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ORIGINAL ARTICLE

Netupitant/palonosetron without dexamethasone for preventing nausea and vomiting in patients with multiple myeloma receiving high-dose melphalan for autologous stem cell transplantation: a single-center experience

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is one of the most frequent adverse events compromising quality of life (QoL) in patients undergoing autologous stem cell transplantation (ASCT). However, CINV prophylaxis is still lacking uniformity for high-dose melphalan (HDM), which is used to condition patients with multiple myeloma (MM). Netupitant/palonosetron (NEPA) is administered with dexamethasone (DEXA) for CINV prevention in several chemotherapy regimens. Our study aims to assess the efficacy of NEPA, without DEXA, in preventing CINV in 106 adult patients with MM receiving HDM and ASCT. All patients had antiemetic prophylaxis with multiple doses of NEPA 1 h before the start of conditioning and after 72 h and 120 h. A complete response (CR) was observed in 99 (93%) patients at 120 h (overall phase). The percentage of patients with complete control was 93%. The CR rate during the acute phase was 94% ($n=100$). During the delayed phase, the CR rate was 95% ($n=101$). Grade 1 nausea and vomiting were experienced by 82% and 12% of the patients, respectively. Grade 2 nausea was reported in 18% and vomiting in 10% of patients. Our results showed, for the first time, that NEPA, without DEXA, was a well-tolerated and effective antiemetic option for MM patients receiving HDM followed by ASCT.

Keywords Chemotherapy-induced nausea and vomiting (CINV) · Netupitant/palonosetron (NEPA) · High-dose melphalan · ASCT · Multiple myeloma

Introduction

A highly emetogenic chemotherapy (HEC) regimen is widely used as a conditioning regimen for patients with multiple myeloma (MM) undergoing autologous stem cell transplantation (ASCT) [6]. Chemotherapy-induced nausea and vomiting (CINV) still represents the most distressing side effects, and nausea is reported by more than 50% of the patients undergoing a transplant [22]. The problem of controlling CINV in ASCT recipients is far from solved [23]. The cause of CINV in ASCT is related to many factors, such as gender, age, number of previous chemotherapy lines, and the use of prophylactic antibiotics and narcotic analgesics in the management of mucositis [15, 29]. CINV may also be influenced by factors related to treatment including conditioning regimens, administration, dose, duration, and schedule of the drugs, along with the possible additive effect of several chemotherapy drugs [27]. Uncontrolled CINV can be detrimental for the patient and cause metabolic alterations,

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such as dehydration, electrolyte imbalance, and malnutrition, and therefore interfere with patient adherence to life-saving treatments.

Melphalan (MEL) remains the most widely used agent in preparative regimens for both ASCT and allogeneic transplants because of its myeloablative properties and broad antitumor effects as a DNA alkylating agent [4]. MM remains the main indication for ASCT worldwide [8, 28]. The current standard approach for ASCT in MM patients is to use high-dose MEL (HDM) 200 mg/m^2 except in those aged over 70 and those with kidney failure, for whom a lower dose of HDM is used (140 mg/m^2) [16, 24]. However, very little information is available about its potential impact on the onset of nausea and vomiting in these patients [33]. The National Comprehensive Cancer Network (NCCN) guidelines recently included parenteral HDM ≥ 140 mg/m^2 in patients with a high emetic risk, and MEL < 140 mg/m^2 in those with a moderate emetic risk [12].

Palonosetron (PALO) with aprepitant, low-dose dexamethasone (DEXA), and olanzapine have been used for preventing nausea and vomiting in patients with MM undergoing ASCT [21, 26, 36]. While these studies have reported a low incidence of emesis (0–41%), other studies have reported delayed vomiting as moderately frequent (12–66%), despite adequate prophylaxis in patients receiving HDM [5, 9]. Recently, Tendas et al. showed that an aprepitant-based, three-drug regimen (aprepitant + serotonin receptor antagonist (5HT3RA) + DEXA) had a better efficacy than a two-drug regimen (5HT3RA + DEXA) without increasing the frequency of adverse events for CINV prophylaxis in MM patients undergoing ASCT with HDM conditioning [12].

Netupitant/palonosetron (NEPA) is the first oral fixed combination of a highly selective Neurokinin 1 (NK1) receptor antagonist (RA) with the second-generation 5-HT3 RA PALO. NEPA has demonstrated superiority in preventing CINV compared with PALO in patients receiving cisplatin and anthracycline/cyclophosphamide-based chemotherapy [2, 19].

A limited number of published studies have reported the impact of NEPA in preventing nausea and vomiting in patients receiving ASCT. Recently, Di Renzo et al. reported the use of NEPA without DEXA in 82 patients undergoing ASCT for NHL[14]. Apolito et al. [3] described 70 patients who underwent ASCT for MM and received NEPA in combination with DEXA before ASCT. However, no published studies report the use of NEPA without DEXA in MM patients receiving HDM and ASCT. We, therefore, evaluated the efficacy of NEPA, without DEXA, for CINV prophylaxis in 106 patients who underwent ASCT for MM.

Patients and methods

Study design

This is a single-center, open-label, prospective, observational study designed to assess the efficacy of NEPA in preventing acute and delayed CINV in patients with MM receiving HDM and ASCT. The local ethics committee approved the study, and all patients signed the informed consent form in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Patients

The inclusion criteria were patients aged ≥ 18 years with a diagnosis of MM, eligible for transplantation, a favorable response (according to the International Myeloma Working Group criteria after induction therapy), and a World Health Organization performance status of 0 to 3.

Treatment

All patients received a bortezomib-based induction therapy in combination with thalidomide, and dexamethasone (VTD) or cyclophosphamide, and dexamethasone (VCD). High-dose cyclophosphamide (2–4 g/m^2) plus granulocyte colony-stimulating factor was used to mobilize peripheral blood stem cells. For the transplant phase, patients were admitted to hospital in a positive-pressure, reverse-isolation room and followed a "complete inpatient" program comprising central venous catheter implantation on day − 2, conditioning regimen on day − 1, stem cell reinfusion on day 0, and supportive care during the aplastic phase. The conditioning regimen was high-dose melphalan (HDM) 200 mg/m^2, given on day − 1, with a single intravenous infusion lasting 30 min. Day 0 was the day of ASCT. During the aplastic phase, patients received oral prophylaxis with ciprofloxacin (500 mg twice daily) or levofloxacin (500 mg daily from day 0 until neutrophil count recovery) and acyclovir (800 mg twice daily from day + 3). Granulocyte colony-stimulating factor (pegfilgrastim) was administered on day + 1. Red blood cell and platelet transfusions were performed when indicated to maintain the hemoglobin level at ≥ 8 g/dL and the platelet count at ≥ 10×10^9/L, or in the presence of symptomatic anemia and/or minimal mucocutaneous bleeding. Patients also received continuous i.v. hydration and electrolyte support. The time to neutrophil engraftment was defined as the interval between day 0 and the first of 3 consecutive days of an ANC > 0.5×10^9/L after transplantation. The time to platelet engraftment was defined as the interval between

day 0 and the first day of a platelet count > 20×10^9/L in the absence of platelet transfusions within the previous 7 days.

Antiemetic prophylaxis

NEPA was administered at a dose of 1 capsule (300 mg netupitant; 0.5 mg palonosetron) 1 h before the start of chemotherapy conditioning (day − 1) and repeated after 72 h (day + 2) and after 120 h (day + 4). Intravenous levosulpiride 25 mg was used as a rescue antiemetic when needed. All patients underwent oral cryotherapy for the prevention of mucositis during the administration of MEL.

Assessment

For 10 days after HDM infusion, the nurses recorded emetic episodes and rated nausea daily. In the 2 h prior to starting chemotherapy, patients recorded whether or not they had suffered from vomiting and the rate of nausea in the previous 24 h. The investigators reviewed the diary in order to ensure the completeness of the data. Rescue therapy (defined as any medication taken to treat established nausea or emesis) was recorded after reviewing the medical and nursing charts. Nausea and vomiting were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.03.

Endpoints and statistical analysis

The primary endpoint was the rate of complete response (no emesis and no rescue medication) (CR) at 120 h after conditioning. Secondary endpoints were defined as the rate of CR during the acute phase (0–24 h) and delayed phase (25–120 h) from the start of HDM. Patients were evaluated every day for up to 10 days after ASCT. The occurrence of breakthrough emesis after 72 h was considered a treatment failure. The safety of NEPA was also evaluated. Qualitative variable data were expressed as frequencies and percentages and were evaluated using the chi-square test. Analyses were performed with SPSS 19 (IBM SPSS Statistics for Windows, version 19.0, IBM Corp, Armonk, NY).

Results

A total of 106 patients were enrolled. The main patient characteristics and transplant outcomes are summarized in Table 1. The median age was 60 (range: 42–72) years. Sixty-seven (63%) patients were male and the Eastern Cooperative Oncology Group (ECOG) performance status was ≤ 1 in 100 (96%). The median body weight was 72.5 (range: 43–170) kg. No treatment-related mortality was registered.

NEPA prophylaxis showed a high efficacy in preventing CINV during the HDM conditioning period, especially for no emesis and no rescue therapy with a proportion of patients of 93.4% and 98% in the overall phase (supplementary table 1), respectively. The primary outcome was largely achieved with a CR observed in 99 (93.3%) patients at 120 h. The CR rate during the acute phase was 94.3% ($n = 100$). During the delayed phase, the CR rate was 95.2% ($n = 101$) (Fig. 1). The percentage of patients who attained complete control in the overall phase was 93%. Grade 1 nausea and vomiting were experienced by 82% and 12% of the patients, respectively. Grade 2 nausea was reported in 18% and vomiting in 10% of patients. No patients had grade 3–4 nausea or vomiting (Fig. 2a and b). Breakthrough emesis occurred in 2% of the patients, who received levosulpiride as a salvage treatment (supplementary table 1). Only one patient had > 2 episodes of vomiting during the first 24 h, but he did not require second-line antiemetic therapy. In all, 71 (67%) patients experienced weight loss at 7 days after ASCT. The median body weight loss was 2 (range: 0.5–8) kg. NEPA showed a good safety profile, resulting in very well tolerated with no TEAEs occurring.

Discussion

Uncontrolled nausea and vomiting still remain two of the main, disabling symptoms for patients undergoing chemotherapy. Several complications such as weight loss, electrolyte imbalance, dehydration, and weakness impair not only the patients' health but also their quality of life. Management of CINV in ASCT is challenging [34, 35] and the guidelines in multiple day/drug regimens, commonly used in conditioning regimens, are very difficult to apply [30]. Over the past few years, several clinical studies have reported the efficacy of the combination of three drugs, 5HT3RA, NK-1RA, and dexamethasone, for antiemetic prophylaxis [19, 20]. Although the superior efficacy of the triple-antiemetic regimen has been widely reported in the literature, adherence to the international antiemetic guidelines (MASCC/ESMO) is still low resulting in a lack of compliance and poor prophylaxis for the patients [5]. The HDM 200 mg/m^2 regimen, which is the "gold standard" in MM patients [10, 11], requires a single-day administration of chemotherapy. Recently, the National Comprehensive Cancer Network (NCCN) guidelines placed intravenous melphalan ≥ 140 mg/m^2 in the highly emetogenic category (> 90%) [13]. Consequently, CINV prophylaxis should be designed with the three-drug (aprepitant, 5HT3RA, dexamethasone) or four-drug (olanzapine, aprepitant, 5HT3RA, dexamethasone) combinations in accordance with the recommended guidelines for patients undergoing ASCT [24].

In the HDM setting, palonosetron [9, 11, 17, 20, 25, 26], granisetron [21, 32, 37], and ondansetron [5, 7, 36] have been investigated. None of the aforementioned studies was

Table 1 Patient characteristics and transplant outcomes

Variable	Value
No. of patients	106
Age, years, median (range)	60 (42–70)
Median weight, range, kg	72.5 (43–170)
Gender	
Male	67 (63%)
Female	39 (37%)
ECOG	
0–1	100 (94%)
2–3	6 (6%)
Induction therapy	
Bortezomib, thalidomide, and dexamethasone (VTD)	96 (91%)
Bortezomib, cyclophosphamide, and dexamethasone (VCD)	10 (9%)
Mobilization regimen	
Cyclophosphamide 2 g/m^2 + G-CSF	106 (100%)
Conditioning regimen	
Melphalan 200 mg/m^2	106 (100%)
Disease status before ASCT	
CR	25 (23.5%)
VGPR	61 (58.4%)
PR	19 (16.4%)
No. of CD34 + infused (106/kg)	4.35 (3.8–5.1)
Incidence of febrile neutropenia	28%
Among patients with fever—days with fever (≥ 38.2 °C)	3 (2–4)
Mucositis	
Yes (WHO 0–1)	69%
Yes (WHO 2–3)	31%
Diarrhea	
Yes (WHO 0–1)	84%
Yes (WHO 2–3)	16%
Red blood cell transfusions	
No	81%
Yes	19%
Among patients with red blood cell transfusions	1 (1–2)
Platelet transfusions	
No	44%
Yes	56%
Among patients with platelet transfusions	2 (1–29)
Days to ANC $\geq 0.5 \times 10^9$ L	10 (9–10)
Days to reach platelet count $\geq 20 \times 10$ [9]/L	13 (12–15)
Days to discharge (after stem cell infusion)	16 (15–19)

The table reports age, gender, the ECOG performance status, and the chemotherapy regimen administered to all 106 patients enrolled in the study. Abbreviations: *ASCT*, autologous stem cell transplantation; *ECOG*, Eastern Cooperative Oncology Group; *CR*, complete remission; *VGPR*, very good partial remission; *PR*, partial remission

randomized and the three drugs can be considered equivalent in terms of efficacy for CINV prevention. In terms of side effects, palonosetron has a better safety profile, as it does not cause heart problems, in particular QTc prolongation [18]. Recently, Tendas et al. reviewed the literature for emetogenicity and the efficacy and safety of CINV during ASCT with HDM conditioning, and concluded that the aprepitant-based three-drug regimen should be the regimen of choice for CINV prophylaxis in these patients, although the heterogeneity of the studies examined does not allow definitive conclusions to be drawn [33].

DEXA is recommended for CINV prophylaxis in ASCT in combination with 5HT3RA and aprepitant. Although the exact mechanism of action of DEXA in CINV prevention is

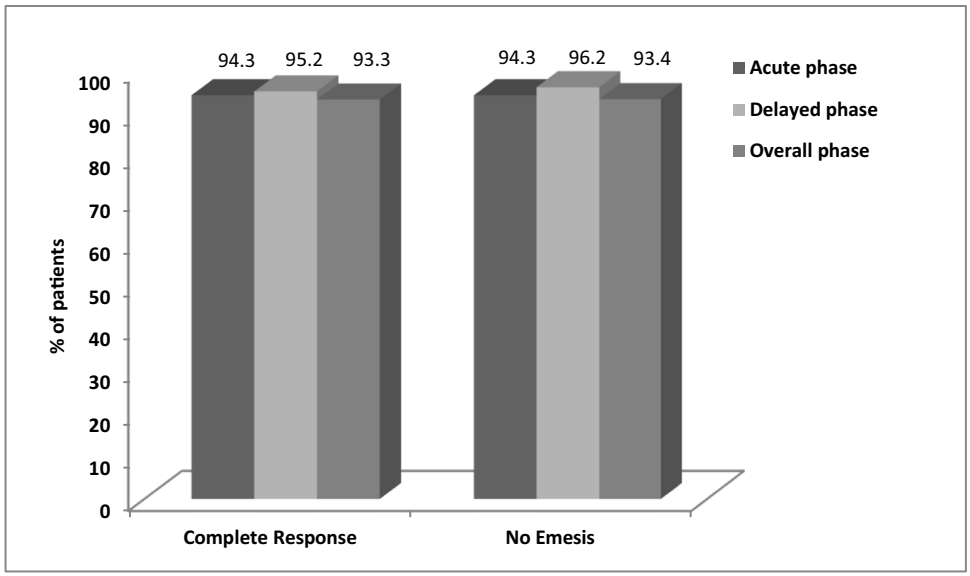

Fig. 1 Proportions of patients with complete response (no emesis and no rescue medication) and no emesis for the acute (0–24 h), delayed (25–120 h), and overall (0–120 h) phases

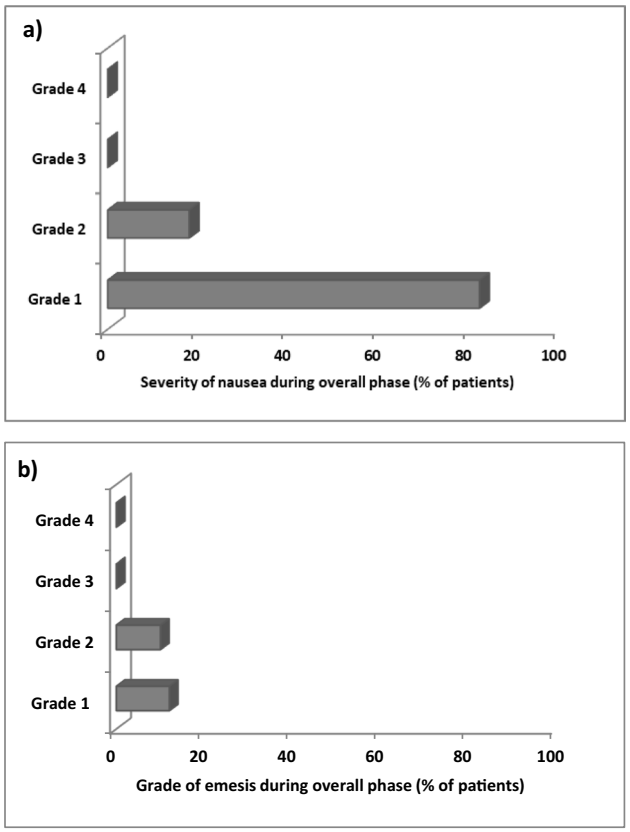

Fig. 2 The histograms show the proportions of patients with grade 1, grade 2, grade 3, and grade 4 of nausea (**a**) and emesis (**b**) during overall phase (120 h) according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.03

unclear, guidelines strongly recommend its administration as CINV prophylaxis [12, 30]. However, the use of DEXA is associated with numerous side effects, such as increased immunosuppression, a higher risk of infections, dysmetabolic alterations, and adrenal insufficiency with suppression of the hypothalamic–pituitary–adrenal axis [10, 31].

Guidelines for CINV prophylaxis recommend the use of olanzapine in high emetic risk chemotherapy, but the advantage of its use in high-dose chemotherapy with ASCT is not clear [13, 16, 25].

The rationale of our study was to explore the efficacy and the safety of NEPA (given as single agent, on days − 1, + 2, and + 4) without DEXA in preventing CINV in patients with MM and treated with HDM 200 mg/m^2 and ASCT. We observed a safe and excellent control of CINV in this cohort of patients treated with a single oral administration with good compliance. NEPA administration resulted in a very high complete response rate during the acute (94.3%), delayed (95.2%), and overall (93.3%) phases. In a similar study, Apolito et al. reported the same type of disease and conditioning regimen but patients received only 1 day of NEPA in combination with 10 mg DEXA [22]. The short duration and schedule may explain the significant difference in the overall CR rate: 56% compared to 93% obtained in our cohort. The use, in our study, of a one-dose drug administration combined an effective antiemetic prophylaxis with a simplification of the therapy, which also enables the use of DEXA in heavily pre-treated and immunocompromised patients to be avoided [1]. In fact, despite the known properties of DEXA for the treatment of patients with MM, its equally known immunosuppressive activity must be evaluated in the management of transplant patients at a high risk of infectious complications. In addition, as recently reported by the ESMO guidance for supportive care, the use of DEXA during this pandemic should be reviewed in patients with established cancer and at a high risk of COVID-19 complications [13].

In conclusion, for the first time, our study provides evidence of the high efficacy of NEPA without DEXA in controlling both emesis and nausea in patients at a high risk of CINV undergoing HDM.

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Author contribution BL and MM designed the study. AP, BL, ADC, and MM wrote the manuscript. AP, PFP, VL, and GP performed the statistical analysis. BL, VN, AF, FAC, MP, TM, GC, FAC, GI, MP, and MM provided cases for the study. FP, GC, LR, NM, VR, DP, SG, TG, and AMR administered the daily questionnaire and sorted the data in nurse files. All the authors edited and approved the final version of the manuscript.

Data availability N/A

Code availability N/A

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Support Care Cancer institutional research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication N/A

Conflict of interest ADC is an employee of Italfarmaco SpA. Other authors have no conflict of interest to disclose.

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