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Chi-Ting Liau
Nei-Min Chu
Hsueh-Erh Liu
Robert Deuson
Jade Lien
Jen-Shi Chen

Incidence of chemotherapy-induced nausea and vomiting in Taiwan: physicians' and nurses' estimation vs. patients' reported outcomes

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C.-T. Liau · J.-S. Chen (✉)
Department of Internal Medicine,
Division of Hematology–Oncology,
Chang Gung Memorial Hospital,
199, Duenhua North Road,
Sungshan Chiu,
Taipei, Taiwan, 105, Republic of China
e-mail: js1101@adm.cgmh.org.tw
Tel.: +886-3-3281200
Fax: +886-3-3278211

N.-M. Chu
Division of Hematology and Medical Oncology, Koo Foundation Sun Yat-Sen Cancer Center,
Taipei, Taiwan

H.-E. Liu
School of Nursing,
Chang Gung University,
Tao-Yuan,Taiwan

R. Deuson
Outcomes Research, Merck & Co., Inc.,
Whitehouse Station, NJ, USA

J. Lien
Medical Department, Merck,
Sharp & Dohme (I.A.) Corp.,
Taipei, Taiwan

Abstract *Background:* The major objective of the study was to determine the incidence and prevalence of acute and delayed chemotherapy-induced nausea and vomiting (CINV) among patients receiving chemotherapy and assess the accuracy with which medical providers perceive the incidence of CINV in their practice. *Methods:* Specialists, residents and nurses (medical providers) from two cancer centers in Taiwan estimated the incidence of acute and delayed CINV. Chemotherapy-naïve patients from the same centers then completed a 5-day nausea and vomiting diary following highly and moderately emetogenic chemotherapy (HEC and MEC) to determine the actual incidence of acute and delayed CINV. Daily nausea ratings were recorded on a 100-mm visual analogue scale (VAS). No nausea was defined as a nausea VAS score <5 mm. Vomiting episodes were also recorded. Nausea and vomiting were defined as acute and delayed based on whether they occurred during the first 24 h after chemotherapy, or during days 2–5 after chemotherapy, respectively. *Results:* In the two oncology centers, 37 medical providers (13 specialists, 4 residents, 20 nurses) and 107 patients were enrolled. The mean patient age was 49.2 years with 76% female and 74% having breast cancer. Of the 107 patients, 39% received HEC and 61% received MEC, and 77% received a 5-HT3 receptor antagonist and 94% received dexamethasone. There were no significant differences between patients with acute CINV and delayed CINV in terms of demographics, chemotherapy treatment or antiemetic treatment. The proportion of patients without alcohol use was significantly higher among patients with delayed CINV than among those with non-delayed CINV. Good control of CINV during the acute period correlated with the control of delayed emesis. There were no significant differences between specialists', residents', and nurses' estimations of the incidence rates of CINV. For HEC given to chemotherapy-naïve patients, the medical providers estimated acute CINV to be 44/41% and delayed CINV to be 61/53%, respectively. However, patient diaries revealed acute CINV to be 43/21% and delayed CINV to be 64/60%, respectively. For MEC given to chemotherapy-naïve patients, medical providers estimated acute CINV to be 39/36% and delayed CINV to be 44/39%, respectively. However, patient diaries revealed acute CINV to be 55/18% and delayed CINV to be 74/55%, respectively. *Conclusions:* Medical providers significantly overestimated the incidence of acute vomiting by 20% and 18% in HEC and MEC patients, respectively. While they correctly estimated the rate of delayed vomiting in HEC patients, they underestimated it by 16% in MEC patients. With respect to nausea, medical providers correctly estimated rates of both acute and delayed nausea in HEC patients, but significantly underestimated rates of acute and delayed nausea by 16% and 30%, respectively, in MEC patients.

Keywords Antiemetic · Chemotherapy · Incidence · Emetogenic · Perception · Delayed

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common complication of cancer treatment, affecting 70–80% of patients [1]. CINV has a significant impact on patients' functional status, compliance with chemotherapy, and costs. Patients may delay scheduled chemotherapy or even refuse potentially curative therapy because of the distress resulting from CINV [2]. Patients who have CINV in their first cycle of chemotherapy tend to have more severe symptoms with each subsequent cycle [3, 4].

There are certain factors that affect the risk of CINV, including sex, alcohol intake, age, history of motion sickness, pregnancy sickness or previous CINV, and factors related to the chemotherapeutic treatment [5–8]. Of these factors, the intrinsic emetogenicity of the chemotherapy is the most important. According to the Hesketh classification, these agents are classified into five levels of emetogenicity, which define their probability of inducing acute CINV in the absence of effective antiemetic prophylaxis [9]. An algorithm has been devised to estimate the potential risk of combination treatments, based on the individual agents comprising it. These classifications and algorithms have been used as the basis for numerous antiemetic treatment guidelines and are frequently referred to in clinical research.

CINV can be classified as acute, delayed, or anticipatory. Acute CINV is defined as occurring within 24 h of chemotherapy. Delayed CINV is usually defined as commencing more than 24 h after administration of chemotherapy and may persist for 6–7 days [2, 10]. Patients who experience acute emesis with chemotherapy are significantly more likely to have delayed emesis. Evidence suggests that good control of acute CINV, particularly during the initial treatment received by chemotherapy-naïve patients, has a positive impact on the control of delayed and, by extrapolation, anticipatory symptoms, as well as of acute- and delayed-onset emesis associated with subsequent cycles of treatment [11–13].

Different mechanisms appear to be responsible for emesis after chemotherapy or radiotherapy and for anticipatory vomiting. The 5-HT3 receptor antagonists, especially ondansetron, in combination with dexamethasone appear to be the most commonly used regimen to treat emesis following chemotherapy with cisplatin [14, 15]. Although the introduction of 5-HT3 receptor antagonist antiemetics has apparently led to a significant reduction in the frequency of post-treatment vomiting, CINV refractory to treatment with 5-HT3 is still a clinical problem for oncologists. A recent survey suggests that physician and nurses often underestimate the occurrence of CINV in cancer patients [16]. This may result from the fact that many health-care professionals no longer consider CINV to be a major clinical problem. Further progress will depend upon an accurate understanding of the present magnitude of the problem. To answer these concerns, we conducted a prospective study to determine oncologists' and oncology nurses' estimates of the extent of CINV in general routine practice, and to determine the proportion of patients still experiencing acute and delayed CINV despite receiving antiemetic prophylaxis.

Patients and methods

Patients

From July to December 2002, all adult patients scheduled to receive highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) for the first time at one of two medical oncology divisions (Chang Gung Memorial Hospital and Koo Foundation Sun Yat-Sen Cancer Center) were enrolled into the study. This survey was reviewed and approved by the institutional review boards of both centers. Written inform consent was obtained from all patients prior to study entry.

As this study was observational in nature, few restrictions were placed on patients' entry into the study. Patients were eligible for the study if they met the following criteria: never received chemotherapy treatment before study entry; male or female; 18 years of age or older; treated with single-agent therapy, or a combination therapy that had an overall emetogenic level of 3, 4 or 5 according to the Hesketh classification [9]; willing to participate in the study, and signed a consent form; willing and able to complete the study forms (i.e., patients' diary) and visual analogue scales (VAS).

Patients were not included in the study if they met any of the following criteria: had vomited during the 24 h prior to their first chemotherapy treatment cycle; were scheduled to receive multiple-day chemotherapy treatment, either as an inpatient or outpatient; had received radiation therapy to the abdomen; had medical conditions such as cancer with brain metastasis, hypercalcemia and intestinal obstruction, which themselves may cause nausea and vomiting; had a life expectancy of less than 3 months.

Treatments

Chemotherapy agents

Chemotherapy regimens were prescribed in accordance with guidelines issued at each institution for each type and stage of cancer. Single antineoplastic agents were classified by emetic risk level (Table 1). For combinations, the emetogenic level was determined by identifying the most emetogenic agent in the combination and then assessing the relative contribution of the other agents (Table 2). The following rules were applied: (1) level-1 agents did not con-

Table 1 Hesketh definition of emetogenic potential of chemotherapeutic agents and combination therapy

Emetogenic potential	Single agent
High emetic risk, levels 4 and 5 (>60% frequency of emesis[a])	Carmustine >250 mg/m^2
	Cisplatin ≧50 mg/m^2
	Cyclophosphamide >750 mg/m^2
	Dacarbazine
	Carboplatin
	Doxorubicin >60 mg/m^2
	Methotrexate >1000 mg/m^2
	Procarbazine (oral)
Moderate emetic risk, level 3 (30–60% frequency of emesis[a])	Cyclophosphamide <750 mg/m^2
	Cisplatin <50 mg/m^2
	Doxorubicin 20–60 mg/m^2
	Epirubicin <90 mg/m^2
	Hexamethylmelamine (oral)
	Ifosfamide
	Methotrexate 250–1000 mg/m^2
	Mitoxantrone <15 mg/m^2
Low emetic risk, level 2 (10–30% frequency of emesis[a])	Docetaxel
	Etoposide
	5-Fluorouracil <1000 mg/m^2
	Gemcitabine
	Methotrexate <250 mg/m^2
	Mitomycin
	Paclitaxel
No emetic risk, level 1 (<10% frequency of emesis[a])	Bleomycin
	Hydroxyurea
	Methotrexate ≦50 mg/m^2
	Vinblastine
	Vincristine
	Vinorelbine

[a]Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
Adapted with permission from Hesketh et al. [9]

tribute to the emetogenic level of a combination; (2) adding one or more level-2 agent increased the emetogenicity of the combination by one level greater than the most emetogenic agent in the combination; and (3) adding level-3 or -4 agents increased the emetogenicity of the combination by one level per agent [9]. Patients were treated with single-agent therapy or a combination therapy that had an overall emetogenic level of three, four or five according to the Hesketh classification. Patients were further divided in two groups: those who received HEC (level 4–5) and those who received MEC (level 3).

Table 2 Combination emetogenicity level

Emetogenic levels of individual agents	Combination level
2+2	3
2+2+2	3
3+2	4
3+2+2	4
3+3+3	5

Antiemetic agents

Antiemetic regimens were also prescribed according to ASCO recommendations for the use of antiemetics and followed at each institution [17]. Guidelines were applied to both HEC-treated patients and MEC-treated patients and usually included dexamethasone in combination with a 5-HT3 antagonist or metoclopramide (Table 3).

Study design

This was a prospective observational study among cancer chemotherapy patients receiving their first cycle of MEC or HEC. MEC was defined as Hesketh level 3 emetogenic potential, and HEC was defined as Hesketh levels 4–5 emetogenic potential. The data for this study were collected from three sources: oncologists, their nurses, and patients. Sample size and power calculations are essentially irrelevant in this observational study as they are based on treatment group differences. Based on previous experience with this type of study, we recruited approximately 50 patients per site. A 20% attrition rate was to be expected (for a variety of reasons such as: incomplete or inaccurate data, patient's withdrawal, accidental violation of inclusion and/or exclusion criteria, etc.).

Table 3 Antiemetic prophylaxis and rescue guidelines by level of emetic risk, days 1–5 (integrated with local reimbursement guidelines)

Level of emetic risk	Antiemetic guidelines
Level 4–5: high emetic risk	Start before chemotherapy, repeat daily for fractionated doses of chemotherapy: dexamethasone 20 mg IV day 1, 8 mg daily or 4 mg twice daily orally or IV days 2–5 and 5-HT3 antagonist: ondansetron 16–24 mg orally or 8 mg IV day 1, ±8 mg orally or IV daily days 2–5 or tropisetron 5 mg orally or IV day 1, ±same dose daily days 2–5 ±lorazepam 0.5–1 mg orally or IV every 6 h days 1–5
Levels 3: moderate emetic risk	Dexamethasone 12 mg orally or IV day 1, ±8 mg daily or 4 mg twice daily orally or IV days 2–5 ±metoclopramide 10–20 mg orally or IV every 6 h days 1–5 ±diphenhydramine 25–50 mg orally or IV every 6 h days 1–5

Assessment tools

The patients' sociodemographics, cancer type and stage, chemotherapy regimen, prescribed antiemetic medications (for acute and delayed phases), and comorbid conditions were recorded by the study coordinator on a form at study entry. The incidence of CINV and its impact on the patients' daily life were evaluated using the self-assessment tools described below. The patients were given both oral and written instructions by the oncology nurse on using these tools.

Patient diary

Patients were given a 5-day diary in which to record daily episodes of CINV. All episodes of vomiting and retching (dry heaves) occurring between days 1 and 5 following the administration of chemotherapy were recorded by the patient with date and time. During that same period, patients also reported any rescue antiemetic therapy taken, in addition to the antiemetic medication that was prescribed at baseline, giving the name and dose and the date and time of administration. Patients assessed their level of nausea using the VAS described below. The patient diary was translated from English to Chinese and culturally validated for use in Taiwan.

Visual analogue scale (VAS)

Patients used a nongraduated 100-mm horizontal VAS to assess their level of nausea for the first 24 h following chemotherapy treatment (day 1) and for days 2–5. This scale was anchored at 0 mm (left side of the scale) and 100 mm (right side of the scale) corresponding to no nausea and nausea as bad as it can be, respectively. Patients were asked to draw a vertical mark on the horizontal line at a point corresponding to their self-assessed level of nausea. The VAS score was taken as the distance in millimeters from the left side of the scale (0 mm) to the patient's vertical mark. Scores of 5 mm and higher were considered as indicative of nausea, and scores of 25 mm or higher indicative of significant nausea [18, 19].

Medical provider survey

In the two oncology centers, 37 medical providers (13 specialists, 4 residents, 20 nurses) were enrolled in the study. The percentage of patients experiencing nausea or vomiting while receiving HEC or MEC with concurrent antiemetic agents were recorded before the start of the study using a self-administered questionnaire used in an earlier study [16] and validated for Taiwan.

Study outcomes

No nausea was defined as a VAS score of <5 mm on the 100-mm scale. A patient was considered to have had acute nausea or delayed emesis if he/she reported a VAS score ≥5 mm or at least one episode of emesis during the first 24 h after chemotherapy treatment. Similarly, a patient was considered to have had delayed nausea or acute emesis if he/she reported a VAS score ≥5 mm or at least one episode of emesis during days 2–5 after chemotherapy treatment.

Analysis

Descriptive analysis was used to describe patients' characteristics and chemotherapy and antiemetic treatment patterns. To compare differences between acute CINV or not and between delayed CINV or not, we calculated two sample *t*-tests for continuous variables and used the chi-squared test or Fisher's exact test for categorical variables. Because of the small sample size, we tested differences in the mean time to the first vomiting episode using the Wilcoxon rank sum test or the Kruskal-Wallis test. The chi-squared test was used to compare the oncologists' and nurses' estimation of CINV with the patients' reported outcomes. All of the statistical comparisons were carried out with a two-tailed test at a 5% level of significance.

Results

Patient disposition

A total of 110 patients were enrolled in the study between July and December 2002. Of these, three patients were excluded for evaluation: two were associated with early deterioration of their condition and one did not complete the patient's diary. The characteristics of the remaining 107 remaining patients are discussed below.

Patient demographics

The patients had a mean age of 49.2±9.5 years (Table 4), and 75.7% were female. Most patients (93.5%) did not consume alcoholic beverages and 94.4% did not experience motion sickness. The most common primary cancer site was the breast (73.8%), followed by the head and neck (14%). Nearly half the patients were diagnosed in stage II (48.6%) and the other half in stages III (25.2%) and IV (22.4%). The most frequent concurrent illnesses for all patients were hypertension (6.5%) and diabetes mellitus (3.7%).

Table 4 Patient characteristics (n=107)

Demographic characteristics	Mean±SD	Number of patients (%)
Age (years)		
Total	49.15±9.52	
Male	51.85±9.91	
Female	48.28±9.28	
Sex		
Male		26 (24.3)
Female		81 (75.7)
Alcohol use		
Yes		7 (6.5)
No		100 (93.5)
Motion sickness		
Yes		6 (5.6)
No		101 (94.4)
Types of primary tumor		
Breast		79 (73.8)
Liver		2 (1.8)
Head and neck		15 (14)
Nasopharynx		9 (8.4)
Prostate		1 (0.9)
Metastases of unknown origin		1 (0.9)
Stage of cancer		
Stage I		4 (3.7)
Stage II		52 (48.6)
Stage III		27 (25.2)
Stage IV		24 (22.4)
Concurrent illnesses		
Diabetes mellitus		4 (3.7)
Hypertension		7 (6.5)
Heart failure		1 (0.9)
Asthma		1 (0.9)
Chemotherapy		
Highly emetogenic		42 (39.3)
Moderately emetogenic		65 (60.7)
Antiemetics		
Dexamethasone		101 (94.4)
Metoclopramide		79 (73.8)
Diphenhydramine		22 (20.6)
5-HT3 antagonists		82 (76.6)

Treatment patterns

Chemotherapy treatments

Of the 107 patients, 42 (39.3%) received HEC and 65 (60.7%) received MEC. On average, patients receiving HEC were given 2.74 agents and those receiving MEC received 2.34 agents. Nearly all those receiving HEC and 83% of those receiving MEC were given at least two cytotoxic drugs (Table 5).

Antiemetic prophylaxis

All patients received antiemetic prophylaxis: 94% received dexamethasone; 74% metoclopramide; 21% diphenhydramine; 77% a 5-HT3 antagonist (Table 4). The pattern of antiemetic prophylaxis differed for both HEC- and MEC-treated patients with respect to the combination dexamethasone, metoclopramide and 5-HT3 antagonist: 8/37 HEC patients (19.1%) vs 29/37 MEC patients (44.6%). Similarly, twice as many HEC-treated patients as MEC-treated patients received combinations of dexamethasone, diphenhydramine and a 5-HT3 antagonist, with or without metoclopramide (Table 5). Overall, antiemetic prophylaxis and guidelines were followed in both oncology centers in this study.

Patient-reported outcomes

Incidence of nausea

Patients recorded their mean VAS scores in both acute and delayed phases as shown (Fig. 1). Incidence rates of CINV as reported by patients in their diary and on the VAS scale are summarized in Table 6. As seen in this table, 43% of HEC patients experienced acute (day 1, postchemotherapy) nausea and 64% delayed nausea (days 2–5, postchemotherapy), despite antiemetic prophylaxis. Among MEC patients, 55% and 74% reported acute and delayed nausea, respectively. Patients treated with HEC or MEC reported nausea (VAS >5 mm) and significant nausea (VAS >25 mm) throughout the acute and delayed phases for a period of 5 days after chemotherapy, peaking on day 2. Slightly more patients treated with MEC reported higher levels of nausea (as measured by the VAS) than patients treated with HEC.

Incidence of vomiting

The incidence of vomiting (emesis) is also shown in Table 6. Observed incidence rates of emesis in the acute phase averaged 21% and 18% in HEC and MEC patients, respectively, while in the delayed phase rates averaged 60% and 55% in HEC and MEC patients, respectively. As for nausea, postchemotherapy vomiting episodes peaked on day 2 with 44/107 patients (41%) vomiting on average twice (Fig. 2).

Antiemetic rescue therapy

Despite the administration of adequate antiemetic prophylaxis, these relatively high incidence rates of CINV,

Table 5 Chemotherapy treatment and antiemetic prophylaxis (*dex* dexamethasone, *diph* diphenhydramine, *MCP* metoclopramide)

Characteristic	All patients		Patients receiving HEC		Patients receiving MEC	
	Percent	Number	Percent	Number	Percent	Number
Chemotherapy agents[a]						
Number of agents used per patient (mean±SD)	2.50±0.69		2.74±0.50		2.35±0.76	
Patients receiving at least two agents	88.8	95	97.6	41	83.1	54
Antiemetic medication						
Dex	0.9	1	2.4	1	0.0	0
Diph	0.0	0	0.0	0	0.0	0
MCP	0.9	1	0.0	0	1.5	1
5-HT3 antagonist	2.8	3	7.1	3	0.0	0
Others[b]	0.0	0	0.0	0	0.0	0
Diph+MCP	0.9	1	0.0	0	0.0	0
Dex+others	1.9	2	2.4	1	1.5	1
Dex+5-HT3	10.3	11	9.5	4	10.8	7
Dex+MCP	20.6	22	21.4	9	20.0	13
Dex+5-HT3+others	0.9	1	0.0	0	1.5	1
Dex+MCP+others	4.7	5	2.4	1	6.2	4
Dex+MCP+5-HT3	34.6	37	19.1	8	44.6	29
Dex+diph+5-HT3	8.4	9	14.3	6	4.6	3
Dex+diph+MCP	2.8	3	2.4	1	3.1	2
Dex+diph+MCP+5-HT3	8.4	9	11.9	5	6.2	4
Dex+diph+MCP+5-HT3+others[b]	0.9	1	2.4	1	0.0	0
Number of observations	107		42		65	

[a]The number of different agents that the patient was treated with during the first cycle; it does not include the same agent reported more than once even if it was given at a different dose

[b]Lorazepam, prochlorperazine

especially in the delayed phase, called for antiemetic rescue therapy. In the acute phase 25 patients (23.4%) received rescue therapy, 24 receiving it again in the delayed phase. In the delayed phase, 70–75 patients received an average of 2.6 rescue medications during days 2–5 (Fig. 3).

Healthcare providers' prediction of CINV

In the two oncology centers, 37 medical providers (13 specialists, 4 residents, 20 nurses) were enrolled in the study. Their estimation of the percentage of patients experiencing CINV while receiving HEC or MEC with con-

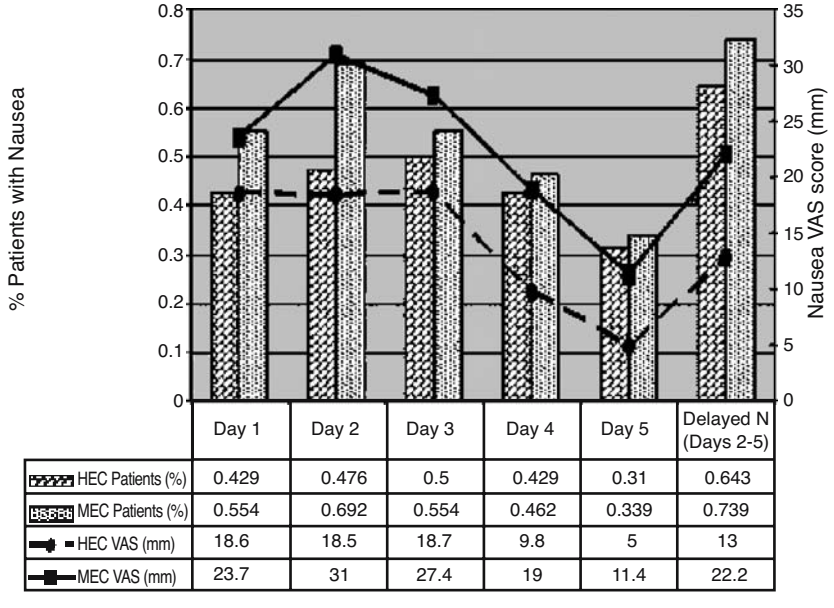

Fig. 1 Nausea: postchemotherapy mean VAS scores per day for HEC (n=42) and MEC (n=65) patients

Table 6 Incidence rates of nausea and emesis and 95% confidence intervals (CI)

Patient group	Sample size	With condition	Without condition	Observed incidence rates	
				Mean	95% CI
HEC (39%)					
Acute nausea	42	18	24	0.43	0.28–0.76
Delayed nausea	42	27	15	0.64	0.50–0.52
Acute emesis	42	9	33	0.21	0.09–0.96
Delayed emesis	42	25	17	0.60	0.45–0.57
MEC (61%)					
Acute nausea	65	36	29	0.55	0.43–0.59
Delayed nausea	65	48	17	0.74	0.63–0.38
Acute emesis	65	12	53	0.18	0.09–0.97
Delayed emesis	65	36	29	0.55	0.43–0.59

current antiemetic agents were recorded (Table 7). Specialists', residents', and nurses' estimations of CINV showed high agreement with the evaluation of patients. There was no significant difference among the medical providers' estimations.

Comparison of patients' actual responses and estimations from oncologists and nurses are also shown in Table 7. For HEC given to chemotherapy-naïve patients, medical providers correctly estimated the level of nausea experienced by patients in the acute (44% vs 43%, NS) and delayed (61% vs 64%, NS) phases, when compared with patients' reported outcomes. This was the case also with respect to vomiting in the delayed phase (53% vs 60%, NS). However, medical providers estimated that 41% of patients had acute vomiting, while only 21% of patients reported acute vomiting ($P<0.001$).

For MEC given to chemotherapy-naïve patients, medical providers under-estimated incidence rates of acute (39%) and delayed (44%) nausea while patients reported 55 and 74% delayed nausea ($p=0.023$ and $p<0.001$, respectively).

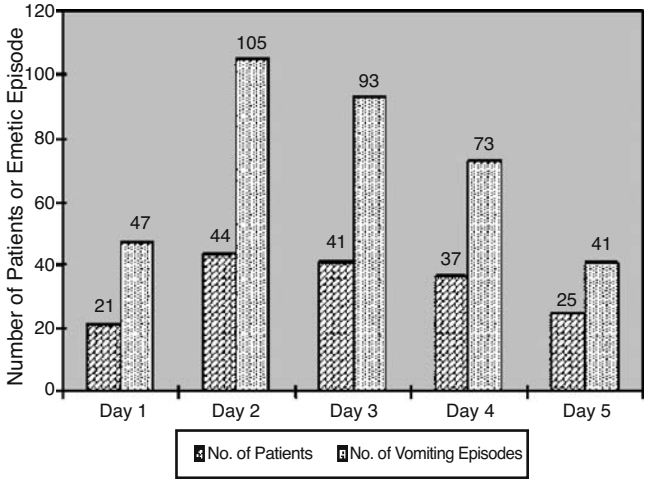

Fig. 2 Postchemotherapy vomiting episodes in 107 patients

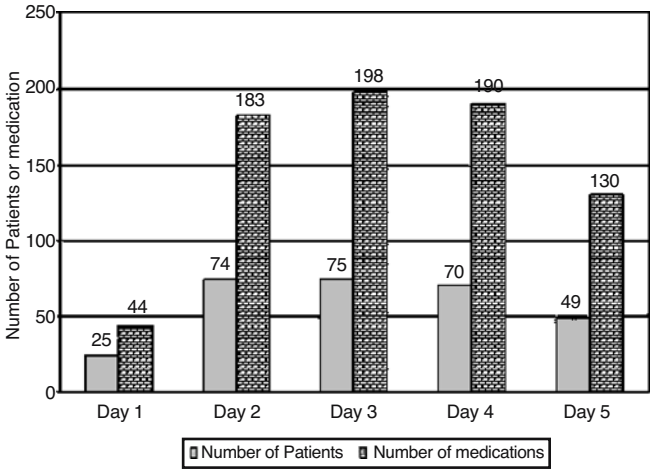

Fig. 3 Rescue antiemetics per day (107 patients)

Table 7 Comparison of patients' actual responses and estimations by oncologists and nurses

Chemotherapy		Specialists, residents and nurses (n=37)	Patients (n=107)	P value (chi-squared test)
HEC (n=42)	Nausea (%)			
	Day 1	44.1	42.9	0.395
	Days 2–5	61.4	64.3	0.560
	Vomiting (%)			
	Day 1	40.7	21.4	<0.001
	Days 2–5	53.0	59.5	0.475
MEC (n=65)	Nausea (%)			
	Day 1	39.1	55.4	0.023
	Days 2–5	43.5	73.9	<0.001
	Vomiting (%)			
	Day 1	36.1	18.5	0.004
	Days 2–5	39.2	55.4	0.023

Medical providers over-estimated rates of acute (36% vs. 18%, $p<0.004$) vomiting when compared with patients' reported rates. However, in the delayed phase medical providers under-estimated vomiting rates (39% vs. 55%, $p<0.023$).

Discussion

Adequate control of CINV is very important in determining patient compliance with either HEC or MEC. Marked progress in the prevention of CINV has been achieved over the past decade. Acute CINV is controlled successfully with a combination of a steroid and a 5-HT3 receptor antagonist or metoclopramide. As a result, many health-care professionals no longer believe CINV to be a major clinical problem. However, the results of this study contradict such a belief.

Emesis, or vomiting, is easily measured by counting the number of vomiting episodes, but levels of nausea can only be determined by the patient. Various questionnaires, using either VAS or categorical scales, are in widespread use [17, 19–22]. Before the start of the study, medical providers (oncology specialists, residents and nurses) were asked to estimate the percentage of patients they expected to experience CINV on the first day (acute phase) and on days 2–5 (delayed phase) after chemotherapy among those who received HEC or MEC. These estimations were then compared with actual incidence rates of CINV as reported by the patients. There was no significant difference among specialists', residents', or nurses' estimation of incidence rates. Hence these estimated incidence rates were combined and compared with patient-reported rates. Significant differences between estimated and reported rates were tested using the Chi-squared test ($P<0.05$). Medical providers significantly overestimated the incidence of acute vomiting by 20% and 18% in HEC and MEC patients, respectively. While they correctly estimated the rate of delayed vomiting in HEC patients, they underestimated it by 16% in MEC patients. With respect to nausea, medical providers correctly estimated rates of both acute and delayed nausea in HEC patients but significantly underestimated rates of acute and delayed nausea by 16% and 30%, respectively, in MEC patients.

These findings are only partly consistent with those of an earlier study [16]. Grunberg et al. compared incidence rates of CINV estimated by 24 physicians and nurses with incidence rates reported by 298 patients (67 receiving HEC and 231 receiving MEC). More than 35% of the patients overall experienced acute nausea, whereas 13% experienced acute emesis. Delayed nausea and emesis were observed in 60% and 50% of HEC patients, respectively, and in 52% and 28% of MEC patients, respectively. Physicians and nurses accurately predicted the incidence of acute CINV but underestimated the incidence of delayed nausea and emesis after HEC by 21% and 28%, respectively, and delayed nausea after MEC by 28%.

In the present study, the overestimation of the incidence of acute emesis in both HEC and MEC patients by medical providers may be, in part, due to the fact that medical providers under-appreciated the improved efficacy of 5-HT3 antagonist or metoclopramide used in combination with dexamethasone in controlling acute emesis. With these findings, oncologists may consider not sacrificing the appropriate dosing of chemotherapy agents because of concern about the emetogenicity of the regimen.

The underestimation of the occurrence of delayed CINV among MEC patients by medical providers is consistent with the study of Grunberg et al. and may be due to underreporting of these symptoms by patients once discharged from hospital. The success of symptomatic control should not be assumed and must be established in direct communication by the physician with, and assessment by, the patient. The finding again confirms the adverse impact of limiting the usage of 5-HT3 antagonist in MEC patients according to local reimbursement guidelines, which has led to unsatisfactorily control of delayed CINV.

Several risk factors for acute emesis, some confirmed by multivariate analysis, have been shown to predict poor antiemetic control. These factors include poor control with prior chemotherapy, female sex, a low chronic alcohol intake or history, and younger age [5–8]. Our data reveal that there are no significant differences between acute CINV and delayed CINV patients in terms of demographics, chemotherapy treatment and antiemetic treatment. This may have been due to the small sample size of our patients.

The neuropharmacologic mechanism of delayed emesis is not well understood. Prevention of this problem has been based on empiric results. Evidence suggests that good control of CINV during the acute period correlates with the control of delayed emesis [17, 23, 24]. Conversely, protection failure during the first 24 h has a high predictive value for delayed emesis in the same cycle. In our study, good control of acute CINV had a highly positive predictive value for delayed CINV, and failure to control acute CINV had a significantly higher negative predictive value for delayed CINV. Our results confirm that protection from acute emesis plays a major role in the occurrence and control of delayed emesis. Patients who experience acute emesis with chemotherapy are significantly more likely to have delayed emesis. Thus, any patient characteristic that predicts a greater risk for acute emesis should be considered as a predictive factor for delayed emesis as well [25]. Although there were only seven patients with alcohol use, the proportion of our patients without alcohol use seemed to be higher in those with delayed CINV than in those with acute CINV.

Fewer agents have been tested or are commonly used for delayed emesis than for acute emesis. Delayed symptoms occur more frequently with HEC [26, 27] and are more difficult to treat than acute CINV. A randomized trial suggests that the addition of the neurokinin 1 (NK_1) receptor antagonist aprepitant to standard antiemetic therapy improves control of CINV [28]. No NK_1 receptor antagonist is currently commercially available in Taiwan. Thus optimal prophylactic control is imperative to minimize occurrence. Our findings confirm the paramount importance of achieving effective control of acute CINV in order to reduce the development of delayed CINV [28, 29], which presents physicians with a clinical challenge. It is important that physicians take a full medical history to identify patients at greatest risk of developing CINV, and ensure that the most effective currently available antiemetic agents are administered prophylactically at optimum doses to control symptoms during the acute phase [30]. All patients at risk of delayed emesis require sustained prophylaxis throughout the post-treatment period. Effective preventative measures serve to enhance the quality of life of the patient and lead to improved patient compliance with subsequent chemotherapy cycles.

In conclusion, despite the use of modern antiemetics, CINV continues to be a significant clinical problem. In controlling CINV, the strategy should always focus on prevention rather than treatment. Good acute control with prophylactic antiemetics has a positive impact on the control of delayed CINV. In this study, medical providers were shown to underestimate the incidence of delayed CINV in MEC patients. The success of symptomatic control should not be assumed and must be established by direct communication with, and assessment by, the patient. Until novel antiemetic agents such as NK_1 receptor antagonists become commercially available in Taiwan, physicians should use the best available and most suitable agents during acute and delayed phases of CINV.

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