Outcomes of Autologous Haematopoietic Stem Cell Transplant in Lymphomas: A Single Centre Study

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ABSTRACT

Objective: To determine the outcomes of autologous haematopoietic stem cell transplant (auto HSCT) in lymphoma patients in terms of overall survival (OS), disease-free survival (DFS), and treatment-related mortality and to identify the associated factors.

Study Design: A descriptive study.

Place and Duration of the Study: Department of Clinical Haematology, The Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Pakistan, from February 2006 to 2023.

Methodology: Clinical records of 59 patients who underwent auto HSCT were analysed. Median of OS and DFS was calculated by applying Kaplan-Meier test. Log-rank test was applied to check the association of OS and DFS with multiple variables. In multivariate analysis, Cox-regression was used to check the hazard ratio of significant variables.

Results: At day 100, the transplant-related mortality of the study was 6.7%, and disease relapse was experienced in 34%. The estimated OS was 82.7% at five years and 77.6% at 14 years with median OS of 117 months. The estimated DFS was 62% at five years and 58.6% at 14 years with median DFS of 97 months. Age was the only factor significantly associated with both OS and DFS. The subtype of lymphoma, indication to transplant, and septic shock were found significantly associated with OS only. While DFS was associated with, time to relapse after first complete remission (CR). However, at multivariate analysis only septic shock and time to relapse after the first CR remained significant

Conclusion: For younger, chemosensitive patients who have experienced their first CR for a longer duration, auto HSCT is a compelling therapy option in the management of lymphoma.

Key Words: *Transplantation, Autologous, Diffuse large cell lymphoma, Hodgkin lymphoma*.

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INTRODUCTION

Worldwide, lymphomas are certainly one of the most common malignancies broadly divided into Hodgkin's (HL 10%) and non-Hodgkin lymphomas (NHL 90%).[1] NHL has more than 60 subtypes of B and T/NK cells,[2] including most aggressive and indolent lymphomas as well.[3] Globally, HL have good outcomes, however, 20-30% will relapse after the first CR, while 10% have refractory disease,[4] whereas different NHL requires different treatment approaches[5] or is left untreated if indolent.[1] Among the treated, 30-40% may have refractory disease or relapse depending on the subtype.[3] However, autologous haematopoietic stem cell transplant (auto HSCT) is a therapeutic option for such relapsed and refractory (rep/ref) cases of HL or NHL or even upfront therapy for some lymphomas.[6]

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Auto HSCT for lymphomas was first reported in 1959 in England and is now the standard of care for lymphoma.[3,4,6] Almost 50% of fit patients with Rep/Ref cHL, chemosensitive to salvage therapy are curable with high-dose chemotherapy followed by auto HSCT.[7,8] Research indicates that 50% of patients who receive transplants experience relapses; nevertheless, there is little data to predict the results of auto HSCT in Pakistan. The purpose of this research was to evaluate the treatment outcomes and survival rates in order to provide insight into prognostic factors for patients who have few post-transplant therapeutic alternatives.

METHODOLOGY

In this descriptive study, a total of 59 patients with lymphoma underwent auto HSCT at the Armed Forces Institute of Bone Marrow Transplant Centre, Rawalpindi, Pakistan, from February 2006 to 2023. The cut-off date for statistical analysis was August 15, 2023 to ensure a minimum of 100 days post-transplantation for all alive patients. The clinical records of these patients were reviewed through non-probability convenience sampling technique. Patients of all age groups, genders and types of lymphoma who underwent auto HSCT were included in the study. Patients with lymphoma who underwent allo BMT were excluded.

Data were analysed through SPSS version 25. In descriptive analysis, percentage and frequency were calculated for categorical variables and mean ± standard deviation for all the continuous variables. In univariate analysis, chi-square test was used to analyse the relationships between categorical data and treatment-related mortality. Median overall survival (OS) and disease-free survival (DFS) were calculated by applying Kaplan-Meier test. Log-rank test was applied to check the association of OS and DFS with age, gender, stage of disease at diagnosis, histological subtype of lymphoma, indication for transplant, pre-transplant lines of chemotherapy received, remission status, and duration, mobilisation regimen, CD34 count, conditioning regimen, and post-transplant complications. In multivariate analysis, Cox-regression was applied to check the hazard ratio of significant variables. A confidence interval of 95% and p-value of <0.05 was considered statistically significant.

RESULTS

Out of the 59 patients in the study cohort, 34 (58%) were in the HD and 25 (42%) in the NHL group. Among the NHL, 10 (40%) had diffuse large B cell lymphoma (DLBCL), 6 (24%) anaplastic large cell lymphoma alkaline negative (ALCL Alk neg), 5 (20%) cases of mantle cell lymphoma (MCL), 2 (8%) Burkitt lymphoma (BL), and other cases, such as small lymphocytic lymphoma (SLL), and T cell lymphoma not otherwise specified (n = 1, 4% each). Mean age at the time of HSCT was 31 years (IQR: 10-64 years), and the male-to-female ratio was 2:1 [male = 40 (68%), female = 19 (32%)]. In the HD group 20 (59) were males and 14 (41%) were females and in the NHL 20 (80%) were males and only 5 (20%) were females. Prior to ASCT, the mean number lines of therapy were 3 (IQR: 1-7), while 20 (59%) of HD, and 8 (32%) of NHL group received more than 3 lines of chemotherapy. Twenty (59%) in HD group and 18 (72%) in the NHL group had advance-stage disease (Stage III or IV) at diagnosis. The indications for auto HSCT included 10 (17%) aggressive lymphomas necessitating an upfront transplant that included BL, MCL, ALCL, 22 (37%) primary refractory disease, and 27 (46%) relapsed disease. Among the patients with relapsed disease, the median time to relapse after the first CR was 16 months (range 6-132 months). Among all, 55 (93%) patients had complete metabolic remission (CMR) prior to auto HSCT, while 4 (7%) had partial remission (PR). Just one patient had an intermediate HCT-CI score, whereas 58 (98%) had low scores. Mobilisation of stem cells was done by Cyclophosphamide-GCSF (CY-G 41, 70%), GCSF (n = 3, 5%), GCSF-Plerixafor (n = 9, 15%), and Cy-G followed by Plerixafor (n = 6,10%) with mean CD34 count of 3.79 (IQR: 2.57-6.28). The conditioning regimen for 57 (96%) ASCT was BEAM (Carmustine + Etoposide + Cytarabine + Melphalan); two patients, however, got BECy (n = 1) and Benda-EAM (n = 1), respectively. Median time to neutrophil engraftment was 11 ± 2 days, and platelet engraftment was 20 ± 12 days. Peri-transplant complications were observed in 56 patients (94%) among which febrile neutropenia (n = 43, 75%) was the most frequently observed followed by 34 (57%) with gut toxicity. However, septic shock was also observed in 12 (20%) patients.

At day 100, treatment-related mortalities were observed in four patients (6.7%). Overall disease relapse was experienced in 19 patients (34%). The estimated OS was 82.7% at five years and 77.6% at 14 years with median OS of 117.4 ± 14.6 months (95% CI = 88.8-146.0). The estimated DFS was 62% at five years and 58.6% at 14 years with median DFS of 97.2 ± 30.93 months (95% CI = 36.6-157.8).

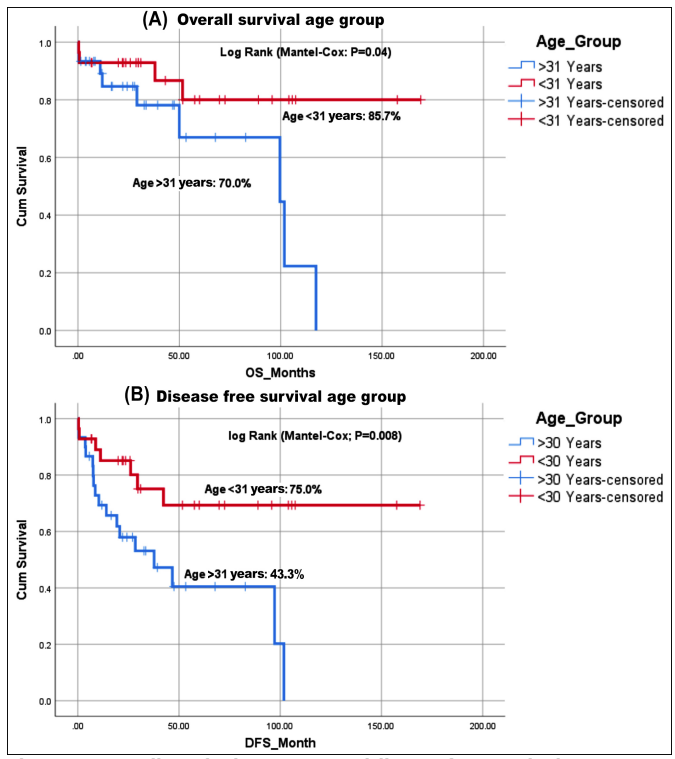

Figure 1: Overall survival age group and disease free survival age group.

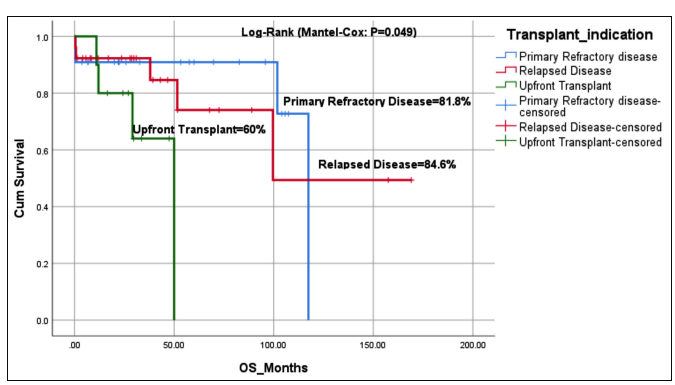

Figure 2: Overall survival auto HSCT indication.

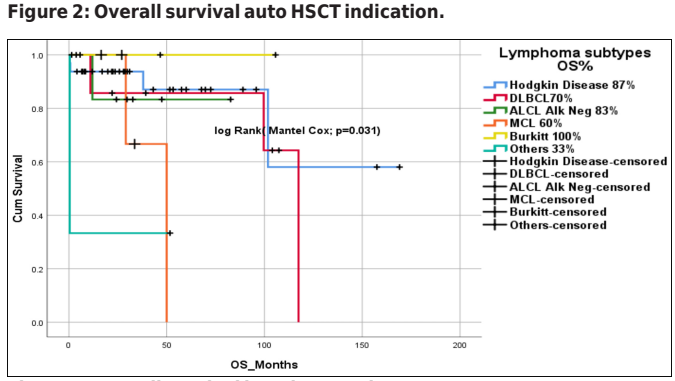

Figure 3: Overall survival lymphoma subtypes.

In univariate analysis, age was the only factor associated with both OS and DFS. Other than age, subtype of lymphoma, indication to transplant, and septic shock were found significantly associated with OS only. While DFS was associated with time to relapse after the first CR. Median OS in patients <30 years was 141.1 ± 12.8 months (95% CI = 116-166) and median DFS was 123.2 ± 14.7 months (95% CI = 94.4-152.1), whereas median OS in patients >30 years was 99.6 ± 44.8 months (95% CI = 11.7-187.4, Figure 1A) and median DFS was 37.7 ± 15.2 months (95% CI = 7.7-67.6, Figure 1B). The median OS in patients with primary refractory disease was 103.9 ± 8.5 months (95% CI = 87.1-120.7), in patients with relapsed disease, median OS was 126.4 ± 19.2 months (95% CI = 88.4-164.4), whereas patient receiving an upfront transplant had median OS of 38.9 ± 6.08 months (95% CI = 27.0-50.8, Figure 2). Subtype of lymphoma was significantly associated with OS (p = 0.031) and was observed in the following order: Burkitt lymphoma (n = 2, 100%), HD (n = 29, 87.9%), ALCL Alk Neg (n = 5, 83%), DLBCL (n = 7, 70%), and MCL (n = 3, 60%, Figure 3). The DFS of subtypes of lymphoma (p = 0.76) was observed as: Burkitt lymphoma (n = 1, 50%), DLBCL (n = 5, 50%), MCL (n = 2, 40%), HD (n = 9, 30.0%), and ALCL Alk Neg (n = 1, 16.7%). OS was associated with septic shock (p <0.001) and was 63% in patients experiencing septic shock during the post-transplant period (median OS of 43 ± 16.0 months, 95% CI = 11.6-74.6) *versus* 84% in those who did not (median OS of 112.4 ± 11.9 months, 95% CI = 89.1-136.2). The DFS was associated with time to relapse after the first CR (p <0.012) and was 30% in <12 months' time to relapse (median OS of 20.7 ± 10.0 months, 95% CI = 1.06-40.34) while in patients with time to relapse of >12 months was 57% (median DFS of 97.2 ± 40.2 months, 95% CI = 18.5-175.8).

By applying Cox-regression with OS, patients experiencing septic shock during the post-transplant period had 88.78 times more chance of hazard ratio than those who did not (p <0.005, CI 95%: 3.7-2088). Nonetheless, DFS patients experiencing relapse within a year of their pre-HSCT initial CR had 24 times more chance than those having pre-HSCT first CR of >12 months (HR = 1.4; CI 95%: 0.35-0.57, p <0.02).

DISCUSSION

Even with the development of new and innovative therapies, auto HSCT is still the main consolidation option for patients with recurrent and unresponsive HD or NHL, improving their prognosis. All forms of lymphoma are included in this 17-year single-centre research, and a sizeable fraction of patients received transplants after 2017. Complications following transplantation were common; of these, one-fourth of patients experienced septic shock, which significantly impacted OS but not DFS. TRM of this study was comparable to previous studies[9] and its superiority above results from local research are noteworthy.[10] The study exceeded previous findings with a five-year OS of 82.7% and a DFS of 62% and relapse rates matched those seen in pertinent research by Ali *et al*., Hajifathali *et al*., and Badar *et al*.[10-12]

According to this research, treatment refractoriness, early relapse, age, and disease subtype are important predictors of OS in auto HSCT. The only factor that was found to affect both OS and DFS was age, with older patients having a significantly higher rate of ASCT failure. The influence of age on treatment response and long-term prognosis has also been highlighted in previous research by Brice *et al*., and Kadkhoda *et al*.[13,14]

This age-restricted study is at odds with Wudhikarn *et al*.'s study which elaborates that auto HSCT is safe for NHL patients over 65 years, with possible long-term DFS and OS improvements.[15] The significance of expanding the eligibility criteria for HSCT beyond age alone was highlighted by Roerden *et al*.[16] While there were differences in OS between lymphoma subtypes, HD Burkitt lymphoma, and ALCL Alk neg lymphoma showed equivalent results to previous studies.[5,7,17] Nevertheless, half of the patients of DLBCL and one-third of HD patients had treatment failure in terms of DFS, nonetheless OS were better.[18,19] With lower survival in initial refractory DLBCL and HD compared to relapsed disease, the result, which is in line with previous studies, emphasise the significance of chemosensitivity for successful auto HSCT salvage.[20] However, Shargian *et al*. discovered no distinction in OS between relapsed and primary refractory disease.[21] Following the conclusions prolonging initial CR has a substantial impact on Auto HSCT efficacy, impacting DFS[22] and HD.[19]

For primary refractory and early relapse cases, consolidation with auto HSCT is still preferable to upfront CAR T treatment.[23] Consistent with previous research, variables such as gender, diagnostic stage, pre-transplant chemotherapy lines, CD34 count and choice of mobilisation, and conditioning regimen did not significantly affect survival.[4,15] Although findings were complementary to previous research that shows a correlation between low HCT CI scores and PET/CT-CR prior to ASCT with high survival rates,[6-8] they did not reach statistical significance. This could be because of stringent HSCT selection criteria that lead to improved OS and DFS.

The retrospective study design, a varied lymphoma-type population, and possible selection bias that would exclude patients with poor performance status, high HCT CI score, older age, comorbidities, PET-positive PR, and failed mobilisation are the main limitations of this study.

CONCLUSION

Auto HSCT is preferred, particularly in younger, chemosensitive patients with prolonged initial CR; nonetheless, DFS is still comparatively poor, perhaps requiring post-transplant maintenance therapy. Future studies should look for the role of novel agents either before or after transplantation, as well as the function of maintenance therapy and allo HSCT in enhancing results.

ETHICAL APPROVAL:

Ethical approval was received from the Institutional Review Board of the Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Pakistan (IRB No: 2105/BMTC/R&P; Dated: 20/11/2021).

PATIENTS' CONSENT:
The study participants and/or their relatives provided their voluntary agreement and approval for the use of the data.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
IH, MAK: Concept, literature search, ethical approval, conduct of the study, data analysis, manuscript writing, and editing.
MNA: Data acquisition, critical revision, and manuscript editing.
AS, NS, HK: Data collection and statistical evaluation.
MAK: Approved the final version of the manuscript to be published.
All authors approved the final version of the manuscript to be published.

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