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

Submitted Feb 24, 2022. Accepted for publication Apr 18, 2022.
doi: 10.21037/tcr-22-595
View this article at: https://dx.doi.org/10.21037/tcr-22-595
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 lymphomas (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.amegis.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 $I^2\geq50\%$, 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 AHSCF (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 AHSCF and those who did not receive AHSCF (P<0.05), which suggested that AHSCF 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.
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.

Table 1 Basic information of the included literature

| First author         | Year of publication | Number of cases | Country | Region |
|----------------------|---------------------|-----------------|---------|--------|
| Houillier C (11)     | 2019                | 38              | France  | Europe |
| Van Den Neste E (12) | 2017                | 16              | United Kingdom | Europe |
| Le Gouill S (13)     | 2017                | 120             | Algeria | Europe |
| Hagiwara S (14)      | 2020                | 5               | Japan   | Asia   |
| Jiménez-Ubieto A (15)| 2018                | 16              | Spain   | Europe |
| Jurinovic V (16)     | 2018                | 63              | Germany | Europe |
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.
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 corresponded 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 $I^2=9\%$, 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.
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
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conclusively improved, and the indications have been continuously clarified (21,22). It can be said that AHSTC 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, AHSTC 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 AHSTC 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 AHSTC 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 AHSTC 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 AHSTC after high-dose chemotherapy was significantly higher than that of patients who did not receive AHSTC. These results demonstrate that treatment with high-dose chemotherapy combined with AHSTC 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.

Acknowledgments

Funding: None.

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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References

1. Bader CS, Barreras H, Lightbourn CO, et al. STING differentially regulates experimental GVHD mediated by CD8 versus CD4 T cell subsets. Sci Transl Med 2020;12:eay5006.
2. Aladag E, Aktimur SH, Aydı̈n Ö, et al. Allogeneic Hematopoietic Stem-Cell Transplantation Improves Disease-Free Survival Compared to Pediatric-Inspired Berlin-Frankfurt-Münster Chemotherapy in Adult Acute Lymphoblastic Leukemia. Clin Lymphoma Myeloma Leuk 2021;21:e147-53.
3. Abdalla A, Hammad M, Hafez H, et al. Outcome predictors of autologous hematopoietic stem cell transplantation in children with relapsed and refractory Hodgkin lymphoma: Single-center experience in a lower-middle-income country. Pediatr Transplant 2019;23:e13531.
4. Pinczés L, Szabó R, Illés Á, et al. Real-world efficacy of brentuximab vedotin plus bendamustine as a bridge to autologous hematopoietic stem cell transplantation in primary refractory or relapsed classical Hodgkin lymphoma. Ann Hematol 2020;99:2385-92.
5. Zheng WS, Guan LX, Cheng LC, et al. Clinical
Characteristics and Prognosis of Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2020;28:1551-7.

6. Fiala MA, Vij R, Wildes TM. A Mixed-Methods Study of Stem Cell Transplantation Utilization for Newly Diagnosed Multiple Myeloma. Clin Lymphoma Myeloma Leuk 2019;19:e521-5.

7. Singer S, Dean R, Zhao Q, et al. BEAM versus BUCYVP16 Conditioning before Autologous Hematopoietic Stem Cell Transplant in Patients with Hodgkin Lymphoma. Biol Blood Marrow Transplant 2019;25:1107-15.

8. Çakar MK, Tekgündüz E, Dal MS, et al. The effect of high-dose cytarabine followed by autologous hematopoietic stem cell transplantation on the outcome of patients with mantle cell lymphoma. J Oncol Pharm Pract 2020;26:273-8.

9. Anuar NA, Tey KWF, Ng SC, et al. Outcomes of high dose therapy and autologous haematopoietic stem cell transplantation for non-hodgkin lymphoma: A retrospective analysis in a resource-limited country. Int J Clin Pract 2021;75:e13823.

10. Moore JJ, Massey JC, Ford CD, et al. Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. J Neurol Neurosurg Psychiatry 2019;90:514-21.

11. Houillier C, Taillandier L, Dureau S, et al. Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. J Clin Oncol 2019;37:823-33.

12. Van Den Neste E, Schmitz N, Mounier N, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Bone Marrow Transplant 2017;52:216-21.

13. Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. N Engl J Med 2017;377:1250-60.

14. Hagiwara S, Nagai H, Uehira T, et al. Autologous peripheral blood stem cell transplantation for relapsed/refractory HIV-associated lymphoma: a phase II clinical study. Int J Hematol 2020;111:434-9.

15. Jiménez-Ubieta A, Grande C, Caballero D, et al. Autologous stem cell transplantation may be curative for patients with follicular lymphoma with early therapy failure who reach complete response after rescue treatment. Hematol Oncol 2018;36:765-72.

16. Jurinovic V, Metzner B, Pfreundschuh M, et al. Autologous Stem Cell Transplantation for Patients with Early Progression of Follicular Lymphoma: A Follow-Up Study of 2 Randomized Trials from the German Low Grade Lymphoma Study Group. Biol Blood Marrow Transplant 2018;24:1172-9.

17. Kallam A, Vose JM. Hope After Salvage Therapy Fails: Novel Agents for Relapsed/Refractory Hodgkin Lymphoma. Oncology (Williston Park) 2019;33:192-8.

18. Trino S, Zoppoli P, Carella AM, et al. DNA methylation dynamic of bone marrow hematopoietic stem cells after allogeneic transplantation. Stem Cell Res Ther 2019;10:138.

19. Steinhardt MJ, Krummenast FC, Rosenwald A, et al. R-CHOP intensification with mid-cycle methotrexate and consolidating AraC/TT with BCNU/aHSCT in primary aggressive lymphoma with CNS involvement. J Cancer Res Clin Oncol 2022;148:205-14.

20. Junfeng L, Lina M, Xinyue C. Autologous hematopoietic stem cell transplantation for human immunodeficiency virus associated gastric Burkitt lymphoma: A case report. Medicine (Baltimore) 2019;98:e16222.

21. Liu W, Wu M, Xie Y, et al. Autologous hematopoietic stem cell transplantation with inadequate stem cell dose in patients with non-Hodgkin lymphoma. Leuk Lymphoma 2021;62:323-9.

22. Lemieux C, Ahmad I, Bamkace NM, et al. Outcome of autologous hematopoietic stem cell transplant in older patients with B cell lymphoma when selected for fitness and chemosensitive disease. Leuk Res 2019;79:75-80.

23. Sapelli J, Filho JS, Matias Vieira GM, et al. BuCyE can safely replace BEAM as a conditioning regimen for autologous stem cell transplantation in the treatment of refractory and relapsed lymphomas. Leuk Res 2021;110:106689.

24. Dong X, Jia Q, Fu W, et al. Two unusual cases of autologous HSCT related TMA with kidney injury. Ann Palliat Med 2021. [Epub ahead of print]. doi: 10.21037/apm-21-226.

25. Gile JJ, Lopez CL, Ruan GJ, et al. Hypomagnesemia at the time of autologous stem cell transplantation for patients with diffuse large B-cell lymphoma is associated with an increased risk of failure. Blood Cancer J 2021;11:65.

(English Language Editor: A. Kassem)