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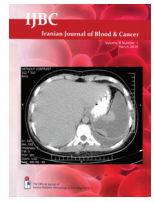

REVIEW ARTICLE

Role of Stem Cell Transplantation in the Treatment of Burkitt Lymphoma; A Systematic Review

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ABSTRACT

Background: Burkitt lymphoma is a common subtype of non-Hodgkin lymphoma in children. It has a rapid and aggressive clinical course with frequent involvement of bone marrow and central nervous system. Systemic chemotherapy is the mainstay of the treatment for this malignancy in children. In this systematic review, we discuss autologous and allogeneic hematopoietic stem cell transplantation (HSCT) and its indications in pediatric patients with Burkitt lymphoma.
Methods: The Medline (PubMed) database was searched using all keywords and phrases. The studies were identified by utilizing a combination of MeSH terms, such as Burkitt lymphoma, stem cell transplantation, autologous transplantation and allogeneic transplantation. Articles which were not published as full articles (conference proceedings excluded) were excluded. Relevant articles published during 2000-2015 were included.
Results: 13 articles met the inclusion criteria and were discussed.
Conclusion: Both autologous and allogeneic HSCT may improve survival in patients with BL. Autologous HSCT is mainly considered for patients with high-risk features of BL at presentation; however, allo-HSCT with non-myeloablative conditioning regimens are preferred for advanced stages and relapsed/refractory disease.

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Introduction

Burkitt lymphoma (BL) is one of the most aggressive types of lymphoma, classified as high grade non-Hodgkin's lymphoma (NHL) according to the REAL classification.[1] Its growth rate is very rapid and doubling time of the tumor is very short. It is usually treated with intensive chemotherapy which gives satisfactory results especially in the group of patients who have good initial response.[2]

The ideal salvage strategy for patients with BL with partial remission or relapsed disease is unknown. Combination salvage chemotherapy is usually attempted. However, very few patients with relapsed BL achieve a meaningful response regardless of the chemotherapy agent used.[3]

Autologous or allogeneic stem cell transplantation (ASCT or Allo-SCT) is recommended; however, the role of HSCT in BL is not well defined since there are limitations such as chemotherapy induced toxicity during conditioning and before HSCT. Transplant-related toxicity, particularly in patients who have received prior multiple intensive chemotherapy is also a poor determining factor.[4] Transplant-related mortality in the group of patients who underwent allogeneic SCT after failure of autologous transplantation approached 50% in one report.[5] Since HSCT in the management of BL is a challengeable topic in adults and pediatric oncology, we

aimed to perform a systematic review to find the best up-to-date available data in the literature.

Methods

The research team initially drew up a study protocol aimed at addressing the research issues raised for patients with BL or leukemia who need HSCT. A systematic search was undertaken. Two or more members of the review team reviewed all references. The Medline (PubMed) database was searched using all keywords and phrases. The studies were identified by utilizing a combination of MeSH terms, such as Burkitt lymphoma, stem cell transplantation, autologous transplantation and allogeneic transplantation. Articles which were not published as full articles (conference proceedings excluded) were excluded. Articles which addressed the clearly focused questions, those to minimise bias, relevant studies, publication dates between 2000-2015, randomized clinical trials (RCT) and other types of original articles published in English and peer-reviewed journals were selected. Recommendation Report SCT-4, a comprehensive guideline regarding HSCT in lymphoma which is a quality Initiative of the Program in Evidence-Based Care (PEBC) in Cancer Care Ontario of Canada and recommendations in 3rd WBMT Scientific Symposium in Cape Town on Nov 2014 were also are included. We decided to evaluate the quality of the studies for methodology, sampling, randomization and examined four potential sources of bias including; study participation, study attrition, confounding variables and measurement of outcomes.

Results

We searched the Medline (PubMed) electronic database by using a broad search strategy. Two reviewers independently screened the list of references to assess their eligibility for inclusion in consultation with another reviewer. Meanwhile, studies/patients meeting all of the following criteria were included in this review: 1) patients who underwent the first transplantation and 2) availability of detailed patients' characteristics and outcome data such as relapse-free survival (RFS), overall survival (OS), relapse rates (RR) and non-relapse mortality.

Finally, 13 main articles were found to form the basis for this narrative review. The flow diagram of the search study and review articles is shown in figure 1.

Discussion

The optimal salvage therapy for patients with relapsed Burkitt lymphoma is unknown.[3] Patients with relapsed/primary refractory B-NHL/B-ALL have a poor prognosis with current treatment approaches, while the patients sensitive to salvage therapy have an acceptable chance to achieve a sustained complete second remission with high-dose chemotherapy and HSCT.[6,7]

Actually, the modern immune-chemotherapy with Rituximab and CNS prophylaxis has resulted in dramatic improvement in the management of patients with NHL, with similar reports to those obtained from less intensive regimens, survival rates close to 90%.[8,9]

There has been a progressive reduction in the use of auto-HSCT as consolidative therapy in first complete remission (CR).[9] Nevertheless, for patients with high risk characteristics including elevated LDH levels, bulky disease at presentation, involvement of bone marrow or CNS or relapsed/refractory disease, HSCT should be considered.[10-14]

In relapsed patients, the disease can be salvaged with high-dose chemotherapy and autologous stem cell transplantation which results in 37% long-term disease-free survival depending on the disease status at the time of transplantation.[15]

Transplant-related toxicity, particularly in patients who have received prior multiple intensive chemotherapy are too high. Transplant-related mortality in the group of patients who underwent allogeneic SCT after autologous transplantation failure approached 50% in one report.[2]

Relapsed patients BL who were heavily treated and had received high doses of multiagent chemotherapy regimens before receiving HSCT may benefit from a non-myeloablative conditioning chemotherapy regimen

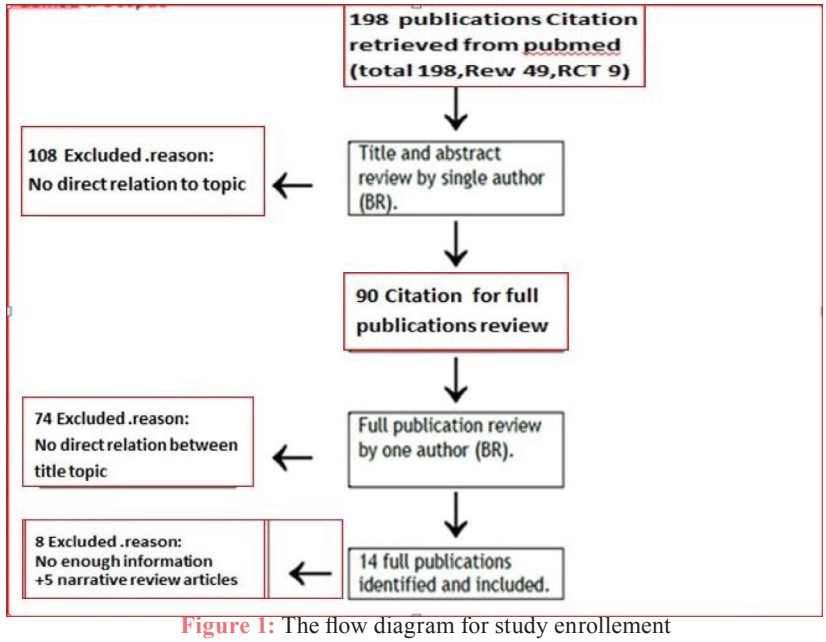

Figure 1: The flow diagram for study enrollement

during allogeneic HSCT.[3,16] One of the major goals in non-myeloablative STC is to establish mixed chimerism with too low toxicity and serious graft-versus-host effects; while retaining graft versus tumor effects which is always associated with conventional conditioning regimens.[17,18] These chimerisms will eventually lead to dominance of a particular population of stem cells, depending upon the balance of donor and recipient T-cell activities.[19]

As a matter of fact, the beneficial effects of graft-versus lymphoma (GVL) in the setting of allogeneic HSCT are not conclusive, particularly when the low response to donor lymphocyte infusion (DLI) in adult acute lymphoblastic leukemia patients is taken into consideration.[20] So, the use of a non-myeloablative regimen permits engraftment of the donor stem cells by creating marrow spacing through the graft-versus-host effect, a phenomenon which usually does not occur by myeloablative regimens or radiation therapy.[21] Although non-myeloablative regimens in other types of NHL are less encouraging due to the high rate of procedure-related complications and also higher risk of relapse. Most patients with lymphoid malignancies undergoing such a procedure have had low or intermediate grade lymphoma while BL is a high grade type of NHL.[22]

Approximately 50% of patients with chemosensitive BL who undergo SCT can be cured; however, a significant number of patients will not proceed to SCT because of early resistance or recurrence.[23]

Conclusion

Both autologous and allogeneic HSCT may improve survival in patients with BL. Autologous HSCT is mainly considered for patients with high-risk features of BL at presentation; however, allo-HSCT with non-myeloablative conditioning regimens are preferred for advanced stages and relapsed/refractory disease.

Conflict of Interest: None declared.

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