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Chemotherapy-Induced Nausea and Vomiting in the Treatment of Gastrointestinal Tumors and Secondary Prophylaxis with Aprepitant

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Key Words

Chemotherapy-induced nausea and vomiting · Gastrointestinal tumors · Aprepitant · Neurokinin-1 receptor

Abstract

Background: Chemotherapy-induced nausea and vomiting (CINV) belongs to the most feared side-effects of cancer treatment. Its incidence during chemotherapy of gastrointestinal tumors (GITs) with highly and moderately emetogenic regimens is not well documented. It is also unknown whether aprepitant, a neurokinin-1 receptor antagonist, can be used as secondary antiemetic prophylaxis in case of CINV during cycle 1. **Patients and Methods:** Patients with GITs who were treated with highly and moderately emetogenic chemotherapy received standard antiemetic prophylaxis including a 5-hydroxytryptamine-3 receptor antagonist and dexamethasone. In case of CINV > grade 1 (National Cancer Institute classification) during the first chemotherapy course, aprepitant was additionally administered with further cycles. **Results:** We screened 109 patients. 16 patients (15%) experienced acute and/or delayed CINV. Features associated with CINV were low-dose cisplatin-containing chemotherapy (15/16 patients), female gender (11/16 patients), abstinence to alcohol (11/16 patients) and former emesis gravidarum (11/16 patients). 11 patients who got further courses of the same chemotherapy received aprepitant. 7 are fully assessable for response. 5 of 7 patients had a complete protection from CINV (71%) and 1 patient had improved symptoms. **Conclusions:** In the majority of cases, primary standard antiemetic prophylaxis provided adequate protection against CINV. In case of failure to primary prophylaxis, secondary prophylaxis with aprepitant showed a high efficacy against CINV.

Schlüsselwörter

Chemotherapie-induzierte Übelkeit und Erbrechen · Gastrointestinale Tumoren · Aprepitant · Neurokinin-1-Rezeptor

Zusammenfassung

Hintergrund: Chemotherapie-induzierte Übelkeit und Erbrechen (CINV) beeinträchtigen die Lebensqualität von Tumorpatienten. Das Auftreten von CINV während einer hoch oder moderat emetogenen Chemotherapie bei Patienten mit Tumoren des Gastrointestinaltraktes (GITs) und der eventuelle Nutzen einer Sekundärprophylaxe mit Aprepitant (Neurokinin-1-Rezeptorantagonist) sind bislang nicht beschrieben. **Patienten und Methoden:** Patienten mit GITs unter hoch oder moderat emetogener Chemotherapie erhielten eine antiemetische Standardprophylaxe mit 5-Hydroxytryptamin-3-Rezeptorantagonist und Dexamethason. Bei Auftreten von CINV > Grad 1 (gemäß National Cancer Institute-Klassifikation) wurde in den weiteren Zyklen zusätzlich Aprepitant verabreicht. **Ergebnisse:** Von 109 untersuchten Patienten entwickelten 16 (15%) akute oder verzögerte CINV. Folgende Faktoren waren mit dem Auftreten von CINV assoziiert: cisplatin-haltige Chemotherapie (15/16), weibliches Geschlecht (11/16), Alkoholabstinenz (11/16) und vorbekannte Hyperemesis gravidarum (11/16). 11 Patienten erhielten weitere Chemotherapiezyklen und 7 Patienten konnten bezüglich des Ansprechens auf eine Sekundärprophylaxe mit Aprepitant ausgewertet werden. 5 dieser Patienten zeigten ein komplettes Ansprechen der CINV (71%) und ein Patient eine Symptombesserung. **Schlussfolgerungen:** Bei den meisten der mit einer hoch oder moderat emetogenen Chemotherapie behandelten Patienten mit GIT war eine antiemetische Standardprophylaxe zum Schutz vor CINV ausreichend. Bei Versagen der Standardprophylaxe zeigte eine Sekundärprophylaxe mit Aprepitant eine gute Wirksamkeit.

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Introduction

Nausea and emesis are among the most feared side-effects of chemotherapy. During the last few decades, definite progress has been made in the management of chemotherapy-induced nausea and vomiting (CINV). The introduction of antiemetic drugs including dopamine receptor and 5-hydroxytryptamine 3 ($5HT_3$) receptor antagonists helped to prevent nausea and vomiting in a significant number of patients. However, despite treatment with $5HT_3$ antagonists a great many patients experience delayed emesis [1, 2]. According to Hesketh [3], $5HT_3$ antagonists have little activity when used to prevent cisplatin-induced delayed emesis and modest activity as antiemetic prophylaxis of delayed emesis caused by moderately emetogenic chemotherapy.

In a trial by Aapro et al. [4], palonosetron, a selective second-generation $5HT_3$ antagonist, in combination with dexamethasone showed a trend toward greater efficacy than ondansetron in preventing delayed CINV. Also in patients who failed to respond to one or two previous antiemetic treatments, the combination of palonosetron and dexamethasone seems to be safe and highly effective in controlling acute and particularly delayed CINV [5].

A few years ago, the most effective available prophylaxis for delayed emesis was the combination of a $5HT_3$ antagonist or metoclopramide with corticosteroids [6, 7]. But even with this combination, approximately 50% of patients receiving highly or moderately emetogenic chemotherapy continued to suffer from delayed vomiting and/or nausea [8–12]. Hence, there was a clear medical need for more effective prevention of CINV in patients receiving highly or moderately emetogenic chemotherapy. Aprepitant (Emend®; MSD Sharp and Dohme, Haar, Germany) antagonizes the effect of substance P on the neurokinin 1 (NK_1) receptor, and showed an increased protection against acute and delayed CINV if given as a primary prophylaxis in patients receiving highly emetogenic chemotherapy [13]. Aprepitant has also been shown to improve antiemetic control in patients receiving emetogenic non-cisplatin-based chemotherapy defined as moderately emetogenic [14]. A trial from our own group focused on health outcomes and also the cost effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. Aprepitant was found to be cost effective when combined with ondansetron plus dexamethasone. 42% of the aprepitant drug cost was offset by lower resource use in terms of lower doses of dexamethasone, reduced use of rescue medication and avoided hospitalizations in the aprepitant group. When receiving highly emetogenic chemotherapy, patients were estimated to have gained an equivalent of 15 additional hours of perfect health per cycle (0.63 quality-adjusted life days) with aprepitant-based antiemetic prophylaxis. Cost per quality-adjusted life year gained with aprepitant was estimated at € 28,891. Therefore, aprepitant substantially improved CINV-related health outcomes in patients undergoing highly emetogenic chemotherapy. Incremental benefits materialized in a cost-effective fashion [15].

To the best of our knowledge, the emetogenic burden of typical chemotherapy regimens given during the treatment of gastrointestinal tumors (GITs) and the effectiveness of a primary or a secondary antiemetic prophylaxis have not been assessed thus far and are therefore unknown.

This trial was conducted to evaluate the incidence of CINV during treatment of GITs with highly and moderately emetogenic chemotherapy receiving a standard antiemetic prophylaxis ($5HT_3$ antagonist plus dexamethasone) and to assess the effect of a secondary antiemetic prophylaxis including aprepitant after failure of first-line standard prophylaxis.

Methods

Patients ≥ 18 years with locally advanced or metastatic GITs treated with highly and moderately emetogenic chemotherapy (criteria of the Multinational Association of Supportive Care in Cancer; *www.mascc.org*) were included. Nausea and vomiting that occurred within 24 h of administration of chemotherapy was termed acute CINV. Patients who had experienced CINV ≥ 2 (according to National Cancer Institute classification) during previous treatments, e.g. during adjuvant chemotherapy or adjuvant chemoradiation, could not enter the study.

For the interventional part of this study, adequate hematologic, renal and hepatic functions were required. In case of CINV ≥ grade 2 during the first course of chemotherapy, patients were prescribed oral aprepitant administered at a dose of 125 mg on day 1, and 80 mg orally on days 2 and 3 in addition to the standard antiemetic prophylaxis ($5HT_3$ antagonist granisetron 1.5 mg intravenously (i.v.) on day 1 plus dexamethasone 12 mg i.v. on day 1 and 8 mg per os on days 2–3). Aprepitant was given until completion of chemotherapy. Data on protection from CINV were obtained from structured inquiries and diaries for the patients' self-assessment.

The primary study endpoint of the screening study was to evaluate the incidence of CINV in patients treated by guideline-based standard antiemetic prophylaxis. A secondary endpoint was to define risk factors for CINV in patients treated with chemotherapy for GITs. The primary objective of the interventional study was to assess the overall response rate for acute (day 1) and delayed (days 2–5) CINV following secondary antiemetic prophylaxis with aprepitant. Complete response was defined as complete relief from CINV; partial response was defined as a decline of CINV of at least one degree (NCI criteria). A response rate for delayed nausea and emesis of ≥ 40% was assumed and the number of patients for inclusion in this study was determined according to Gehan's two-stage design. Initially, 6 patients had to be included in the first stage of the trial to warrant a precision of 0.1 in estimation of the expected response rate of ≥ 40% with a power of 95%.

In the recruiting phase, a low prevalence of CINV was observed (see results). Therefore, the power considerations within the chosen Gehan-design were reduced to 90%, resulting in a required subtotal of 5 patients in the first stage and another 16–20 patients in the second stage. After 3 responses were observed in the first 5 patients treated with aprepitant, a total of 109 patients had to be screened to achieve the required number of 16 patients with CINV treated by standard antiemetic prophylaxis.

A one-sided exact binomial test was provided to evaluate success of therapy regarding the expected response rate. 95% confidence intervals (CI) were calculated for response rates using StatXact (version 5; Cytel, Inc., USA). All analyses were performed at a 0.05 level of significance. The trial was approved by the Ethics Committee of the Medical Faculty, Technische Universität München, Munich, Germany. All patients had to

Table 1. Highly and moderately emetogenic chemotherapy regimens administered in the study population

Regimen	Dose, mg/m^2	Patients	
		screening n = 109	included patients n = 16
Cisplatin, 5-FU, folinic acid	50/2000/500	59	12
Docetaxel, cisplatin, 5-FU, folinic acid	40/40/2000/200	7	0
Oxaliplatin, 5-FU, folinic acid	50/2000/500, 85/200/600, 85/400/200, 85/2000/500	16	0
Paclitaxel, cisplatin, 5-FU, folinic acid	80/50/2000/500	13	3
Oxaliplatin, cetuximab, 5-FU, folinic acid	50/250/2000/200, 100/250/2400/400	5	1
Irinotecan, 5-FU, folinic acid	180/2000/500, 180/2400/400	2	0
Gemcitabin, oxaliplatin	1200/100	2	0
Docetaxel, oxaliplatin, 5-FU, folinic acid	40/85/2000/200	1	0
Irinotecan, cisplatin	65/30	1	0
Capecitabine, cisplatin	2000/80	1	0
Capecitabine, oxaliplatin, cetuximab	1650/50/250	1	0
Irinotecan, cetuximab, 5-FU, folinic acid	180/250/2400/400	1	0

5-FU: 5-Fluorouracil.

provide their written informed consent for the screening part and for the interventional part of this study.

Results

We screened 109 patients with cancer of the esophagus (39%), stomach (47%), pancreas (2%) and colorectum (12%). 88 patients had locally advanced disease and 21 patients were treated for metastatic disease. Median age was 61 years (range 29–78) and 32 patients were female. 22 of the screened female patients had a history of emesis gravidarum and 35 patients in the screening group were abstinent to alcohol. In the majority of cases (87%), the therapy intention was neoadjuvant, 3 patients received adjuvant treatment and 11 patients were given chemotherapy in palliative intention. The applied chemotherapy regimens are listed in table 1. One patient was erroneously included because he received a higher dose of cisplatin (80 mg/m^2). This patient was included in the screening part of the study.

The detailed classification of acute and delayed CINV observed in the 16 patients who entered the interventional part of the study is outlined in table 2.

Patient characteristics associated with CINV were as follows: low-dose cisplatin-containing chemotherapy (15/16 pts, 1 patient was treated with an oxaliplatin-based regimen), female gender (11/16 pts), complete abstinence to alcohol (11/16 pts). All female patients who experienced CINV previously had suffered from emesis gravidarum (11/16 pts).

Eleven patients who were given further courses of chemotherapy received aprepitant (intent-to-treat population) as secondary prophylaxis. 7 patients are fully assessable for response; 4 patients did not return their study diaries. 5 patients had a complete secondary protection from CINV (per-protocol population: 71% (5/7; CI 0.29–0.96, p = 0.096), and 45% (5/11) in the intent-to-treat population; CI 0.17–0.77, p = 0.47). One patient had an improvement in emesis from grade 2 to grade 1, corresponding to a partial response. The overall response rate was 86% (6/7) (CI 0.42–0.99, p = 0.019) in the per-protocol population and 55% (6/11) (CI 0.23–0.83, p = 0.25) in the intent-to-treat population. One patient who had experienced delayed nausea grade 2 during cycle 1 had no benefit from aprepitant. This patient was female, completely abstinent to alcohol and got a cisplatin-based chemotherapy.

As we mentioned before, only one patient with a non-cisplatin-based chemotherapy regimen experienced CINV (acute nausea grade 2, delayed nausea grade 1). This patient had a complete response to a secondary prophylaxis with aprepitant.

Table 2. Acute and delayed CINV observed in the study population (one patient can be mentioned for both acute and delayed CINV)

	Patients (%)
Acute and delayed CINV	16 (15%)
Acute N grade 1	3 (3%)
Acute N grade 2	8 (7%)
Acute V grade 1	2 (2%)
Acute V grade 2	2 (2%)
Delayed N grade 1	4 (4%)
Delayed N grade 2	11 (10%)
Delayed N grade 3	3 (3%)
Delayed V grade 1	1 (1%)
Delayed V grade 2	5 (5%)

N: Nausea; V: vomiting.

Discussion

This trial showed an unexpected low rate of CINV in patients with GITs receiving highly and moderately emetogenic chemotherapy and standard antiemetic prophylaxis. In those patients who experienced CINV during cycle 1, the addition of aprepi-

tant to standard prophylaxis brought at least some relief from CINV in the majority of subjects. Known risk factors for CINV were identified.

Many GITs are treated with moderately emetogenic or cisplatin-based chemotherapy. In our trial, cisplatin ≤ 50 mg/m^2 was defined as highly emetogenic according to Hesketh [3], who categorizes cisplatin-based chemotherapy independent from dose as highly emetogenic.

The incidence rate of CINV in gastrointestinal cancer is unknown to date. The effectiveness of secondary prophylaxis of CINV using aprepitant in GITs is also undetermined. In the present trial, 85% of the chemotherapy patients treated by a primary antiemetic prophylaxis with a $5HT_3$ antagonist plus dexamethasone showed an adequate protection against CINV. To the best of our knowledge, this is the first time that the response to a standard antiemetic prophylaxis was analyzed in this specific patient population. This observation is of particular interest as one must assume that patients with GITs might be predetermined to experience nausea and emesis due to impairment of the intestinal passage caused for example by esophageal obstruction or impaired gastric emptying. Protection for acute CINV was particularly good, whereas the majority of patients who experienced CINV suffered from delayed nausea and vomiting on days 2–5.

The incidence of CINV under standard antiemetic prophylaxis was very low in comparison with other studies. In a trial by Al-Batran and colleagues [16], patients treated with oxaliplatin-based chemotherapy experienced nausea in 53% and vomiting in 31%. In case of a cisplatin-based regimen chemotherapy-induced nausea and vomiting occurred even more frequently in 70 and 52%, respectively [16]. Notably, the current trial is a single-center study. Treatment was given at a high-volume center with a particular concentration on the treatment of gastrointestinal cancers, which allows for a highly accurate implementation of standard antiemetic guidelines. The known differences between single-center experiences and multi-center trials in terms of patient selection and accuracy of treatment application make a direct comparison with reports from multi-institutional trials difficult and may explain the relatively low rate of observed CINV in our study.

In case of CINV, we could identify emetogenic risk factors that are well known from the literature [17–19], like female gender, platin-based chemotherapy, alcohol abstinence and previous emesis gravidarum. It should be pointed out that, during chemotherapy based on other than low-dose cisplatin-containing combinations, almost no significant CINV was observed. This indicates that for oxaliplatin-based regimens standard antiemetic prophylaxis with $5HT_3$ antagonists plus dexamethasone definitely seems to protect almost all patients from significant CINV. The number of patients treated by an irinotecan-based regime in this trial is too small to make a statement in this regard.

In case of failure to primary prophylaxis, aprepitant demonstrated protection against CINV in 6/7 patients (86%), which suggests that the secondary addition of aprepitant to $5HT_3$ antagonists and dexamethasone in patients failing to primary prophylaxis is associated with improved control of CINV. It is important to emphasize that the number of analyzable patients treated by aprepitant is very small. Nevertheless, this is in line with results from a trial conducted by Oechsle et al. [20] where aprepitant demonstrated significant activity in patients with nausea/vomiting refractory to prophylaxis with $5HT_3$ antagonists and dexamethasone treated with cisplatin-based chemotherapy. The number of patients with nausea for > 4 days decreased from 71 to 12% ($p < 0.001$), and the number of those with emesis for > 2 days decreased from 77 to 0% ($p < 0.001$).

It is a common observation that some patients experience anticipatory nausea and vomiting in response to a conditioned reflex – the sight, smell and sounds of the treatment room or other sensory perceptions can lead to nausea or vomiting. Therefore, it has been postulated that optimal protection from CINV from the first exposure to chemotherapy is important because otherwise anticipatory nausea and vomiting may be triggered. This hypothesis cannot be supported by the results of these two trials, but the number of patients investigated with an aprepitant-based salvage prophylaxis is clearly too small to draw definitive conclusions.

The present study assessed the activity of a standard antiemetic prophylaxis and the effectiveness of secondary addition of aprepitant in patients with GITs treated with highly and moderate emetogenic chemotherapy. In the majority of cases with GITs, primary standard antiemetic prophylaxis provided adequate protection against CINV, but it was also shown that a thorough medical history is key and that well-defined clinical risk factors may help to identify those patients who are at increased risk of developing CINV.

Our results suggest that patients presenting with particular risk factors for CINV may be considered for primary prophylaxis with aprepitant. However, in case of failure to primary standard prophylaxis, aprepitant still can protect from CINV during further chemotherapy cycles when given as secondary prophylaxis.

References

1 Roila F, Bracardia S, Tonato M, Maranglo M, Bella M, Donati D: Ondansetron in the prophylaxis of acute and delayed cisplatin-induced emesis. Clin Oncol 1990;2:268–272.

2 Hesketh P: Management of cisplatin-induced delayed emesis. Oncology 1996;1:78–85.

3 Hesketh PJ: Chemotherapy-induced nausea and vomiting. N Engl J Med 2008;358:2482–2494.

4 Aapro MS, Grunberg SM, Manikhas GM, Olivares G, Suarez T, Tjulandin SA, Bertoli LF, Yunus F, Morrica B, Lordick F, Macciocchi A: A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol 2006;17:1441–1449.

5 Massa E, Astara G, Madeddu C, Dessì M, Loi C, Lepori S, Mantovani G: Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced nausea and vomiting following highly or moderately emetogenic chemotherapy in pre-treated patients who have failed to respond to a previous antiemetic treatment: Comparison between elderly and non-elderly patient response. Crit Rev Oncol Hematol. 2008, in press.

6 Kris MG, Gralla RJ, Tyson LB, Clark RA, Cirrincione C, Groshen S: Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. J Clin Oncol 1989;7:108–114.
7 Gralla RJ, Rittenberg C, Peralta M, Lettow L, Cronin M: Cisplatin and emesis: aspects of treatment and a new trial for delayed emesis using oral dexamethasone plus ondansetron beginning at 16 hours after cisplatin. Oncology 1996;1:86–91.
8 Grunberg SM, Deuson RR, Mavros P: Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Cancer 2004;100:2261–2268.
9 The Italian Group for Antiemetic Research: Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. N Engl J Med 2000;342:1554–1559.
10 Perez EA, Hesketh P, Sandbach J: Comparison of single-dose oral granisetron versus intravenous ondansetron in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: A multicenter, double-blind, randomized parallel study. J Clin Oncol 1998;16:754–760.
11 Kaizer L, Warr D, Hoskins P: Effect of schedule and maintenance on the antiemetic efficacy of ondansetron combined with dexamethasone in acute and delayed nausea and emesis in patients receiving moderately emetogenic chemotherapy: A phase III trial by the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1994;12:1050–1057.
12 The Italian Group for Antiemetic Research: Delayed emesis induced by moderately emetogenic chemotherapy: Do we need to treat all patients? Ann Oncol 1997;8: 561–567.
13 De Wit R, Herrstedt J, Rapoport B, Carides AD, Guoguang-Ma J, Elmer M, Schmidt C, Evans JK, Horgan KJ: The oral NK_1 antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. Eur J Cancer 2004;40: 403–410.
14 Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenberg PD, Raftopoulos H, Grunberg SM, Gabriel M, Rodgers A, Bohidar N, Klinger G, Hustad CM, Horgan KJ, Skorbienda F: Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 2005;23:2822–2830.
15 Lordick F, Ehlken B, Ihbe-Heffinger A, Berger K, Krobot KJ, Pellissier J, Davies G, Deuson R: Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. Eur J Cancer 2007;43:299–307.
16 Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, Rethwisch V, Seipelt G, Homann N, Wilhelm G, Schuch G, Stoehlmacher J, Derigs HG, Hegewisch-Becker S, Grossmann J, Pauligk C, Atmaca A, Bokemeyer C, Knuth A, Jäger E; Arbeitsgemeinschaft Internistische Onkologie: Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008;26:1435–1442.
17 Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW: Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. J Clin Oncol 1999;17:2971–2994.
18 Osoba D, Zee B, Pater J, Warr D, Latreille J, Kaizer L: Determinants of post chemotherapy nausea and vomiting in patients with cancer. J Clin Oncol 1997;15: 116–123.
19 Pollera CF, Giannarelli D: Prognostic factors influencing cisplatin-induced emesis. Cancer 1989;64:1117–1122.
20 Oechsle K, Müller MR, Hartmann JT, Kanz L, Bokemeyer C: Aprepitant as salvage therapy in patients with chemotherapy-induced nausea and emesis refractory to prophylaxis with 5-HT(3) antagonists and dexamethasone. Onkologie 2006;29: 557–561.