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REVIEW ARTICLE

Prevention of chemotherapy-induced nausea and vomiting after high-dose melphalan and stem cell transplantation: review of the evidence and suggestions

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Abstract

Introduction High-dose melphalan (HDMel) is the most common conditioning chemotherapy regimen for autologous stem cell transplantation (SCT) in patients affected by multiple myeloma (MM). No consensus exists for the emetogenicity or prophylaxis of chemotherapy-induced nausea and vomiting (CINV) in this regimen.

Methods Data on the incidence and efficacy/safety of CINV prophylaxis among patients affected by MM undergoing autologous SCT with the HDMel regimen was extracted from electronic databases and analyzed.

Results Eleven studies involving multiple CINV prophylaxis regimens were identified and included. No consensus on HDMel emetogenicity was reached, but most studies summarized the emetogenicity as moderate-high risk. An aprepitant-based three-drug regimen (aprepitant + serotonin receptor antagonist (5HT3RA) + dexamethasone) showed better efficacy than a two-drug regimen (5HT3RA + dexamethasone) for CINV prevention without increasing the frequency in adverse events.

Conclusions The aprepitant-based three-drug regimen should be the regimen of choice for CINV prophylaxis for MM patients undergoing autologous SCT with HDMel conditioning.

Keywords Chemotherapy-induced nausea and vomiting · Stem cell transplantation · High-dose melphalan · Aprepitant · Quality of life

Introduction

Management of chemotherapy-induced nausea and vomiting (CINV) in high-dose chemotherapy with hemopoietic stem cell transplant (SCT) is challenging [1, 2]. However, two features identified in this setting should help facilitate CINV management: First, the same conditioning regimens are often used for different diseases, for example, in autologous SCT, BEAM conditioning is used in both Hodgkin and non-Hodgkin lymphoma, and in allogenic SCT, conditioning has both a myeloablative and immunosuppressive function. Second, the predominantly inpatient management of SCT facilitates both the monitoring and assessment of CINV.

On the contrary, several aspects make it difficult to understand the mechanism and management of CINV during SCT, which includes the following: (i.) the variability in age, gender, and diagnoses as barriers to epidemiological analysis and evaluation of prophylactic and therapeutic measures; (ii.) the

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fragmentation of available data due to the large amount of bone marrow transplantation units that often perform a limited number of transplants; (iii.) the confounding factors present during HSCT, such as the nausea and vomiting invoked side effect of cryopreservation mean dimethylsulfoxid (DMSO), of cytokines released from infused cells [3], and of supportive therapies, such as antimicrobial prophylaxis or analgesic drugs; (iv.) the limited knowledge about quality of life (QoL) topics, such as CINV, in the practice of SCT and hematology in general; and the (v.) International guidelines suggest the use of the three-drug combination (aprepitant, 5HT3RA, and dexamethasone) in the setting of SCT, but the application of guidelines in multiple days and multiple drugs regimens (commonly used in high-dose chemotherapy conditioning for SCT) is difficult.

However, not all conditioning regimens require multiple days of multiple drug administration. For instance, the high-dose melphalan (HDMel) regimen, which is one of the most broadly used, requires either a single day administration of melphalan 200 mg/sqm (MEL200) or a two-consecutive day administration of melphalan 100 mg/sqm (MEL100×2). Thus, HDMel is an ideal testbed for the study of CINV in SCT.

The National Comprehensive Cancer Network (NCCN) guidelines recently placed intravenous melphalan, regardless of the dosage, in the moderately emetogenic category (30–90%) [4]. Whereas, the guidelines previously distinguished between doses, placing a melphalan dose less than 50–100 mg/sqm in the low emetogenic risk category (10–30%) and a melphalan dose greater than 50–100 mg/sqm in the moderate emetogenic risk category (30–90%). Another emetogenic classification resource, [5] placed melphalan with a dose greater than 50 mg/sqm among class 4 drugs (CINV risk 60–90% [6]).

This data suggests that an increase in dosage correlates with an increase in emetogenicity. In fact, recent literature reports that increasing melphalan dosage from 140 mg/sqm to 200 mg/sqm leads to an increase in CINV probability, despite adequate to high-dose prophylaxis [7]. Therefore, in our opinion, the HDMel regimen should be considered from moderate to high emetogenicity. 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 high-dose chemotherapy and hemopoietic stem cell transplantation or chemotherapy with high emetogenicity drugs [4, 8, 9].

Methods

Review themes

In this paper, we will review the literature for the emetogenicity and the efficacy and safety of CINV prophylaxis in the HDMel regimen, try to identify the best CINV prophylaxis schedule for HDMel conditioning, examine the safety of the identified schedule in the setting of autologous SCT in multiple myeloma, and provide our recommendation for CINV prophylaxis in this situation.

Search strategy

Clinical studies reporting on CINV during autologous SCT with HDMel conditioning were included to assess the emetogenicity of HDMel and the efficacy and safety of the antiemetic regimen. The entire PubMed and Google Scholar databases were searched using the following keywords: “chemotherapy-induced nausea and vomiting,” “CINV,” “nausea,” “vomiting,” “melphalan,” “bone marrow transplantation,” “stem cell transplantation,” “transplantation,” “transplant.” Only English language papers were included, and all duplicated studies were removed.

Results

Results of the search

Fifteen studies were identified that matched the search criteria. Of the 15, 3 were excluded due to patient treatment with multiple conditioning regimens and due to data not reported separately for patients treated with HDMel.

Melphalan emetogenicity during transplants

Emetogenicity is defined as the capacity of an antineoplastic drug to induce emesis (vomiting or retching). In addition to emesis, an emetogenic drug can induce nausea or anorexia as an adverse effect on gastrointestinal receptors by stimulating conduction routes and central nervous system centers that control nausea and vomiting. The evaluation of emetogenic potential of a certain drug is important because the antiemetic treatment guidelines consider acute emetogenicity, as a criterion for recommendations on CINV prevention [4, 8]. While, for certain drugs, data on emetogenicity are easily available, for other drugs data are still lacking. Melphalan has been in use for nearly 60 years. However, since the phase I trial results are not available in the literature, the data on acute emetogenicity without prophylaxis is unknown. Recently, HDMel toxicity was examined by Abidi MH et al. [10], but the data for acute and delayed emesis was not reported separately. Nevertheless, in the last years, data on the acute and delayed emetogenicity of HDMel were reported in articles that presented the results of clinical trials evaluating the efficacy of new antiemetic drugs. Four detailed articles [11–14] evaluating the acute emetogenicity of HDMel in patients undergoing CINV prophylaxis with different schedules reported a low

emesis incidence (0–41%). Other research on HDMel reported delayed vomiting as moderately frequent (12–66%), despite adequate prophylaxis [11, 13–16]. Finally, our analysis of the literature showed a similar rate of CINV in the two melphalan schedules (MEL200×1 and MEL100×2).

Efficacy of combination antiemetic therapy

Eleven papers, reporting results of clinical trials, that explored the effectiveness of a certain prophylaxis for CINV in patients undergoing HDMel conditioning for autologous SCT are included (Table 1). Of these 11 studies, 2 are randomized, comparative, and prospective [7, 18], 6 are single-arm prospective [7, 12, 15, 16, 18, 20], 2 are comparative and retrospective [10, 19], and 1 is single-arm retrospective [13] (Table 1). From these experiments, only aprepitant, fosaprepitant, and olanzapine were compared to standard therapy in the setting of HDMel. There was no data comparing palonosetron or any other drug, such as Nepa, with the standard CINV regimen.

The prospective study by Girault assessed the effects of different palonosetron dosages [11], which is useful for the efficacy and safety of CINV prophylaxis with palonosetron, but not for the comparison of different schedules (Table 1).

The trial by Schmitt [17], comparing a three-drug regimen (aprepitant + granisetron + dexamethasone) with a two-drug regimen (granisetron + dexamethasone), contained 181 patients in each arm. The study was randomized and blinded with placebo administered to patients in the two-drug regimen. The three-drug regimen was significantly more effective especially when comparing emesis. The complete response, which included no emesis or rescue for 0–120 h, in the aprepitant versus placebo was 58% versus 41%, and the result for no nausea in aprepitant versus placebo was 85% versus 78%.

The study by Clark SM et al. [18] compared a three-drug regimen, which was administered prospectively, to a historical cohort of patients treated with a two-drug regimen. The three-drug (Fos) aprepitant-containing treatment was more effective when compared to the two-drug 5HT3RA + dexamethasone regimen (see, Table 1). This is similar to the results of the randomized comparative study by Clark SM above.

The retrospective comparative study by Uchida M. et al. [19] was small, *n* of 48 with only 15 patients treated with HDMel conditioning, and compared a two-drug aprepitant + granisetron against granisetron alone. It is important to note that both regimens were steroid-free. The complete response rate, which involved no vomiting or mentioning of rescue therapy, was 81.8% in the two-drug aprepitant + granisetron group that had 11 patients compared to 25.0% in the granisetron only group that had four patients.

The retrospective comparative study by Trifilio S et al. [14] compared an olanzapine-containing triplet therapy with an aprepitant or fosaprepitant-containing triplet therapy. The emesis and nausea control rates were superior for patients treated with the olanzapine-containing regimen (see, Table 1).

The six noncomparative, single-arm, prospective studies [7, 12, 15, 16, 18, 20] investigated the efficacy of an aprepitant-containing three-drug regimen (four studies [12, 15, 16, 20]), a fosaprepitant-containing three-drug regimen (one study [18]), and a palonosetron-containing two-drug regimen (one study [7]). The results disclosed a high probability of protection from emesis with rescue medication (80–88%) and a lower, although different between trials, probability of protection from emesis without rescue medication (0–52%).

No trials compared the efficacy of different 5HT3RAs in the setting of HDMel. When analyzing the data of the five trials [7, 11, 13, 15, 20] in which palonosetron was used as an 5HT3RA in a two or three-drug regimen, it is impossible to decipher the difference with the other 5HT3RAs (Table 1).

Overall, the (fos)aprepitant-containing three-drug regimen seemed to be superior to the two-drug regimen of 5HT3RA + dexamethasone (Table 1).

Drug-focused overview

5HT3RA 5HT3RAs are recommended by guidelines for CINV prophylaxis in autologous SCT, as well as for highly emetogenic drugs as part of a three-drug combination (aprepitant + 5HT3RA + dexamethasone) [4, 8, 9]. In the setting of HDMel, palonosetron was investigated in five trials [7, 11, 13, 15, 20], granisetron in three trials [12, 17, 19], and ondansetron in three trials [14, 16, 18]. The efficacy of different 5HT3RA drugs was not evaluated in the setting of HDMel; therefore, they should perhaps be considered equivalent in terms of efficacy for CINV prevention.

On the contrary, in terms of safety, palonosetron differs from the other 5HT3RAs. The side effects of 5HT3Rs are well-known. They are frequent and often arise almost acutely, although they are rarely severe [21]. The most important and dangerous side effect is QTc prolongation [22, 23], which can result in arrhythmia, most commonly, tachyarrhythmia, ventricular arrhythmia, and torsade de pointes. This side effect is magnified when 5HT3Rs are administered in patients affected by congenital QTc prolongation syndrome or by electrolytes abnormalities such as hypokalemia and hypomagnesemia. Side effects are also exacerbated when 5HT3Rs are co-administrated with drugs that can affect QT prolongation, such as quinolones, antifungal, and azoles, which are often administered concomitantly during conditioning for autologous transplant. However, in terms of side effects, palonosetron has an advantage, when comparing it with other 5HT3RAs, because it does not cause the QTc prolongation [24] that is common among older generation 5HT3RAs. As such, palonosetron may be preferred over older 5HT3RA agents due to its ability to reduce the risk of QTc prolongation and accompanying arrhythmias.

Table 1 Literature data analysis

Reference	Study design (number of patients)	Patient population/ chemotherapy	Treatment groups	Response			Safety
				Protection (no emesis with rescue)	Response (no rescue medication)	No nausea	
Girault [11]	Randomized, double-blind pilot study ($N = 73$)	MM, MEL200 (100/d × 2 dd)	PALO IV: 0.25 mg × day −2 DEX IV: 20 mg × day −2, −1 vs. PALO IV: 0.25 × day −2, −1 DEX IV: 20 mg × day −2, −1 vs. PALO IV: 0.25 × day −2,− 1, 0 DEX IV: 20 mg × day −2, −1	Complete protection (no emesis with rescue medication) from − 2 to + 4 = 41.7% vs. 41.7% vs. 44% (NS)	Complete response (no rescue medication) from − 2 to + 4 = 8.3% vs. 20.8% vs. 20.0% (NS)	No nausea from − 2 to + 4 = 8.3% vs. 29.2% vs. 16.0% (NS)	No AE related to drugs
Schmitt [17]	Randomized Placebo-controlled Phase III trial ($N = 362$, 181 vs. 181)	MM, MEL200 (100/d × 2 dd, − 3, − 2)	APR PO: 125 mg × day − 3, 80 mg × day − 2,− 1 GRA PO: 2 mg × day −3 ,− 2, − 1.0 DEX PO: 4 mg × day − 3, 2 mg × day − 2, − 1 vs. PLACEBO PO × day − 3, − 2, − 1 GRA PO: 2 mg x day − 3, − 2, − 1.0 DEX PO: 4 mg × day − 3, 2 mg × day − 2, − 1	Complete protection (no emesis with rescue medication, 0–120) APR vs. PLA = 78% vs 65% ($p = 0.00436$)	Complete response (no emesis, no rescue, 0–120) APR vs. PLA = 58% vs. 41% ($p = 0.0042$)	85% vs. 78% ($p = 0.106$)	AE identical in the 2 arms; no data on engraftment, PFS and OS
Bechtel [16]	Prospective, single-arm study ($N = 26$)	MM, MEL200 (200/d × 1 dd)	APR PO: 125 mg × day − 2, 80 mg × day − 1.0 OND PO: 16 mg × day − 2 DEX PO: 12 mg × day − 2, 8 mg × day − 1, 0, + 1	Complete protection (no emesis with rescue medication) Delayed CINV (≤ 1 episode) (24–120 hh) = 96% (92% no episodes)	ne	No nausea 24-120hh = 11.6%	No effect on engraftment; 3 readmission for nausea, vomiting, dehydratation
Musso [7]	Prospective, single-arm study ($N = 134$; MEl200/140, $N = 52$))	MM/Lym/other, MEL200 (single day), MEL140, BEAM, FEAM, other	PALO IV: 0.25 mg × day −2 DEX IV: 8 mg x day −2	ne	Complete response (no emesis, no rescue) MEL200 = 24% MEL140 = 58%	Complete protection (no emesis, no significant nausea, no rescue) MEL200 = 18% MEL140 = 42%	Headache 13% of all patients (all diagnoses)

Table 1 (continued)

Reference	Study design (number of patients)	Patient population/ chemotherapy	Treatment groups	Response			Safety
				Protection (no emesis with rescue)	Response (no rescue medication)	No nausea	
Clark [18]	Prospective, single arm, comparison with hystorical cohort ($N = 126$, MEL200 = 96, FOSAPR = 40)	MM-PCN/LYM, BEAM/ME-L200 (100 × 2) ($N = 126$, MEL200 = 96, FOSAPR = 40)	FOSAPR IV: 150 mg × day − 2 OND IV: 16 mg × day − 2 DEX IV: 12 mg × day − 2, − 1 vs. 20 mg × day − 2, − 1 LOR IV/PO: 1 mg × day − 2, − 1.0 vs. OND IV: 16 mg × day − 2 DEX IV: 12 mg × day − 2, − 1 vs. 20 mg × day − 2, − 1 LOR IV/PO: 1 mg × day − 2, − 1.0	Complete protection (no emesis with rescue possible) 80% vs. 66% ($p = 0.068$)	Complete response (no emesis no rescue) 12.5% vs. 3% ($p = 0.077$)	Total no nausea MEL200 FOS = 13% (no control group)	No adverse effects related to FOSA
Deauna-Limayo [15]	Prospective, single arm, two cohorts, MEL ($N = 9$) and BEAM ($N = 9$)	MM (MEL140/200 (70/100 × 2)-3,--2); LYM (BEAM)	APR PO: 125 mg × day − 3, 80 mg × day − 2, − 1 PALO IV: 0.25 mg × day − 3, − 2, − 1 DEX IV: 4 mg × 4 dd − 3, − 2, − 1, + 3 LOR IV: 1 mg × day 0 (pre-infusion)	ne	Complete emetic response (no vomiting, no rescue medication, any grade nausea; acute = 11%; delayed = 11%; extended = 0%; overall = 0%	No significant nausea Overall (acute to extended phase) = 6/9 (66.7%); acute 9/9 (100%); delayed ne; extended = ne	1/18 (6%) MM/Lyp pts. grade 2 cardiac AE (possible correlation)
Uchida [19]	Retrospective, comparative, apr vs. standard, no steroid ($N = 48$; MEL200 only, $N = 15$; apr 11 vs no Apr 4))	Mixed diagnosis, MM MEL200 (100 × 2) disaggregate	APR PO: 125 mg × day 1, 80 mg × day 2, 3 GRA IV: 3 mg twice × day 1, 2 vs. GRA IV: 3 mg twice × day 1, 2	Complete response (no vomiting, no mention of rescue therapy) 81.8% vs. 25.0% ($p = 0.077$)	ne	ne	No difference (data aggregate)
Jordan [12]	Prospective, single-arm ($N = 64$; MEL200/140 (100 × 2/70 × 2) $N = 21$)	(N = 64; MEL200/140 (100 × 2/70 × 2) $N = 21$)	APR PO: 125 mg × day − 3, 80 mg × day − 2, − 1.0 GRA IV: 1 mg × day − 3, − 2 DEX IV: 8 mg × day − 3, − 2, − 1, 0	ne	Complete response in the overall phase (day 1 until 5 days after end of chemotherapy), defined as no vomiting and no use of rescue therapy in this period = 52%; acute = 100%; delayed = 52%	No nausea in the overall period = 33%	No comparison; data aggregate; apparently normal toxicity
Trifilio [14]	Retrospective, comparative,	MM (MEL200)		Complete protection (overall only)		APR vs. OLA vs. FOSAPR	No difference

Table 1 (continued)

Reference	Study design (number of patients)	Patient population/ chemotherapy	Treatment groups	Response			Safety
				Protection (no emesis with rescue)	Response (no rescue medication)	No nausea	
	olanzapine vs. aprepitant vs. fosaprepitant ($N = 117$, olanzapine 43 aprepitant 54 fosaprepitant 20)		APR PO: 125 mg × day − 1, 80 mg × day 0, + 1 ONDA IV: 16 mg × day − 1, 8 mg IV TID × day 0–6 mPDN IV: 125 mg × day − 1 DEX IV: 10 mg × day 0, 4 mg BID × day + 1, + 2 vs. FOSAPR IV: 150 mg × day − 1 ONDA PO: 16 mg × day − 1, 8 mg IV TID × day 0−+ 6 mPDN IV: 125 mg × day − 1 DEX IV: 10 mg × day 0, 4 mg BID × day + 1, + 2 vs. OLA PO: 5 mg BID × day − 1, 0, + 1, + 2 (or more) ONDA PO: 16 mg × day − 1, 8 mg IV TID × days 0, + 1, + 2 (or more) mPDN IV: 125 mg × day − 1 DEX IV: 10 mg × day 0	APR vs. OLA vs FOSAPR 85% vs. 91% vs. 80%	Complete response (no emesis no medication) APR vs. OLA vs. FOSAPR Acute 59% vs. 81% vs. 75% Delayed 35% vs. 66% vs. 35%	No nausea Acute 65% vs. 98% vs. 80% Delayed 37% vs. 75% vs. 55%	Probable QTc tract prolongation (evaluated in OLA arm only)
Marquez [13]	Retrospective, single-arm study ($N = 31$)	MM, MEL200 (single day, day − 4)	PALO: unspecified administration schedule DEXA: unspecified administration schedule	Acute phase: no emesis (no mention of rescue medication) 71% Delayed phase: no emesis (no mention of rescue medication) 61.3%	ne	Acute phase: no nausea = 45.2% Delayed phase: no nausea = 38.7	AE: constipation: 6.4%
Isoda [20]	Prospective, single arm ($N = 24$; MEL (100 × 2))	MEL (100 × 2)	APR PO: 125 mg × day − 3, 80 mg × day − 2, − 1,0	Complete protection (no emesis with rescue medication) acute	Complete response (no emesis, no rescue therapy) acute (0–48 hh) 87.5%; delayed	ne	No adverse effects related to drugs

Table 1 (continued)

Reference	Study design (number of patients)	Patient population/ chemotherapy	Treatment groups	Response			Safety
				Protection (no emesis with rescue)	Response (no rescue medication)	No nausea	
			PALO IV: 0.75 mg × day − 3 DEX IV: 6.6 mg × day − 3, − 2, − 1, 0	(0–48 hh) 91.7%; delayed (48–120 hh) 100%; extended (> 120 hh) 91.7%; overall (0–120) 91.7%	(48–120 hh) 75%; extended (> 120 hh) 66.6%; overall (0–120) 75%; complete control (no emesis, no rescue therapy, only mild nausea) acute (0-48hh) 86.4%; delayed (48–120 hh) 68.2%; extended (> 120 hh) 59.1%; overall (0–120) 68.2%		

PALO palonosetron, *APR* aprepitant, *FOSAPR* fosaprepitant, *DEX* dexamethasone, *mPDN* methilprednisone, *OND* ondansetron, *GRA* granisetron, *LOR* lorazepam, *ne* not evacuate, *MEL* high-dose melphalan, *BEAM* bcnu+etoposide+aracytin+melphalan regimen, *FEAM* fotemustine+etoposide+aracytin+melphalan regimen, *MM* multiple myeloma, *LYM* lymphoma, *PCN* plasma cell neoplasm; not evaluated

5HT3RA interactions with drugs frequently used during SCT are reported in Table 2.

Aprepitant and Fosaprepitant As for 5HT3RA, NK1RAs are recommended for CINV prophylaxis in autologous SCT and highly emetogenic chemotherapy in combination with 5HT3RA and dexamethasone. In the setting of HDMel, aprepitant or fosaprepitant were investigated in eight different trials [12, 14–20]. Two trials compared a three-drug regimen (aprepitant or fosaprepitant +5HT3 + dexamethasone) with a two-drug regimen (5HT3RA + dexamethasone), concluding that the three-drug regimen was more effective [16, 17]. The results from the noncomparative trials confirmed the efficacy of the three-drug regimen that was mentioned above [12, 15, 18–20]. Data from the trial comparing olanzapine-containing therapy with an aprepitant or fosaprepitant-containing three-drug regimen [14] are discussed below.

Aprepitant side effects are infrequent. In fact, literature shows a similar incidence of side effects with aprepitant when compared to control groups [25, 26] when a standard dose is administered (125 mg on day 1, 80 mg on day 2 and 3) and corticosteroids are reduced as recommended.

Aprepitant interactions are mainly cause by cytochrome dose-dependent inhibition (moderate competitive inhibition of cytochrome CYP4503A4) or induction (mild induction of both cytochrome CYP4503A4 and cytochrome CYP4502C9). Aprepitant is a substrate and weak inhibitor of P-glycoprotein, but this activity seems to be clinically insignificant when aprepitant is co-administered with other P-glycoprotein substrates [27]. By examining drug label information and online drug interaction calculators [28–30], only a few drug-drug associations are clinically significant when considering aprepitant. Table 2 summarizes, grades, and proposes possible solutions for these drug-drug interactions. Aprepitant interactions during SCT are mainly caused by co-administration with corticosteroids, such as dexamethasone for CINV prophylaxis. This interaction is well-documented. It is caused by aprepitant induced inhibition of cytochrome CYP4503A4, the metabolic pathway for both dexamethasone and methylprednisolone [31], thus increasing corticosteroid serum half-life. The international guideline solution to this adverse drug interaction during co-administration of aprepitant with a corticosteroid is to reduce dexamethasone dosage as CINV prophylaxis and to carefully evaluate a reduction in corticosteroid dosage when it is being given with an indication other than CINV prophylaxis (e.g., as an antineoplastic treatment).

No significant interaction was found for the co-administration of aprepitant and 5HT3RA. The co-administration of aprepitant and azoles, as antifungal prophylaxis, should be avoided or restricted (fluconazole, voriconazole, or posaconazole are acceptable). Azoles significantly increase the concentration or potency of aprepitant,

and inversely, aprepitant induces a mild increase in the concentration or potency of itraconazole by affecting hepatic CYP4503A4-mediated metabolism. The interaction between ondansetron and azoles should be avoided or strictly monitored, due to the risk of QTc prolongation and arrhythmias.

The co-administration of aprepitant and proton-pump inhibitors (PPI) should be limited, because PPIs are metabolized by CYP4503A4. However, pantoprazole and omeprazole are considered safe since they are metabolized by different cytochrome isoforms.

The co-administration of aprepitant and quinolones is possible because there is no significant drug-drug interaction. However, quinolones should be used with caution when given with ondansetron and azoles, due to the risk of clinically significant QTc prolongation.

No significant interactions are reported between DMSO or allopurinol and aprepitant.

Corticosteroids Dexamethasone is recommended for CINV prophylaxis in autologous SCT and highly emetogenic chemotherapy in combination with 5HT3RA and (fos)aprepitant. Corticosteroids were co-administered in most trials of CINV prevention in HDMel [7, 11–18, 20], with the exception of one study [19]. From the ten studies that used corticosteroids, dexamethasone was the corticosteroid of choice, used in nine trials [7, 11–13, 15–18, 20], methylprednisolone was used in the remaining trial [14].

The exact mechanism of action of corticosteroids for CINV prevention is unclear, and their use in this setting should be considered off-label. However, guidelines strongly recommend their administration as CINV prophylaxis based on the amount of supportive research data available [4, 8, 32].

The side effects of corticosteroids are well-known. They can be either acute or delayed due to chronic administration [33] (endocrine, neurological/psychiatric, muscle/skeletal [34, 35], immunological [36], etc.). Corticosteroid-induced immunosuppression is directly proportional to the extent of duration and total dose administered, but it is impossible to identify a threshold below which immunosuppression will be absent or clinically insignificant. Therefore, although the duration of administration for CINV prophylaxis is limited, in certain situations, the effect could be relevant and dangerous. For example, in the setting of SCT, patients undergoing high-dose chemotherapy will develop a noteworthy, although transient, immunosuppression due to a decrease in white blood cell count. In this case, any additional immunosuppression could result in an increased risk of infection. This is confirmed by a study that attempted to establish the dose of aprepitant for the prevention of CINV [37]. It was reported that high-dose dexamethasone administered with higher doses of aprepitant caused an increased risk of febrile neutropenia due to CYP3A4-mediated steroid metabolism reduction induced by aprepitant-mediated CYP3A4 inhibition [31]. Based on this interaction, a corticosteroid dosage reduction is recommended whenever aprepitant is co-administered [4, 8].

Corticosteroid interactions with drugs frequently used during SCT are reported in Table 2.

Olanzapine Guidelines for CINV prophylaxis recommend the use of olanzapine in high emetic risk chemotherapy, but not in high-dose chemotherapy with SCT [4, 8, 9]. However, olanzapine is an atypical antipsychotic drug and is currently considered as an off-label treatment for CINV prophylaxis.

The retrospective comparative study by Trifilio S. et al. [14] compared an olanzapine-containing triplet therapy to an aprepitant or fosaprepitant-containing triplet therapy, both in the setting of HDMel. The CINV control rate for the patients treated with the olanzapine-containing regimen was reported as more effective.

The common side effects of olanzapine after short-term administration are sedation, orthostatic hypotension, fatigue, and extrapyramidal disorders [14, 38]. The potential for interaction between olanzapine and drugs commonly administered during SCT is low (Table 2). Co-administration of olanzapine and metoclopramide increases the risk of adverse neurological events due to antidopaminergic activity, such as extrapyramidal symptoms and neuroleptic malignant syndrome [28–30].

In conclusion, the side effects and drug-drug interactions caused by olanzapine are manageable. Therefore, olanzapine is a potential candidate for CINV prevention in the setting of autologous transplantation. However, its use for CINV prevention is currently off-label; thus, it should not be recommended as a CINV prophylaxis. New prospective comparative trials are warranted to confirm its role as an alternative or partner drug of the NK1RA-containing a three-drug regimen.

Conclusion

The studies examined in this article provide sufficient data to suggest that the three-drug regimen (NK1RA + 5HT3RA + dexamethasone) is recommended for prevention of CINV in patients undergoing autologous SCT with high-dose melphalan conditioning. The ideal choice of 5HT3RA is palonosetron, due its reduced incidence of cardiac toxicity, such as QTc prolongation, when compared to older generation 5HT3RAs [24]. This is especially the case when other QTc-affecting drugs are co-administered.

The NK1RA of choice is aprepitant (orally) or fosaprepitant (intravenously), since no data exists on the efficacy or safety of different NK1RA drugs in the setting of autologous SCT with HDMel conditioning.

Olanzapine, an atypical antipsychotic drug that is currently not indicated for use in CINV prophylaxis, has common side effects that have the potential to interfere with quality of life. Therefore, olanzapine-containing regimens should be

Table 2 Clinically significant interactions for aprepitant, olanzapine, setrons and dexamethason with drugs commonly administered during HDMel conditioning for SCT

Aprepitant < > azoles	+++	Itraconazole will increase the level or effect of aprepitant by affecting hepatic/intestinal enzyme CYP3A4 metabolism (competitive inhibition). Avoid or use alternate drug.
Aprepitant < > azoles	++	Fluconazole, posaconazole and voriconazole will increase the level or effect of aprepitant by affecting hepatic/intestinal enzyme CYP3A4 metabolism (competitive inhibition). Use caution/monitor.
Aprepitant < > azoles	+	Aprepitant will increase the level or effect of itraconazole by affecting hepatic/intestinal enzyme CYP3A4 metabolism (competitive inhibition).
Aprepitant < > azoles	±	Aprepitant will slowly induce CYP4503A4 thus potential reducing the level or effect of azoles.
Aprepitant < > quinolones	–	No interaction found for levofloxacin and ciprofloxacin
Aprepitant < > antiviral agents	–	No interaction found for acyclovir and valaciclovir
Aprepitant < > melfalan	–	No interaction found
Aprepitant < > proton pomp inhibitors	+	No interaction found for omeprazole and pantoprazole; aprepitant could increase the level or effect of lansoprazole and rabeprazole by affecting hepatic/intestinal enzyme CYP3A4 metabolism.
Aprepitant < > 5HT3RAs	–	No interaction found for ondansetron, palonosetron, tropisetron, and granisetron
Aprepitant < > corticosteroids	++	Aprepitant will increase the level or effect of dexamethasone and methylprednisolone by inhibition of CYP3A4-mediated corticosteroids metabolism. Reduce corticosteroids dosage (25–50%).
Aprepitant < > corticosteroids	+	Dexamethasone and methylprednisolone will decrease the level or effect of aprepitant by inducing hepatic CYP3A4-related aprepitant metabolism. Use caution/monitor.
Aprepitant < > corticosteroids	±	Aprepitant will slowly induce CYP4503A4 thus potential reducing level or effect of corticosteroids.
Aprepitant < > Allopurinol	–	No interaction found
Aprepitant < > metoclopramide or olanzapine	–	No interaction found for metoclopramide and olanzapine (when used separately)
Olanzapine < > azoles or quinolones or antiviral drugs	–	No interaction found
Olanzapine < > melphalan	–	No interaction found
Olanzapine < > proton pump inhibitors	–	No interaction found
Olanzapine < > 5HT3RAs or corticosteroids	–	No interaction found
Olanzapine < > Allopurinol	–	No interaction found
Olanzapine < > metoclopramide	++	Increased risk of neurological adverse events due to antidopaminergic activity (extrapyramidal symptoms, neuroleptic malignant syndrome)
5HT3RA <> melphalan	–	No interaction found
5HT3RA <> quinolones	++	Moderate risk of QTc elongation and cardiac arrhythmia with ondansetron or tropisetron, low risk with granisetron; no interaction found with palonosetron
5HT3RA <> antiviral drugs	–	No interaction found
5HT3RA <> proton pump inhibitors	–	No interaction found
5HT3RA <> azoles	++	Moderate risk of QTc elongation and cardiac arrhythmia with ondansetron, tropisetron, posaconazole and voriconazole; low risk with granisetron; no interaction found with palonosetron
5HT3RA <> azoles	+	Itraconazole will increase the level or effect of ondansetron by inhibition of CYP3A4-mediated ondansetron metabolism. Caution; no dosage reduction needed.
5HT3RA <> Allopurinol or metoclopramide	–	No interaction found
5HT3RA <> corticosteroids	±	Dexamethasone (but not methylprednisolone) will decrease the level or effect of 5HT3RA by inducing hepatic CYP3A4-related metabolism. Use caution/monitor. No drug dosages adjustments are needed.
Corticosteroids <> melphalan	–	No interaction found
Corticosteroids <> proton pump inhibitors	±	Dexamethasone and methylprednisolone will decrease the level or effect of proton pump inhibitors by inducing hepatic CYP3A4-related metabolism. Use caution/monitor. No drug dosages adjustments are needed.
Corticosteroids <> metoclopramide or allopurinol	–	No interaction found
Corticosteroids <> antiviral drugs	–	No interaction found
Corticosteroids <> azoles	++	Azoles will increase the level or effect of corticosteroids by inhibition of CYP3A4-mediated metabolism and P-glycoprotein-mediated efflux. Avoid.
Corticosteroids <> azoles	±	Corticosteroids will decrease the level or effect of itraconazole by inducing hepatic CYP3A4-related metabolism. Use caution/monitor. No drug dosages adjustments are needed.

+++ serious interaction, ++, moderate interaction, + mild interaction, – no interaction

Table 3 Suggested schedule as CINV prophylaxis for HDMel conditioning regimen

	− 2	− 1	0	+ 1
Aprepitant	125	80	80	
5HT3RA	X*			
Dexamethasone	4-8 mg	2–4 mg	2–4 mg	

*Palonosetron should be preferred; if other than palonosetron 5HT3RA are administered avoid the co-administration of drugs-inducing QTc prolongation 5HT3RA dosage as for guidelines [4, 5]: ondansetron 8 mg iv; palonosetron 250 mcg iv; granisetron 1 mg iv; tropisetron 5 mg iv; dolasetron 100 mg iv

In any case, avoid the co-administration of azoles and aprepitant

evaluated in prospective clinical trials to adequately assess safety and efficacy in comparison with other standard regimens in the setting of autologous SCT with HDMel conditioning [39].

Currently, there is doubt concerning the risk of steroid therapy in patients undergoing high-dose chemotherapy. For example, despite known corticosteroid ability to help treat multiple myeloma, it is rarely administered during HDMel active therapy due to the potential risk of infectious complications. This concern is also palpable in general practice where hematologists are reluctant to administer steroids. Therefore, in the setting of transplant, our opinion is to limit the usage of corticosteroids, because the value lost in steroids-free CINV prophylaxis [32] should be contained by NK1 antagonist or new generation 5HT3RA, such as palonosetron. The suggested schedule is stated in Table 3.

A limitation of this review arises from the heterogeneity of the studies examined. An example is the administration of different HDMel regimens, MEL100×2 and MEL200, which contain potentially different effects on CINV probability. However, we do not believe this is a limitation that invalidates our conclusion. Instead, it emphasizes the necessity to standardize the management of patients undergoing SCT, even in the setting of ameliorative care, such as CINV prophylaxis.

Continuous monitoring on the efficacy and safety of the three-drug regimen that is suggested above for the prophylaxis of CINV in autologous SCT after HDMel conditioning will be essential not only to expand on the availability of data that supports this regimen but also to encourage its use with different conditioning regimes and in allogeneic transplantations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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