Control of chemotherapy-induced nausea and vomiting in patients with gastrointestinal tumours

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ABSTRACT

Objectives During cancer treatment, many patients experience chemotherapy-induced nausea and vomiting (CINV), which leads to a lower quality of life and poorer adherence to the subsequent chemotherapy cycles. The aim of the study was to assess antiemetic therapy prescribing and CINV control in the acute phase (24 hours post-chemotherapy) and the delayed phase (days 2–4 post-chemotherapy). Factors influencing CINV control were also determined.

Methods Information on antiemetic premedication was gathered from patient medical records. Data regarding antiemetic therapy post-discharge and CINV control were in both phases obtained using patient questionnaires. Antiemetic therapy prescribing was compared with internal CINV prevention and control guidelines. Predictive factors for CINV control were evaluated using binary logistic regression.

Results There were 62 patients enrolled in the study, out of which 50 (80.6%) received adequate antiemetic premedication. In the acute phase, 46 (74.2%) patients reported well-controlled CINV, whereas 16 (25.8%) reported uncontrolled CINV. None of the patients was prescribed post-discharge antiemetic therapy as per guidelines. In the delayed phase, CINV was more frequent as 39 (62.9%) patients reported well-controlled CINV, whereas uncontrolled CINV was reported in 23 (37.1%) patients. The predictive factors for overall CINV control were prescription of corticosteroids (OR=9.025, $p=0.019$) and patient age (OR=0.851, $p=0.002$). The delayed CINV control was dependent on age (OR=0.885, $p=0.030$) and acute CINV control (OR=17.377, $p=0.001$).

Conclusions The majority of the patients were prescribed adequate antiemetic therapy for the acute phase but not for the delayed phase, which may have resulted in more patients experiencing delayed CINV.

INTRODUCTION

During cancer treatment, many patients experience chemotherapy-induced nausea and vomiting (CINV), which leads to lower quality of life and poorer adherence to subsequent chemotherapy cycles.^{1,2} It depends on chemotherapy-related risk factors, such as chemotherapy emetogenic potential, dosage, route of administration, duration of intravenous chemotherapy and number of chemotherapy cycles, as well as other, mainly patient-related risk factors.^{2–4} Chemotherapy emetogenic potential is defined by the proportion of patients who experience CINV in the absence of antiemetic therapy. The occurrence of CINV is expected in 90% of patients receiving chemotherapy with high emetogenic potential, 30–90% of patients with

moderate, 10–30% of patients with low and <10% of patients with minimal emetogenic potential.⁵ Additionally, patient-related risk factors for CINV are patient age, gender, alcohol consumption, anamnesis of motion or morning sickness, depression and anxiety.^{2–4}

There are different types of CINV that can occur in different phases after chemotherapy. Acute CINV occurs in the acute phase, minutes to hours after starting chemotherapy, up to 24 hours post-chemotherapy. The delayed CINV occurs more than 24 hours after administration of chemotherapy and can persist up to 7 days. The term overall CINV refers to both acute phase and delayed phase together.^{3,6} Uncontrolled CINV in previous cycles can induce anticipatory CINV that occurs before the administration of chemotherapy in the following cycle and has a strong psychogenic potential.⁷

Regular monitoring and adequate antiemetic therapy are essential for appropriate control of CINV. The most frequently used methods for CINV monitoring are patient questionnaires and patient diaries.^{2,4}

Several CINV prevention guidelines exist in clinical practice on local, national or international level. However, according to studies performed in various clinical settings, low adherence to these guidelines was reported.^{1,8,9}

At the ambulatory clinic for patients with gastrointestinal cancer (Clinical Department for Gastroenterology at the University Medical Centre Ljubljana), internal CINV prevention and control guidelines ('Guidelines') have been established in 2014, based on recognised international guidelines from National Comprehensive Cancer Network (NCCN),⁵ Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO)¹⁰ and American Society of Clinical Oncology (ASCO).¹¹ The Guidelines are available in the online supplementary tables S6–S9. Depending on the emetogenic potential, corticosteroids (dexamethasone 8–20 mg intravenously), neurokinin 1 receptor (NK₁) antagonists (aprepitant 125 mg orally), serotonin type 3 receptor (5-HT₃) antagonists (granisetron 1 mg intravenously) and benzodiazepines (lorazepam 1–2 mg intravenously) are recommended as premedication for acute CINV prevention and control. For the delayed CINV prevention and control, corticosteroids (dexamethasone 4 mg orally, from the evening on the day of chemotherapy up to 4 days after chemotherapy), NK₁ antagonists (aprepitant 80 mg orally on days 2 and 3 after chemotherapy) and dopamine antagonists (metoclopramide 10–40 mg orally daily as needed or thiethylperazine 6.5 mg orally up to 3 times daily as needed, days 2–5 after chemotherapy) are recommended post-discharge.^{5,10–12}

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The aim of the study was to assess CINV control separately in the acute phase and the delayed phase and overall. We determined the factors influencing CINV control, including consistency of antiemetic therapy with the Guidelines (altogether and by specific antiemetic groups), and other factors such as age, gender and CINV control in the acute phase.

METHODS

Study design

The prospective observational study was conducted at the ambulatory clinic for patients with gastrointestinal cancer, Clinical Department for Gastroenterology at the University Medical Centre Ljubljana, from May to July 2015.

Patients over 18 years old, treated for gastrointestinal tumours who received at least one cycle of *intravenous* (with or without *orally*) chemotherapy with high, moderate or low emetogenic potential during the study period, were eligible for inclusion in the study. Patients who received oral chemotherapy only or chemotherapy with minimal emetogenic potential were excluded from the study. All patients gave written informed consent prior to inclusion in the study.

Procedures

Information on received chemotherapy and antiemetic premedication was gathered from patient medical records. Data regarding antiemetic therapy post-discharge and the level of acute and delayed CINV control were obtained using translated MASCC Antiemesis Tool (MAT) questionnaire for the patients (available online in the supplementary material).^{13 14} The emetogenic potential of a chemotherapy regimen was defined by the antineoplastic agent with the highest emetogenic potential in the regimen, which is in accordance with the internal Guidelines.^{3 12} Patients who had not vomited nor had experienced any nausea $\geq$ level 3 (on a 10-point Visual Analogue Scale marked on the MAT questionnaire) were defined as patients with 'controlled CINV', whereas patients who had vomited or had experienced nausea $\geq$ level 3 at least once were defined as 'uncontrolled CINV'. Antiemetic therapy as well as CINV control were monitored separately for the acute phase and the delayed phase and overall. The therapy for CINV prevention and control for both the acute phase and delayed phase was termed 'overall antiemetic therapy'. Received antiemetic therapy was compared with the Guidelines, where therapy, inconsistent with the Guidelines, was defined as any difference in the antiemetic agents, regimens or doses.^{5 10 11} The anticipatory phase was not monitored.

Statistical analysis

Data on patient characteristics and data from the questionnaires were analysed using descriptive statistics. Predictive factors for the acute, the delayed and overall CINV control were evaluated using binary logistic regression with backward likelihood ratio method. All of the predictive factors included in the binary logistic regression analysis are shown in [table 1](#). Statistical analyses were carried out by statistical software SPSS for Windows, V.19.0.

RESULTS

Patients and chemotherapy

Sixty-seven (n=67) eligible patients agreed to participate in the study and 89 questionnaires were distributed. Altogether, 62 (69.7%) questionnaires from 42 patients were successfully completed and returned. Each questionnaire was treated as a separate case, since in each cycle different antiemetic therapies may have been prescribed. Among all patients, 35 (56.5%) were men

Table 1 Predictive factors included in the binary logistic regression analysis for the acute, the delayed and overall CINV control

	Acute CINV control	Delayed CINV control	Overall CINV control
Predictive factors			
Age	X	X	X
Gender	X	X	X
Acute CINV control	/	X	/
Consistency with the guidelines			
Corticosteroids—acute phase	X	X	X
NK ₁ antagonists—acute phase	X	X	X
5-HT ₃ antagonists—acute phase	X	X	X
Corticosteroids—delayed phase	/	X	X
NK ₁ antagonists—delayed phase	/	X	X
Corticosteroids—overall	/	/	X
NK ₁ antagonists—overall	/	/	X

CINV, chemotherapy-induced nausea and vomiting; 5-HT₃ antagonists, serotonin type 3 receptor antagonists (granisetron); NK₁ antagonists, neurokinin 1 receptor antagonists (aprepitant); X, the predictive factor was included in the logistic regression analysis; /, the predictive factor was not included in the logistic regression analysis.

Table 2 Chemotherapy emetogenic potential

Chemotherapy emetogenic potential; n (%)		
Low*	Moderate†	High‡
27 (43.6)	32 (51.6)	3 (4.8)

n (%), number (and percentage) of patients.

*Chemotherapy regimen: 5-fluorouracil+leucovorin; gemcitabine+paclitaxel and gemcitabine monotherapy.

†Chemotherapy regimen: cisplatin+gemcitabine; oxaliplatin+gemcitabine; oxaliplatin+epirubicin+capecitabine; oxaliplatin+capecitabine+bevacizumab and oxaliplatin+capecitabine.

‡Chemotherapy regimen: cisplatin+trastuzumab+capecitabine.

and 27 (43.5%) were women. The median age of patients was 66.5 years (range 41–81 years).

Chemotherapy regimen with regard to emetogenic potential is presented in [table 2](#). Among 62 patients, 27 (43.6%) received chemotherapy with low, 32 (51.6%) received chemotherapy with moderate and 3 (4.8%) received chemotherapy with high emetogenic potential.

CINV control

Better CINV control was achieved in the acute phase, where 16 patients experienced nausea $\geq$ level 3, out of which 3 vomited. In the delayed phase one patient experienced nausea < level 3 but vomited, while 22 patients experienced nausea $\geq$ level 3, out of which 4 vomited. Forty-six (46) and thirty-nine (39) patients had well-controlled CINV during the acute phase and the delayed phase, respectively ([table 3](#)). Data from patients' questionnaires with level of nausea and number of emetic episodes in the acute phase and the delayed phase are available online in supplementary table S10.

Consistency of antiemetic therapy with the Guidelines

[Table 4](#) shows the consistency of the antiemetic therapy with the Guidelines. All received combinations of antiemetics can be seen online in supplementary table S11.

Table 3 CINV control in the acute phase and the delayed phase and overall

	CINV; n (%)	
	Well controlled	Uncontrolled
Acute CINV	46 (74.2)	16 (25.8)
Delayed CINV	39 (62.9)	23 (37.1)
Overall	37 (59.7)	25 (40.3)

CINV, chemotherapy-induced nausea and vomiting.
n (%), number (and percentage) of patients.

Table 4 Consistency of the antiemetic therapy with chemotherapy-induced nausea and vomiting (CINV) prevention and control guidelines

	Guidelines-consistent antiemetic therapy	Guidelines-inconsistent antiemetic therapy
Acute phase	n (%)	
Corticosteroids	51 (82.3)	11 (17.7)
5-HT ₃ antagonists	62 (100)	0 (0)
NK ₁ antagonists	61 (98.4)	1 (1.6)
All	50 (80.6)	12 (19.4)
Delayed phase		
Corticosteroids	0 (0)	62 (100)
NK ₁ antagonists	61 (98.4)	1 (1.6)
All	0 (0)	62 (100)
Overall		
Corticosteroids	0 (0)	62 (100)
5-HT ₃ antagonists	62 (100)	0 (0)
NK ₁ antagonists	61 (98.4)	1 (1.6)
All	0 (0)	62 (100)

n (%), number (and percentage) of patients.

5-HT₃ antagonists, serotonin type 3 receptor antagonists (granisetron);
NK₁ antagonists, neurokinin 1 receptor antagonists (aprepitant).

In the acute phase, corticosteroids (dexamethasone) were not received in consistence with the Guidelines in 11 (17.7%) cases. All of these cases occurred in patients treated with single agent chemotherapy regimens that presented low emetogenic potential. Regardless of the received chemotherapy regimen, the prescription of corticosteroids in the delayed phase was inconsistent with the Guidelines in all cases (100%). In contrast, all patients had 5-HT₃ antagonists prescribed in consistence with the Guidelines for the acute phase. Two patients (n=2) with high and six patients (n=6) with moderate emetogenic potential received NK₁ antagonist aprepitant, suggesting that the vast majority of patients had NK₁ antagonists prescribed consistently with the Guidelines in both phases.

Influence of predictive factors on CINV control

Table 5 shows predictive factors included in the final logistic models for the acute, the delayed and overall CINV control, with the relevant statistical data.

For the acute CINV control, age and consistency of corticosteroids prescription with the Guidelines for the acute phase were included as predictive factors in the final logistic model. Both failed to show statistical significance ($p=0.052$ and $p=0.059$, respectively). One-year increase in age resulted in 7.5% risk reduction for the acute CINV. Patients with Guidelines-inconsistent corticosteroids prescription for the acute

Table 5 Final logistic models for the acute, the delayed and overall CINV control

Variable	95% CI for OR			p Value
	Lower bound	OR	Upper bound	
Predictive factors, influencing acute CIN V				
Age	0.855	0.925	1.001	0.052
Corticosteroids—acute phase	0.945	4.236	18.988	0.059
Predictive factors, influencing delayed CIN V				
Acute CIN V	3.465	17.377	87.149	0.001
Age	0.792	0.885	0.988	0.030
Gender	0.073	0.300	1.229	0.094
Predictive factors, influencing overall CIN V				
Age	0.771	0.851	0.941	0.002
Corticosteroids—acute phase	1.446	9.025	56.347	0.019

CINV, chemotherapy-induced nausea and vomiting; Corticosteroids—acute phase, consistency of corticosteroids prescription with the Guidelines for the acute phase.

phase indicated 4.2 times risk growth for the acute CINV occurrence, compared with patients with Guidelines-consistent therapy regimen.

For the delayed CINV control, age, gender and acute CINV control were included as predictive factors in the final logistic model. Patients with acute CINV had 17.4 times higher probability to experience delayed CINV ($p=0.001$) than those with controlled acute CINV. There was 11.5% risk reduction for delayed CINV with every 1-year increase in age ($p=0.030$). Gender did not demonstrate statistical significance; however, an unexpected trend towards higher risk for men compared with women (70% increase in risk, $p=0.094$) was observed.

For overall CINV control, the age and corticosteroids prescription consistent with the Guidelines for the acute phase were included as predictive factors in the final logistic model. Both were statistically significant, with p values equal to 0.002 and 0.019, respectively. One-year age increase resulted in 14.9% risk reduction of overall CINV. Patients with Guidelines-inconsistent corticosteroids for the acute phase showed 9 times higher risk for overall CINV compared with patients receiving corticosteroids for the acute phase.

DISCUSSION

Patients and chemotherapy

Patients treated in one of the main centres for gastrointestinal tumours in Slovenia were followed in this prospective study. In Slovenia, the prevalence of patients with gastrointestinal tumours is 645 per 100 000 inhabitants. Of the patients with gastrointestinal tumours, 55.8% are men and 44.2% women.¹⁵ In this respect, our study sample represents the national population of patients with gastrointestinal cancer relatively well, despite the fact that the majority of these patients (also depending on the type of treatment) receive chemotherapy in other centres. The study population was mainly represented by older patients, since the frequency of gastrointestinal tumours increases with patient age.¹⁶

CINV control

CINV control was described in two groups of patients: those with well-controlled CINV and those with uncontrolled CINV. The similar principle has been used in several other studies.^{14 17 18} In our study, score ≥ 3 on a 10-point Visual

Analogue Scale for nausea was used as the limit value between well-controlled CINV and uncontrolled CINV, based on the study performed by Hsieh *et al.*¹⁴ In that study, the same score was used for defining ‘clinically significant nausea’. An additional criterion for the well-controlled group in our study was the absence of vomiting, which has not been reported in similar studies. Delayed CINV control was less well controlled, which could be partly due to the Guidelines-inconsistent antiemetic therapy for the delayed phase (see below).

Consistency of antiemetic therapy with the Guidelines

We reviewed the consistency of antiemetic therapy with the Guidelines for all groups of antiemetics—separately for corticosteroids, NK₁ antagonists and 5-HT₃ antagonists, and altogether, for the acute, the delayed phase and overall. For the acute phase, the consistency to the Guidelines was higher than for the delayed phase. Patients received corticosteroids and 5-HT₃ antagonists *intravenously*, whereas aprepitant was administered *orally* in premedication. Of the three groups, there was a low, but nevertheless relevant deviation from the Guidelines observed for the acute phase only for corticosteroids. On the other hand, for the delayed phase, when corticosteroid dexamethasone should have been prescribed and administered *orally*, none of the patients received it consistently with the Guidelines. In comparison with previous studies, consistency of antiemetic therapy with the Guidelines was not evaluated separately for each antiemetic group. Aapro *et al* discovered 55% and 46% of patients received antiemetic therapy consistent with the Guidelines during acute and delayed phases, respectively.¹⁷ Similar results were also observed by Caracul *et al.*¹ Our results showed higher consistency with the Guidelines for the acute phase (80.6%), but lower for the delayed phase (0%) due to the discrepancies in the prescription of corticosteroids.

Regarding the NK₁ antagonists, in patients receiving chemotherapy with high emetogenic potential, aprepitant was prescribed in two cases. The reason it was not prescribed for the third patient could not be established. Aprepitant was also prescribed in six patients receiving chemotherapy with moderate emetogenic potential. In these cases, administration of aprepitant is based on physician’s clinical judgement, depending on the presence of additional risk factors for CINV, which in our study, apart from age and gender, were not possible to monitor systematically. Therefore, all patients with moderately emetogenic chemotherapy were attributed to the Guidelines-consistent group for NK₁ antagonists.

Dopamine antagonists and benzodiazepines could not be assessed because of the pro re nata prescribing recommendation defined in the Guidelines. Even though diazepam was being prescribed without justification instead of lorazepam (with the latter being recommended in the Guidelines), patients receiving diazepam were not attributed to the Guidelines-inconsistent group for benzodiazepines.

Influence of predictive factors on CINV control

The predictive factors included in the final logistic models for the acute and overall CINV control were the consistency of corticosteroids with the Guidelines for the acute phase and patient age. The final logistic model for the delayed CINV control included the acute CINV control, age and gender. The acute CINV control was only considered as a predictive factor for the delayed CINV control, as overall, it was already incorporated in the term ‘overall CINV control’ by definition.

Younger patients in our study were at higher risk for CINV occurrence, which is consistent with the literature data.^{1 2 5}

It was established that the gender influenced CINV control opposite to the literature data, as women showed lower risk for CINV occurrence.^{1 2 5} However, statistical significance in our study was not detected.

We concluded that consistency of corticosteroids with the Guidelines for acute phase affects the overall CINV control. Due to insignificant p values, we could not definitely confirm the relationship with the acute CINV control. Nevertheless, a visible trend towards influence on the acute CINV control was observed. Certain planned risk factors analyses were not possible, due to the high level of Guidelines-consistent or inconsistent antiemetic therapy, for example, all patients had Guidelines-consistent 5-HT₃ antagonists for the acute phase and Guidelines-inconsistent corticosteroids for the delayed phase; only one patient had Guidelines-inconsistent NK₁ antagonists in any phase.

Study limitations

The major limitation of our study was the relatively small study sample, due to short study period, and limited number of patients who received therapy at the ambulatory clinic. A longer study could have provided more reliable results and would probably have increased the statistical significance; therefore, studies on large scale are warranted. Second, the selected study sample was based only in one Medical centre and therefore conclusions on the national level could have been unjustified. Third, uncontrolled CINV in previous cycles of chemotherapy, which could have affected CINV control in the following cycles was not monitored in our study. We followed each chemotherapy cycle as a separate case, since in each cycle different antiemetic treatments may have been prescribed. Moreover, to confirm the benefit of strict adherence to the Guidelines, a follow-up study would be reasonable.

Conclusions

Ambulatory clinic for patients with gastrointestinal cancer did not fully adhere to the CINV prevention and control guidelines. The situation with antiemetic premedication was better than

Key messages

What is already known on this subject

- ▶ Chemotherapy-induced nausea and vomiting (CINV) can be successfully prevented or treated using different types of antiemetic drugs and their combinations.
- ▶ Patients with gastrointestinal tumours are treated with various chemotherapy regimens that demonstrate different emetogenic potentials, from minimal to high.
- ▶ Chemotherapy-related risk factors for CINV, such as emetogenic potential, route of administration, number of chemotherapy cycles and patient-related risk factors, such as age and gender, are well recognised.

What this study adds

- ▶ Antiemetic prescription for the treatment of patients with gastrointestinal cancer for the acute phase was guidelines consistent. In the delayed phase, corticosteroids were not prescribed as per guidelines.
- ▶ Overall predictive factors for CINV control in patients with gastrointestinal tumours were prescription of corticosteroids and age, whereas the delayed phase was dependent on age and acute CINV control.

post-discharge. To a certain extent, lack of CINV control could be attributed to inadequate antiemetic therapy; however, other risk factors affected CINV control as well. Implementing regular monitoring of CINV, for example, using a standardised questionnaire for patients with gastrointestinal cancer might be rational. By identifying higher risk patients, their antiemetic treatment and therefore CINV control might be improved.

Contributors RBs contribution to the research: acquisition, analysis and interpretation of data, design of the work, drafting the manuscript. TVs contribution to the research: design of the work, critical revision of the draft manuscript. BŠs contribution to the research: allowing access to the research site, patients and medical records, critical revision of the draft manuscript. MDVs contribution to the research: design of the work, analysis of data, critical revision of the draft manuscript.

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