https://www.scientificarchives.com/journal/journal-of-clinical-haematology

Journal of Clinical Haematology Mini Review

BeEAM Conditioning for Autologous Transplant in Lymphoma: A Review of the Evidence, Safety and Efficacy

Logan Hahn[1], Mark Bosch[2*]

[1]Department of Medicine, University of Saskatchewan, Saskatoon, SK, Canada

[2]Provincial Hematology and Blood and Marrow Transplant Program, Saskatchewan Cancer Agency, Saskatoon, SK, Canada

[*]Correspondence should be addressed to Mark Bosch; mark.bosch@saskcancer.ca

Received date: September 09, 2021, **Accepted date:** September 23, 2021

Abstract

High dose chemotherapy (HDCT) and subsequent autologous stem cell transplantation (ASCT) has become an immensely valuable treatment option in both Hodgkin's and Non-Hodgkin's Lymphoma. In recent years, some stem cell transplant centres have begun implementing bendamustine, etoposide, cytarabine and melphalan (BeEAM) as a preferred HDCT regimen. This change mostly stemmed from economic concerns related to a scarcity of other chemotherapeutic agents and a need to improve upon current outcomes. Despite the common use of BeEAM chemotherapy, there is a paucity of data on the efficacy, tolerability and safety of the regimen. The following review article will discuss the current literature pertaining to BeEAM chemotherapy and compare the regimen to the formerly widely-used BCNU, etoposide, cytarabine and melphalan (BEAM) regimen.

Keywords: Bone marrow transplant, Chemotherapy, Nephrotoxicity, Idiopathic pneumonia syndrome, Mucositis, Economic analysis

The Introduction of BeEAM Chemotherapy

The ground-breaking PARMA and CORAL trials have substantiated high dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) as standard of care in the treatment of chemosensitive and relapsed Non-Hodgkin's Lymphoma (NHL) [1,2]. Additionally, the regimen has proven effective in the treatment of relapsed and resistant Hodgkin's Lymphoma (HL) [3,4]. Globally, carmustine (BCNU), etoposide, cytarabine and melphalan (BEAM) has been the most widely used conditioning regimen of the past 30 years [5]. BEAM conditioning is generally well-tolerated and effective, with the most common toxicity being oral and gastrointestinal mucositis [5]. Despite this, some transplant centres have transitioned from BEAM HDCT to a newer regiment referred to as BeEAM, which replaces BCNU for bendamustine. The movement appears to be primarily driven by a worldwide scarcity of BCNU, which has led to affordability issues. This dramatic rise in drug cost is not insignificant. Between 2013 and 2015, the price of BCNU increased from $200 (CAD) / 100 mg vial to $4,965.14 (CAD) / 100 mg vial.

Bendamustine was first synthesized in the former German Democratic Republic in the 1960s [6]. The mechanism of action of bendamustine is unlike that of other alkylating agents and its activity includes apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe [7]. A phase I-II trial conducted by Visani et al. found bendamustine to be safe and efficacious in the transplant setting, reporting a 100-day transplant-related mortality of 0%. Additionally, 81% of the 77-patient cohort was in complete remission at a median observation of 18 months [6].

The Benefits of BeEAM

The most apparent advantage of BeEAM over its predecessors is affordability. Few studies have conducted economic comparisons of HDCT regimens. However, our research group recently published an economic analysis of BeEAM and BEAM regimens based on local data from our provincial transplant centre located in Saskatoon, Saskatchewan, Canada. The cost of a BEAM ASCT at our centre was found to be $33,381 CAD, whereas a BeEAM

ASCT only resulted in a gross cost of $12,181 CAD [8]. While this data is certainly limited geographically, it does suggest that the implementation of BeEAM chemotherapy has the potential to financially benefit transplant centres. In our small centre, for instance, the transition from BEAM to BeEAM chemotherapy has resulted in a net savings of approximately $890,000 CAD from 2015 to 2019. Presumably, this relates to the current scarcity of BCNU and the marked increase in costs.

Prior to the introduction of bendamusine-containing HDCT regimens, BCNU was widely-used. BCNU is associated with idiopathic pneumonia syndrome (IPS). IPS is a devastating lung transplant complication associated with higher rates of treatment-related mortality (TRM) and reduced progression-free survival (PFS) and overall survival (OS) [9]. While the mechanism of action of BCNU-induced IPS has not yet been elucidated, it appears to be dose-dependent [9]. The incidence of IPS associated with BCNU varies widely in the literature, with rates of 1-64% reported [9-12]. Unsurprisingly, BCNU doses below 450 mg/m^2 appear to be far less problematic [10]. To our knowledge, the newer BeEAM regimen, which utilizes bedamustine instead of BCNU, has only been implicated in one case of IPS. The dreaded transplant complication was reported in one BeEAM patient in a study conducted by Gilli et al., suggesting that IPS is a possible, albeit rare, consequence of BeEAM HDCT [13]. Nonetheless, the risk of IPS is far more apparent in BCNU-containing regimens, thus suggesting a potential advantage of BeEAM HDCT.

Too Good to Be True? The Case of BeEAM Nephrotoxicity

The largest concern that has been raised about BeEAM HDCT is nephrotoxicity. Reports of BeEAM nephrotoxicity vary widely in the literature from clinically insignificant creatinine rises to kidney injury necessitating dialysis. Overall, the incidence of nephrotoxicity has been reported to be between 1.6-48% [14-18]. A study conducted by Noesslinger et al. found that roughly 80% of BeEAM patients experienced transient increases in creatinine within a few days of bendamustine administration [19]. However, none of these patients required any therapeutic intervention or delays in administration of chemotherapy [19]. In contrast to this, one study reported a 10% incidence of Grade III-IV renal toxicity (based on Common Terminology Criteria for Adverse Events v4.0) following bendamustine administration, with one patient even requiring dialysis [13]. A recent study published by our group, found the overall rate of nephrotoxicity to be 32% in our cohort of 41 BeEAM patients. However, 92% of these toxicities were Grade I-II, and the clinical course was not affected for any patient. Interestingly, 9/13 patients in our study who developed renal toxicity had elevated creatinine levels at discharge, suggesting some persistence of renal impairment [8].

Unsurprisingly, stem cell transplants are medically intensive, and other factors such as concomitant antibiotic use could contribute to acute kidney injury. Cohort studies comparing the incidence of nephrotoxicity between BeEAM and other HDCT regimens have garnered mixed results. A cohort study conducted by Garciaz et al. reported nephrotoxicity in 48% of BeEAM patients, whereas only 7% of BEAM patients developed the complication ($p<0.001$) [17]. It should be noted, however, that the cohorts were studied at different times, and the intergroup differences may reflect differences in monitoring and management. However, another cohort study performed in 2018 also seems to suggest bendamustine-associated kidney injury. In a retrospective, matched cohort study, Saleh et al. report the rate of nephrotoxicity to be 12% in BeEAM patients and 6% in patients receiving BEAM [16]. Additionally, the authors report BeEAM dosages above 160 mg/m^2 to be an independent prognostic factor predisposing to acute renal failure [16]. However, another cohort study reported BeEAM and BEAM to cause statistically-insignificant rates of nephrotoxicity at 1.6% and 0.6%, respectively [18].

While the true impact of BeEAM nephrotoxicity is difficult to determine at this point, our centre is reassured by the fact that acute kidney injury rarely seems to impact the course of the ASCT. Renal insufficiency during ASCT has not been implicated with increased transfusion requirements or mucositis incidence [20]. Furthermore, there does not seem to be any association between renal insufficiency and engraftment rate [20]. Common sense precautions such as providing adequate hydration and the avoidance of bendamustine dose escalations beyond 200 mg/m^2/day are generally recommended and employed by our institution [16,19].

Other Toxicities

Digestive toxicities, such as oral mucositis, typhlitis and diarrhea, are among the most common complications of HDCT. In our previous study, we found the incidence of oral mucositis to be 88% [8]. Similarly, a study conducted by Gilli et al. reports the incidence of oral mucositis to be 84%, suggesting that this is a nearly ubiquitous complication [13]. Most (94%) of the cases of oral mucositis reported in our study were Grade I-II and managed expectantly [8]. However, in our experience, the complication is distressing for patients and affects their perception of quality of care. In this respect, it appears that BeEAM does not disadvantage patients, with cohort studies reporting similar rates of oral mucositis associated with BEAM HDCT [15-18]. The incidence of typhlitis associated with BeEAM HDCT appears to range from 17-35%, and represents a serious transplant complication with mortality rates as high as 50% [6,8,14,16,21]. As

with mucositis, typhlitis does not appear to be unique to BeEAM HDCT, with the BEAM regimen causing similar rates of complication [17]. Interestingly, diarrhea does appear to be significantly more common in patients treated with BeEAM as compared to BEAM [15,16]. For instance, Ribrag et al. found that Grade III diarrhea occurred in 44% of BeEAM patients, compared to 13.2% of BEAM patients ($p<0.001$) [15].

Aside from gastrointestinal toxicities, infections are a common consequence of stem cell transplantation. For instance, in our cohort of 41 patients undergoing BeEAM HDCT, 23 (56%) developed bacteremia [8]. However, cohort studies have not revealed BeEAM HDCT to be an independent risk factor when compared to the older BEAM regimen [15-17]. Other complications, such as cardiotoxicity and transaminitis, appear rare and comparable between conditioning regimens, although the evidence is currently limited [16].

Remission and Survival

BeEAM appears to have comparable OS and PFS compared to BEAM HDCT. For instance, a phase I-II trial, reported BeEAM to have a 3-year PFS of 72% [22]. Additionally, TRM appears to be low with BeEAM, with many studies reporting a TRM of less than 5% [6,8,14,19]. In our recently published study, for instance, one death occurred at day +14 from stem cell infusion, yielding a TRM of 2.4%. The death was believed to be due to cardiac arrest in a patient with known cardiovascular disease [8]. To our knowledge, no cohort study has showed a survival advantage between BeEAM or BEAM in terms of OS or PFS [8,16].

Conclusion and Future Directions

Based on the current available data, BeEAM remains the HDCT regimen of choice at our centre. Firstly, there appears to be no difference in OS and PFS between BeEAM and prior HDCT regimens. Additionally, we are satisfied with the safety profile associated with BeEAM. In our experience, the nephrotoxicity associated with the regimen is 'clinically-silent' and has not resulted in increased mortality or delay of therapy. BeEAM seems comparable to BEAM in terms of other toxicities, however BeEAM does appear to carry a greater risk of diarrhea. The increased risk of gastrointestinal upset can be offset by the apparent reduction in IPS, which represents a much more substantial transplant complication. Lastly, our centre reports tremendous cost-savings associated with BeEAM HDCT. Safely implementing cost-saving measures has become increasingly important to health systems, especially amid the COVID-19 pandemic.

However, there are certainly unanswered questions pertaining to the choice of HDCT. Firstly, the current literature is limited in terms of large, prospective cohort studies directly comparing HDCT regimens. Thus, current studies could be insufficiently powered to detect differences between regimens in terms of rare complications, such as cardiotoxicity. Additionally, BeEAM is a relatively new therapy. At our centre, for instance, BeEAM only became standard of care in 2015. As a result, there is a paucity of data surrounding long-term survival, latent complications and secondary malignancies. However, BeEAM seems promising as a safe, efficacious and economical HDCT option.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgements

We would like to thank our patients and the Saskatchewan Cancer Agency for their assistance. Also, we wish to thank the University of Saskatchewan College of Medicine's Dean's project program for fostering collaboration between the authors.

Author Contributions

L.H. and M.B. wrote the paper. All authors reviewed and approved the paper.

Additional Information

Correspondence and requests for materials should be addressed to M.B.

References

1. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van Der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. New England Journal of Medicine. 1995 Dec 7;333(23):1540-5.

2. Gisselbrecht C, Glass B, Mounier N, Gill DS, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. Journal of Clinical Oncology. 2010 Sep 20;28(27):4184.

3. Fermé C, Mounier N, Diviné M, Brice P, Stamatoullas A, Reman O, et al. Intensive salvage therapy with high-dose chemotherapy for patients with advanced Hodgkin's disease in relapse or failure after initial chemotherapy: results of the Groupe d'Etudes des Lymphomes de l'Adulte H89 Trial. Journal of Clinical Oncology. 2002 Jan 15;20(2):467-75.

4. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM,

Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. The Lancet. 2002 Jun 15;359(9323):2065-71.

5. Galieni P, Troiani E, Bigazzi C, Mazzotta S, Ruggieri M, Pezzoni V, et al. Modified BEAM as conditioning regimen for lymphoma patients undergoing autologous hematopoietic stem cell transplantation. Bone Marrow Transplantation. 2018 Jan;53(1):91-3.

6. Visani G, Malerba L, Stefani PM, Capria S, Galieni P, Gaudio F, et al. BeEAM (bendamustine, etoposide, cytarabine, melphalan) before autologous stem cell transplantation is safe and effective for resistant/relapsed lymphoma patients. Blood, The Journal of the American Society of Hematology. 2011 Sep 22;118(12):3419-25.

7. Leoni LM, Bailey B, Reifert J, Bendall HH, Zeller RW, Corbeil J, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. Clinical Cancer Research. 2008 Jan 1;14(1):309-17.

8. Hahn L, Lim H, Dusyk T, Sabry W, Elemary M, Stakiw J, et al. BeEAM conditioning regimen is a safe, efficacious and economical alternative to BEAM chemotherapy. Scientific Reports. 2021 Jul 7;11(1):1-9.

9. Till BG, Madtes DK. BCNU-associated pneumonitis: portrait of a toxicity. Leukemia & lymphoma. 2012 Jun 1;53(6):1019-20.

10. Lane AA, Armand P, Feng Y, Neuberg DS, Abramson JS, Brown JR, et al. Risk factors for development of pneumonitis after high-dose chemotherapy with cyclophosphamide, BCNU and etoposide followed by autologous stem cell transplant. Leukemia & Lymphoma. 2012 Jun 1;53(6):1130-6.

11. Afessa B, Abdulai RM, Kremers WK, Hogan WJ, Litzow MR, Peters SG. Risk factors and outcome of pulmonary complications after autologous hematopoietic stem cell transplant. Chest. 2012 Feb 1;141(2):442-50.

12. Olivieri J, Mosna F, Pelosini M, Fama A, Rattotti S, Giannoccaro M, et al. A comparison of the conditioning regimens BEAM and FEAM for autologous hematopoietic stem cell transplantation in lymphoma: an observational study on 1038 patients from Fondazione Italiana Linfomi. Biology of Blood and Marrow Transplantation. 2018 Sep 1;24(9):1814-22.

13. Gilli S, Novak U, Taleghani BM, Baerlocher GM, Leibundgut K, Banz Y, et al. BeEAM conditioning with bendamustine-replacing BCNU before autologous transplantation is safe and effective in lymphoma patients. Annals of Hematology. 2017 Mar 1;96(3):421-9.

14. Chantepie S, Tchernonog E, Peyrade F, Larcher MV, Diouf M, Fornecker LM, et al. Bendamustine-based (BeEAM) conditioning before autologous stem cell transplantation: result of a French multicenter study of 386 patients from Lysa Centers. Blood. 2016 Jan 1;128(22):3450.

15. Ribrag V, Saleh K, Danu A, Koscielny S, Pilorge S, Ghez D, et al. BEAM or BeEAM High-Dose Chemotherapy Followed By ASCT: A Single Center Comparative Analysis of Toxicity. Blood. 2016 Jan 1;128(22):4648.

16. Saleh K, Danu A, Koscielny S, Legoupil C, Pilorge S, Castilla-Llorente C, et al. A retrospective, matched paired analysis comparing bendamustine containing BeEAM versus BEAM conditioning regimen: results from a single center experience. Leukemia & Lymphoma. 2018 Nov 2;59(11):2580-7.

17. Garciaz S, Coso D, De Collela JS, Broussais F, Stoppa AM, Aurran T, et al. Bendamustine-based conditioning for non-Hodgkin lymphoma autologous transplantation: an increasing risk of renal toxicity. Bone Marrow Transplantation. 2016 Feb;51(2):319-21.

18. Frankiewicz A, Saduś-Wojciechowska M, Najda J, Czerw T, Mendrek W, Sobczyk-Kruszelnicka M, Soska K, et al. Comparable safety profile of BeEAM (bendamustine, etoposide, cytarabine, melphalan) and BEAM (carmustine, etoposide, cytarabine, melphalan) as conditioning before autologous haematopoietic cell transplantation. Contemporary Oncology. 2018;22(2):113-7.

19. Noesslinger T, Panny M, Simanek R, Moestl M, Boehm A, Menschel E, et al. High-dose Bendamustine-EAM followed by autologous stem cell rescue results in long-term remission rates in lymphoma patients, without renal toxicity. European Journal of Haematology. 2018 Sep;101(3):326-31.

20. Farnault L, Venton G, Pourroy B, Jourde-Chiche N, Ivanov V, Arcani R, et al. Severe renal insufficiency is not an absolute pitfall to autologous stem cell transplantation with BeEAM (bendamustine, etoposide, cytarabine, melphalan) conditioning regimen. Bone marrow Transplantation. 2019 Jul;54(7):1173-5.

21. Ullery BW, Pieracci FM, Rodney JR, Barie PS. Neutropenic enterocolitis. Surgical Infections. 2009 Jun 1;10(3):307-14.

22. Visani G, Stefani PM, Capria S, Malerba L, Galieni P, Gaudio F, et al. Bendamustine, etoposide, cytarabine, melphalan, and autologous stem cell rescue produce a 72% 3-year PFS in resistant lymphoma. Blood, The Journal of the American Society of Hematology. 2014 Nov 6;124(19):3029-31.