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Management of chemotherapy induced emesis

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ABSTRACT

Important progress has been achieved in the last few years in the prevention of chemotherapy-induced nausea and vomiting thanks to the introduction in clinical practice first of the 5-HT3 antagonists and of the NK1 antagonists more recently. To prevent acute emesis induced by cisplatin/moderately emetogenic chemotherapy, a combination of aprepitant plus a 5-HT3 antagonist and dexamethasone/a 5-HT3 antagonist plus dexamethasone, is now the most efficacious regimen. For the prevention of delayed emesis induced by cisplatin/moderately emetogenic chemotherapy, a combination of dexamethasone plus aprepitant or metoclopramide or a 5-HT3 antagonist/dexamethasone or a 5-HT3 antagonist are the preferred antiemetic regimens. For the prevention of acute emesis induced by low emetogenic chemotherapy a prophylaxis with a single antiemetic drug such as dexamethasone is suggested while no antiemetic prophylaxis should be administered to prevent acute emesis induced by minimal emetogenic chemotherapy or to prevent delayed emesis induced by low or minimal emetogenic chemotherapy. In this last case a rescue therapy should be administered in patients presenting acute or delayed emesis.

KEY WORDS: *Antineoplastic Agents; Nausea; Vomiting; Antiemetics; Dexamethasone; Metoclopramide; Serotonin Antagonists; Receptors, Neurokinin-1*

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INTRODUCTION

Patients submitted to antineoplastic chemotherapy present three different types of emesis that, because each has particular characteristics, require different prophylactic and therapeutic approaches:

- Acute emesis that starts in the first 24 hours after chemotherapy administration;
- Delayed emesis that arbitrarily has been defined as emesis starting 24 hours after chemotherapy administration and can persist for some days and sometimes until the next course of chemotherapy;
- Anticipatory emesis that starts immediately before the chemotherapy administration in patients with previous experience of chemotherapy-induced acute and delayed emesis. It is generally induced by the sight and smell of the place in which the chemotherapy is administered. In Tables 1 and 2 the classification of antineoplastic agents according to their emetogenic potential proposed by the Perugia Consensus Conference on antiemetics (March, 29-31, 2004) is reported. The emetogenic potential of antineoplastic agents, both intravenously and orally administered, has been classified in 4 groups: high (emetic risk >90%), moderate (between 30% and 90%), low (between 10% and 30%) and minimal (<10%). This classification, as well as the others previously available (1,2), is arbitrary because emetogenic characteristics of many agents such as frequency, intensity, duration, starting time after the administration, etc., are not known.

Furthermore, emesis induced by an antineoplastic agent is also different according to its combination with other chemotherapeutic agents, its dose, its duration of infusion and some patient characteristics such as sex, age, previous experience of emesis during pregnancy, kinetosis, etc.

Table 1. Emetogenic potential of intravenous antineoplastic agents

Degree	Drug
High	Cisplatin
	Mecloretamine
	Streptozotocin
	Cyclophosphamide > 1500 mg/m^2
	Carmustine
	Dacarbazine
Moderate	Oxaliplatin
	Cytarabine > 1 gr/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide ≤ 1500 mg/m^2
	Doxorubicin
	Epirubicin
	Idarubicin
	Irinotecan
Low	Docetaxel
	Paclitaxel
	Mitoxantrone
	Topotecan
	Etoposide
	Pemetrexed
	Methotrexate
	Mitomicin C
	Gemcitabine
	Cytarabine ≤ 100 mg/m^2
	5- Fluorouracil
	Bortezomib
	Cetuximab
	Trastuzumab
Minimal	Bleomycin
	Busulfan
	2-Clorodeossiadenosine
	Fludarabine
	Vinblastine
	Vincristine
	Vinorelbine
	Bevacizumab

Table 2. Emetogenic potential of oral antineoplastic agents

Degree	Drug
High	Exametilmelamine
	Procarbazine
Moderate	Cyclophosphamide
	Etoposide
	Temozolomide
	Vinorelbine
	Imatinib
Low	Capecitabine
Minimal	Clorambucil
	Idrossiurea
	L-Fenilalanine mustard
	6-Tioguanine
	Methotrexate
	Gefitinib

In this review the guidelines of antiemetic prophylaxis suggested by randomized clinical trials or meta-analysis in patients submitted to chemotherapy are reported (Table 3).

Table 3. Guidelines for antiemetic prophylaxis*

Chemotherapy	Antiemetics
High single doses of cisplatin	
Acute emesis	Aprepitant + 5-HT3 antagonist + dexamethasone
Delayed emesis	- Metoclopramide + dexamethasone - 5-HT3 antagonist + dexamethasone - (Aprepitant + dexamethasone)**
Dacarbazine, mechloretamine, streptozotocin, nitrosoureas	
Acute emesis	5-HT3 antagonist + dexamethasone
Moderately emetogenic chemotherapy (cyclophosphamide, epirubicin, doxorubicin, carboplatin)	
Acute emesis	5-HT3 antagonist + dexamethasone
Delayed emesis	Dexamethasone or a 5-HT3 antagonist
Low and repeated doses of cisplatin	- 5-HT3 antagonist + dexamethasone - (dexamethasone for delayed vomiting)**
C.M.F. (oral cyclophosphamide)	- Metoclopramide + dexamethasone - 5-HT3 antagonist
Low emetogenic chemotherapy	
Acute emesis	- Dexamethasone or other antiemetics different from 5-HT3 antagonists**
Delayed emesis	- Only rescue therapy
Minimal emetogenic chemotherapy	
Acute emesis	- Only rescue therapy
Delayed emesis	- Only rescue therapy
All chemotherapeutic agents	
Anticipatory emesis	- Psychological techniques - Hypnosis
High-dose chemotherapy	
Acute emesis	- 5-HT3 antagonist ± dexamethasone

* See text for recommended doses and schedules of administration
** See text for a discussion of this indication

Prevention of acute emesis induced by a high single dose of cisplatin

The combination of a 5-HT3 antagonist plus dexamethasone has been shown in at least two double-blind studies to have superior efficacy (complete protection from vomiting in about 80% of patients) and better tolerability with respect to the combination of high-dose metoclopramide plus dexamethasone plus diphenhydramine or lorazepam. Therefore, the combination of a 5-HT3 antagonist plus dexamethasone has been considered until now the treatment of choice for the prevention of cisplatin-induced acute emesis.

This recommendation is probably valid also for the prevention of acute emesis induced by dacarbazine, mecloretamine, streptozotocin and nitrosoureas, even if at present controlled clinical trials are lacking.

In the last few years some phase II studies have reported interesting results with the association of a NK1 antagonist, aprepitant, to the standard combination of a 5-HT3 antagonist plus dexamethasone (3).

Table 4. Doses and schedules of administration of 5ht3 antagonists in the prevention of acute emesis

Drug	Dose	Schedule	Administration
Ondansetron	8 mg or 0.15 mg/kg	Single Dose	IV
	16 mg*	Single Dose	Oral
Granisetron	1 mg or 0.01 mg/kg	Single Dose	IV
	2 mg	Single Dose	Oral
Tropisetron	5 mg	Single Dose	IV
	5 mg	Single Dose	Oral
Dolasetron	100 mg or 1.8 mg/kg	Single Dose	IV
	100 mg	Single Dose	Oral
Palonosetron	0.25 mg	Single dose	IV

* In two doses. In patients treated with cisplatin the oral dose of ondansetron is 24 mg

Two randomized, double-blind studies in chemotherapy-naive patients submitted to cisplatin chemotherapy at the dose ≥70 mg/m^2 have been published (4,5). In these the standard treatment (ondansetron 32 mg IV plus dexamethasone 20 mg orally in the first 24 hours and dexamethasone 8 mg orally twice on days 2-4 after cisplatin) has been compared with an antiemetic combination including aprepitant (aprepitant 125 mg orally plus ondansetron 32 mg iv plus dexamethasone 12 mg orally in the first 24 hours, aprepitant 80 mg orally plus dexamethasone 8 mg orally on days 2 and 3 and dexamethasone 8 mg orally on day 4). In these studies the dexamethasone dose was reduced on the first day (12 mg instead of 20 mg) and on the following days (8 mg instead of 16 mg) due to a pharmacokinetic interaction with aprepitant that more than doubles plasmatic levels of dexamethasone. This reduction has been made to avoid confounding the interpretation of the study results in terms of efficacy and tolerability that the different exposition to dexamethasone could cause.

In the first study 569 patients were enrolled (4). Complete response (no vomiting and no rescue therapy) was significantly superior with aprepitant (62.7% versus 43.3% on days 1-5, 82.8% versus 68.4% on day 1 and 67.7% versus 46.8% on days 2-5). Complete protection from nausea was also significantly superior on days 1-5 (49% versus 39%) and on days 2-5 (53% versus 40%). The incidence of adverse events was not significantly different between the two antiemetic regimens.

In the other study 530 patients were enrolled (5). Complete protection was significantly superior with aprepitant on days 1-5 (72.7% versus 52.3%), on day 1 (89.2% versus 78.1%) and on days 2-5 (75.4% versus 55.8%). Instead, complete protection from nausea was not significantly different on days 1-5 (47.5% versus 44.2%) and on days 2-5 (51.0% versus 47.7%). Again in this study the adverse events were not significantly different between the two groups of patients.

In conclusion, in both studies aprepitant combined with ondansetron and dexamethasone significantly increased the antiemetic protection with respect to the standard therapy and was generally well tolerated. Therefore, a combination of aprepitant plus a 5-HT3 antagonist and dexamethasone is to be considered the treatment of choice to prevent cisplatin-induced acute emesis. The suggested dose of aprepitant (125 mg orally 1 hour before cisplatin administration) has been identified in a recently published dose-finding study (6).

In spite of the fact that all agree that the 5-HT3 antagonists should be administered as a single dose immediately before chemotherapy, there is a large variation in the single dose approved for intravenous administration. For example, in the USA the approved dose of ondansetron (32 mg) is 4 times higher than the approved dose in Europe (8 mg) while the opposite is valid for granisetron (1 mg with respect to 3 mg).

Table 4 reports the doses and schedules of administration considered therapeutically equivalent in the prevention of acute emesis induced by cisplatin or by moderately emetogenic chemotherapy. Several randomized, double-blind controlled studies have demonstrated the similar efficacy and tolerability of the different 5-HT3 antagonists. Therefore, the choice

between them should be based on their acquisition cost. Recently, some studies have compared the efficacy of palonosetron, a new 5-HT3 antagonist with a longer half-life (about 40 hours), with other 5-HT3 antagonists. Two of these carried out in patients submitted to moderately emetogenic chemotherapy compared palonosetron to dolasetron and ondansetron (7,8). These studies showed statistically significant differences in terms of complete protection from acute and delayed emesis in favor of palonosetron but were not well planned studies from a methodological point of view (the 5-HT3 antagonists were not associated with dexamethasone to prevent acute and delayed emesis, several enrolled patients had previously been submitted to chemotherapy with the possibility of having mild nausea, and their distribution between the two arms of the studies was not well clarified). Therefore, more studies are needed to define whether palonosetron is a real therapeutic innovation. The recommended single dose of intravenous dexamethasone is 20 mg.

Prevention of cisplatin-induced delayed emesis

Due to its high incidence, all patients submitted to high single doses of cisplatin should receive an antiemetic prophylaxis against delayed emesis.

The 5-HT3 antagonists, used alone, have demonstrated at the most only moderate efficacy against cisplatin-induced delayed emesis. Instead, the combinations of oral or intramuscular dexamethasone (8 mg twice on days 2-3 and 4 mg twice on days 4-5) with metoclopramide (0.5 mg/kg or 20 mg orally 4 times a day on days 2-5) or a 5-HT3 antagonist (for example, oral ondansetron 8 mg twice on days 2-5) starting 24 hours after chemotherapy and continuing for a minimum of 72 hours, have been shown efficacious and should be considered the best treatment to prevent cisplatin-induced delayed emesis.

In the two-phase III aprepitant studies summarized above, complete protection from delayed emesis (days 2-5) was significantly superior in patients that received the combination of aprepitant (80 mg orally on days 2 and 3 after cisplatin) plus dexamethasone with respect to those submitted to dexamethasone alone (4-5).

Unfortunately, in these two studies patients did not receive the suggested treatment to prevent cisplatin-induced delayed emesis that, as stated before, is represented by a combination of dexamethasone plus metoclopramide or a 5-HT3 antagonist. The Perugia Consensus Conference stated that for the prevention of cisplatin-induced delayed emesis in patients that in the first 24 hours had been treated with a combination of aprepitant, a 5-HT3 antagonist and dexamethasone to prevent acute emesis, a combination of aprepitant plus dexamethasone is recommended because it is superior to dexamethasone alone.

Instead, I think that to define the role of aprepitant in the prevention of cisplatin-induced delayed emesis it is necessary to carry out further studies in which all patients have received the new standard prophylaxis of cisplatin-induced acute emesis (aprepitant + ondansetron + dexamethasone) and starting from 24 hours after cisplatin administration, patients should be randomized to receive the standard regimen (dexamethasone + metoclopramide or dexamethasone + a 5-HT3 antagonist) or the same standard regimen combined with aprepitant. At present it is not known if it is necessary to administer a prophylaxis for delayed emesis in patients submitted to dacarbazine, mecloretamine, streptozotocin, and nitrosoureas.

Prevention of acute emesis induced by moderate emetogenic chemotherapy (single doses IV of cyclophosphamide, doxorubicin, epirubicin and carboplatin, used alone or in combination)

High and repeated doses of corticosteroids (dexamethasone or methylprednisolone), as well as the 5-HT3 antagonists, induce complete protection from vomiting in about 60%-80% of patients. The combination of a 5-HT3 antagonist plus dexamethasone has been shown significantly more efficacious than dexamethasone alone or a 5-HT3 antagonist alone and should be considered the recommended regimen for the prevention of acute emesis induced by moderately emetogenic chemotherapy. No randomized comparative trials are available regarding patients submitted to antineoplastic agents of moderate emetogenic potential different from cyclophosphamide, doxorubicin, epirubicin and carboplatin, used alone or in combination. In any case, it is probable that such recommendations are also valid for these drugs. Also in this situation the 5-HT3 antagonists can be used both intravenously and orally (Table 4). The recommended dose and schedule of administration of dexamethasone in the prevention of acute emesis induced by moderately emetogenic chemotherapy has recently been identified in a randomized double-blind study; it is 8 mg single dose IV before chemotherapy administration (9).

Prevention of delayed emesis induced by moderately emetogenic chemotherapy

Only a few studies have been carried out to evaluate the efficacy of antiemetic drugs against delayed emesis. Orally administered dexamethasone or a 5-HT3 antagonist have been shown efficacious (complete protection from delayed emesis in about 40%-60% of patients). In these patients, protection from acute emesis significantly influences the incidence of delayed emesis. In fact, the incidence of delayed vomiting and nausea is inferior to 20%-30% in patients that did not have acute vomiting and moderate-severe nausea, and it is about 55%-75% in those that had acute vomiting and moderate-severe nausea.

A double-blind comparative study has demonstrated the necessity to administer an antiemetic prophylaxis to prevent delayed emesis in all patients submitted to moderately emetogenic chemotherapy (10). The recommended drug, at least for the patients who have not presented acute vomiting and moderate-severe nausea, is oral dexamethasone 4 mg twice on days 2-5 after chemotherapy. More studies are necessary to identify the optimal treatment for patients having acute vomiting and moderate-severe nausea.

Prevention of emesis in patients submitted to low and repeated doses of cisplatin (20-40 mg/m2/day for 3-5 days)

An intravenous combination of a 5-HT3 antagonist plus dexamethasone has been shown efficacious in determining complete protection from vomiting in about 55%-83% of patients during the 3-5 days of cisplatin administration. This combination has been shown superior to high dose IV metoclopramide plus dexamethasone, to alizapride plus dexamethasone and to a 5-HT3 antagonist alone. Therefore, this combination, administered every day of cisplatin chemotherapy, should be considered the treatment of choice.

To identify the optimal dose of the 5-HT3 antagonists and of dexamethasone in this subgroup of patients dose-finding studies, still lacking, are necessary. In the studies carried out until now the 5-HT3 antagonists have been administered as a single vial a day for all days of chemotherapy administration while the dexamethasone dose has been 8-20 mg iv.

The Perugia Consensus Conference has recommended administering in such patients dexamethasone for the prevention of delayed emesis even if data supporting this choice are lacking.

Prevention of emesis induced by oral cyclophosphamide in combination with intravenous methotrexate and 5-fluorouracil (C.M.F.)

Despite the wide use of this regimen, only two controlled studies have been published. A combination of dexamethasone, in a single IV dose (10 mg) on day 1 and 8, plus a 14-day administration of oral metoclopramide (10 mg three times a day) has been shown to be the treatment of choice. An orally administered 5-HT3 antagonist is a valid alternative treatment in patients that do not tolerate this combination.

Prevention of acute emesis induced by low emetogenic chemotherapy (i.e., mitoxantrone, 5-fluorouracil)

In patients submitted to these chemotherapies, despite the lack of randomized clinical trials, the Perugia Consensus Conference recommended using an antiemetic prophylaxis (i.e., dexamethasone 4 or 8 mg IV) immediately before their administration.

Prevention of acute emesis induced by minimal emetogenic chemotherapy and of delayed emesis induced by low and minimal emetogenic chemotherapy

In these indications antiemetics should not be routinely administered. Rescue antiemetic treatment should be administered if patients have acute and/or delayed emesis.

Prevention of anticipatory emesis

This appears only if the patients suffered previously from frequent and/or severe nausea and vomiting post-chemotherapy. Therefore, the best preventive therapy is to avoid acute and delayed emesis from the very first course of chemotherapy. The pharmacological treatment now available is not able to achieve complete protection from anticipatory nausea and vomiting. In several studies, psychological techniques and hypnosis have been shown efficacious to prevent anticipatory nausea and vomiting.

Prevention of emesis induced by high-dose chemotherapy

Only a few studies have described the natural history of emesis induced by high-dose chemotherapy. Three small, randomized studies have shown the superiority of the 5-HT3 antagonists with respect to older antiemetic drugs. More studies are necessary to identify the optimal dose and schedule of the 5-HT3 antagonists as well as their efficacy in combination with dexamethasone or other drugs such as aprepitant. No therapy has been shown efficacious in the prevention of delayed emesis induced by high-dose chemotherapy.

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Corrigendum

Because of the technical error that appeared in the 2/3 of the circulation, issue 12/3, pages 172-177, and because of the ethical and educational reasons we publish again the paper titled Management of chemotherapy induced emesis by F. Roila. We apologize once more to the author and the organizers of The First Belgrade Educational Symposium, October 2004, and to the readers.

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