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REVIEW ARTICLE

Fausto Roila
Donatella Donati
Stefano Tamberi
Guido Margutti

Delayed emesis: incidence, pattern, prognostic factors and optimal treatment

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F. Roila (✉) · D. Donati · S. Tamberi
G. Margutti
Medical Oncology Division,
Arcispedale S. Anna, Ferrara, Italy
e-mail: roila fausto@libero.it
Tel.: +39-075-5783968
Fax: +39-075-57209990

F. Roila
Policlinico Hospital, Via Brunamonti,
06122 Perugia, Italy

Abstract Delayed emesis has been arbitrarily defined as vomiting and/or nausea beginning, or persisting for, more than 24 h after chemotherapy administration. Acute emesis is the most important prognostic factor for delayed emesis. Owing to the relatively high incidence and severity all patients treated with cisplatin ≥50 mg/m^2 should receive antiemetic prophylaxis. In these patients a combination of dexamethasone plus metoclopramide or a 5-HT3 antagonist is the most efficacious regimen. All patients submitted to moderately emetogenic chemotherapy, such as cyclophosphamide, carboplatin, doxorubicin and epirubicin, should also receive antiemetic prophylaxis with oral dexamethasone to prevent delayed emesis.

Keywords Delayed emesis · Antiemetic prophylaxis · 5-HT3 antagonists · Dexamethasone · Metoclopramide

Introduction

In the last 20 years important progress has been achieved in the prevention and treatment of chemotherapy-induced nausea and vomiting. Factors contributing to the improved control of emesis include: enhanced knowledge of the pathophysiology of emesis; the completion of large methodologically sound clinical studies on antiemetics; and the discovery of new and more efficacious antiemetic drugs, in particular the 5-HT3 receptor antagonists.

While our understanding of chemotherapy-induced emesis was improving, it soon became clear that we were confronted with two types of emesis: acute and delayed. Delayed emesis has been arbitrarily defined as emesis that begins or persists more than 24 h after chemotherapy.

Until the last decade little attention had been addressed to the delayed emesis phenomenon. There are various reasons for this:

- Primarily it is a less severe event than acute emesis.
- Delayed emesis occurs when the patients are at home and away from direct observation by the oncologists.
- An animal model for the study of this condition has not been available until recently [33, 43].

The inevitable consequence has been that only a few, and often not well-conducted, studies have been published on this topic.

Pathophysiology

The pathophysiology of delayed emesis is unknown. Though not proven, various mechanisms have been postulated:

1. Disruption of the blood–brain barrier. Antineoplastic agents, especially cisplatin, can disrupt the blood–brain barrier, determining a mild and reversible cerebral oedema. The increased intracranial pressure may potentiate other emetic inputs. This has been demonstrated in the dog after cisplatin administration via the

carotid artery [37]. When the drug was intravenously administered instead there was no neurotoxicity; but if the blood–brain barrier was opened using mannitol then intravenous cisplatin also induced significant neurotoxicity. The documented activity of corticosteroids in the treatment of cerebral oedema and delayed emesis gives some support to this hypothesis.

2. Disruption of gastrointestinal motility and/or permeability. Chemotherapeutic agents, in particular cisplatin, can cause temporary disturbances of gastrointestinal tract function, such as hypomotility and gastroparesis, that are capable of inducing protracted nausea and vomiting [3, 6].
   On the other hand, the gut mucosa normally provides an effective barrier against the entry of macromolecules into the bloodstream, but it has been postulated that the cytotoxic effects of cisplatin on the gut mucosa can stimulate the release of hormones, many of which can induce emesis when given in high doses [3, 6].
3. Role of endogenous or exogenous adrenal hormones. Corticosteroids and noradrenaline (but not adrenaline) may have a role in chemotherapy-induced delayed emesis. In fact, urinary cortisol excretion was inversely related and noradrenaline excretion was directly related to the intensity of chemotherapy-induced delayed nausea [7, 8]. The anti-inflammatory properties of cortisol may act as an antiemetic by preventing the release of serotonin in the gut or preventing the activation of 5-HT3 receptors in the gastrointestinal system [7]. Noradrenaline, however, may have an emetogenic effect promoting the release of serotonin in the gut or alternatively affecting 5-HT3 receptor sensitivity [8].
   Moreover, corticosteroids (dexamethasone) are frequently used for the prevention of acute emesis, and it has been suggested that their abrupt discontinuation can bring about adrenal failure, which may be responsible for the occurrence of the delayed emesis [2]. On the other hand, two recent studies showed that dexamethasone administration before chemotherapy led to a significant decline in endogenous cortisol levels in 24 h and to a subsequent, rapid, significant recovery in the next 24 h [30, 41].
4. Accumulation of emetogenic metabolites from chemotherapeutic agents. Others have postulated that delayed emesis may be the result of an accumulation of metabolites of chemotherapy agents (those of cisplatin have been identified in the body fluid and tissues over 24 h after its administration) or of the hypomagnesaemia induced by cisplatin.

It is likely that delayed emesis is a multifactorial phenomenon with relative contributions from each of the above factors or others not yet determined.

Incidence and pattern of delayed emesis

Delayed emesis has been studied mainly in cisplatin-treated patients, but it also occurs with moderately emetogenic chemotherapy, especially carboplatin and cyclophosphamide. The incidence and characteristics of delayed emesis differ between patients receiving cisplatin-based and those receiving moderately emetogenic chemotherapy, and we will therefore describe the two phenomena separately.

Cisplatin

Cisplatin induces a biphasic pattern of emesis. In one study, all patients not receiving antiemetic prophylaxis following cisplatin, 120 mg/m^2, experienced nausea and vomiting within the first 24 h after chemotherapy [11]. Symptoms begin with a short latency period of 2–3 h and peak around 6–8 h after cisplatin administration. This acute phase lasts for 10–18 h before subsiding. It is followed by a separate phase occurring more than 24 h later.

Recently, a new definition of cisplatin-induced delayed emesis has been proposed [28]). In fact, in patients treated with cisplatin and receiving placebo, metoclopramide or ondansetron as antiemetics, there appear to be two vomiting peaks: one at approximately 4 h and one at 18 h, with a period of virtually no vomiting between them, even in patients receiving placebo. While both metoclopramide and ondansetron attenuate the first peak significantly, neither eliminates or attenuates the second peak at 18 h. These observations suggest that the phenomenon of delayed emesis may begin at 16 h rather than 24 h after cisplatin [28]. However, this pattern of emesis induced by cisplatin was not confirmed in 196 cisplatin-treated patients who had acute emesis despite prophylaxis with ondansetron or granisetron combined with dexamethasone. In this study the start of vomiting was uniformly distributed during the first 24 h [17].

The incidence and pattern of delayed emesis have been described in one study on 86 patients receiving cisplatin, 120 mg/m^2, and treated for the prevention of acute emesis with metoclopramide, dexamethasone and diphenhydramine or lorazepam, who were monitored for 5 days after the chemotherapy without receiving any antiemetic treatment other than that received for acute emesis [26]. During the first 24 h, 38% of patients had vomiting. Over the next 4 days, 93% of patients experienced some degree of delayed nausea and vomiting. The incidence and intensity of symptoms peaked during the 48- to 72-h period following chemotherapy administration, when 61% of patients had vomiting and 78% had nausea. The incidence and intensity of the phenomenon decreased during the subsequent days. In any case, the symptoms experienced during the delayed phase were less severe than those during the acute phase.

Moderately emetogenic chemotherapy

Less information is available on the incidence and characteristics of delayed emesis induced by moderately emetogenic chemotherapy. One difference is that the emetic symptoms follow a monophasic pattern after moderately emetogenic chemotherapy. The onset of emesis after carboplatin and cyclophosphamide occurs with a latency period of 6–12 h, which is longer than that observed with cisplatin. Symptoms are most intense in the first 24 h, but nausea and vomiting can persist over a 24- to 36-h period [31]. In a study in which 31 breast cancer patients treated with 5-fluorouracil, doxorubicin and cyclophosphamide were observed for 4 consecutive days without receiving any antiemetic prophylaxis, most of them had vomiting for 2 or more days [31].

In another study, performed in 28 patients treated with carboplatin (300–400 mg/m^2), the peak intensity of emesis occurred between 8 and 12 h after chemotherapy and, although symptoms subsided significantly by 24 h, some patients (11%) continued to have emesis 48 h after this [31].

On the basis of these observations, Martin has suggested the opportunity of distinguishing the two patterns of delayed emesis by reserving the term 'delayed emesis' for the biphasic pattern of symptoms which follow cisplatin treatment and using the term 'prolonged emesis' for the late emesis following non-cisplatin chemotherapy [31].

Moreover, Morrow has proposed considering delayed emesis as only that occurring after an initial 24 h free of nausea and vomiting and considering 'persistent emesis' as emesis that continues beyond the day of chemotherapy administration [35].

Data on the incidence of delayed emesis in patients treated with moderately emetogenic chemotherapy are scanty. In a large study by the Italian Group for Antiemetic Research, evaluating patients treated with cyclophosphamide, doxorubicin, epirubicin and carboplatin, on days 2–5, when patients were monitored without receiving any antiemetic prophylaxis, the incidence of moderate to severe vomiting and nausea was approximately 20% and 25%, respectively [19]. However, studies often differ in the incidence of delayed emesis observed, and the differences can sometimes be explained by patient/treatment characteristics that represent important prognostic factors.

Prognostic factors in delayed emesis

Few studies have evaluated the prognostic factors predisposing patients to delayed emesis, and almost all of them have been performed in cisplatin-treated patients.

- The most important prognostic factor to emerge from these studies is obtaining complete protection from nausea and vomiting during the first 24 h [16, 26, 27, 42]. This factor is independent of the type of antiemetic treatment received for acute or delayed emesis.

In patients followed for more than one cycle of chemotherapy the incidence of delayed vomiting in the second/third cycles was dependent on the results obtained in the first 24 h of the same cycles of chemotherapy. Not only that, but the incidence of delayed vomiting in the second/third cycles was also dependent on the incidence of delayed vomiting in the first/second cycles [16]. Furthermore, the study showed that delayed vomiting was a prognostic factor for acute emesis in the subsequent cycles [16].

Even in patients treated with moderately emetogenic drugs the most important prognostic factor is obtaining complete protection in the first 24 h after chemotherapy administration [19, 21]. The incidence of delayed vomiting/moderate to severe nausea is low (<15%/<15%) in patients who did not have acute vomiting/moderate-severe nausea, but is high (55%/75%) in patients who did [19, 21].

- Another important prognostic factor for delayed emesis is the dose of cisplatin administered. In fact, two studies have shown that doses ≤90 mg/m^2 induced delayed emesis less frequently than doses >90 mg/m^2 (22% versus 43% in one study [42] and 19.4% versus 46.9% in another [16]).
- Sex is also a significant prognostic factor, independent of the antiemetic treatment received. In one study 76% of females versus 39% of males had delayed vomiting after cisplatin chemotherapy [42].
- In patients treated with cisplatin, age, tumour burden and tumour localisation also seem to be important. In fact, patients with ovarian cancer with diameter of the greatest residual tumour <2 cm had less delayed nausea than those with diameter ≥2 cm [15], patients with supradiaphragmatic localisation less than those with infradiaphragmatic localisation, and older patients less than younger ones [5]. However, these results require confirmation in larger studies.

Treatment of delayed emesis

Owing to its relatively high incidence and severity, at least in some high-risk patients, delayed emesis causes distress and discomfort to many patients and can contribute to reducing the compliance in subsequent cycles of chemotherapy. For these reasons it is important to know and utilize the best available preventive treatment.

The objectives of treatment for delayed emesis should be: (1) to provide patients with the best treatment able to obtain complete protection from acute emesis starting from the first cycle of chemotherapy; (2) to use regimens

Table 1 Cisplatin-induced delayed emesis: comparative studies without 5-HT3 antagonists (*O* open, *SB* single blind, *DB* double-blind, *PL* placebo, *ALZ* alizapride, *MTC* metoclopramide, *DEX* dexamethasone, *PCP* prochlorperazine, *C.P.* complete protection from delayed vomiting, *N.S.* not specified)

Type of study	No. of patients	Cisplatin dose (mg/m²)	Antiemetics	C.P. (%)	Results		Reference
					Vomiting	Nausea	
DB	91	120	MTC+DEX DEX PL	52.0 35.0 11.0	MTC+DEX>DEX>PL	MTC+DEX and DEX>PL	[27]
SB	120	≥50	MTC DEX PL	69.0 65.4 56.7	MTC=DEX=PL	MTC and DEX>PL	[42]
SB	63	60–120	DEX ALZ+DEX MTC+DEX	44.0 30.0 70.0	MTC+DEX>ALZ+DEX and DEX	MTC+DEX=ALZ+DEX=DEX	[34]
O	70	80 or 100	DEX+PCP No therapy	28.6 20.0	DEX+PCP≥No therapy	DEX+PCP≥No therapy	[32]
O	42	80	MTC+DEX PL	75.0 50.0	MTC+DEX>PL	MTC+DEX>PL	[44]
DB	60	≥60	ACTH PL	67.0 43.0	ACTH >PL	ACTH=PL	[38]
DB	152	60–120	ACTH 1 mg ACTH 2 mg+1 mg after 72 h PL	62.0 71.4 35.3	ACTH 2 mg≥ACTH 1 mg>PL	ACTH 2 mg≥ACTH 1 mg>PL	[39]

that consist of oral agents, facilitating easy outpatient use; (3) to use regimens that contain agents proven to be efficacious and tolerable in this setting; (4) to use treatments that take account of cost factors whenever possible.

In this section the results of comparative studies specifically planned to evaluate different antiemetic treatments in the prevention of delayed emesis will be presented. Studies with the primary objective of evaluating different antiemetic drugs in the prevention of acute emesis, and in which the same drugs were continued in the following days, will not be reported. This is because in such studies the superiority of one drug with respect to another in the prophylaxis of delayed emesis could mean either that the drug is superior or that the superiority of a drug is due to better results obtained with this drug in the first 24 h that persist in the following days and, therefore, to a dependence effect. To distinguish these two results a multifactorial analysis comparing the results obtained in the prevention of delayed emesis balancing those obtained in the prophylaxis of acute emesis should be carried out. Unfortunately, no such analysis was performed in these studies.

In evaluating antiemetic efficacy against delayed emesis, considering the differing incidence and characteristics of the phenomenon, it is necessary to plan studies in which patients subjected to cisplatin chemotherapy are clearly separated from those subjected to moderately emetogenic chemotherapy. Instead, two recently published studies enrolled both types of patients [1, 23]. In these studies, from day 2 to day 5 all patients received dexamethasone (4 mg or 10 mg orally) and were randomised to receive granisetron (1 mg or 2 mg orally) or metoclopramide (10 mg or 20 mg three times a day). The proportion of patients who achieved complete protection from delayed emesis was similar with both regimens (68% versus 55% and 81% versus 84%, respectively with granisetron and metoclopramide).

Following cisplatin

Antiemetic activity of drugs other than 5-HT3 receptor antagonists

In Table 1 the comparative studies between different antiemetics (used alone or in combination) or with respect to placebo in the prevention of delayed emesis are summarized [27, 32, 34, 38, 39, 42, 44].

From these data it appears clear that the efficacy shown by metoclopramide, dexamethasone or ACTH, when used alone, although superior to placebo in the prevention of delayed nausea or vomiting, is often of limited clinical significance. A combination of oral metoclopramide (0.5 mg/kg, or 20 mg, every 6 h on days 2–5) plus dexamethasone (8 mg every 12 h on days 2 and 3 after cisplatin and 4 mg every 12 h on days 4 and 5) is the most efficacious antiemetic treatment for the prevention

Table 2 Cisplatin-induced delayed emesis: comparative studies with 5-HT3 antagonists (*OND* ondansetron, *GRAN* granisetron)

Type of study	No. of patients	Cisplatin dose (mg/m^2)	Antiemetics	C.P. (%)	Results		Reference
					Vomiting	Nausea	
DB	48	≥100	OND PL	40.0 33.0	OND≥PL	OND=PL	[9]
DB	538	≥70	OND PL	36.0 26.0	OND≥PL	OND≥PL	[36]
DB	434	≥50	DEX+PL DEX+GRAN	35.0 38.0	GRAN+DEX=DEX	GRAN+DEX=DEX	[29]
DB	619	≥69	DEX+PL DEX+GRAN	58.4 57.2	GRAN+DEX=DEX	GRAN+DEX=DEX	[10]
DB	527	≥50	GRAN+PL GRAN+DEX	58.0 78.9	GRAN+DEX>GRAN	GRAN+DEX>GRAN	[22]
DB	236	≥50	OND+PL OND+DEX	50.0 63.0	OND+DEX≥OND	OND+DEX≥OND	[13]
DB	322	≥50	MTC+DEX OND+DEX	60.0 62.0	MTC+DEX=OND+DEX	MTC+DEX=OND+DEX	[18]

of delayed emesis. Nonetheless, as shown in two large studies in 249 and in 522 patients, therapy of this phenomenon is far from being optimal: about 40–60% of patients had delayed nausea and/or vomiting despite treatment with metoclopramide plus dexamethasone [16, 20].

Antiemetic activity of 5-HT3 receptor antagonists

Only recently has the role of the 5-HT3 receptor antagonists in the prevention of cisplatin-induced delayed emesis been clarified. In Table 2 the results of the most important comparative studies performed with the 5-HT3 receptor antagonists are reported [9, 10, 13, 18, 22, 29, 36]. The analysis of all these studies suggests that 5-HT3 receptor antagonist activity in the prevention of delayed emesis is probably not as good as it is in the prevention of acute emesis and that their efficacy, when used alone, is only moderate. Furthermore, in two studies the addition of a 5-HT3 antagonist to dexamethasone did not result in more cases of complete protection from delayed vomiting and nausea than were achieved with dexamethasone alone [10, 29]. On the other hand, the addition of dexamethasone to a 5-HT3 antagonist decreased the incidence of delayed emesis to a lower level than was seen with a 5-HT3 antagonist alone [13, 22].

Finally, in a double-blind randomised study, oral ondansetron (8 mg every 12 h on days 2–4) combined with dexamethasone showed similar antiemetic activity as standard metoclopramide plus dexamethasone in the prevention of cisplatin-induced delayed emesis, and these two regimens should be considered the antiemetic prophylaxis of choice for delayed emesis [18]. Considering the higher cost, metoclopramide remains the standard treatment, but, according to the results of this study, preference should be given to ondansetron in patients who do not tolerate metoclopramide or who had emesis in the first 24 h [18].

Following moderately emetogenic chemotherapy

Until recently the problem of delayed emesis due to moderately emetogenic chemotherapy has received little attention. At present, three comparative studies on the prevention of delayed emesis induced by moderately emetogenic drugs show ondansetron, granisetron and dexamethasone to be superior to placebo [14, 24, 25] (Table 3). In none of these three studies did patients receive the optimal antiemetic prevention of acute emesis (a combination of dexamethasone plus a 5-HT3 receptor antagonist) in the first 24 h [4, 12], and this increased the incidence of delayed emesis. In another open study the addition of a 5-HT3 antagonist (ondansetron or dolasetron) to dexamethasone did not increase the proportion of patients with complete protection from delayed emesis over that achieved with dexamethasone alone [40].

Finally, the Italian Group for Antiemetic Research carried out a double-blind study in which, 24 h after chemotherapy, patients were divided into two groups: patients who did not have either vomiting or moderate to severe nausea (the low-risk group) and patients who had one or both (the high-risk group) [21]. Patients in the low-risk group were then randomly assigned to receive one of the following from day 2 to day 5 after chemotherapy: oral placebo, 4 mg of dexamethasone given orally twice daily, or 8 mg of ondansetron in combination with 4 mg of dexamethasone, given orally twice daily. Patients in the high-risk group were randomly assigned to receive oral dexamethasone alone or in combination with ondansetron at the same doses as were used in the low-risk group.

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