

# Revision of nausea and vomiting in patients with haematological malignancies and hematopoietic transplantation

## Abstract

Nausea and vomiting induced by chemotherapy in the context of hematopoietic transplantation is a frequent adverse effect that negatively influences the clinical course of patients. To date, its management continues to be a challenge for health professionals dedicated to the care of these patients. Therefore, there is little evidence on the effectiveness of the new anti-emetics and their combinations in patients treated with high doses of chemotherapy and subsequent infusion of hematopoietic precursors and few studies with validity and sufficient significance due to fragmentation (multiple transplant centers) in order to extrapolate their findings to clinical practice. In our hospital we used high-doses melphalan administered in a single day (200mg/m<sup>2</sup>) to condition the patients with multiple myeloma (MM). To prevent chemotherapy-induced nausea and vomiting (CINV) we used the combination of palonosetron plus dexamethasone administered half an hour before the start of chemotherapy. Our experience with this combination is very satisfactory.

**Keywords:** palonosetron, melphalan, multiple-day chemotherapy, high-dose chemotherapy, dexamethasone, netupitant

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**Abbreviations:** CINV, chemotherapy induced nausea and vomiting; HSTC, hematopoietic stem cell transplantation; MM, multiple myeloma; 5-HT3 RAs, 5-HT3 receptor antagonists; NHL, non hodgkin lymphoma; HL, hodgkin lymphoma; AML, ACUTE MYELOID LEUKemia; MASCC, multinational association for supportive care in cancer; ESMO, European society for medical oncology; NCCN, national comprehensive cancer network; NK1, neurokinin 1; CI, confidence interval; CR, complete response

## Introduction

Nausea and vomiting induced by chemotherapy in the context of hematopoietic transplantation is a frequent adverse effect that negatively influences the clinical course of patients. To date, its management continues to be a challenge for health professionals dedicated to the care of these patients. Multiple mechanisms have been linked to the pathophysiology of nausea and vomiting. Several neurotransmitters function as mediators in peripheral and/or central nausea and vomiting including dopamine, serotonin and substance P. In each type of emesis several of these transmitters and their respective receptors with different relative importance are involved. Since there is no single pathway and mediator for all forms of emesis a family of drugs with absolute global efficacy has not been found. Not even a family of these drugs is able to control, in all cases, both acute and delayed emesis.

## Own experience

In our hospital we used high-doses melphalan administered in a single day (200mg/m<sup>2</sup>) to condition the patients with multiple myeloma (MM). To prevent chemotherapy-induced nausea and vomiting (CINV) we used the combination of palonosetron plus dexamethasone administered half an hour before the start

of chemotherapy. Our experience with this combination is very satisfactory and we summarize it in the following point

31patients, 20womens(64.5%) and 11men, mean age 59.4years old received melphalan (200mg/m<sup>2</sup>) on day -4. Previously, as prophylaxis of CINV, palonosetron plus dexamethasone was given. At the moment of the admission for the transplant only two patients had anticipatory nausea. In the first 24hours after melphalan infusion and palonosetron administration 54.8%(n=17) suffered an episode of nausea (eight patients grade 1, eight grade 2 and one grade 3) and only nine had vomits (seven grade 1, one grade 2 and one grade 3). Between the next 24-96hours 19patients (61.3%) had nausea (14 grade 1, two grade 2 and three grade 3) and 12 patients (38.7%) vomit (nine grade 1 and three grades 2). As rescue medication levomepromazine was used in the 35.5%. All the others were treated with metoclopramide, dexamethasone, domperidone and/or benzodiazepines. The only adverse effect documented after Palonosetron administration was constipation (n=2, 6.4%). We can confirm the effectiveness and security of palonosetron in the prevention of nausea and vomits induced for high dose of melphalan.

## Discussion

Studies of prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) include a pull of patients with various pathologies (Hodgkin lymphoma, multiple myeloma...) in which patients who are going to undergo hematopoietic stem cell transplantation (HSTC) are often not involved. Therefore, there is little evidence on the effectiveness of the new anti-emetics and their combinations in patients treated with high doses of chemotherapy and subsequent infusion of hematopoietic precursors and few studies with validity and sufficient significance due to fragmentation (multiple transplant centers) in order to extrapolate their findings to clinical

practice. The lack of uniformity in the study periods, the response criteria and the conditioning regimens used (although all of them include highly emetogenic chemotherapy) are added to the lack of studies. Important differences between HTSC and conventional chemotherapy regimens should be taken into account when evaluating their emetogenic capacity:

- i. HSTC, conditioning chemotherapy is usually administered several consecutive days
- ii. High-dose emetogenic drugs are used in the HSTC at very high doses
- iii. Total body irradiation, included in certain conditioning regimens, which produces almost constant emesis in these patients.

High-dose multiple-day melphalan is a commonly used conditioning regimen for patients with MM who are undergoing HSCT. In this context, the control of nausea and vomiting is more difficult. In recent years, a series of studies have been presented that aim to find the best antiemetic prophylaxis in MM patients conditioned with high-dose melphalan regimen. Giralt et al.<sup>1</sup> have published their experience in a randomized, double-blind pilot study in 73 patients with MM undergoing HSTC conditioned with high-dose melphalan regimen (100mg/m<sup>2</sup> x 2days). Patients received 1, 2 or 3 days 0.25mg palonosetron (30-minute IV bolus) 30 minutes before to administration of melphalan on days -2, -1 and day 0 of the infusion. Dexamethasone (20mg IV) was administered on days -2 and -1 followed by palonosetron dose or placebo. Complete protection (non-emesis) was achieved in 41.7%, 41.7% and 44.0% of patients receiving 1, 2, or 3 days of palonosetron respectively. A complete response (without emesis or salvage treatment) was achieved in 8.3%, 20.8% and 20.0% (P=0.14) respectively. The most common adverse events were moderate diarrhea or constipation, headache, insomnia and flatulence. Repeated doses of palonosetron are safe and effective. In this regime the administration of two days is better than the single dose and equal to three consecutive doses; the key benefit is the decrease in inter current vomiting and the need for rescue treatment. The conclusions urged to develop more effective combinations from this scheme.<sup>1</sup> Musso et al.<sup>2</sup> reported an observational study of 134 patients with hematologic malignancies (52 MM, 50 NHL, 13 HL and 19 AML) receiving, during conditioning period, palonosetron (0.25mg on the 1st day of chemotherapy) and dexamethasone as prophylaxis of the CINV in the context of the HSTC. A second dose of palonosetron was administered at 72 hours in the case of inter current vomiting. Complete response and complete protection was achieved in 36% and 26% of patients, respectively. In addition, one-half of the patients, re-treated with palonosetron for breakthrough emesis, were successfully rescued.<sup>2</sup>

### Regarding to guideline review

**Guidelines 2016 updated MASCC/ESMO:** Recommend the combination of three drugs, a 5-HT3 RA with dexamethasone and aprepitant, in patients with high-dose of chemotherapy with stem cell transplant.

**NCCN guidelines version 1 2017 anti-emesis:** There is no specific recommendation for patients who are undergoing HSTC.

Aprepitant and fosaprepitant are selective antagonists of high affinity for receptors of substance P neurokinin 1 (NK1) human. There is limited experience with the use of aprepitant in the context of HSTC. Aprepitant exerts modest inhibitory effect on CYP3A4 and modest inductive effect on CYP2C9 substrates which could be a

problem when it is associated with anti-neoplastic drugs metabolized by this route. However, the evidence and impact of drug interactions with aprepitant is still limited.<sup>3</sup> The safety and efficacy of aprepitant was evaluated in a phase II study in 24 patients undergoing to HSCT and conditioned with high-dose melphalan regimen (100mg/m<sup>2</sup> on days 1-2). Intravenous palonosetron (0.75mg on day 1), oral aprepitant (125mg on day 1; 80mg on days 2-4) and intravenous dexamethasone (6.6mg on days 1-4) were administered for prevention of CINV. Complete response (no emesis and no rescue antiemetic) and complete control (no emesis, no rescue antiemetic and no more than mild nausea) rates were 75 and 68% during the overall phase (0-120h), while they were 88 and 86% in the acute phase (0-48h), 75 and 68% in the delayed phase (48-120h) and 67 and 59% in the extended phase (120-168h), respectively. No serious adverse events were detected in relation to antiemetic prophylaxis.<sup>4</sup>

In 2014, Schmitt and cols reported a phase III study, patients with MM were randomized to receive either aprepitant administered at a dose of 125mg orally on day 1 and 80mg orally on days 2 to 4, granisetron (given at a dose of 2mg orally on days 1 to 4) and dexamethasone (given at a dose of 4mg orally on day 1 and 2mg orally on days 2 to 3) or placebo, granisetron at the same dose as in the investigational arm and dexamethasone at a dose of 8mg orally on day 1 and 4mg orally on days 2 to 3. The high-dose chemotherapy regimen consisted of melphalan at a dose of 100mg/m<sup>2</sup> administered intravenously on days 1 to 2. The autologous stem cell transplant was performed on day 4. The primary end point was a complete response, defined as no emesis and no rescue therapy within 120h of melphalan administration. A total of 362 patients were available for the efficacy analysis, with 181 in each treatment arm. The CR rate was significantly higher in the aprepitant arm compared to the control group (58 vs. 41%; 95% CI, 1.23 to 3.00; p=.0042). Absence of major nausea (94 vs. 88%; 95% CI, 1.09 to 5.15; p=.026) and emesis (78 vs. 65%; 95% CI, 1.25 to 3.18; p=.0036) within 120h was significantly improved by aprepitant.<sup>5</sup> Netupitant is a novel selective antagonist of human NK1 receptors and is marketed in combination with palonosetron in a oral fixed-dose containing 300mg of netupitant and 0.5mg of palonosetron (NEPA). Palonosetron is a second-generation serotonin receptor antagonist (5-HT3 RAs). Compared with first-generation 5-HT3 RAs, it has a half-life significantly longer and a relatively high binding affinity for the 5-HT3 receptor.<sup>6</sup> Furthermore, QTc prolongation has not been described with palonosetron.<sup>7</sup>

### Conclusion

We have different therapeutic options with acceptable effectiveness. Within the 5-HT 3 RAs, palonosetron seems the most valuable option. Possibly palonosetron could be beneficial in combination with aprepitant, for this would be necessary prospective and individualized studies for haematological neoplasia and treatment scheme.

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### Conflict of interest

The author declares no conflict of interest.

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