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ORIGINAL ARTICLE

Triple drug combination in the prevention of nausea and vomiting following busulfan plus cyclophosphamide chemotherapy before allogeneic hematopoietic stem cell transplantation

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Summary

Purpose: *A clinical study of triple drug combination (aprepitant+palonosetron+ dexamethasone) was carried out to evaluate its efficacy in preventing both acute and delayed emesis after high-dose chemotherapy (HDC) with busulphan+cyclophosphamide (BuCy) before hematopoietic stem cell transplantation (HSCT).*

Methods: *The study enrolled 60 patients suffering from various hematological malignancies: 20 in the triple drug antiemetic group and 20 in each of two historical control groups that received dexamethasone plus either ondansetron or palonosetron. The groups were comparable for statistical analysis. The observation period started with the initiation of chemotherapy (0 h) and continued for 24 h after its completion for the acute phase, and during 5 days after finishing chemotherapy for the delayed phase. The response rate of the study drugs was evaluated by a 4-grade scale based on the condition of nausea and vomiting: highly, moderately or slightly effective and not effective.*

Results: *Patients treated with the triple drug combination had significantly higher response rates than those receiving palonosetron or ondansetron (+ dexamethasone) during both the acute and delayed phases: highly effective in early + late phases: 55 vs. 30 vs. 20%; highly effective in early phase: 70 vs. 30 vs. 20%; highly effective in late phase: 55 vs. 55 vs. 30%; highly + moderately effective in early phase: 75 vs. 32 vs. 25%; highly + moderately effective in late phase: 85 vs. 60 vs. 40% for triple drug combination, palonosetron + dexamethasone and ondansetron + dexamethasone, respectively.*

Conclusion: *This triple drug combination was more effective than ondansetron or palonosetron (+ dexamethasone) in preventing acute (especially), and delayed nausea and vomiting following BuCy chemotherapy before HSCT.*

Key words: antiemetic therapy, hematopoietic stem cell transplantation, high-dose chemotherapy, NK1 receptor antagonists, serotonin receptor antagonists, steroids

Introduction

Cancer patients frequently cite nausea and vomiting as one of the most distressing and debilitating side effects of chemotherapy [1-8]. Chemotherapy-induced nausea and vomiting (CINV) can be divided into acute (24 or fewer hours after chemotherapy), delayed (more than 24 hours after chemotherapy) or anticipatory (before chemotherapy) [9]. This distinction is made because acute CINV is believed to be mediated through serotonin receptor stimulation while delayed CINV is thought to involve multiple neurotransmitters, including opioid and neurokinin receptors [10]. Chemotherapeutic agents have variable emetogenic potential that is affected by dose and method of administration [11-13].

HDC, often combined with total body irradiation (TBI) or total nodal irradiation of a varied amount, and stem cell rescue is a treatment modality applied to a wide variety of medical conditions [14]. The delivery of high-dose therapy is almost always associated with a great degree of nausea and vomiting. A number of studies have been published regarding control of nausea and vomiting during the time when such therapy is delivered up until or shortly after the stem cell infusion. A variety of antiemetic regimens have been studied to control nausea and vomiting associated with the preparative

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therapy phase of HSCT [1]. The "no emesis" rate for 5 days (120 h) following chemotherapy is the primary endpoint of modern antiemetic trials. Researchers also consider control during the initial 24 h after chemotherapy (acute emesis) and prevention from 24 to 120 h (delayed emesis) as additional parameters to be evaluated in antiemetic drug trials [15].

The American Society of Clinical Oncology (ASCO) guidelines contain no explicit recommendation for use of antiemetics with HDC. However, in the ASCO guidelines for the control of emesis associated with chemotherapy, there is the suggestion that all preparative therapies for HSCT fall into the category of highly emetogenic chemotherapy. Thus, patients should receive the recommended antiemetic control as given to other patients receiving similar highly emetogenic chemotherapy [16].

To prevent acute and delayed nausea and vomiting following chemotherapy of high emetic risk, it is recommended a multiday drug regimen including a 5-HT3 receptor antagonist, dexamethasone and aprepitant beginning before chemotherapy [1,15,16-18]:

MASCC level of consensus: high
MASCC level of confidence: high
ESMO level of evidence: I
ESMO grade of recommendation: A

In this study a triple drug combination was carried out to evaluate its efficacy in preventing both acute and delayed emesis after HDC (BuCy) before HSCT by using a historical control group of patients treated with dexamethasone and ondansetron or palonosetron.

Methods

This study enrolled 60 patients suffering from various hematological malignancies (acute and chronic leukemias or myelodysplastic syndrome/MDS). Hospital Ethics Committee approved the study and patients scheduled to receive the triple drug antiemetic therapy gave signed informed consent (n=20). They received BuCy (busulphan total dose 13.2 mg/kg i.v. or 16 mg/kg orally, and cyclophosphamide i.v., total dose 120 mg/kg before grafting) as conditioning regimen. Antiemetic triple drug combination consisted of aprepitant p.o. 1 h before HDC (day 1: 125 mg, days 2 and 3: 80 mg daily) + 0.25 mg palonosetron i.v. 30 min before chemotherapy on the first day of the conditioning regimen and dexamethasone 20 mg i.v. 15 min before HDC (day 1) and 12 mg daily in the remaining days of the conditioning regimen. The patient historical control groups (n=20 each) received either ondansetron 32 mg i.v.+ dexamethasone daily through HDC or palonosetron + dexamethasone as described above. Patient characteristics are shown in Table 1. The patient groups were comparable for statistical analysis. The observation period started with the initiation of chemotherapy (0 h) and continued for 24 h after the completion of chemotherapy for the acute phase, and during 5 days after finishing chemotherapy for the delayed phase. The severity of nausea was evaluated according to the following 4-grade scale: none (no nausea); mild (slight nausea but no disruption of daily activities); moderate (nausea+some disruption of daily activities); and severe (extreme nausea+ severe disruption of daily

Table 1. Patient characteristics

Characteristics	*Triple antiemetic drugs group n= 20*	*Palonosetron + dexamethasone group n= 20*	*Ondansetron + dexamethasone group n= 20*
Age, years			
Median	38	42	40
Range	19-64	22-62	22-64
Gender			
Male	11	10	12
Female	9	10	8
Diagnosis (patients, n)			
Acute myelogenous leukemia	14	15	14
Myelodysplastic syndrome	5	3	3
Chronic myeloid leukemia	1	2	3
Conditioning regimens (patients, n)			
Bu IV/Cy	16	16	13
Bu PO/Cy	4	4	7
Type of HSCT (patients, n)			
Autologous	3	3	4
Allogeneic	17	17	16

Bu: busulphan, Cy: cyclophosphamide, IV: intravenously, PO: per os, HSCT: haematopoietic stem cell transplantation

Table 2. Evaluation of response rate of the study antiemetic drugs by the 4-grade scale based on the condition of nausea and vomiting

Antiemetic response	*Grade of nausea*		
	A- none or mild	*B- moderate*	*C- severe*
Complete	Highly effective	Highly effective	Moderately effective
Major	Highly effective	Moderately effective	Slightly effective
Minor	Moderately effective	Slightly effective	Not effective
Failure	Not effective	Not effective	Not effective

activities). The antiemetic response was evaluated using the following criteria: complete (no emetic episode); minor (1-2 episodes); major (3-5 episodes); and failure (>5 episodes). The response rate of the study drugs was evaluated by the following 4-grade scale based on the condition of nausea and vomiting: highly, moderately or slightly effective and not effective (Table 2).

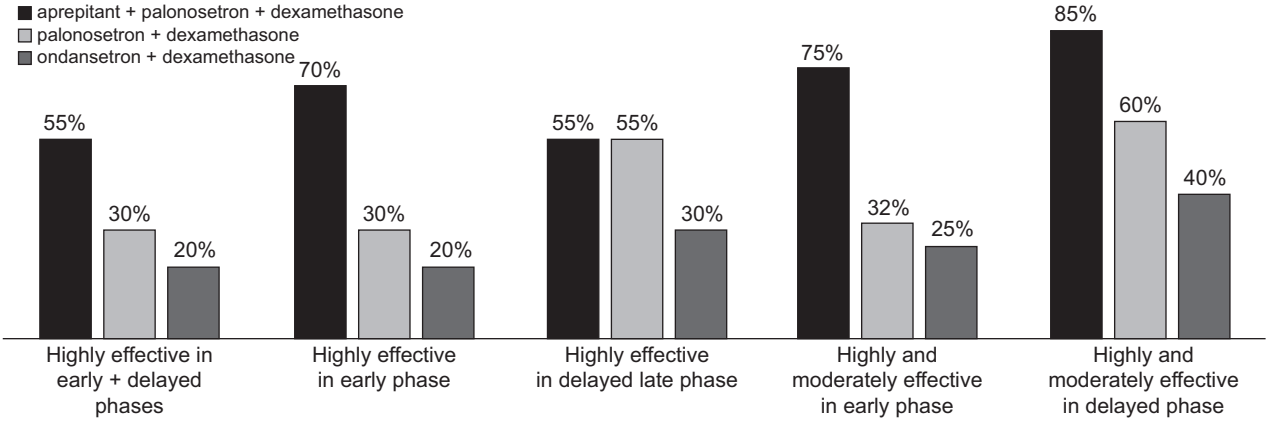
Statistical analysis

The baseline characteristics of the patients (age, diagnosis, sex and conditioning regimens, type of transplantation) were compared between the groups using one-way ANOVA. Wilcoxon test was used for analysis of differences between groups. The statistical analysis was performed using the program Statistica 9.0, with p-value <0.05 considered significant. The safety of a drug was assessed on the basis of the incidence of adverse events, graded on a 5-point scale (a score of 1 indicated mild adverse effects, and a score of 5 fatal adverse effects).

Results

Patients treated with the triple drug combination had significantly higher response rates than those receiving palonosetron or ondansetron (+ dexamethasone) during both the acute and delayed phases: highly effective in early + late phases: 55 vs. 30 vs. 20%; highly effective in early phase: 70 vs. 30 vs. 20%; highly effective in late phase: 55 vs. 55 vs. 30%; highly+moderately effective in early phase: 75 vs. 32 vs. 25%; highly+moderately effective in late phase: 85 vs. 60 vs. 40%, for triple drug combination, palonosetron + dexamethasone and ondansetron + dexamethasone, respectively (all p-values appear in Figure 1). All antiemetic regimens were well tolerated. There were no

Figure 1. Efficacy of triple drug regimen vs. palonosetron/ondansetron plus dexamethasone.



Type of antiemetic regimen	*Activity of antiemetic regimens (p-values)*				
	Highly effective in early + delayed phases	*Highly effective in early phase*	*Highly effective in delayed phase*	*Highly and moderately effective in early phase*	*Highly and moderately effective in delayed phase*
APD vs. PD	0.04	0.01	NS	0.008	0.04
APD vs. OD	0.02	0.005	0.04	0.005	0.007
PD vs. OD	NS	NS	0.04	NS	0.07

APD: aprepitant/palonosetron/dexamethasone, PD: palonosetron/dexamethasone, OD: ondansetron/dexamethasone, NS: non significant

differences in safety among the regimens and adverse events were generally mild and transient (only constipation was observed).

Discussion

In recent years, significant improvements have been made in the management of neutropenia and thrombocytopenia and other potentially life-threatening complications of ablative chemotherapy. While these complications are of particular concern to physicians, patients receiving ablative therapy with bone marrow or blood stem cell transplants are often troubled by other side effects such as nausea, vomiting, diarrhea and stomatitis [1,19]. Bellm et al. conducted in-depth interviews with 38 subjects (10 men, 28 women; mean age 46.9 years) who had received ablative therapy with bone marrow and/or peripheral blood stem cell transplants. Twenty-eight (74%) patients received autologous stem cell transplants and 10 (26%) received allogeneic transplants. Participants reported stomatitis, nausea and vomiting, diarrhea, and fatigue as the most troubling side effects. Stomatitis was selected as the single most debilitating side effect (42%), followed by nausea and vomiting (13%) [19]. CINV is associated with a significant deterioration in quality of life. Serotonin 5-HT3 receptor antagonists plus dexamethasone have significantly improved the control of acute CINV, but delayed CINV remains a significant clinical problem [20]. Two new agents, palonosetron and aprepitant, have recently been approved for the prevention of both acute and delayed CINV. Palonosetron is a second-generation 5-HT3 receptor antagonist with longer half-life and higher binding affinity than first-generation 5-HT3 receptor antagonists. Aprepitant is the first agent available in the new drug class of neurokinin-1 (NK-1) receptor antagonists. The introduction of these new agents has generated revised antiemetic guidelines for the prevention of CINV [16,21-23].

Palonosetron is a recent, strong and selective antagonist of 5-HT3 receptors. Initially, 3 main trials have compared palonosetron to other 5-HT3 receptor antagonists [24-26]. These trials have shown at least equal efficiency and even superiority of palonosetron. But these trials were criticized because the study population was quite heterogeneous and patients didn't receive the optimal antiemetic treatment (only 0, 5 and 63% of patients received dexamethasone in each study). A recent meta-analysis (5 trials) stating the same favorable findings may be the subject of the same criticism [27].

Another recent study evaluated the efficacy of the association of palonosetron, aprepitant and dexamethasone [28]. This study wasn't comparative but the results showed an excellent control of emesis (emesis-free rate 92.8%) and a good control of nausea (nausea-free rate 59.9%) in patients treated by highly emetogenic chemotherapy. Optimal comparative studies are expected.

Aprepitant is the first NK-1-receptor antagonist. It is a potent selective, central nervous system-penetrant, oral non-peptide antagonist of the NK1 receptor. The first trials evaluated the efficiency of aprepitant in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy. The results proved that aprepitant alone or in association with dexamethasone was inferior to 5-HT3 receptor antagonists [29-31]. Thus, aprepitant can't replace 5-HT3 receptor antagonists in the prevention of the acute nausea and vomiting induced by highly emetogenic chemotherapy. But aprepitant increases the efficiency of the association between dexamethasone and 5-HT3 receptor antagonists [32-34]. Besides, studies showed that aprepitant has very important activity against delayed CINV [32-34].

Our study showed that the addition of aprepitant to palonosetron and dexamethasone was significantly superior to palonosetron or ondansetron with dexamethasone in both acute and delayed CINV. Future studies are needed to establish standard antiemetic therapy for patients treated with HDC with stem cell rescue. There are many factors that are important to consider for patients undergoing HSCT when studying the incidence and severity of nausea and vomiting. The preparative therapy, which may be chemotherapy alone or a combination of chemotherapy and TBI, results in significant gastrointestinal dysfunction that may last for days to weeks. Dysfunction of the gastrointestinal tract may result in a continual source of serotonin release. This continued source of serotonin and the release of substance P may serve as a constant stimulus to nausea and vomiting. Transplanted patients have past records of varied nutrition support, varied history of nausea, vomiting and sometimes anticipatory vomiting, variable use of antiemetic regimens, and a variety of current and past infections. Often, SCT patients will then have different health care providers at different centers, with different regimens for controlling nausea and vomiting. These factors may make it difficult to control anticipatory nausea and vomiting or prevent nausea and vomiting from the planned preparative therapy [1].

Several protocols are in place looking at the triple antiemetic combination (steroid combined with a 5-HT3 antagonist and aprepitant) for those undergoing HSCT preparative therapy, but the reported results are preliminary. The studies by Bubalo et al. from Oregon included a novel way of giving a prolonged course of aprepitant (10-12 days, including the preparative ther-

apy period and for several days after the infusion of the stem cells) [34,35]. In the meantime, ASCO guidelines suggest the use of the triple antiemetic combination for such therapy (steroid combined with a 5-HT3 antagonist and aprepitant) for patients treated with HDC, based on the emetic risk posed by this kind of treatment [16]. However, minimal data exist for assessing the success of this combination in a large patient population.

Future studies may consider the use of palonosetron, aprepitant and casopitant with new antiemetic agents in patients receiving HDC with bone marrow transplantation. Gabapentin, midazolam and olanzapine are potential new antiemetics. The most promising among them seems to be olanzapine with very high complete response rates of both nausea and vomiting, when combined with a 5-HT3 receptor antagonist and a corticosteroid [36]. Ghrelin, a peptide secreted by the gastric mucosa, increases the gut motility, protects the gastric mucosa (e.g. against ethanol) and increases appetite. In a study using the ferret as a model, ghrelin decreased the number of vomiting episodes induced by cisplatin [37].

Little is known about why antiemetics are ineffective in some patients. A recent study demonstrated that lack of antiemetic effect could be due to a specific deletion variation on the 5-HT3B receptor gene [38]. Further studies exploring the possibility of prescribing antiemetics on a pharmacogenetic basis are needed.

Conclusion

Triple drug antiemetic combination with aprepitant, palonosetron and dexamethasone was more effective than ondansetron or palonosetron (+ dexamethasone) in preventing acute (especially) and delayed nausea and vomiting following HDC with BuCy before HSCT.

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