attempt a meta-analysis comparing BuFlu with BuCy as a conditioning regimen prior to HSCT in patients with hematologic neoplasms.

**Materials and methods**

**Inclusion and exclusion criteria**

All reports comparing BuFlu with BuCy as myeloablative conditioning regimens prior to HSCT in patients with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) or chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS) and other hematologic neoplasms were considered eligible for inclusion. Non-randomized comparisons from retrospective studies were also included. All reports from clinical trials randomly or non-randomly assigning patients to either BuFlu regimen or BuCy were considered for pooling in the meta-analysis. Trials comparing different doses of Flu or different chemotherapy regimens were not considered for inclusion. Studies on autoimmune diseases and non-myeloablative or reduced-intensity conditioning were also not considered.

**Literature search strategy**

We used Medical Subject Headings (MeSH), Professional terminology and searched term in all electronic databases: (busulfan and cyclophosphamide OR BuCy) AND (busulfan and fludarabine OR BuFlu) AND allogeneic [MeSH] and crossed with the search sentence: prospective OR longitudinal OR cohort OR randomized controlled trial OR controlled clinical trial, searched the Cochrane Library (current) and PubMed, science and used Chinese with the same method searched the sinoMed VIP, CNKI, WanFang. Cross-references from selected articles were also used for retrieving relevant studies. Two reviewers independently selected studies according to inclusion and exclusion criteria, extracted data, in case of disagreements were resolved by discussion.

**Outcome measures**

The primary outcome of interest was efficacy as measured by overall survival (OS) and event-free survival (EFS or leukemia-free survival). Secondary outcomes included acute graft-versus-host-disease (aGVHD, we chose to evaluate cumulative incidence at day 100 post HCT based on the classical definition of GVHD), chronic GVHD, liver related toxicity, CMV infection, relapse or progression incidence, RRM. These outcomes were evaluated according to the study definition.

**Quality assessment**

We used the Cochrane Collaboration’s tool for assessing risk of bias for randomized controlled trials. It provided a description of what was reported in the study and gave a subjective judgment regarding protection from bias: low risk, high risk of bias or unclear risk (according to Cochrane Review’s handbook 5.3, updated March 2011; available from www.cochrane-handbook.org) by Table 1. We used the Newcastle-Ottawa scale [5] (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), for non-randomized studies, to assess whether the study adjusted for the confounders listed in Table 2.
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Table 2. Quality assessment of included non-randomized controlled trials

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the non exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Comparability of cohorts</th>
<th>Assessment of outcome</th>
<th>Duration of follow up</th>
<th>Adequacy of follow up</th>
<th>Adequacy Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>YS Chae 2007 [11]</td>
<td>b</td>
<td>a</td>
<td>d</td>
<td>a</td>
<td>d</td>
<td>b</td>
<td>a</td>
<td>4</td>
</tr>
<tr>
<td>Joseph 2010 [12]</td>
<td>b</td>
<td>a</td>
<td>d</td>
<td>c</td>
<td>d</td>
<td>b</td>
<td>a</td>
<td>3</td>
</tr>
<tr>
<td>BorjeS 2008 [13]</td>
<td>b</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>d</td>
<td>a</td>
<td>a</td>
<td>6</td>
</tr>
<tr>
<td>HuKai 2014 [14]</td>
<td>b</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>d</td>
<td>b</td>
<td>a</td>
<td>5</td>
</tr>
<tr>
<td>Roberta 2014 [15]</td>
<td>b</td>
<td>a</td>
<td>d</td>
<td>a</td>
<td>d</td>
<td>b</td>
<td>a</td>
<td>4</td>
</tr>
</tbody>
</table>

Adapted from http://www.endoedu.com/mobile/guideline/NOS cohort.pdf Newcastle-Ottawa Quality Assessment of Cohort Studies. Representativeness of the cohort: (a’) truly representative, (b’) somewhat representative, (c) selected group, (d) ND. Selection of non-exposed cohort: (a’) same community, (b) different source, (c) ND. Ascertainment of exposure: (a’) secure record, (b’) structured interview, (c) written self report, (d) ND. Comparability of cohorts: (a’) study controls for % of disease risk, (b’) study controls for age, sex, stem sell source and donor type, (c) study is not controlled. Outcome assessment: (a’) independent blind, (b’) record linkage, (c) self report, (d) ND. Duration of follow up: (a’) adequate-at least 5 years (if outcomes other than 5 years OS are reported) or at least 3 months (if only acute GVHD was reported), (b) not adequate-does not fit (a). Adequacy of follow up: (a’) complete, (b’) <10% lost, (c) >20% lost, (d) ND. ND-no description; “—adequate. Adequacy score was summarized for each study by addition the number of subjects with adequate score (mark with ""). Maximal score was seven.

Data analysis

Meta-analysis for any outcome of interest was attempted only if relevant data could be extracted from three or more trials. All meta-analyses were performed using the random effects model (assuming the existence of heterogeneity) to provide a more conservative yet robust estimate of effect. Review Manager (RevMan version 5.3, Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration 2011) was used for performing the meta-analyses. Relative risk or risk ratio (RR) and 95% confidence interval (CI) were calculated for each outcome and presented as forest plots after pooling. The pooled RR, symbolized by a solid diamond at the bottom of the forest plot (the width of which represents the 95% CI) is the best estimate of the pooled outcome. Sensitivity or influence analysis was carried out to assess the influence of each study on the overall summary effect. The heterogeneity analysis included in the study was done by chi-square test according to Higgins’ study [6] and P<0.1 means the heterogeneity exists. The size of the heterogeneity [7] was judged by the I² (the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error) and I²>50% means the heterogeneity is bigger.

Results

The search yielded 389 potentially relevant trials of which twelve trials [8-19] were considered for further investigation. Of them, 3 studies were excluded [17-19]. Nine trials, enrolling 1155 patients treated in between 2008 and 2014, met the inclusion criteria [8-16]. Four trials were randomized controlled trials [8-10, 16] (enrolling 584 patients: 292 patients in BuCy group, 292 patients in BuFlu group). One of the randomized clinical controlled trials was an interim analysis report and the authors reported on data of 126 out of 130 patients originally recruited to the study [8]. Three trials were prospective one arm interventional trials with comparison to historical controls [11-13]. All other 2 trials were retrospective comparative studies [14, 15]. Data regarding demographics, host and donor characteristics, transplantation protocol, GVHD prophylaxis and the median follow-up time are summarized in Table 3.

Primary outcomes

Acute GVHD

Acute GVHD generally occurs within first 100 days of transplantation, while chronic GVHD occurs beyond 100 days. Data on the incidence of acute GVHD could be extracted from 5 trials that were pooled for meta-analysis. There was no difference in the incidence of grades 3-4 acute GVHD between BuCy group and BuFlu group (RR 2.58, [95% CI 0.56-11.76], 5 studies, Figure 1). Sensitivity analysis for grades 3-4 acute GVHD, including only RCTs showed similar results (RR 2.44, [95% CI 0.25-23.60], 3 studies). Subgroup analysis according to the studies in which only patients received intravenous busulfan were included showed a similar
### Table 3. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>NO. Of patients</th>
<th>median age (years)</th>
<th>conditioning regimen (range)</th>
<th>Included disease</th>
<th>GVHD prophylaxis</th>
<th>Graft source</th>
<th>Donor’s characteristic</th>
<th>The median follow-up time (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2011 [8]</td>
<td>40</td>
<td>40.5 (17-63)</td>
<td>Bu3.2 mg/kg/d iv - 7 d~ 4 d; Cy60 mg/kg/d iv - 3 d~ 2 d</td>
<td>AL; CML; MDS</td>
<td>CsA; MTX; MMF</td>
<td>BM (n=56); PB (n=68); CB (n=2)</td>
<td>RD (n=96); NRD (n=30)</td>
<td>27 (4-56)</td>
</tr>
<tr>
<td>Liu H 2013 [9]</td>
<td>40</td>
<td>30.5 (12-52)</td>
<td>Bu3.2 mg/kg/day iv - 7 d~ 4 d; Cy60 mg/kg/d iv - 3 d~ 2 d</td>
<td>AML; ALL; CML; MDS</td>
<td>CsA; MTX; MMF</td>
<td>BM (n=103); PB (n=2)</td>
<td>RD (n=93); NRD (n=15)</td>
<td>31 (23-40)</td>
</tr>
<tr>
<td>Chung 2014 [10]</td>
<td>50</td>
<td>64 (17-49)</td>
<td>Bu3.2 mg/kg/d iv - 7 d~ 4 d; Cy60 mg/kg/d iv - 3 d~ 2 d</td>
<td>AML</td>
<td>CsA; MTX; MMF; ATG</td>
<td>BM (n=19); PB (n=73); NRD (n=15)</td>
<td>RD (n=80); NRD (n=15)</td>
<td>10 (1-94)</td>
</tr>
<tr>
<td>Joseph 2010 [11]</td>
<td>51</td>
<td>100</td>
<td>Bu4 mg/kg/d po - 7 d~ 4 d; Cy60 mg/kg/d iv - 3 d~ 2 d</td>
<td>AML</td>
<td>CsA; MTX; MMF; RAPA</td>
<td>BM (n=37); PB (n=114)</td>
<td>RD (n=112); NRD (n=113)</td>
<td>8 (1-90)</td>
</tr>
<tr>
<td>Borje S 2008 [12]</td>
<td>148</td>
<td>46 (19-66)</td>
<td>Bu3.2 mg/kg/d iv - 7 d~ 4 d; Cy60 mg/kg/d iv - 3 d~ 2 d</td>
<td>AML; MDS; ALL</td>
<td>CsA; MTX; MMF; MP</td>
<td>BM (n=84); PB (n=131); NRD (n=84)</td>
<td>RD (n=132); NRD (n=131)</td>
<td>74.6 (unclear)</td>
</tr>
<tr>
<td>HuKai 2014 [13]</td>
<td>28</td>
<td>28 (7-45)</td>
<td>Bu3.2 mg/kg/d iv - 6 d~ 4 d; Cy1.8 g/m²/d iv - 3 d~ 2 d; Ara-C2 g/m²/d iv - 3 d~ 2 d; Me-CCNU1250 mg/m²/d po -1d</td>
<td>AML; MDS; ALL</td>
<td>CsA; ATG; Pentostatin</td>
<td>BM (n=17); PB (n=45)</td>
<td>RD (n=37); NRD (n=8)</td>
<td>17 (7-108)</td>
</tr>
<tr>
<td>Roberta 2014 [14]</td>
<td>48</td>
<td>42 (14-57)</td>
<td>Bu3.2 (4) mg/kg/d iv (po) - 8 d~ 5 d; Cy60 mg/kg/d iv - 3 d~ 2 d</td>
<td>AML</td>
<td>CsA; ATG</td>
<td>BM (n=26); PB (n=39)</td>
<td>RD (n=65); NRD (n=65)</td>
<td>69 (0.4-199)</td>
</tr>
<tr>
<td>Rambaldi 2014 [15]</td>
<td>121</td>
<td>50 (unclear)</td>
<td>Bu3.2 mg/kg/d iv, 4 consecutive days; Cy60 mg/kg/d iv, 2 consecutive days</td>
<td>AML</td>
<td>CsA; MTX</td>
<td>BM (n=77); PB (n=168)</td>
<td>RD (n=112); NRD (n=113)</td>
<td>8 (1-90)</td>
</tr>
</tbody>
</table>

**Notes:** BU: busulfan; Flu: fludarabine; Cy: cyclophosphamide; Ara-C: cytosine arabinoside; Me-CCNU: semustine; CsA: cyclosporin A; MTX: methotrexate; MMF: mycophenolate mofetil; ATG: Antithymocyte globulin; MP: methylprednisolone; RAPA: Rapamycin; AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; MDS: myelodysplastic syndrome; CML: chronic myeloblastic leukemia; NHL: non-Hodgkin lymphoma; HLH: hemophagocytic lymphohistiocytosis; BM: bone marrow; PB: peripheral blood; cord blood; RD: related donors; NRD: unrelated donors.
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Figure 1. Meta analysis of acute GVHD.

A

B

Test for subarous differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%
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incidence of grades 3-4 acute GVHD in both the two groups (RR 2.84, [95% CI 0.48-16.70], 4 studies). Five tries reported the incidence of severe (grades 2-4) acute GVHD. There was no significant increase in the rate of aGVHD in patients given BuCy compared to patients given BuFlu (RR 1.33, [95% CI 0.58-3.08], 5 studies, Figure 1). Subgroup analysis according to the studies in which only patients received intravenous busulfan were included showed a similar incidence of grades 2-4 acute GVHD in both the BuCy and the BuFlu groups (RR 0.94, [95% CI 0.43-2.04], 2 studies).

Overall survival

All studies provided data overall survival. The use of BuCy was associated with a 4% reduction in OS at 2-years (RR 0.96, [95% CI 0.80-1.15], 9 studies) compared to BuFlu (Figure 2A) that was not statistically significant. Sensitivity analysis including RCTs showed similar non-significant results (RR 1.06, [95% CI 0.86-1.31], 4 studies). Subgroup analysis according to the studies in which only patients received intravenous busulfan were included also showed a similar incidence of 2 years OS in both the two groups (RR 1.01 [95% CI 0.85-1.21], 6 studies). Four studies reported the incidence of 5 year OS. There was no difference in 5 year OS between the two groups (RR 0.86, [95% CI 0.71-1.04], 4 studies, Figure 2B).

Event free survival

Seven studies provided data on event-free survival. The use of BuCy was associated with a 12% reduction in EFS at 2-years (RR 0.88 [95% CI 0.69-1.13], 7 studies) compared to BuFlu (Figure 3A) that was not statistically significant. Sensitivity analysis including RCTs showed similar non-significant results (RR 1.05 [95% CI 0.83-1.32], 4 studies). Four studies reported the incidence of 5 year EFS. There was no difference in 5 year EFS between the two groups (RR 1.07 [95% CI 0.81-1.41], 4 trials, Figure 3B).

Non-relapse mortality

Nine tries [7-14] reported the incidence of NRM. The use of BuCy was associated with a 48% increment in NRM (RR 1.48 [95% CI 0.97-2.26], 9 studies) compared to BuFlu (Figure 4).
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that was not statistically significant. Sensitivity analysis including RCTs showed similar non-significant results (RR 1.14 [95% CI 0.56-2.30], 4 studies). Subgroup analysis according to the studies in which only patients received intravenous busulfan were included showed a similar incidence of NRM in both the two groups (RR 1.37 [95% CI 0.80-2.36], 6 studies).

Chronic GVHD

Data on the incidence of chronic GVHD could be extracted from 8 trials that were pooled for meta-analysis. There was no difference in the incidence of chronic GVHD between BuCy group and BuFlu group (RR 0.94 [95% CI 0.68-1.31], 8 studies, Figure 5A). Sensitivity analysis for cGVHD including only RCTs showed similar results (RR 1.03 [95% CI 0.84-1.25], 3 studies). Seven studies reported the incidence of extensive cGVHD. The use of BuCy was associated with a 6% increment in extensive cGVHD (RR 1.06 [95% CI 0.83-1.36], 7 studies) compared to BuFlu (Figure 5B) that was not statistically significant. Subgroup analysis according to the studies in which only patients received intravenous busulfan were included showed a similar non-significant incidence of extensive cGVHD in both the two groups (RR 0.99 [95% CI 0.74-1.31], 5 studies).

Figure 4. Meta analysis of non-relapse mortality.

Figure 5. Meta analysis of chronic GVHD.
Regimen-related toxicity

Six trials reported the incidence of liver related toxicity. BuCy was associated with a significant increment (90%) in the risk of RRT (Figure 6) compared to the BuFlu regimen (RR 1.90 [95% CI 1.00-3.61], 6 trials). However, there was no significant increment in subgroup analysis according to the studies in which only patients received intravenous busulfan were included in both the BuCy and the BuFlu groups (RR 1.39 [95% CI 0.86-2.25], 3 studies). Three studies [8, 10, 15] reported heart related toxicity. The incidence of cardiac toxicity was 10.8% in BuCy group and 4.5% in BuFlu group. Roberta’s [15] study was comprehensive reported the early regimen-related toxicity in the two groups. The result showed that the gastrointestinal damage, nerve toxicity, the incidence of lung, bladder, and kidney toxicity were higher in BuCy group than BuFlu group.

CMV infection

Five studies provided data on CMV infection. There was no significant difference in the inci...
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Table 1: Comparison of incidence of CMV infection between the two groups (RR 1.25 [95% CI 0.99-1.58], 5 trials, Figure 7). Similar results were seen when only the three RCTs were included in sensitivity analysis (RR 1.18 [95% CI 0.89-1.56], 3 studies).

**Relapse or progression incidence**

The incidence of relapse or progression from six studies was very similar (Figure 8) in the two treatment groups (RR 0.98 [95% CI 0.70-1.38], 6 trials). Similar results were seen when only the four RCTs were included in sensitivity analysis (RR 0.92 [95% CI 0.62-1.37], 4 studies).

**Relapse related mortality**

There was no significant difference in the incidence of relapse related mortality between the two groups (RR 1.14 [95% CI 0.91-1.44], 6 trials, Figure 9). Similar results were seen when only the two RCTs were included in sensitivity analysis (RR 0.93 [95% CI 0.55-1.57], 2 studies).

**Discussion**

Allo-HSCT is an effective, even the only curative option for patients with hematologic malignancies. The conditioning regimen before stem cell transplantation is an important factor affecting the prognosis of patients [20]. Successful bone marrow transplantation (BMT) with a combination of cyclophosphamide (Cy) and total body irradiation (TBI) was reported in the 1970s [21]. In 1980s, a new regimen with BuCy was found for allogeneic marrow transplantation [22]. Accordingly Cy-TBI and BuCy regimens have been regarded as the standard conditioning regimens with sufficient anti-leukemia effect, but they also have a very high incidence of pre-treatment-related toxicity [23]. BuCy is associated with significant risks of cardiotoxicity, hemorrhagic cystitis, hepatic veno-occlusive disease (HVOD). Some scholars [24, 25] found the incidence of life-threatening cardiac toxicity accounted for 5% to 10% and hemorrhagic cystitis incidence up to 70% after accepting the conditioning regimen containing cyclophosphamide. Interactions between busulfan and cyclophosphamide might result in increased liver toxicity, especially the incidence of HVOD. Regimens combined busulfan with cyclophosphamide, when the oral busulfan substitute for intravenous, still cause the HVOD increasing as the metabolites of them are conjugated with glutathione (GSH) [26].

Fludarabine is a purine analog that inhibits DNA replication and repair. As it has shown a safe toxicity profile, strongly immunosuppressive activity and synergistic tumor-killing effect with busulfan, many researchers used BuFlu in myeloablative and non-myeloablative conditioning regimens for allo-HSCT in hematological malignancies. In the study of Iravani et al [27] and Ma et al [28], the application of BuFlu conditioning regimen in myeloid malignancies can reduce acute and chronic GVHD, HVOD, TRM, but there is no significant difference in EFS, OS compared with the classical conditioning regimen. In this study, we compared and analyzed the efficacy and toxicity between BuCy and BuFlu regimens and the results show that BuCy and BuFlu regimen has no significant difference in the incidence of acute and chronic GVHD, relapse rate and non-relapse mortality, EFS, OS, etc. But the BuFlu may have lower incidence of hepatic toxicity due to the small sample size. This suggests that patients with liver dysfunction cloud choose BuFlu as a myeloab-
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relative conditioning regimen when undergoing allo-HSCT, and it may be able to reduce the complications of liver.

In every study, the BuCy or BuFlu regimen are consistent in the aspects of pretreatment method, dosage of medication, underlying disease, GVHD prophylaxis, stem cell sources, donor type and follow-up time, and baseline equilibrium. The study results don’t change significantly by analyzing the heterogeneous sensitivity, indicating that the combined results are more reliable and also have a certain reference value to guide follow-up study of positive significance. However, there exists selected bias in the included studies and the date is not complete. In addition, the included studies are mostly retrospective controlled study, and the cases were collected in different ways as it was from a variety of countries and regions. Meta-analysis is unable to obtain more detailed information than the literature. Thus some potential factors such as duration of disease, pre-transplant chemotherapy, diet, physical condition, may impact on the results. Large randomized controlled studies are needed to enhance proof strength and provide high quality research evidence for the second evaluation.

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Disclosure of conflict of interest

None.

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