Bone Marrow Versus Peripheral Blood Stem Cell Transplant in Lymphoma: A Systematic Review and Meta-Analysis

Yanxia Jiang, Yue Zhen, Qian Xu, Dong He, Guoan Chen, Yan Chen

Abstract

Objectives: The choice of whether to use bone marrow or peripheral blood in autologous transplantation remains controversial. Posttransplant relapse and long-term survival are critical issues.

Materials and Methods: Studies that compared bone marrow transplant versus peripheral blood stem cell transplant in lymphoma patients were searched. Our search resulted in 15 studies.

Results: Pooled data showed contradictory results with no conclusive differences in overall survival (for randomized controlled trials vs nonrandomized controlled trials: hazard ratio = 0.69 vs 1.17; 95% confidence interval, 0.44-1.10 vs 0.90-1.51; and \( P = .12 \) vs \( P = .25 \)), progression-free survival (for randomized controlled trials vs nonrandomized controlled trials: hazard ratio = 0.89 vs 1.14; 95% confidence interval, 0.57-1.38 vs 0.82-1.58; and \( P = .60 \) vs \( P = .43 \)), and relapse rates. However, we observed an overall trend toward lower relapse rate after bone marrow transplant. Lower relapse rate was likely associated with better progression-free survival (\( P = .052 \)), and lower transplant-related mortality was associated with better overall survival (\( P = .043 \)).

Conclusions: Autologous bone marrow transplant with mobilization should be reconsidered for lymphoma patients to reduce recurrence and improve quality of life. More powered randomized controlled trials are warranted to update our findings.

Key words: Autologous transplantation, Bone marrow transplant, Hematopoietic stem cells

Introduction

High-dose chemotherapy followed by autologous hematopoietic stem cell transplant (auto-HSCT or ASCT) has been a standard treatment modality for refractory or relapsed non-Hodgkin lymphoma (NHL) and Hodgkin disease. Early consolidative transplant improves the prognosis of patients with high-risk aggressive lymphoma who gain little benefit from conventional regimens alone. Autologous bone marrow and peripheral blood progenitor cells permit the use of significantly intensified chemotherapy or radiotherapy irrespective of fatal myelosuppression or hematologic toxicity. As a first-line treatment, high-dose chemotherapy plus ASCT substantially reduces the bone marrow tumor load, resulting in a high rate of complete response, but late relapses are common. Bone marrow transplant (BMT), which contains a number of different stem cell populations, including hematopoietic stem cells, mesenchymal stem cells, endothelial progenitor cells, and fibroblasts, may have a protective effect. Peripheral blood progenitor cells have become more popular due to their faster trilineage engraftment or because NHL usually involves the bone marrow. However, whether bone marrow or mobilized peripheral blood has more tumor cell contamination or greater clonogenic potential is unclear because tumor cells can also be mobilized to the peripheral blood. Although “solid tumors” like lymphoma are distinct from leukemia or other blood cancers, most systematic reviews and meta-analyses on this topic have taken all hematologic malignancies into account. To further investigate whether the stem cell source is associated with better survival outcomes, lower relapse rates, or nonrelapse mortality, we did a meta-analysis to compare BMT and peripheral blood stem cell transplant (PBSCT) among lymphoma patients.
Materials and Methods

This meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO, Centre for Reviews and Dissemination, University of York, York, UK) on March 6, 2016 (Registration No. CRD42016036152). We prepared a prospective protocol a priori in adherence to PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 20151 and MOOSE (Meta-analysis of Observational Studies in Epidemiology),2 which are centered around the PICO principle.

Literature search
PubMed, EMBASE, and the Cochrane Library were searched for electronic records to be exported into EndNote X7.5 (Thomson Reuters, New York, NY, USA), augmented by Google Scholar, the Lymphoma Research Foundation, the National Cancer Institute, the Center for International Blood and Marrow Transplant Research, OpenGrey, and ClinicalTrials.gov. The databases were searched from their inception until January 3, 2016. No language or outcome restrictions were imposed. The search strategy was uploaded to PROSPERO. In addition, we scanned the obtained full-text articles and scrutinized the references of included papers and pertinent reviews. We also manually searched abstracts from conference proceedings of annual meetings of the American Society of Hematology, American Society of Clinical Oncology, European Hematology Association, and the European Bone Marrow Transplantation Group from 2000 to 2015 for other eligible studies.

Inclusion and exclusion criteria
All randomized controlled trials (RCTs), controlled clinical trials, and cohort or case-control studies comparing PBSCT with BMT for lymphoma patients of any age, with at least one of the quantitative data sets for survival or death, progression/relapse, and engraftment (absolute neutrophil count > 0.5 x 10^9/L; platelet count > 20 x 10^9/L), whether in a full-text or an abstract format, were included. Those studies that compared either PBSCT or BMT with a mixed combination of the 2 or a second HSCT were ineligible. We intended to include hematologic malignancies if the data of lymphoma patients could be separately extracted, but no population in our practice fit this case.

We also questioned whether the differences between peripheral blood and bone marrow varied with donor type (ie, allogeneic or autologous donors); therefore, the initial search strategy was designed not to exclude allogeneic HSCT for lymphoma. However, only 3 documents (2 full-text articles3,4 and 1 abstract5) were returned, which were inadequate to answer this question. Thus, “allo-HSCT” studies were excluded. Although no language restriction was imposed during the search, only English and Chinese studies were eligible for comprehension. Two reviewers (YZ and YC) independently evaluated all selected articles meeting the predefined criteria, and the strength of agreement on the final inclusion was graded using the Cohen statistic.6

Data extraction
Data were extracted by YZ and confirmed by YC. The extracted data were filled into a standardized Excel file (Microsoft Corporation, Redmond, WA, USA). If data at both diagnosis and transplant were provided, we chose the latter one for analysis. Median (range) days to neutrophil and platelet recovery were converted to the mean and standard deviation using estimation methods recommended by Hozo and associates.7 The original publication was retained to clarify the study characteristics, using other updated versions only to supplement longer follow-up data. Standard error and the natural logarithm of hazard ratio (HR) were indirectly calculated from the reported number of events with the log-rank P value or by digitizing the Kaplan-Meier curves using Engauge Digitizer8 version 4.1 (Mark Mitchell) and Adobe Photoshop CS6 Extended as described by Tierney and colleagues.9 An attempt was made to contact all primary authors for incomplete information by sending E-mails and Research Gate messages; however, no responses were received. Any discrepancies would be addressed by joint crosschecks for validity.

Quality assessment
We applied the revised Cochrane “risk of bias” tool (described in version 5.1.0) to estimate the methodologic quality of included RCTs, whereas non-RCT comparative studies were critically appraised using the ROBINS-I tool (Risk of Bias in Non-randomized Studies of Interventions) version 7 (March 2016),10 which considers 7 domains of bias.
and 1 overall bias. Each domain is judged as low, moderate, serious, or critical risk or as having too little information to determine. One study mixed the randomized and nonrandomized data and was assessed using both tools. Disagreements would be resolved through discussions to reach a consensus.

Data synthesis and statistical analyses
Data from interventional and observational studies were synthesized separately. Subgroup analyses were performed according to study design. In sensitivity analyses, we tested whether omitting a single study affected the final results. Continuous outcomes were expressed as the mean differences and binary outcomes as odds ratios (ORs) with 95% confidence interval (95% CI). In time-related adverse events, an HR > 1 favored BMT over PBSCT. Interstudy heterogeneity was explored using the Cochran’s Q test with significance set at \( P < .1 \) and \( I^2 \) statistic with a cut-off value of > 50%, which indicated severe heterogeneity. A random-effects model would then be chosen; otherwise, the fixed-effects model would be used. An L’Abbé plot mirrored the relapse rate in the experimental group versus in the control group and reflected the heterogeneity of binary variables. Meta-regression models helped to investigate potential covariates that might contribute to the heterogeneity of continuous variables.

Publication bias was visualized by funnel plots and quantified by using the Egger test. Meta-regression and publication bias were not conducted routinely when the study number was less than 10. Unless otherwise specified, \( P < .05 \) (2-sided) was considered statistically significant. All statistical analyses were performed using RevMan 5.3.5 (Nordic Cochrane Centre, Copenhagen, Denmark) and Stata/MP 14.1 (StataCorp LP, College Station, TX, USA).

Results
Search results
Study selection results are illustrated in Figure 1. Our initial search returned 8596 citations, which included 5113 from EMBASE, 3085 from PubMed, and 398 from Cochrane Central Register of Controlled Trials, without additional sources of publications identified. Of the 7024 nonduplicate records, 6962 were quickly discarded (reviews, case reports, biomarker and animal/cell studies, and those not relevant). The remaining 62 references were retrieved for eligibility assessment, and 46 publications were excluded for reasons shown in Figure 1. Finally, 15 studies (5 RCTs, 11-16 2 controlled clinical trials, 17,18 and 8 observational studies 19-26) comprising 16 publications (15 accessed as full text 11-18,20-26 and 1 as an abstract 19) were included in this meta-analysis. The Cohen statistic for agreement was 0.90.

Study characteristics
Of the 8 observational studies, four were cohort studies (2 prospective studies 20,22 and 2 retrospective studies 19,25) and four 21,23,24,26 were retrospective case-control studies (3 with matched-pair designs 21,24,26). The main study characteristics and summary outcomes are shown in Tables 1 to 3. Nine studies originated from Europe, 5 from the United States, and 1 from Asia. These studies were published between 1994 and 2005, enrolling a total of 1993 patients with lymphoma, among whom 1949 patients received high-dose chemotherapy plus ASCT (988 PBSCT and 961 BMT). Data from 1883 patients were analyzed. Sample sizes varied across studies, ranging from 26 to 710. Most patients were 30 to 50 years old and diagnosed with advanced relapsed/refractory NHL or Hodgkin disease. The median age was generally larger within the PBSCT groups.
Quality assessment
The risk of bias assessment of the included studies is presented in Tables 4 and 5.

Primary outcomes
No studies provided HR information directly on overall and progression-free survival (PFS) assessments. By indirect means, 12 studies qualified for overall survival (OS) analysis in 1543 patients (Figure 2a) and 10 for PFS analysis in 1570 patients (Figure 2b). When RCTs and non-RCTs were examined, the opposite results were shown. We found a significant heterogeneity ($I^2 = 51\%$) within the non-RCT subgroup regarding PFS. Therefore, a random-effects model was applied. No significant heterogeneity was found in both OS subgroups ($I^2 = 0\%$ and 49\%, respectively); however, given the subgroup differences ($P = .05$), we strongly estimated a publication bias for RCTs, which is mostly dotted on the left side of the OS funnel plot (Figure 2c).
<table>
<thead>
<tr>
<th>Author</th>
<th>Conditioning Regimen</th>
<th>Mobilization (PBSC)</th>
<th>HLC Regimen ≥ 3</th>
<th>Radiotherapy (with TBI)</th>
<th>Elevated LDH*</th>
<th>Disease Status (% CR or PR)</th>
<th>Tumor Mass &gt; 10 cm</th>
</tr>
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<tbody>
<tr>
<td>Randomized controlled trials</td>
<td></td>
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</tr>
<tr>
<td>Vose11</td>
<td>BEAC</td>
<td>G-CSF SC 10 µg/kg/d (day -4 to -1)</td>
<td>PB: 32% BM: 13%</td>
<td>No</td>
<td>(&gt; normal) PB: 21% BM: 3 (6%)</td>
<td>PB: 3  (7%)</td>
<td></td>
</tr>
<tr>
<td>Schmitz13</td>
<td>BEAM</td>
<td>G-CSF SC 10 µg/kg/d (day -6 to -1)</td>
<td>PB: 30% BM: 23%</td>
<td>PB: 33% BM: 45%</td>
<td>Unknown</td>
<td>PB: 0 BM: 0</td>
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</tr>
<tr>
<td>Vellenga13</td>
<td>BEAM</td>
<td>GM-CSF SC 5 µg/kg/d (day 4 after the 2nd DHAP)</td>
<td>Unknown</td>
<td>PB: 29% BM: 31%</td>
<td>(≥ 2 x normal) PB: 9% BM: 10%</td>
<td>Unknown</td>
<td></td>
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<tr>
<td>Kanteti14</td>
<td>Thiotepa, CTX, carboplatin, VP16</td>
<td>G-CSF SC 10 µg/kg/d (day -4 to -1)</td>
<td>PB: 12% BM: 43%</td>
<td>PB: 41% BM: 29%</td>
<td>Unknown</td>
<td>PB: 12% BM: 21%</td>
<td></td>
</tr>
<tr>
<td>Damiani12</td>
<td>BEAC (NHL) BEAM (HD)</td>
<td>G-CSF SC 16 µg/kg/d (day -4 or -5 to -1 [PB]; day -3 to -1 [BM])</td>
<td>Lines ≥ 2: PB: 16% BM: 11%</td>
<td>PB: 21% BM: 22%</td>
<td>Unknown</td>
<td>PB: 100% BM: 100%</td>
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<tr>
<td>Controlled clinical trials</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Weisdorf17</td>
<td>CTX (BCNU, VP16 or TBI)</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>PB: 80% BM: 85%</td>
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<td>Hou18</td>
<td>CBV</td>
<td>G/G-CSF 5 µg/kg/d x 5 days, CTX 2-3 g/m²/d x 2 days</td>
<td>Unknown</td>
<td>Unknown</td>
<td>PB: 29% BM: 14%</td>
<td>PB: 100% BM: 100%</td>
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</tr>
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<td>Cohort studies</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brice25</td>
<td>BEAC, CBV, BEAM, TBI</td>
<td>G-CSF 5 µg/kg/d day 6 after CT</td>
<td>PB: 28% BM: 36% (n =34)</td>
<td>(&gt; normal) PB: 0 BM: 0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sharp20</td>
<td>VP16-CTX and unknown</td>
<td>No</td>
<td>Unknown</td>
<td>BM: 11%</td>
<td>BM: 18%</td>
<td>Unknown BM: 18%</td>
<td></td>
</tr>
<tr>
<td>Geisler22</td>
<td>BEAM</td>
<td>CTX 3-4 g/m²/day 1; G-CSF SC 5 µg/kg from day 2</td>
<td>PB: 8% BM: 0f</td>
<td>Unknown</td>
<td>Unknown</td>
<td>PB: 95% BM: 84%</td>
<td></td>
</tr>
<tr>
<td>Goldzak19</td>
<td>DexamBEAM, CBV, BuCy2</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>PB: 100% BM: 100%</td>
<td></td>
</tr>
<tr>
<td>Case-control studies</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perry26</td>
<td>BEAM</td>
<td>G-CSF² SC 263 µg/d or 300 µg/d, CTX 1-5 g/m²</td>
<td>PB: 17% BM: 19%</td>
<td>Pre-HSCT: 40%/46%; Post-HSCT: 16%/29%</td>
<td>Unknown</td>
<td>PB: 21% BM: 5 (7%)</td>
<td></td>
</tr>
<tr>
<td>Libert21</td>
<td>No</td>
<td>Unknown</td>
<td>Both: 20%</td>
<td>Unknown</td>
<td>BM: 43%</td>
<td>Unknown</td>
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<tr>
<td>Bierman23</td>
<td>TBI+CTX (+Ara-C), BEAM and CBV (+Hu)</td>
<td>No</td>
<td>Unknown</td>
<td>Both: 40%</td>
<td>77%</td>
<td>(≥ normal) Both: 23%</td>
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<tr>
<td>Majolino24</td>
<td>CBV or BEAM or unknown</td>
<td>G/G-CSF or EPO, GF, EPO, GF; (HD)</td>
<td>(NHL/HD)</td>
<td>PB: 10% BM: 19%</td>
<td>(NHL/HD)</td>
<td>PB: 70%/66% BM: 71%/66%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Ara-C, cytarabine; BEAC, carmustine, etoposide, cytarabine, cyclophosphamide; BEAM, carmustine, etoposide, cytarabine, melphalan; BCNU, carmustine; BM, bone marrow group; BMT, bone marrow transplant; BuCy2, BuCy2 and CTX; CBV, cyclophosphamide, carmustine, etoposide; CK, cytokine; CR, complete response; CT, computed tomography; CTX, cyclophosphamide; Dexam, dexamethasone; DHAP, dexamethasone, cytarabine, cisplatin; EBMT, European Bone Marrow Transplantation; EPO, erythropoietin; GF, growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte/macrophage colony-stimulating factor; HD, Hodgkin disease; HLC, high-dose chemotherapy; HSCT, hematopoietic stem cell transplant; Hu, hydroxyurea; IL, interleukin; NHL, non-Hodgkin lymphoma; PB, peripheral blood stem cell group; PBSC, peripheral blood stem cell; PR, partial response; SC, subcutaneous; TBI, total body irradiation; VP16, etoposide

*More patients in PB group had lactate dehydrogenase (LDH) above the upper limit of normal level (P > 0.05).

**In Geisler’s study, 2 subgroups of BMT were reported, and patients who had high-dose chemotherapy or radiotherapy (≥ 3) regimens were classified as BMT or else as BMT with outcomes showing significant difference from the former.

***Because only 3 patients (8%) of the PBSC cohort had ≥ 3 regimens (compared with 61% of the whole BMT cohort), we used BMT data alone to guarantee outcome comparability. There was imbalance in terms of chemotherapy or radiation therapy in other studies.

****Doses × 2 if patient body weight was > 100 kg.
We found that RCTs might favor PBSCT that improved OS (pooled HR of 0.69; 95% CI, 0.44-1.10; \( P = 0.12 \)) and PFS (pooled HR of 0.89; 95% CI, 0.57-1.38; \( P = 0.60 \)) and non-RCTs might favor BMT that improved OS (pooled HR of 1.17; 95% CI, 0.90-1.51; \( P = 0.25 \)) and PFS (pooled HR of 1.14; 95% CI, 0.82-1.58; \( P = 0.43 \)). However, no significant differences were found between PBSCT and BMT regarding OS and PFS.

Incidence of relapse was derived from 13 of 15 studies with 1584 patients analyzed. Great discrepancies were observed among different study types (Figure 3a). Overall, the L’Abbe plot indicated large heterogeneity and a higher relapse rate after PBSCT.

No significant publication bias regarding relapse rate was determined from the funnel plot (Figure 3b) or the Egger test (\( P = 0.157 \)). In cohort studies, BMT resulted in significantly lower relapse rates than PBSCT (pooled OR of 0.30; 95% CI, 0.13-0.69; \( P = 0.005 \)). However, no significant differences were found in RCT (pooled OR of 2.13; 95% CI, 0.74-6.13; \( P = 0.16 \)) and in case-control studies (pooled OR of 0.63; 95% CI, 0.27-1.47; \( P = 0.29 \)).

**Secondary outcomes**

Ten studies involving 1368 patients reported nonrelapse mortality or early toxic death events (Figure 4a).
Eleven studies of 845 patients and 7 studies of 453 patients reported the median days and ranges to recovery for neutrophils and platelets, respectively. A significantly faster engraftment was shown after PBSCT (Figure 4b and 4c). Further removal of any single study did not virtually change the total effects.

Abbreviations: “Favours” suggests better OS or PFS; IV, generic inverse variance method; RCT, randomized controlled trial; SE, standard error of the mean

Table 4. Risk of Bias Assessment of the Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of Participants and Personnel</th>
<th>Blinding of Outcome Assessment</th>
<th>Incomplete Outcome Data</th>
<th>Selective Reporting</th>
<th>Other Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vose11</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>High risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
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</tr>
<tr>
<td>Schmitz9</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Vellenga13</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>High risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Kanteti14</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>High risk</td>
<td>Unclear risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Weisdorf17</td>
<td>High risk</td>
<td>High risk</td>
<td>High risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
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</tr>
<tr>
<td>Damiani12</td>
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<td>Unclear risk</td>
<td>High risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

Quality assessment was made using the Cochrane risk of bias tool (version 5.1.0). Blinding of participants seemed impossible for all randomized controlled trials due to the intrinsic nature of the intervention. Blinding of outcome assessment was achieved only in Damiani’s study. No studies except Schmitz and associates reported a computer-generated random list and allocation concealment. Weisdorf and associates mixed the data of randomized and assigned patients, some of whom meanwhile received interleukin 1 in another trial. Therefore, their random allocation was of high risk and not free of other bias. Most studies described censored data, and 4 randomized controlled trials mentioned the intention-to-treat analyses for handling. Three studies neglected to report full subset data.

Abbreviations: BMT, bone marrow transplant; CI, confidence interval; PBSCT, peripheral blood stem cell transplant
In non-RCTs, PBSCT had a significantly reduced transplant-related mortality (TRM) (pooled OR of 0.52; 95% CI, 0.33-0.80; \( P = .003 \)). In RCTs, no statistical significance was found that BMT increased TRM (pooled OR of 0.34; 95% CI, 0.11-1.06; \( P = .06 \)). Both subgroups had little heterogeneity (\( I^2 = 0 \% \)).

**Discussion**

Relapse occurs in more than 50% of lymphoma patients after autologous transplant\(^{27,28} \) and is undoubtedly the main reason for rehospitalization. Indeed, relapse-free survival is always of paramount concern to any patient with malignancy. For lymphoma, “relapse-free” is simply “disease-free” (ie, complete remission). Once relapse occurs, it means progression, because relapse is also a type of progression. Progression has a broader definition that includes partial remission and refractory disease. Because relapse rate more directly describes relapse than relapse-free survival and because relapse-free survival is closer to describing OS if there is a rare relapse over a short time, PFS was used more often than relapse-free survival in our included studies.

In this study, we found that PFS was not different between BMT and PBSCT studies; however, significant heterogeneity was observed regarding PFS in individual studies, which might be explained by different relapse rates. Relapse rate varied by study design, but subgroup analysis and meta-regression analysis failed to reveal the cause of lymphoma relapse. However, stem cell source was highly suspected, and the overall results appeared to favor BMT. Overall survival was more closely related to TRM than relapse rate. Both TRM and engraftment favored PBSCT, and their pooled results were highly consistent. However, PBSCT had no significant OS benefit.

We found no reasons why RCTs and non-RCTs showed conflicting results. Indeed, relapse itself is a disputed issue. Tumor burden originates from minimal residual disease after high-dose chemotherapy or from reinfused contaminating autografts. However, some groups have found that peripheral blood progenitor...
cells contain more tumors,29,30 others have found that bone marrow contains more tumors,31-33 and others have shown that peripheral blood progenitor cells and bone marrow are similarly contaminated.20,34,35 One study revealed that peripheral blood progenitor cell contamination was highly variable.27 However, all studies implied that peripheral blood progenitor cells were frequently contaminated. In fact, tumor cells were found in the blood before mobilization or were mobilized into the circulation regardless of marrow infiltration circulating tumor cells, although the blood was initially polymerase chain reaction negative.26 Because Hodgkin disease has notoriously poor peripheral blood progenitor cell collections,37 it may result in repeated mobilization. Because more cells are required for peripheral blood progenitor cell infusion than for BMT, peripheral blood progenitor cell autografts may actually be even more contaminated by lymphoma cells.26

We speculated that immunosurveillance may play a role in the lower relapse rate of patients after BMT. This was based on the evidence that all subsets of natural killer T cells in malignant marrow were more activated than in peripheral blood and that long-lasting expansion of the CD56+ and CD16+ natural killer T-cell subsets was observed only in BMT.39 Natural killer cells are known to monitor cancer development and to kill tumor cells. Natural killer T cells are T cells that express killer cell immunoglobulin-like receptors; these receptors can recognize the down-regulated major histocompatibility complex class I-like molecule CD1d on the tumor cell surface or secrete cytokines such as interferon gamma and tumor necrosis factor alpha, which participate in the antitumor immune response.40 The invariant natural killer T cells are a type I CD1d-reactive natural killer T-cell subset that can protect host immunosurveillance against a B-cell lymphoma.41 A high-level invariant natural killer T-cell line within the graft is the only subset associated with less recurrence and improved PFS.42 In BMT, faster recovery predominantly involved
CD8+ cytotoxic T cells and CD19+/CD20+ B cells. Conversely, PBSCT was more profound for CD4+ helper T and T regulatory cells. Peripheral blood progenitor cells were reported to have an increased secondary cancer risk, particularly for myelodysplastic syndrome/acute leukemia occurrences. Transplanted bone marrow cells might be capable of mounting an immunologic assault against the chemoresistant residual lymphoma cells, resembling a graft versus leukemia effect.

Because high-dose chemotherapy and radiation therapy damage the hematopoietic system, especially the immune system, TRM basically refers to infection as its adverse event. Because of mobilization required for PBSCT, both hematopoietic recovery and immunologic reconstitution can be quicker, resulting in reduced infectious complications and thus significantly lower TRM in PBSCT. Although OS but not relapse is dependent on TRM, PBSCT is not associated with a better OS, indicating that OS might have other confounding factors besides nonrelapse mortality. However, the use of granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor could result in inconclusive outcomes. In the study from Weisdorf and associates, both bone marrow collection and PBSC collection were unmobilized, with the collections in the study from Damiani and associates being mobilized. Interestingly, in both studies, use of BMT had better results. We attributed the severe heterogeneity of neutrophil recovery to diverse granulocyte colony-stimulating factor doses in the studies. Despite rapid blood cell recovery, mobilization impaired the long-term marrow reconstitutive ability of autografts in lymphoma patients, which caused persistent deficiency for several years after PBSCT.

Hemopoietic stem cells are the most relevant targets for high-dose stem cell toxic drugs. Hemopoietic stem cells residing in the bone marrow microenvironment maintain a lifelong self-renewal capacity to repopulate the blood system. It has been reported that peripheral blood progenitor cell grafts are more easily affected by previous cytotoxic chemotherapy, whereas bone marrow progenitor cells are not as sensitive as peripheral blood progenitor cells, since little or no impact was found in early and long-term recovery after hemopoietic stem cell BMT. This was particularly advantageous in heavily pretreated lymphoma patients with poor peripheral blood progenitor cell mobilization. Epigenetic detection revealed that only bone marrow-derived mesenchymal stem cells exhibited hypomethylation and increased expression of transcriptional genes, which facilitated hematopoietic niche formation and permitted homing and maintenance of long-term hemopoietic stem cells. Mesenchymal stem cells have also been shown to promote early immune reconstitution for lymphomas after ASCT.

To our knowledge, this is the second systematic review but the first meta-analysis comparing bone marrow versus peripheral blood ASCT in patients with lymphoma with a focus on survival and relapse. The previous systematic review only included RCTs and focused on engraftment. This meta-analysis had several limitations. First, only 5 studies were included in the meta-analysis, which might be one of the most important reasons for publication bias and subgroup disparity. However, because observational studies tend to reflect more real world situations, objective phenomena can be shown versus with the more idealized RCTs. Second, there have been advances in transplant methods, with established transplant methods in all hematologic malignancies. Because solid tumors are different from blood cancers, future studies should separate leukemia and lymphoma as much as possible. Other factors, including patient age, adjuvant therapy, disease stage, and treatment protocols, may have also affected the strength of the study conclusion. Further meta-analyses should be performed to verify our study based on better-powered RCTs with comparable disease stages and treatment protocols.

**Conclusions**

Our meta-analysis shows contradictory results from RCTs and non-RCTs, and we failed to determine whether BMT or PBSCT showed superior OS and PFS. Nevertheless, the strong likelihood that lower TRM is associated with better OS and that less relapse is associated with better PFS suggest that physicians should choose a proper ASCT according to patient’s conditions and prognosis.

Mobilization with growth factors is encouraging especially in BMT, but caution is warranted. The protective role that bone marrow plays in relapse-free survival needs further consideration. Large-
volume and well-designed RCTs with longer follow-up are warranted to update our findings. Future translational research studies are needed to confirm our ideas.

References


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