

Aspects of interest related to antiemesis in haematological patients

Abstract

Few side effects of cancer treatment are more fearsome for patients than nausea and vomiting. Although both can result from surgery or radiation therapy, chemotherapy-induced nausea and vomiting (CINV) are potentially the most severe and the most distressing ones. Despite recent advances in the prevention of emesis induced by chemotherapy, its control remains to be insufficient in 20-25%¹ of patients, with the ensuing negative impact on their quality of life. In this small review, we intend to analyze some critical aspects related to the approach of antiemetic therapy in the clinical practice in haematological patients.

Keywords: chemotherapy, radiation therapy, surgery, prophylaxis, antiemetic, cyclophosphamide, emetogenic, cytotoxic agents

Volume 7 Issue 2 - 2019

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Received: August 18, 2019 | **Published:** September 24, 2019

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; ECG, electro-cardiogram; TdP, torsade de pointes; RA, receptor antagonists; NETU, Netupitant

Introduction

Good symptomatic control in haematological patients is essential not only to improve the quality of life but also to maintain the intensity of treatment and that the patient's prognosis is not compromised. A greater knowledge of the factors affecting the control of nausea and vomiting are keys to improving the situation:

- Several studies have shown that there is a difference between the perception of CINV by the health care provider and patients, thus leading to a general underestimation of the risk of CINV.^{2,3}
- Another important issue is that most clinical trials evaluating CINV have focused on antiemetic prophylaxis for solid tumor chemotherapy. Consequently, evidenced-based guidelines for antiemetic prophylaxis with haematological malignancies cytotoxic agents are not well established. The definition of AC regimens (Adriamycin plus cyclophosphamide) as highly emetogenic came exclusively from studies of women with breast cancer. It is not clear whether other combination regimens used within AC in other diseases or in more diverse groups of subjects: For example, in non-Hodgkin lymphoma, CHOP (doxorubicin plus cyclophosphamide, vincristine and prednisone) would be highly emetogenic.
- Moreover, it should be noted that most regimens of haematological chemotherapy, include more than one agent and a multiday therapy. This situation adds an extra complexity. Patients, who receive multiday chemotherapy, are at risk of suffering both acute and delayed nausea and vomiting.
- Current recommendations are based on the emetogenic potential of cytotoxic agents. However, there are some factors related to the patient's condition which have been usually overloaded.

Role of NK1 receptor antagonists (NK1RA)

Aprepitant and fosaprepitant, NK₁R antagonists, have a moderate inhibition effect on the cytochrome CYP₃A₄ (P₄₅₀ 3A₄ enzyme), which has a special relevance in drug metabolism.⁴ CYP₃A₄ is responsible for the metabolism of glucocorticoids, and thus, few clinical trials recommend the reduction of dexametasone from 20 to 12mg on first day and from 8mg twice daily to 8mg daily on days two and three when given in combination with aprepitant.⁵⁻⁷ This dose reduction applies only when glucocorticoids are used as antiemetic in conjunction with NK₁RA, not when given as an antitumor agent as part of the chemotherapy scheme. Many combinations of drugs used for the treatment of malignant homeopathies include corticosteroids, strengthening the need for using NK₁R antagonists with caution in this type of patients.

In addition, it is supposed that aprepitant can decrease the clearance of drugs metabolized by CYP₃A₄ such as cyclophosphamide, docetaxel, etoposide, irinotecan or Vinca alkaloids, resulting in extended exposure and increased toxicity. However, there is no clinical evidence that this actually occurs.^{7,8}

Role of palonosetron

Palonosetron, a second-generation agent, has a 30-100 fold higher affinity for the 5-HT₃ receptor and a salient longer half life (40hours) in comparison to first-generation 5-HT₃ receptor antagonists (5-HT₃ RA) such as granisetron, ondansetron and dolasetron.

Besides, palonosetron, as a single agent, is more effective than ondansetron or dolasetron in prevention of emesis owing to chemotherapy agents with different emetogenic potential.⁹⁻¹¹ This was reflected in the results of a multicenter trial in 592 patients, most of them had received doxorubicin and cyclophosphamide (AC) for breast cancer; a small group of subjects were treated with cisplatin/carboplatin based chemotherapy regimens.⁹ Patients were randomly assigned to a single intravenous dose of palonosetron at 0.25 or 0.75mg or dolasetron at 100mg. More patients treated with

palonosetron (0.25mg) have achieved control of both acute (63% vs 53%) and delayed emesis (54% vs 39%) compared with dolasetron. The dose of 0.75mg was not significantly superior in comparison with 0.25mg.

Another trial with similar design as mentioned above, has also demonstrated better results for palonosetron versus ondansetron.¹⁰ Additionally, palonosetron plus glucocorticoids, provides a better control of delayed emesis in comparison with first generation 5-HT₃ RA combined with glucocorticoids.^{12–14} In hematological setting, particularly in patients with non Hodgkin lymphoma, an open label trial with a single arm, has found that overall complete response rate of 86% was reached with a single dose of 0.25mg intravenously palonosetron administered prior to chemotherapy: 75% receiving CHOP plus rituximab.¹⁵ Palonosetron has also shown efficacy in patients who underwent hematopoietic transplantation with high dose therapy conditioning regimens such as melphalan given intravenously at a total dose of 200mg/m² divided over two consecutive days¹⁶

Safety aspects

Changes in the electrocardiogram interval (ECG) are a class effect of first generation 5-HT₃RA, although they have not been reported with both transdermal or prolonged-release subcutaneous granisetron formulations.^{17,18}

Changes in the ECG interval appear to be more pronounced between one-two hours after a dose has been administered. They are usually not clinically significant and in 24hours this effect is reversed.^{19–21} However, potentially fatal cardiac arrhythmias, including Torsade de pointes (TdP), have been reported in relation to QTc prolongation.^{19–23} The FDA has warned about potentially fatal cardiac arrhythmias related to QT prolongation in subjects treated with ondansetron.²⁴ QT prolongation appears to be a dose dependent effect and, particularly, an intravenous single dose of 32mg would be enough to trigger this adverse event.

In the United States it is recommended not to exceed the dose of 16mg given intravenously. In patients with congenital long QT syndrome avoid use of ondansetron and monitoring ECG in special populations, such as those with hypo kalemia or hypo-magnesaemia, heart failure, and Brady-arrhythmias, and in patients taking other medications that could increase the risk of QTc prolongation. As opposed to first generation 5-HT₃ RA, QTc prolongation has not been documented with palonosetron.^{25,26}

Role of netupitant + palonosetron

Netupitant (NETU) is a new highly selective NK₁ RA that has been formulated in combination with palonosetron as an oral fixed dose (AKYNZEO®, also known as NEPA). Palonosetron was selected for the AKYNZEO® combination because of its interesting pharmacological²⁷ and clinical²⁸ profile. Palonosetron is distinguished from first generation 5-HT₃ RAs because of its singular receptor binding, its ability to promote NK₁ receptor internalization and its synergistical effect associated to NETU in the inhibition of the substance P response, as well as its remarkable better efficacy in delayed emesis.^{27,29–30} Accordingly, it has the potential to increase prophylaxis of delayed CINV when used combined with NETU. Another interesting aspect is that NEPA formulation may improve guideline adherence by targeting two critical pathways involved in emesis with a convenient, single oral dose and having an effect on acute and delayed emesis.

Role of olanzapine

Olanzapine is a second generation antipsychotic that blocks serotonin type two 5-hydroxytryptamine receptors (5-HT₂) and dopamine receptors (D2). In a double-blind randomized trial involving 80 patients receiving highly emetogenic chemotherapy, superiority for olanzapine was shown over metoclopramide for treatment of breakthrough nausea and vomiting. Olanzapine was administered 10mg orally, daily for 3days and metoclopramide 10mg orally; three times daily during 3days,³¹ during the observation period (72hours), more subjects receiving olanzapine had no nausea (68% vs 23%) and no recurrent emesis (70% vs 31%). These data suggest that olanzapine is preferred over metoclopramide alone. Even if the optimal dose is not well established, it is expected that a lower dose could provide similar efficacy with a more favorable side effect profile.^{32–33}

Emesis is a very common adverse reaction to chemotherapy that is generally predictable and potentially preventable. The main goal of antiemetic therapy is to control emesis in all situations without adding side effects. In addition, a secondary objective would be controlling or reducing the number of hospitalizations and therefore optimizing the use of health resources. It is very important to carry out preventive measures from the first cycle because a good prophylaxis can reduce the risk of developing nausea and anticipatory vomiting throughout the treatment, as well as the negative impact that both entail.

Acknowledgments

None

Conflicts of interest

The author declares that there are no conflicts of interest.

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