Original Article

Efficacy and safety of autologous hematopoietic stem cell transplantation in the treatment of malignant lymphoma after chemotherapy: a systematic review and meta-analysis

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Background: Autologous hematopoietic stem cell transplantation (AHSCT) is a common method for the clinical treatment of malignant lymphomas that recur after conventional chemotherapy. It has been reported that its efficacy is better than conventional chemotherapy, but the efficacy of its first-line treatment is controversial, and the existing clinical randomized controlled trials have not yet reached a unified conclusion. This work intended to use meta-analysis to systematically evaluate the efficacy and safety of AHSCT in the treatment of malignant lymphoma after high-dose chemotherapy, and draw reliable conclusions to provide reference and basis for clinical application.

Methods: The inclusion and exclusion criteria were formulated based on the PICOIS principle. Relevant articles were retrieved from Medline, Excerpta Medica Database (EMBASE), Elton B. Stephens. Company (EBSCO), Ovid Technologies (OVID), China Biomedical Database, and Wanfang. The search period was limited the study published between January 1, 1980 and November 2021. The search terms included malignant lymphoma, autologous hematopoietic stem cell transplantation, AHSCT, high-dose chemotherapy, etc. The study subjects were diagnosed as malignant lymphoma patients. The experimental group was defined as AHSCT after high-dose chemotherapy, and the control group was defined as conventional chemotherapy (the chemotherapy regimen was not limited). The outcome indicators were overall survival (OS), complete remission rate [complete response (CR) + partial response (PR)], and event-free survival (EFS). RevMan5.3 software provided by the Cochrane Collaboration was used for meta-analysis.

Results: A total of 6 pieces of literature were included, with 264 cases in the experimental group and 389 cases in the control group. There was no risk of bias in the included literature. The intervention method in the control group was conventional chemotherapy (chemotherapy regimen was not limited). The differences in the rates of overall survival and progression-free survival between the groups were compared, and it was found that the overall survival between groups was [odds ratio (OR) =2.88; 95% confidence interval (CI): 1.78–4.66; Z=4.31; P<0.0001] and progression-free survival rate was (OR =2.70; 95% CI: 1.86–3.92, Z=5.21; P<0.00001).

Discussion: AHSCT treatment can significantly prolong the overall survival and progression-free survival rates of patients with malignant lymphoma after chemotherapy.

Keywords: Malignant lymphoma; chemotherapy; autologous hematopoietic stem cell transplantation (AHSCT); meta-analysis

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Introduction

Lymphoma is a general term for malignant tumors derived from immune cells in lymph nodes or peripheral lymph node tissues. According to histopathology, lymphomas can generally be divided into non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) (1). NHL is a type of heterogeneous proliferative lymphatic disease, and its sources include B lymphocytes, T lymphocytes, and natural killer cells (2). The subtypes of the disease in Western countries are mostly diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, border zone cell lymphoma, mantle cell lymphoma, and peripheral T-cell lymphoma-non-specific finger type, etc. (3,4). The subtype distribution of lymphoma in China differs from that in Western countries. Chronic lymphocytic leukemia/small lymphocytic lymphoma is relatively rare, and lymphomas derived from T cells and natural killer cells are more common (5-7).

Survival of patients with this disease depends primarily on prognostic factors and patient response to first-line therapy (8). Long-term survival and prognosis of patients have not been significantly improved, despite a number of current treatment options available for this disease (9). Autologous hematopoietic stem cell therapy (AHSCT) is a commonly used treatment for malignant lymphoma recurrence after conventional chemotherapy. At present, it has been reported that AHSCT has certain advantages compared with conventional chemotherapy, but its efficacy and safety in the first-line treatment are still controversial (10). Existing limited clinical randomized controlled trial data also did not draw consistent conclusions. To address the above limitations, this meta-analysis systematically and comprehensively analyzed the efficacy of AHSCT in the treatment of malignant lymphoma after high-dose chemotherapy, aiming to a provide reference and basis for the clinical application of this technology. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-595/rc).

Methods

Article retrieval

Relevant articles were retrieved from Medline, Excerpta Medica Database (EMBASE), Elton B. Stephens. Company (EBSCO), Ovid Technologies (OVID), China Biomedical Database, and Wanfang Database. The search period restriction limited the results to study published between January 1, 1980 and November 2021. The relevant keywords and medical subject heading terms were combined for blood analysis of patients with chronic obstructive pulmonary disease in the acute exacerbation stage. The search terms included malignant lymphoma, autologous hematopoietic stem cell transplantation, AHSCT, high-dose chemotherapy, randomized controlled trial (RCTs) study, and risk factors. The full texts of the retrieved documents were obtained in accordance with the pre-established inclusion and exclusion criteria, and then it should manually search the documents to avoid losing important documents.

Inclusion and exclusion criteria

The inclusion criteria were defined as follows: (I) the type of study was a RCTs study; (II) the study subjects were clearly defined as patients with malignant lymphoma; (III) the treatment method of the experimental group was AHSCT after high-dose chemotherapy, and the treatment method of the control group was conventional chemotherapy; (IV) patient-related data or outcome indicators were clear and complete, and the study can provide data for analysis.

The exclusion criteria were defined as follows: (I) articles without effect size available for analysis (i.e., those lacking the numbers of cases or controls); (II) reports that do not provide original data (comments, series reports, letters, case reports, and other zoology studies and *in vivo* studies were excluded); and (III) low quality literature was excluded.

Literature retrieval

The articles were independently screened, and the data were extracted and finally cross-checked. Differences of opinion were resolved by expert consultation to decide the data selection.

Data extraction

Two researchers independently read the literature. According to the requirements of meta-analysis, all relevant studies that met the inclusion criteria were screened out, and the quality of each article was evaluated. Studies that had duplicate reports, poor quality, and those with too little confidence in the report to be used were eliminated. Data extraction was performed according to the established tables, and a database was constructed to check the data. If the research report was incomplete, the author was

contacted for verification, and those documents that were confirmed to be unavailable were excluded from this meta-analysis. Disagreements between the two researchers were resolved through discussion or third-party arbitration.

The data was extracted following full-text retrieval. In cases of repeated reports, the most recent research was selected. The data extracted in this research included the basic information of the document (document title, first author, publication year, author information, and document source), basic characteristics of the study subjects (gender, age, research sample size, and baseline comparability), literature research methods, research plan design, intervention measures in the experimental and control groups, outcome evaluation indicators, and outcome data.

Quality evaluation

The methodological quality of the included studies was assessed using the Cochrane Reviewers' Handbook 5.3 tool as the criterion for quality evaluation of the included literature. The Cochrane Reviewers' Handbook 5.3 tool mainly evaluated the quality of included studies based on criteria such as randomization, blinding, and allocation concealment: (I) what random allocation method was used, and whether the method was correct; (II) whether allocation concealment was performed, and whether the method was correct; (III) whether blinding was used, and who was blinded; (IV) whether there was loss to follow-up and exit, whether to use intention-to-treat analysis; (V) other.

Statistical analysis

RevMan5.3 (International Cochrane Collaboration) software provided by the Cochrane Collaboration was employed for meta-analysis. The calculation method used OR as the effect size, and 95% CI was used to express the result. OR = (number of exposed persons/number of non-exposed persons in the case group)/(number of exposed persons/number of non-exposed persons in the control group). The effect scale was calculated for the collected studies, and the I^2 statistic was used to test the heterogeneity of the included literature. When I^2<50%, it was considered that there was no obvious heterogeneity in the test results, and a fixed effect model can be selected for meta-analysis; when I^2≥50%, it was considered that the test results have obvious heterogeneity, and a random effect model can be selected for meta-analysis. If there was serious heterogeneity, it was not suitable for pooling, and subgroup analysis or sensitivity analysis should be performed according to the characteristics of the study. The final meta-analysis results were displayed using forest plots.

Results

Literature retrieval results

A total of 3,349 related documents were retrieved in this study, 1,949 documents were obtained after eliminating documents that did not meet the exclusion and inclusion criteria. Next, after reading the titles and abstracts and excluding documents that obviously did not meet the standards, 374 documents were included. After reading the full texts of these articles, 362 documents that did not meet the requirements were excluded. After further reading of the full text, six articles that did not meet the requirements were excluded. Finally, six documents that met the inclusion criteria were finally included (11-16). The literature retrieval and selection process are shown in *Figure 1*, and *Table 1* displays the basic information of the included literature.

Bias risk of included articles

The Cochrane Handbook version 5.3 systematic review writing manual was adopted to evaluate the bias risk of the 6 documents included in this study and output the bias risk chart, as shown in *Figures 2,3*.

General survival rate

The overall survival of the experimental and control groups was analyzed by literature survey and screening of the six included studies. Meta-analysis of the overall survival of patients receiving AHSCT (*Figure 4*) was performed, and the heterogeneity analysis results showed I^2=0%, so the FEM was used for analysis. After meta-analysis of the comprehensive structure model, the results showed that OR =2.88, 95% CI: 1.78–4.66, Z=4.31, and P<0.0001, which indicated that there was a significant difference between the survival rate of patients receiving AHSCT and those who did not receive AHSCT (P<0.05), which suggested that AHSCT was more effective in improving the survival rate of patients with malignant lymphoma and poor chemotherapy response. *Figure 5* displays a funnel chart analysis of the overall survival rate results of patients; the funnel chart was basically symmetrical, and most of the data corresponded to points within the 95% CI, which indicated that the publication bias was low.

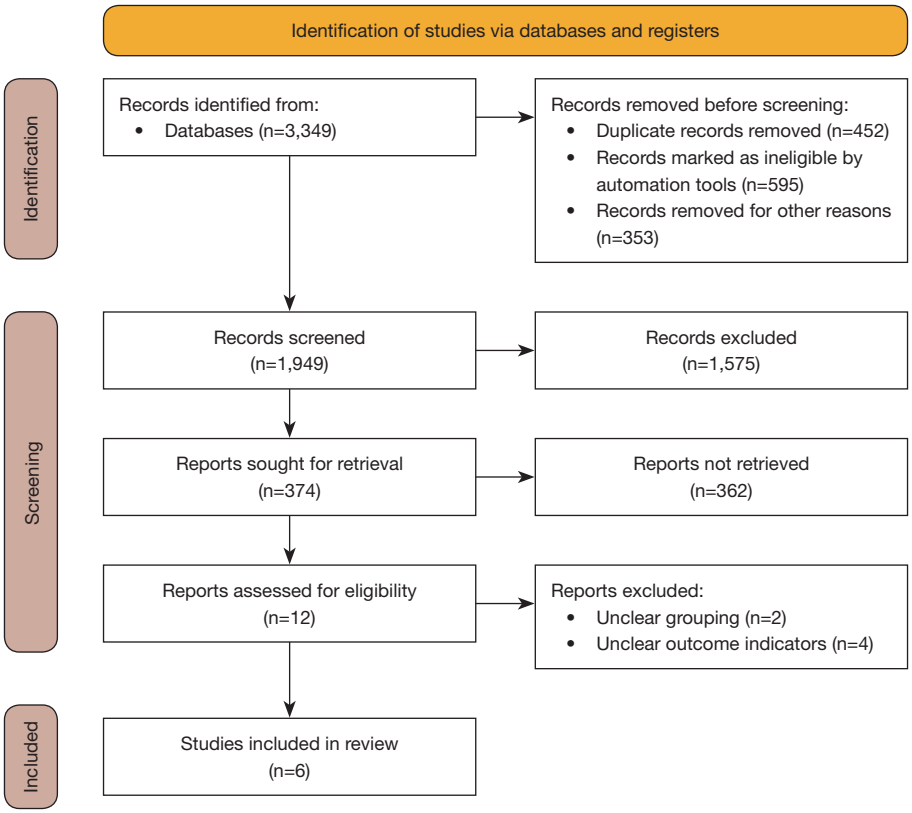

Figure 1 Literature retrieval process.

Table 1 Basic information of the included literature

First author	Year of publication	Number of cases		Country	Region
		Experimental group	Control group		
Houillier C (11)	2019	38	36	France	Europe
Van Den Neste E (12)	2017	16	58	United Kingdom	Europe
Le Gouill S (13)	2017	120	120	Algeria	Europe
Hagiwara S (14)	2020	5	7	Japan	Asia
Jiménez-Ubieto A (15)	2018	16	52	Spain	Europe
Jurinovic V (16)	2018	63	99	Germany	Europe

Comparison of partial remission rates between the two groups

The partial remission rates of the experimental and control groups were analyzed by literature survey and screening of two articles. Meta-analysis of the partial remission rate of patients receiving AHSCT (*Figure 6*) was performed, and the heterogeneity analysis results showed that I^2=63%, so the random effects model (REM) was used for analysis. After meta-analysis of the comprehensive structure model, the results showed that OR =0.60, 95% CI: 0.11–3.21, Z=0.60, and P=0.55, which indicated that there was not a significant difference in partial remission rates of patients receiving AHSCT and those who did not receive AHSCT (P>0.05). *Figure 7* displays a funnel chart analysis of the partial remission rate of patients; the funnel chart was basically symmetrical, and most of the data corresponded to points within the 95% CI, which indicated that the publication bias was low.

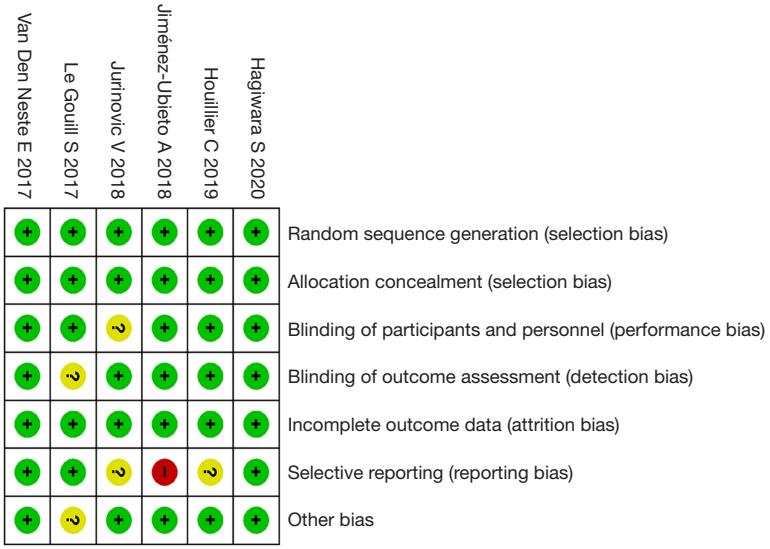

Figure 2 Bias risk assessment diagram of the included literature.

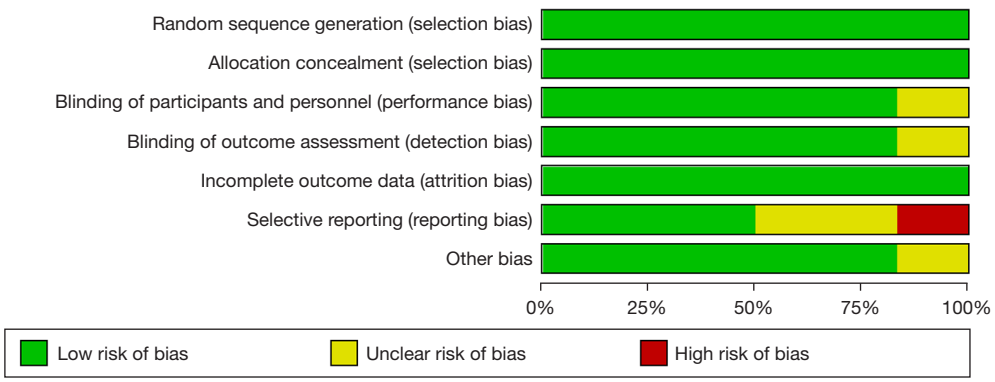

Figure 3 Bar chart of the bias risk assessment of the included literature.

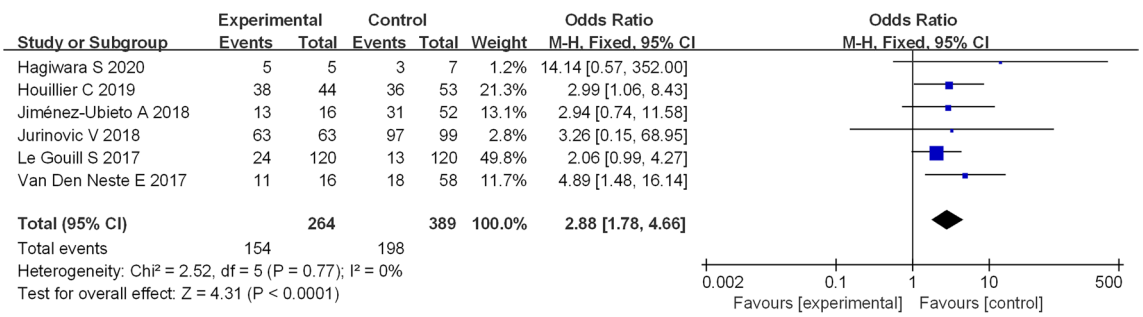

Figure 4 Forest plot showing the overall survival rate results of patients.

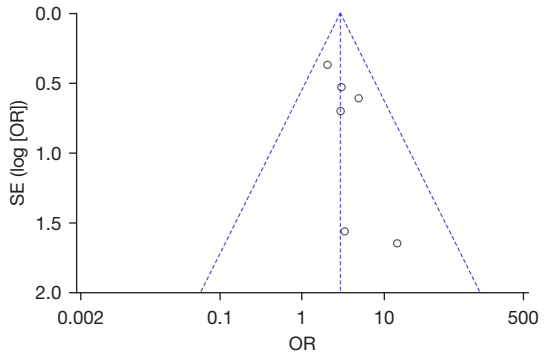

Figure 5 Funnel chart analysis of the overall survival rate.

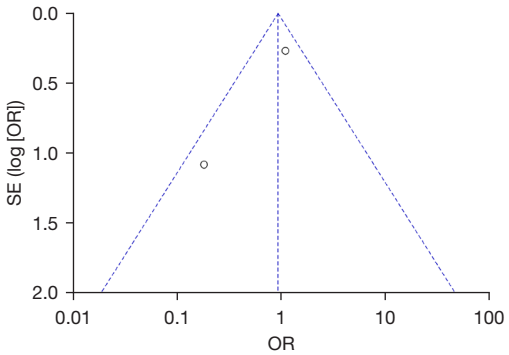

Figure 7 Funnel chart analysis on the partial remission rate.

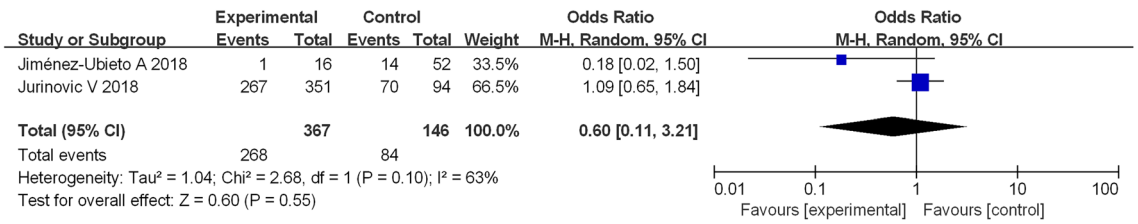

Figure 6 Forest diagram analysis of the partial remission rate.

Comparison of complete remission rate between the two groups

The complete remission rates of the experimental and control groups were analyzed via literature survey and screening of three studies. Meta-analysis of the partial remission rate of patients receiving AHSCT (*Figure 8*) was conducted, and the heterogeneity analysis results showed that I^2=61%, so the REM was used for analysis. After meta-analysis of the comprehensive structure model, the results showed that OR =1.00, 95% CI: 0.38–2.63, Z=0.00, and P=1.00, which indicated there was no a significant difference in the partial remission rate between patients receiving AHSCT and those who did not receive AHSCT (P>0.05). *Figure 9* displays a funnel chart analysis of the complete remission rate of patients; the funnel chart was basically symmetrical, and most of the data correspond to points within the 95% CI, which indicated that the publication bias was low.

Comparison on progression-free survival rate of two groups

The progression-free survival rates of the experimental and control groups were analyzed through literature survey and screening of four articles. Meta-analysis of the progression-free survival rate of patients receiving AHSCT (*Figure 10*) was performed, and the heterogeneity analysis results showed that I^2=0%, so the FEM was used for analysis. After meta-analysis of the comprehensive structure model, the results showed that OR =2.70, 95% CI: 1.86–3.92, Z=5.21, and P<0.00001, indicating that there was a significant difference in the progression-free survival rates of patients receiving AHSCT and those who did not receive AHSCT (P<0.05). *Figure 11* displays a funnel chart analysis of the progression-free survival rates of patients; the funnel chart was basically symmetrical, and most of the data corresponded to points within the 95% CI, which indicated that the publication bias was low.

Discussion

Lymphoma is the general term for malignant tumors of lymph nodes and lymphoid tissues outside the nodules. According to histopathology, lymphomas can generally be divided into NHL and HL (17). There are many types of this disease, its incidence rate is high, and it can easily metastasize, thus making it more complicated and difficult to treat. Lymphomas are typically sensitive to chemotherapy, with some patients being relieved of the disease and having long-term survival after conventional

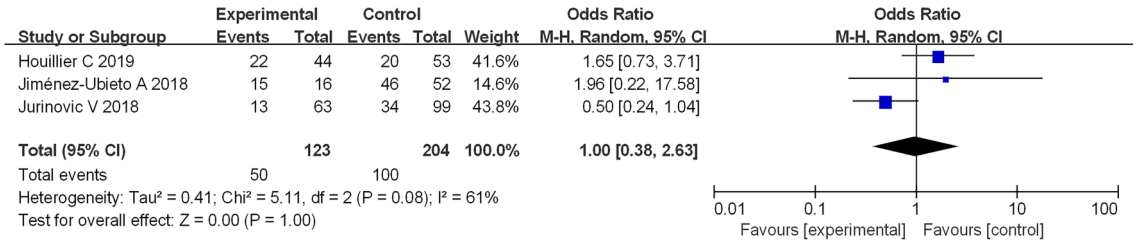

Figure 8 Forest diagram analysis of the complete remission rate.

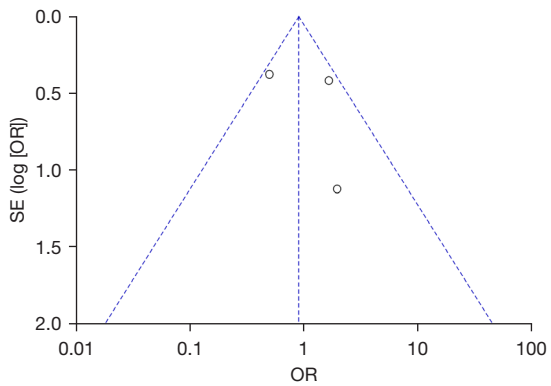

Figure 9 Funnel chart analysis of the complete remission rate.

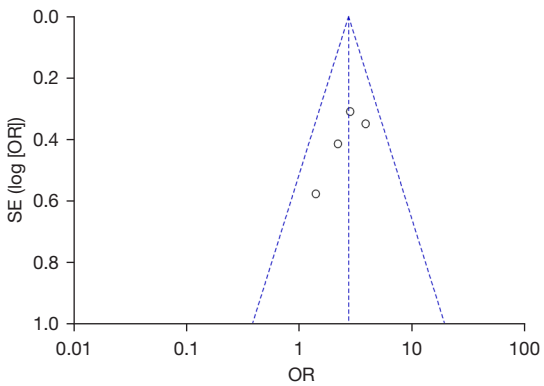

Figure 11 Funnel chart analysis of the progression-free survival rate.

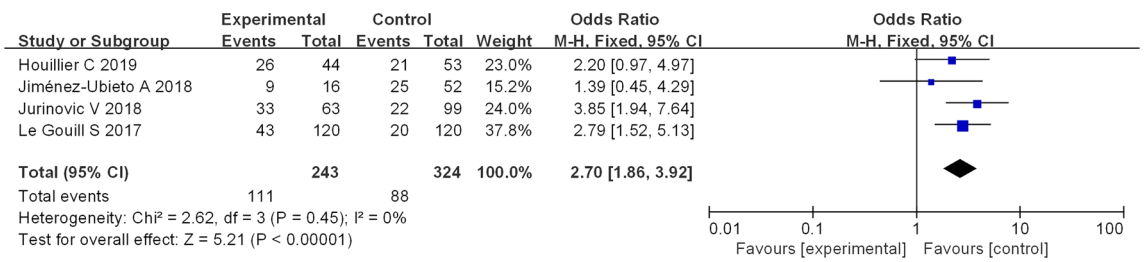

Figure 10 Forest diagram analysis of the progression-free survival rate.

chemotherapy. However, there are still a large number of patients with poor results after conventional chemotherapy, which leads to further deterioration of the patient's condition and ultimately death (18).

In response to the above challenges, doctors began to increase the dose of chemotherapeutic drugs, striving for better curative effects. However, the results of clinical research data showed that although high-dose chemotherapy drugs can kill tumor cells, it also results in considerable damage to the patient's bone marrow hematopoietic and immune functions, which seriously affects their survival and prognosis (19). Therefore, AHSCT technology was developed; the core technology of AHSCT is to collect the patient's own hematopoietic stem cells and then cryopreserve them *in vitro*. After the patient has undergone high-dose chemotherapy or combined whole-body irradiation or total lymph node irradiation, these cells will then be infused back into the patient's body, so that their hematopoietic and immune functions can be restored (20). The advantage of this method is that it can kill tumor cells to the greatest extent, while also guaranteeing the safety of patients. A large number of clinical studies have confirmed that high-dose chemotherapy combined with AHSCT is effective for the treatment of lymphoma. At the same time, the safety

and effectiveness of this treatment have been continuously improved, and the indications have been continuously clarified (21,22). It can be said that AHSCT is currently the most important and effective method for the treatment of lymphoma. It is an effective initial treatment plan for some young relapsed/resistant patients and chemotherapy-sensitive patients. For some suitable patients older than 65 years old, AHSCT is also a good treatment option (23).

However, this method remains controversial. For example, a large number of prospective randomized trials are still needed to verify and evaluate whether this method can be used as a first-line treatment for lymphoma treatment (24). Although there is still a lack of strong evidence on the adverse effects of first-line application of AHSCT for the treatment of lymphoma, it can improve the control rate of the disease and even enable some patients to obtain a cured disease-free survival. Generally, the efficacy of AHSCT in the treatment of lymphoma is positive, but information regarding its safety, indications, and adverse reactions still requires further in-depth and comprehensive research (25).

Conclusions

In this study, we searched the literature related to lymphoma patients treated with AHSCT after high-dose chemotherapy. Meta-analysis was conducted on 6 articles from multiple aspects, including the rates of overall survival, partial remission, complete remission, and event-free survival. It was found that the survival rate of patients receiving AHSCT after high-dose chemotherapy was significantly higher than that of patients who did not receive AHSCT. These results demonstrate that treatment with high-dose chemotherapy combined with AHSCT has a good therapeutic effect for patients for whom conventional chemotherapy was ineffective, and has a higher application prospect for the treatment of malignant tumors.

It can be said that this study provides new ideas and a reference basis for the treatment of malignant lymphoma in patients with an ineffective response to conventional chemotherapy. However, the articles included in this meta-analysis were not comprehensive enough, and thus, may result in some deviations in the research results of this study. In future studies, we will further expand the scope of the search to include in-depth and comprehensive research.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-595/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-595/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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