Case Report

Access this article online

Quick Response Code:

Website: https://journals.lww.com/ijhm

DOI: 10.4103/ijh.ijh_118_24

Shorting of existing conditioning regimen for relapsed/refractory gastric diffuse large B-cell lymphoma transplant and studying its related outcomes: A first of its kind case report

Priyatesh Chandra Dwivedi, Yasam Venkata Ramesh[1], Raj Nagarkar[2]

Abstract:

Using single-agent high-dose melphalan for multiple myeloma and refractory or relapsed (R/R) lymphomas transplant was reported to be clinically beneficial. In view of earlier literature, we opted for this new, modified conditioning regimen (carmustine and melphalan instead of BEAM; B – Carmustine, E – Etoposide, A– Cytarabine, and M– Melphalan) in our patient for autologous hematopoietic stem cell transplantation (aHSCT) to treat relapsed/refractory gastric diffuse large B-cell lymphomas (DLBCLs) in resource-limiting counties like India. In this report, we have articulated all our clinical experiences and insights related to our patient pre- and post-aHSCT in terms of treatment outcomes and survival. Here, we report a case of a 63-year-old male diagnosed with gastric DLBCL and no history of smoking, alcohol, or use of illicit drugs. Routine positron emission tomography–computed tomography (PET-CT) revealed abnormally increased fluorodeoxyglucose (FDG) uptake in parts of the stomach (maximum standardized uptake value: 51.2). Immunohistochemistry revealed high-grade non-Hodgkin's lymphoma of B-cell phenotype (DLBCL of stomach). The patient was started on 6 cycles of R-CHOP (R – Rituximab, C – Cyclophosphamide, H – Doxorubicin, O – Vincristine, *P* – Prednisone) regimen. End-of-treatment FDG PET-CT revealed persistent disease. Hence, the patient received radiation therapy (involved-field radiotherapy-45 Gy/25#). Later, the patient was planned for salvage chemotherapy followed by aHSCT. It's been > 18 months' post-aHSCT, the patient is event-free and is on a 6-monthly follow-up.

Keywords:

Autologous hematopoietic stem cell transplantation, case report, conditioning regimen, gastric diffuse large B-cell lymphoma

Departments of Hematology, [1]Academics and [2]Surgical Oncology, HCG Manavata Cancer Centre, Nashik, Maharashtra, India

Address for correspondence:
Dr. Priyatesh Chandra Dwivedi, Department of Hematology, HCG Manavata Cancer Centre, Nashik - 422 011, Maharashtra, India.
E-mail: academics@manavatacancercentre.com

Submission: 07-10-2024
Revised: 03-12-2024
Accepted: 15-12-2024
Published: 12-03-2025

Introduction

Non-Hodgkin's lymphoma (NHL) is a predominant form of lymphoma, that accounts for 4% of all cancers.[1] Of all NHLs, stomach (30%–40%) was observed to be the most common extranodal site of all extranodal lymphomas and gastrointestinal lymphomas (55%–65%).[2] Of the extranodal primary gastric lymphomas of NHL, low-grade are referred to as mucosa-associated lymphoid tissue lymphomas and aggressive ones as diffuse large B-cell lymphomas (DLBCL). Among the 30 odd subtypes of NHLs, the DLBCL subtype accounts for around 25%–30% of all NHL cases reported worldwide.[3] DLBCL is also further divided into two subtypes based on the cell of origin as activated B-cell type (ABC) and germinal center type (GCB). Where GCB type is reported to have better prognosis and

How to cite this article: Dwivedi PC, Ramesh YV, Nagarkar R. Shorting of existing conditioning regimen for relapsed/refractory gastric diffuse large B-cell lymphoma transplant and studying its related outcomes: A first of its kind case report. Iraqi J Hematol 2025;14:131-4.

average survival rate (75%) than ABC type (40%, average survival rate).[4]

The management of DLBCL in Asia is also largely varied due to its dysregulated healthcare system, wide disparity in resources, heterogeneity of local clinical guidelines, suboptimal treatment options, and large diversity in the population.[5] For the first time, due to the patient's financial constraint, instead of complete BEAM; B – Carmustine, E – Etoposide, A – Cytarabine, and M – Melphalan conditioning regimen, we used only two drugs (carmustine and melphalan) conditioning regimen for autologous transplantation. In this case report, we have articulated our clinical experience and insights related to our patient pre- and postautologous hematopoietic stem cell transplantation (aHSCT) findings, treatment outcomes, and survival.

Case Report

In August 2021, a 63-year-old male and a diagnosed case of NHL (distal body and antrum of stomach) presented to our center for treatment. The patient had no history of smoking, alcohol, or use of illicit drugs. Routine positron emission tomography–computed tomography (PET-CT) revealed abnormally increased fluorodeoxyglucose (FDG) uptake in diffuse, concentric wall thickening lesion involving distal body, and pyloric part of the stomach (maximum standardized uptake value: 51.2, thickness: 28 mm). Immunohistochemistry revealed high-grade NHL of B-cell phenotype (DLBCL of stomach). The patient was started on 6 cycles of R-CHOP (R – Rituximab, C – Cyclophosphamide, H – Doxorubicin, O – Vincristine, *P* – Prednisone) regimen. Interim PET-CT was not done as the patient was not willing due to financial constraints. End-of-treatment FDG PET-CT revealed persistent disease. Hence, the patient received radiation therapy (involved-field radiotherapy-45 Gy/25#), which was well tolerated with only grade 2 skin and Grade 1 upper gastrointestinal toxicity.

Later, the patient was planned for salvage chemotherapy followed by aHSCT. As a part of salvage chemotherapy, patient received 4 cycles of rituximab/dexamethasone high-dose cytarabine (Ara-C)/cisplatin (RDHAP) regimen. Post 4 cycles, the patient had favorable partial response and was planned for aHSCT. After 5 days of mobilization with granulocyte colony-stimulating factor (G-CSF) at 5 μg/kg twice daily, the first stem cell harvest was done on July 2022, but the CD34 + count was only ~ 0.6 million. The second stem cell harvest was done after 5 days of mobilization with G-CSF at 5 μg/kg twice daily. Injection plerixafor (24 mg) was given on the night before harvesting and the CD34 + count was reported to be still low (~ 0.4 million). Preharvest peripheral blood CD34 + count was not done in our patient due to financial constraints and the unavailability of in-house flow cytometry.

In due course, the patient was started on monthly rituximab with prednisolone due to poor mobilization and inadequate stem cell dose (<2 million). After 3 cycles of rituximab and prednisolone, follow-up PET-CT revealed increased lymphomatous involvement but decrease in diffuse, concentric wall-thickening lesions involving the distal body and pyloric part of the stomach.

To increase the stem cell yield, etoposide chemomobilization was done and adequate stem cell dose (~10 million) was achieved. During pretransplant workup, the patient was diagnosed with acute hepatitis B with very high viral load and moderately deranged liver function test (LFT). Tablet tenofovir AF (25 mg, tenofovir alafenamide) was started and the transplant was deferred. The collected stem cell product was cryopreserved.

On of February 2, 2023, the patient underwent aHSCT. Due to the patient's financial constraint, instead of complete BEAM regimen, only two drugs (carmustine 300 mg/m^2 and melphalan 200 mg/m^2) were used as conditioning regimen for the transplantation.

After 2 months of transplantation, the patient was presented with fever and cough. High-resolution CT chest showed well-defined consolidation involving the posterior basal segment of the left lower lobe and inferior lingual region. Rest there are scattered patches of ground-glass opacities seen in bilateral lung parenchyma (right more than left) with the presence of alveolar nodular consolidation within it. Well-defined hypodense node of 15 mm × 10 mm was noted in the right hilar region. Supportive care was provided. Post 6 months, whole-body PET-CT was performed revealing mildly increased FDG uptake in thin-walled cavitating lesion at the upper lobe of the right lung and moderately FDG avid, subpleural, irregular nodular opacity lesions with peripheral "tree-in-bud" appearance at the anterior segment of the right upper lobe. Along by, moderate FDG avid, small necrotic appearing mediastinal lymph nodes were also reported. Low-grade diffuse FDG uptake was also noted in the wall of the distal body and pyloric part of the stomach. Overall above described pulmonary lesions and necrotic appearing mediastinal nodes were more in favor of infective pathology rather than lymphomatous lesions. Bronchoscopy was done and bronchoalveolar lavage sample was sent for GeneXpert. The outcome was reported to be positive and the patient was started on anti-tubercular therapy.

Seven months later from the last follow-up, the patient again presented to our center with cough with

expectoration and shortness of breath. Whole-body PET-CT was performed, revealing increased multiple small centrilobular nodular densities with branching giving rise to tree-in-bud appearance, diffusely involving bilateral lung parenchyma more in lower lobes. Whereas stable multiple calcific densities and nodular densities were observed in both the lungs. Previously seen ill-defined multiple nodular densities are still present and stable in both the lungs, where the largest measured 6 mm (previous size: 10 mm) in the posterior segment of the right upper lobe. Patchy areas of ground-glass opacity and diffuse reticular thickening are seen in bilateral upper lobes. With intravenous antibiotics and supportive care, the patient recovered and was kept on follow-up. It's been >20 months' post-aHSCT, the patient is doing well and is on 6-month follow-up. The next follow-up visit and PET-CT is planned for January 2025.

Etoposide chemomobilization protocol

On day 1 and day 2, injection etoposide was given at a dose of 375 mg/m^2 and G-CSF injection (5 μg/kg) twice daily was started, when absolute neutrophil count was <500/mm^3. Alternate day complete blood count was done and stem cell collection was done using peripheral line once the white blood cell count was >5000/μL. A total of 280 mL was collected with a CD34 + cell dose of 10 × 10^6/kg. The whole chemomobilization procedure and stem cell harvest were done on outpatient basis.

Discussion

DLBCL treatment is largely dependent on the stage, molecular subtype, and type of the disease. In patients with advanced diseases like ours, the treatment regimen includes chemotherapy followed by radiation.[3,6] Studies conducted by MInT group[7] and Lamy *et al*.[8] has also confirmed the R-CHOP therapy followed by radiation as an effective treatment for better prognosis and favorable outcomes.

As a standard of care in relapsed or refractory NHL patients, salvage chemotherapy (RDHAP regimen) followed by aHSCT was reported to be effective.[9-11] Same procedure was followed in our patient, but due to the patients financial constraints and limited resources in tier 3 cities in a developing country like India, preharvest peripheral blood CD34 + count was not performed in many cases. In such poor mobilizer patients, etoposide chemomobilization + G-CSF + plerixafor was reported to be an effective regimen for salvage stem cell mobilization with a success rate of 91.53% and the same was followed in our patient too.[12]

Whereas with the conditioning regimen modifications, reports from Fernández-Gutiérrez *et al*.[13] used high-melphalan alone and reported its noninferiority to other combination conditioning regimens such as BEAM. The use of such modified conditioning regimens (TECAM,[14] BuME,[15] BuCE,[16] etc.) was also reported in some earlier studies and their outcomes were also encouraging.[13-15,17] In view of our patients' financial condition, for the first time in the world, instead of complete BEAM regimen (6 days), we have used the modified conditioning regimen (carmustine and melphalan, for 2 days) for transplantation. We also observed to found many other advantages with such modified conditioning regimens in resource-limited countries like India in terms of their delivery on an outpatient basis, avoiding cryopreservation costs, decreased hospital stay, lowered hospitalization costs, decreased hospitalization-related trauma, safety profile, and economical. However, in our patient, cryopreservation was inevitable due to acute hepatitis and deranged LFT. Where transplantation time was slightly differed till the patient's LFT recovered and viral load decreased significantly.

Overall procedural and drug costs over a period of time are also lot lower in developing countries compared to West.[13] In our patient, the entire hospitalization and medical/pharmacy costs in a tier 3 city in India are summed up ~ 8,000 ± 1500 US dollars, which is far less compared to the USA (~$125,000 ± 25,000)[18,19] and Europe (~€107,457 ± 54,679/patient, autologous).[20] In terms of survival, the comparative observation study conducted by Fernández-Gutiérrez *et al*.[13] clearly observed no statistically significant differences between clinical response, event-free survival, and overall survival at the end of 3 years between high-dose melphalan versus BEAM. As on date, it's been >20 months' post-aHSCT, and our patient is still doing well without any events and is on 6-month follow-up. Being a single case, the outcome can be the major limitation with our present study.

Conclusion

From our clinical observation, we can suggest this new, modified conditioning regimen (carmustine and melphalan instead of BEAM) for aHSCT for relapsed/refractory gastric DLBCL and other NHLs in resource-limiting tier-3 cities in a developing country like India, where affordability is a major hurdle and majority patients do not have health insurance.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Acknowledgment

The authors would like to thank Dr. Yasam Venkata Ramesh from HCG Manavata Cancer Centre, Centre for Difficult Cancers (CDC), Nashik, India, for his medical writing assistance.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Non-Hodgkin Lymphoma — Cancer Stat Facts. Available from: https://seer.cancer.gov/statfacts/html/nhl.html. [Last accessed on 2024 Sep 04].
2. Juárez-Salcedo LM, Sokol L, Chavez JC, Dalia S. Primary gastric lymphoma, epidemiology, clinical diagnosis, and treatment. Cancer Control 2018;25:1073274818778256.
3. Padala SA, Kallam A. Diffuse Large B-Cell Lymphoma. StatPearls; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557796/. [Last accessed on 2024 Sep 04].
4. NCI Study Offers Genetic Insights into Common Lymphoma-NCI. Available from: https://www.cancer.gov/news-events/press-releases/2018/lymphomaa-genetic-subtypes. [Last accessed on 2024 Sep 04].
5. Tan D, Chan JY, Wudhikarn K, Wong RS, Poon L, Norasetthada L, *et al.* Unmet needs in the first-line treatment of diffuse large B-cell lymphoma: Expert recommendations from the Asia-pacific region with a focus on the challenging subtypes. Clin Lymphoma Myeloma Leuk 2024;24:e320-8.
6. Lewis CS, Joy G, Jensen P, Barraclough A, Franco N, Talaulikar D, *et al.* Primary gastric diffuse large B-cell lymphoma: A multicentre retrospective study. Br J Haematol 2024;205:534-41.
7. Pfreundschuh M, Trümper L, Osterborg A, Pettengell R, Trneny M, Imrie K, *et al.* CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: A randomised controlled trial by the MabThera international trial (MInT) group. Lancet Oncol 2006;7:379-91.
8. Lamy T, Damaj G, Soubeyran P, Gyan E, Cartron G, Bouabdallah K, *et al.* R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. Blood 2018;131:174-81.
9. Witzig TE, Geyer SM, Kurtin PJ, Colgan JP, Inwards DJ, Micallef IN, *et al.* Salvage chemotherapy with rituximab DHAP for relapsed non-Hodgkin lymphoma: A phase II trial in the North central cancer treatment group. Leuk Lymphoma 2008;49:1074-80.
10. Schirmbeck NG, Mey UJ, Olivieri A, Ko YD, Kaiser U, Flieger D, *et al.* Salvage chemotherapy with R-DHAP in patients with relapsed or refractory non-Hodgkin lymphoma. Cancer Invest 2016;34:361-72.
11. Hafez R, Hussein S, Ismail M. Definitive salvage chemotherapy for the treatment of refractory/relapsed non-Hodgkin lymphoma, a single center experience. Alexandria J Med 2018;54:679-83.
12. Zucenka A, Peceliunas V, Maciutaite E, Chaleckaite J, Jakimaviciute R, Griskevicius L. Etoposide toposideiuseAlexandria J Med J Meditive salvage chemoplerixafor in patients who failed chemomobilization with or without plerixafor. Biol Blood Marrow Transplant 2019;25:1304-11.
13. Fernández-Gutiérrez JA, Reyes-Cisneros OA, Litzow MR, Bojalil-Alvarez L, Garcia-Villasenor E, Gómez-Gomez ET, *et al.* High dose melphalan is an adequate preparative regimen for autologous hematopoietic stem cell transplantation in relapsed/refractory lymphoma. Hematology 2022;27:449-55.
14. Joffe E, Rosenberg D, Rozovski U, Perry C, Kirgner I, Trestman S, *et al.* Replacing carmustine by thiotepa and cyclophosphamide for autologous stem cell transplantation in Hodgkin's and non-Hodgkin's B-cell lymphoma. Bone Marrow Transplant 2018;53:29-33.
15. Kim KH, Kim WS, Kim SJ, Yoon DH, Suh C, Kang HJ, *et al.* Treatment with intravenous busulfan, melphalan, and etoposide followed by autologous stem cell transplantation in patients with non-Hodgkin's lymphoma: A multicenter study from the consortium for improving survival of lymphoma. Transpl Int 2020;33:1211-9.
16. Kim KH, Lee JH, Lee M, Kim HG, Do YR, Park Y, *et al.* Busulfan, melphalan, and etoposide (BuME) showed an equivalent effect to busulfan, cyclophosphamide, and etoposide (BuCE) as conditioning therapy for autologous stem cell transplantation in patients with relapsed or high-risk non-Hodgkin's lymphoma: A multicenter randomized phase II study bythe consortium for improving survival of lymphoma (CISL). Cancer Res Treat 2023;55:304-13.
17. Marchesi F, Capria S, Pedata M, Terrenato I, Ballotta L, Riccardi C, *et al.* BEAM conditioning regimen ensures better progression-free survival compared with TEAM but not with FEAM in lymphoma patients undergoing autologous stem cell transplant. Leuk Lymphoma 2020;61:2238-41.
18. Acheampong T, Gu T, Le TK, Keating SJ. Treatment patterns and costs among US patients with diffuse large B-cell lymphoma not treated with 2L stem cell transplantation. Futur Oncol 2024;20:623-34.
19. Harkins RA, Patel SP, Flowers CR. Cost burden of diffuse large B-cell lymphoma. Expert Rev Pharmacoecon Outcomes Res 2019;19:645-61.
20. Mayerhoff L, Lehne M, Hickstein L, Salimullah T, Prieur S, Thomas SK, *et al.* Cost associated with hematopoietic stem cell transplantation: A retrospective claims data analysis in Germany. J Comp Eff Res 2019;8:121-31.