DOI: 10.46765/2675-374X.2023V4N2P187

ANTIEMETICS IN HEMATOPOIETIC CELL TRANSPLANTATION: AN OVERVIEW OF RANDOMIZED TRIALS

Leonardo Javier Arcuri [1,2]

1 Academic Research Organization, Hospital Israelita Albert Einstein, Sao Paulo, Brazil
2 Bone Marrow Transplantation Unit, Instituto Nacional de Cancer, Rio de Janeiro, Brazil

Corresponding author: Leonardo Javier Arcuri - leonardojavier@gmail.com - ORCID: 0000-0002-9673-1945

Received: 12 Jul 2022 • Revised: 11 Apr 2023 • Accepted: 12 May 2023.

ABSTRACT

Antiemetics play a key role in hematopoietic cell transplantation (HCT). High-dose chemotherapy and total body irradiation (TBI) have a high emetogenic potential, and vomiting and nausea during conditioning regimen and thereafter impair oral intake, which can lead to weight loss, hyperglycemia due to parenteral nutrition, infectious disease, and increased transplant-related mortality. We searched for randomized trials on antiemetics in HCT. Triplet prophylaxis with a 5-HT antagonist, an NK-1 antagonist, and dexamethasone is a common practice in hematopoietic cell transplantation. Prophylaxis is usually given during the conditioning regimen and sometimes up to a few days later. NK-1 antagonist usage is supported by randomized trials. Olanzapine reduces nauseas, based on a randomized trial. Although recommended by the ASCO guideline, the use of dexamethasone should be considered controversial given the higher incidence of adverse events with this medication in a randomized study and given a possible higher risk of infections, and therefore dexamethasone should be used with caution as an antiemetic in hematopoietic cell transplantation. Metoclopramide, diphenhydramine, and lorazepam are other drugs that also have antiemetic activity, have been used in HCT, and can be used in selected cases.

INTRODUCTION

Antiemetics play a key role in hematopoietic cell transplantation (HCT). High-dose chemotherapy and total body irradiation (TBI) have a high emetogenic potential[1] antiemetics, and antiemetic regimens and to provide recommendations on the use of dexamethasone as a prophylactic antiemetic in patients receiving checkpoint inhibitors (CPIs, and vomiting and nausea during conditioning regimen and thereafter impair oral intake, which can lead to weight loss, hyperglycemia due to parenteral nutrition, infectious disease, and increased transplant-related mortality[2].

With the novel antiemetics, namely serotoninergic (5-HT) antagonists and neurokinin-1 (NK-1) antagonists, acute chemotherapy-induced nausea and vomiting (CINV) can be adequately controlled while control of delayed CINV is somewhat poorer[3]. The objective of this study is to review the randomized studies of antiemetics in HCT.

METHODS

We searched PubMed for (antiemetic*[Title] OR nausea[Title] OR vomit*[Title]) AND (transplant*[Title] OR (high[Title] NEXT dose[Title])) AND (randomized[Title/Abstract] OR randomised[Title/Abstract]) from 2000 and for (metoclopramide[Title] OR diphenhydramine[Title] OR promethazine[Title]) transplant*[Title] without any time limit.

RESULTS

The search yielded 19 studies. We found a total of 11 randomized trials, which are outlined below. Another study was added because of its historical importance.

Serotoninergic Receptor Antagonists

Okamoto et al[4] have compared granisetron with prophylaxis based on metoclopramide and found that granisetron was superior to metoclopramide in preventing CINV in HCT ($p < 0.001$). The use of 5-HT antagonists is now standard in HCT. Constipation and headaches are the main adverse effects of 5-HT antagonists.

Different serotoninergic antagonists

Fox-Geiman et al[5] compared three regimens: oral granisetron 1 mg twice daily, oral ondansetron 24 mg/day, and intravenous bolus ondansetron 32 mg/day until 1 day after the completion of the chemotherapy, all with dexamethasone 10 mg/day. All three regimens demonstrated similar efficacy.

Bubalo et al[6] compared granisetron (2-3 mg/day) or ondansetron (up to 32 mg/day), with dolasetron (1.8 mg/kg, capped at 100 mg, which could be increased to 200 mg/day for refractory patients), combined with dexamethasone, with or without lorazepam and prochlorperazine, during chemotherapy or TBI. Dolasetron-treated patients had fewer days free from emetic episodes ($p < 0.005$). Major or complete responses were also lower with dolasetron.

Slaby et al[7]granisetron, tropisetron and ondansetron, during conditioning for autologous stem cell transplantation (ASCT compared ondansetron 8 mg twice daily, granisetron 3 mg/day, and tropisetron 5 mg/day for 7 days. Dexamethasone was given only in case of failure. Emesis control with ondansetron 8 mg twice daily was significantly poorer than the other two regimens.

Neurokinin-1 receptor antagonists

Bubalo et al[8] et al tested the addition of aprepitant 125 mg followed by 80 mg daily until D+4 to ondansetron 8 mg (twice daily, and 4 times daily in patients receiving busulfan 4 times daily) and dexamethasone (before TBI or cyclophosphamide). Conditioning regimens were BuCy or CyTBI. Complete and major responses were higher in the aprepitant group (85% vs 45%, $p = 0.02$).

Svanberg & Gunnar[9] also tested the addition of aprepitant until 7 days after the end of the chemotherapy. The standard prophylaxis included tropisetron 5 mg/day and betamethasone (6 mg/day). There was a significantly lower number of vomiting episodes in the aprepitant group ($p = 0.001$).

Schmitt et al[10], in patients with multiple myeloma, added aprepitant 125 mg on day 1 and 80 mg/day on days 2 to 4 to granisetron 2 mg D1-4 and dexamethasone 4 mg on D1 and 2 mg on D2-3. Melphalan 100 mg/m2 was given on days 1 and 2. Complete response was achieved more frequently in the group that received aprepitant (58% vs 41%, $p = 0.004$).

Stiff et al[11] added aprepitant 125 mg on day 1 and 80 mg/day for 4 days to ondansetron 8 mg three times daily and dexamethasone 7.5-10 mg/day until the following day of chemotherapy completion. Complete response rates were higher in the aprepitant arm (82% vs 66%, $p < 0.001$).

In summary, these studies demonstrate that the addition of aprepitant is effective and safe in preventing nausea and vomiting in the context of high-dose therapy and hematopoietic cell transplantation and should be offered to all patients.

Dexamethasone

Matsuoka et al[12] tested the addition of dexamethasone to granisetron in patients receiving high-dose chemotherapy with or without total body irradiation (TBI). Patients received 40 mcg/kg with or without 4 mg dexamethasone 30 minutes before each dose of chemo or radiotherapy and repeated 12 hours after the first dose. Granisetron and dexamethasone were given no more than twice daily. Although complete emesis control was higher with dexamethasone (100% vs 63%, $p = 0.02$), adverse reactions were more frequent in the dexamethasone group (68% vs 5%), even though the authors have not specified the rates of infectious complications. The use of corticoids has been associated with higher rates of invasive fungal infections[13] and, in patients with acute myeloid leukemia (AML), with higher infectious death rate even with a low median number of days of corticosteroid administration[14]. In the haploidentical setting, the use of corticosteroid as premedication before graft infusion has been linked to higher CMV reactivation[15].

Olanzapine

Clemmons et al[16] tested the addition of olanzapine 10 mg/day to an antiemetic scheme that included ondansetron 8-16 mg/day, dexamethasone 8-20 mg/day, and fosaprepitant 150 mg/day, given until 3 days after the chemo/radiotherapy. Complete protection (no emesis, rescue antiemetic, or significant nausea) was seen in 55% of the patients who received olanzapine, against 26% ($p = 0.003$) in the control group. The main side effect of olanzapine is sedation.

Dopaminergic receptor antagonists

Gilbert et al[17] cyclophosphamide, and carmustine with autologous bone marrow support were randomized to receive one of four double-blinded antiemetic regimens: 4-day continuous infusion prochlorperazine (6 mg/m2 intravenous [i.v.] loading dose followed by 1.5 mg/m2/hour compared metoclopramide 20 mg/m2.hour with prochlorperazine 1.5 mg/m2.hour, both in combination with diphenhydramine 25 mg 4 times daily and lorazepam 1 mg/m2 every 4 hours, with either dronabinol 5 mg/m2 or placebo. Both metoclopramide and prochlorperazine in combination with lorazepam and diphenhydramine offered similar control of nausea and vomiting, although dose reductions due to toxicity were frequent. The addition of dronabinol did not improve the results.

CONCLUSION

Triplet prophylaxis with a 5-HT antagonist, an NK-1 antagonist, and dexamethasone is a common practice in hematopoietic cell transplantation. Prophylaxis is usually given during the conditioning regimen and sometimes up to a few days later. NK-1 antagonist usage is supported by randomized trials. Olanzapine reduces nauseas, based on a randomized trial. Although recommended by the ASCO guideline[1] antiemetics, and antiemetic regimens and to provide recommendations on the use of dexamethasone as a prophylactic antiemetic in patients receiving checkpoint inhibitors (CPIs, the use of dexamethasone should be considered controversial given the higher incidence of adverse events with this medication in a randomized study and given a possible higher risk of infections, and therefore dexamethasone should be used with caution as an antiemetic in hematopoietic cell transplantation. Metoclopramide, diphenhydramine, and lorazepam are other drugs that also have antiemetic activity, have been used in HCT, and can be used in selected cases.

REFERENCES

1. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update. JCO. 2020;38(24):2782-97. doi:10.1200/JCO.20.01296
2. Yuda S, Fuji S, Savani B, Gatwood KS. Antiemetic Strategies in Patients Who Undergo Hematopoietic Stem Cell Transplantation. Clin Hematol Int. 2022;4(3):89-98. doi:10.1007/s44228-022-00012-8
3. Trigg ME, Inverso DM. Nausea and vomiting with high-dose chemotherapy and stem cell rescue therapy: a review of antiemetic regimens. Bone Marrow Transplant. 2008;42(8):501-6. doi:10.1038/bmt.2008.257
4. Okamoto S, Takahashi S, Tanosaki R, et al. Granisetron in the prevention of vomiting induced by conditioning for stem cell transplantation: a prospective randomized study. Bone Marrow Transplant. 1996;17(5):679-83.
5. Fox-Geiman MP, Fisher SG, Kiley K, Fletcher-Gonzalez D, Porter N, Stiff P. Double-blind comparative trial of oral ondansetron versus oral granisetron versus IV ondansetron in the prevention of nausea and vomiting associated with highly emetogenic preparative regimens prior to stem cell transplantation. Biology of Blood and Marrow Transplantation. 2001;7(11):596-603. doi:10.1053/bbmt.2001.v7.pm11760147
6. Bubalo J, Seelig F, Karbowicz S, Maziarz RT. Randomized open-label trial of dolasetron for the control of nausea and vomiting associated with high-dose chemotherapy with hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2001;7(8):439-45. doi:10.1016/S1083-8791(01)80011-2
7. Slabý J, Trnený M, Procházka B, Klener P. Antiemetic efficacy of three serotonin antagonists during high-dose chemotherapy and autologous stem cell transplantation in malignant lymphoma. Neoplasma. 2000;47(5):319-22.
8. Bubalo J, Mulverhill K, Meyers G, Hayes-Lattin B, Maziarz R. A randomized, placebo-controlled pilot trial of aprepitant combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients undergoing cyclophosphamide-based conditioning regimens prior to hematopoietic stem cell transplant (HSCT). Bone Marrow Transplant. 2018;53(8):1010-8. doi:10.1038/s41409-018-0106-8

9. Svanberg A, Birgegård G. Addition of Aprepitant (Emend®) to Standard Antiemetic Regimen Continued for 7 Days after Chemotherapy for Stem Cell Transplantation Provides Significant Reduction of Vomiting. Oncology. 2015;89(1):31-6. doi:10.1159/000371523

10. Schmitt T, Goldschmidt H, Neben K, et al. Aprepitant, Granisetron, and Dexamethasone for Prevention of Chemotherapy-Induced Nausea and Vomiting After High-Dose Melphalan in Autologous Transplantation for Multiple Myeloma: Results of a Randomized, Placebo-Controlled Phase III Trial. JCO. 2014;32(30):3413-20. doi:10.1200/JCO.2013.55.0095

11. Stiff PJ, Fox-Geiman MP, Kiley K, et al. Prevention of Nausea and Vomiting Associated with Stem Cell Transplant: Results of a Prospective, Randomized Trial of Aprepitant Used with Highly Emetogenic Preparative Regimens. Biology of Blood and Marrow Transplantation. 2013;19(1):49-55. e1. doi:10.1016/j.bbmt.2012.07.019

12. Matsuoka S, Okamoto S, Watanabe R, et al. Granisetron Plus Dexamethasone Versus Granisetron Alone in the Prevention of Vomiting Induced by Conditioning for Stem Cell Transplantation: A prospective Randomized Study. Int J Hematol. 2003;77(1):86-90. doi:10.1007/BF02982608

13. Shi J min, Pei X ying, Luo Y, et al. Invasive fungal infection in allogeneic hematopoietic stem cell transplant recipients: single center experiences of 12 years. J Zhejiang Univ Sci B. 2015;16(9):796-804. doi:10.1631/jzus.B1500005

14. Dix D, Cellot S, Price V, et al. Association Between Corticosteroids and Infection, Sepsis, and Infectious Death in Pediatric Acute Myeloid Leukemia (AML): Results From the Canadian Infections in AML Research Group. Clin Infect Dis. 2012;55(12):1608-14. doi:10.1093/cid/cis774

15. Saad A, Taneja A, Di Stasi A, et al. Impact of high-dose steroid premedication on the outcome of myeloablative T-cell replete haploidentical peripheral blood stem cell transplant. Bone Marrow Transplant. 2018;53(10):1345-8. doi:10.1038/s41409-018-0185-6

16. Clemmons AB, Orr J, Andrick B, Gandhi A, Sportes C, DeRemer D. Randomized, Placebo-Controlled, Phase III Trial of Fosaprepitant, Ondansetron, Dexamethasone (FOND) Versus FOND Plus Olanzapine (FOND-O) for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients with Hematologic Malignancies Receiving Highly Emetogenic Chemotherapy and Hematopoietic Cell Transplantation Regimens: The FOND-O Trial. Biol Blood Marrow Transplant. 2018;24(10):2065-2071. doi:10.1016/j.bbmt.2018.06.005

17. Gilbert CJ, Ohly KV, Rosner G, Peters WP. Randomized, double-blind comparison of a prochlorperazine-based versus a metoclopramide-based antiemetic regimen in patients undergoing autologous bone marrow transplantation. Cancer. 1995;76(11):2330-2337. doi:10.1002/1097-0142(19951201)76:11<2330::aid-cncr2820761122>3.0.co;2-f