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ORIGINAL ARTICLE

Using aprepitant as secondary antiemetic prophylaxis for cancer patients with cisplatin-induced emesis

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Abstract
Purpose Chemotherapy-induced emesis remains a problem despite prophylaxis with 5-hydroxytryptamine (5-HT3) antagonists and dexamethasone. The purpose of the current study was to evaluate the efficacy of adding aprepitant, a neurokinin-1(NK-1) receptor antagonist, as a secondary antiemetic prophylaxis in cases failing to achieve full protection against emesis during the first cycle of a cisplatin-based regimen.
Methods Patients receiving chemotherapy with a dose of at least 50 mg/m^2 of cisplatin-based regimens were eligible. If patients failed to achieve complete protection against vomiting when antiemetics (5-HT3 antagonists and dexamethasone) were given in cycle 1, aprepitant was added in subsequent cycles. The primary endpoint was complete response (no emetic episodes and no rescue antiemetics) during days 1–6.
Results We analyzed 257 patients consecutively. Forty-nine patients (19%) had acute and/or delayed emesis during the first cycle of chemotherapy. Forty of 49 patients received aprepitant for secondary prophylaxis of emesis in the second cycle. Complete protection from vomiting and nausea was achieved in 63% and 55% of patients, respectively. Thirty-five patients received aprepitant for the third cycle. Complete protection from vomiting and nausea was achieved in 77% and 71% of patients, respectively.
Conclusions Primary antiemetic prophylaxis with 5-HT3 antagonists plus dexamethasone provided more than 80% complete protection against cisplatin-induced emesis. Addition of aprepitant as secondary antiemetic prophylaxis in subsequent cycles provided adequate emesis protection in patients who failed primary prophylaxis. Using aprepitant as secondary antiemetic prophylaxis for cancer patients with cisplatin-induced emesis is feasible and cost-effective.

Keywords Aprepitant · NK-1 receptor antagonist · Cisplatin · Chemotherapy · Antiemesis · Secondary prophylaxis

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of cancer therapy [2]. 5-Hydroxytryptamine (5-HT3) antagonists and dexamethasone have been the conventionally standard prophylactic antiemetic regimen before aprepitant [3]. Primary antiemetic prophylaxis with 5-HT3 antagonist plus dexamethasone provides 70%–90% complete protection against cisplatin-induced acute emesis [3, 12, 14, 15], but delayed emesis remains an unsolved problem and only approximately one-half of the patients have achieved complete control of emesis in previous studies.

Multiple neurotransmitters are implicated in CINV [4]. Substance P via binding to the neurokinin-1 (NK-1) receptor is a relevant neurotransmitter in CINV. Based on two prospective phase 3 trials [5, 10], aprepitant (Emend; Merck), a NK-1 antagonist, was approved by the Food and Drug Administration (FDA) in 2003 as a new antiemetic drug to prevent both acute and delayed CINV. Aprepitant is the first FDA-approved treatment that prevents delayed CINV and should always be used in combination with two other antiemetic agents. Although clinical guidelines [7, 11] all recommend that a three-drug combination consisting of 5-HT3 antagonists, dexamethasone and aprepitant should be used as the standard

antiemetic agents for patients receiving chemotherapy at high risk for emesis, this combination was not routinely used in our clinical practice because aprepitant is only reimbursed by the National Health Insurance (NHI) in patients who are refractory to 5-HT3 antagonists and dexamethasone in Taiwan.

Reports on aprepitant for secondary antiemetic prophylaxis are sparse. The purpose of the current study was to evaluate aprepitant used as secondary antiemetic prophylaxis in patients who fail 5-HT3 antagonists and dexamethasone during the first cisplatin-based chemotherapy cycle and the feasibility of this setting.

Patients and methods

Patients

All patients in this study were scheduled to receive chemotherapy with a dose of at least 50 mg/m^2 of cisplatin followed immediately by a continuous infusion of 5-fluorouracil (5-FU) with or without other chemotherapeutic agents. Cisplatin was given on day 1 and the other drugs on day 1 and subsequent days (Table 1). Eligibility criteria included the following characteristics: age at least 16 years, no prior experience with cisplatin-containing chemotherapy and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3. Exclusion criteria included a concurrent severe illness, nausea or vomiting in the last 24 h before chemotherapy, other known causes of nausea or vomiting (e.g., central nervous system metastases, gastrointestinal obstruction and hypercalcemia), or concurrent therapy with corticosteroids or benzodiazepines (unless given for night sedation). All patients were hospitalized during the administration of chemotherapy. The study was approved by the local Ethics Committee. All patients gave verbal informed consent to participate.

Table 1 Patients' characteristics (N=257)

Characteristics	N	%
Gender		
Male	181	70.4
Female	76	29.6
Age group, years		
16–49	45	17.5
50–64	96	37.4
65–82	116	45.1
Performance status		
0, 1	233	90.6
2	20	7.8
3	4	1.6
Previous chemotherapy		
No	250	97.3
Yes, without cisplatin	7	2.7
Primary site of malignancy		
Lung	9	3.5
Breast	10	3.9
Head and neck	34	13.2
Genitourinary	135	54.6
Gastrointestinal	52	20.2
Other	17	6.6
Chemotherapy regimen, dose (mg/m^2), and days		
F500D1-3/L30-35D1-3/A35/P50	1	0.4
F500D1-3/L30-35D1-3/B10/P50	7	2.7
F500D1-3/L30-35D1-3/E30-50/P50	4	1.6
F500D1-3/L30-35D1-3/G1000/P50	63	24.5
F500D1-3/L30-35D1-3/M6/P50	17	6.6
F500D1-3/L30-35D1-3/P50	130	50.5
F500D1-3/L30-35D1-3/V30/P50	21	8.2
FP	14	5.5
F1000D1-4/P100	1	
F1000D1-4/P75	2	
F500D1-4/P75	11	

F 5-fluorouracil, *P* cisplatin, *A* adriamycin, *B* bleomycin, *M* mitomycin, *E* epirubicin, *G* gemcitabine, *L* leucovorin, *V* vinorelbine, *D* day

Antiemetic therapy

This was a single institution study. The same chemotherapeutic drug was used during each cycle using identical doses. Each chemotherapy cycle consisted of cisplatin (50–100 mg/m^2), dexamethasone (20 mg) and 20% mannitol (100–150 cc) administered in 500 cc of 5% dextrose in normal saline (D_5S) for 3 h. Granisetron (Kytril, Roche Laboratories, Inc., Nutley, NJ; Otril, TTY Biopharm, Taipei, Taiwan) 3 mg in 100 ml of dextrose was given as a 15-min intravenous infusion starting 30 min before cisplatin administration. In addition, all patients received 5 mg of dexamethasone intravenously every 12 h after cisplatin administration, and the drug was discontinued after the completion of chemotherapy.

Intramuscular (IM) diphenhydramine was given to patients for antiemetic rescue. The rescue dose of diphenhydramine was 30 mg every 6 h as needed (prn).

If patients failed to achieve complete protection from vomiting with 5-HT3 antagonists and dexamethasone in cycle 1, oral aprepitant was added in subsequent cycles at a dose of 125 mg on day 1 and 80 mg once daily on days 2 and 3.

Response assessment and statistical analysis

Data pertaining to vomiting and nausea were recorded daily by the investigators (physicians and special nurses) commencing

at the time of patient admission. Patients were asked to record their symptoms daily during the days after discharge. These records were collected at out-patient department (OPD) or next admission. We recorded that if this patient experienced CINV or not and the severity of CINV if CINV occurred. An emetic episode was defined as vomiting or retching or continuous vomiting or retching (<1 min between episodes). The efficacy of therapy on vomiting was defined as follows: complete response (no emetic episodes and no rescue antiemetics), major response (one to two emetic episodes), minor response (three to five emetic episodes) and failure (more than five emetic episodes) [8]. The patients assessed the severity of nausea using the following descriptions: none, mild (no interference with daily life), moderate (interference with daily life) and severe (bedridden because of nausea). Analysis of vomiting and nausea was performed separately for day 1 (acute episodes) and days 2–6 (delayed episodes). The severity of delayed vomiting was based on the day between days 2 and 6 with the most emetic episodes. The intensity of delayed nausea was recorded as the worst nausea experienced during days 2–6.

The primary endpoint was complete response (no emetic episodes and no rescue antiemetics) during the 6-day study period. The four secondary endpoints were the response to treatment of acute and delayed emesis and the severity of acute and delayed nausea. Data were analyzed using descriptive statistics.

Results

Two hundred fifty-eight patients were analyzed consecutively between May 2006 and December 2010 at Chang-Gung Memorial Hospital. During the first cycle of chemotherapy, 257 patients were evaluated for emesis; one patient was not evaluated due to a previous cycle of cisplatin-containing chemotherapy. The population consisted of 181 men and 76 women who ranged in age from 26 to 82 years (median, 62 years). Nearly all patients (98%) had an ECOG performance status <2. The majority of patients (97%) were chemotherapy naïve. Greater than one-half of our patients had primary malignancies of the genitourinary system including the bladder, ureters, renal pelves and kidneys. Detailed characteristics of the patients are listed in Table 1.

During the first cycle of chemotherapy, 49 of 257 patients (19%) had acute and/or delayed emesis; the remaining 208 patients (81%) had complete protection from emesis. All 49 patients also had acute and/or delayed nausea. The detailed status of chemotherapy-induced nausea and vomiting during the first cycle is listed in Table 2. Six patients with acute emesis and seven patients with acute nausea also experienced delayed emesis and nausea, respectively, resulting in an equal number of patients with acute and delayed CINV.

Forty of the 49 patients who received aprepitant for secondary prophylaxis from emesis were evaluated in the second cycle of chemotherapy. Nine patients were not evaluated for the following reasons: progression or death due to neoplasm (n=6), refusal of chemotherapy due to side effects (n=1) and antiemetic treatment not given as scheduled (n=2). The antiemetic efficacy data of the 40 patients who received aprepitant for secondary prophylaxis from emesis in the second cycle are listed in Table 3. Complete protection from acute vomiting and nausea was obtained in 98% and 93% of the patients, respectively. Complete plus major protection from acute vomiting and nausea was obtained in all patients. Complete protection from delayed vomiting and nausea was obtained in 65% and 60% of patients, respectively. Complete plus major protection from delayed vomiting and nausea was obtained in 88% and 78% of patients, respectively. Overall, complete protection of vomiting and nausea was achieved in 63% and 55% of the patients, respectively.

Compared to CINV during the first cycle of chemotherapy, 31 patients (78%) had complete protection from emesis (or improvement) and 33 patients (83%) had complete protection from nausea (or improvement).

Thirty-five of 40 patients who received aprepitant for secondary prophylaxis from emesis were evaluated in the third cycle of chemotherapy. Five patients were not evaluated for the following reasons: progression or death due to neoplasm (n=2), loss to follow-up (n=1), refusal of chemotherapy due to side effects (n=1) and complications or death due to other illnesses (n=1). The antiemetic efficacy data of adding aprepitant during the third cycle are listed in Table 4. Complete protection from acute vomiting and nausea was obtained in all patients. Complete protection from delayed vomiting and nausea was obtained in 77% and 71% of patients, respectively. Complete plus major protection from

Table 2 Patients receiving first chemotherapy (N=257)

	Va		Vd			Na		Nd	
	N	%	*N*	%		*N*	%	*N*	%
Complete response	251	97.6	208	81.0	None	250	97.2	203	79.0
Major response	4	1.6	24	9.3	Mild	4	1.6	23	9.0
Minor response	1	0.4	16	6.2	Moderate	2	0.8	25	9.7
Failure	1	0.4	9	3.5	Severe	1	0.4	6	2.3

Va acute vomiting, *Vd* delayed vomiting, *Na* acute nausea, *Nd* delayed nausea

Table 3 Patients receiving aprepitant for secondary prophylaxis (N=40) during cycle 2

	Va		Vd			Na		Nd	
	N	%	*N*	%		*N*	%	*N*	%
Complete response	39	97.5	26	65.0	None	37	92.5	24	60.0
Major response	1	2.5	9	22.5	Mild	3	7.5	7	17.5
Minor response	0	0.0	2	5.0	Moderate	0	0.0	8	20.0
Failure	0	0.0	3	7.5	Severe	0	0.0	1	2.5

Va acute vomiting, *Vd* delayed vomiting, *Na* acute nausea, *Nd* delayed nausea

delayed vomiting and nausea was obtained in 91% of patients. Overall, complete protection from vomiting and nausea was achieved in 77% and 71% of patients, respectively.

Among 35 patients who underwent cycles 2 and 3 of chemotherapy, 23 were completely protected from nausea and vomiting in both cycles, and six were refractory to aprepitant in both cycles. Two patients were completely protected from nausea and vomiting during cycle 2 only, and four patients were completely protected from nausea and vomiting during cycle 3 only.

Among 40 patients who were administered aprepitant, the adverse effects during cycle 1 included hiccups (n=5) and constipation (n=4). Aprepitant did not increase the incidence of adverse effects during cycles 2 and 3.

Discussion

Aprepitant is reimbursed by the NHI in Taiwan for patients who have failed a cisplatin (≧50 mg/m^2)-based regimen with 5-HT3 antagonists and dexamethasone antiemetics. The goal of this study was to evaluate the feasibility of this clinical setting. We assessed CINV using ordinal rather than nominal categories [5, 10] because ordinal categories can simplify the assessment and are more comparable to our daily practice. This study showed that primary antiemetic prophylaxis with 5-HT3 antagonists and dexamethasone provided 81% complete protection from cisplatin-induced emesis. For patients who failed primary prophylaxis, secondary antiemetic prophylaxis with aprepitant provided 65% and 77% complete protection from vomiting during cycles 2 and 3, respectively.

Medical economics is an important issue in our daily practice and must be balanced with evidence-based medicine. Although phase III studies [5, 10] and clinical guidelines [7, 11] suggest that a three-drug combination including aprepitant should be used as primary antiemetic prophylaxis for patients receiving highly emetogenic chemotherapy, the incremental costs for antiemetics are considerable. The current study setting was cost-effective because more than 80% of the patients who received a cisplatin (≧50 mg/m^2)-based regimen did not need aprepitant to achieve complete protection during their first and/or subsequent cycles. In addition, the benefit of aprepitant in secondary prophylaxis was not compromised because the small percentage of patients who experienced emesis during the first cycle achieved more than 60% complete protection from emesis in subsequent cycles.

Aprepitant has been evaluated as secondary antiemetic prophylaxis in patients who were refractory to 5-HT3 antagonists and dexamethasone in the previous cycle [1, 6, 9]. However, the number of patients in those studies was relatively small and the chemotherapy regimens were different. The current study is the first to assess aprepitant as secondary antiemetic prophylaxis solely for a cisplatin-based regimen and is the largest study of aprepitant as secondary prophylaxis for cisplatin-induced CINV.

There are some limitations to the current study. First, there are several emetogenic cytotoxic agents and we evaluated only cisplatin-based regimens. Therefore, our results may not be applicable to other highly emetogenic chemotherapies. Second, the incidence of CINV in our study was much lower than in previous multicenter trials, suggesting that our study may underestimate the role of aprepitant. There are several possible explanations for the lower incidence of CINV in our study; treatment was administered at a high volume cancer center [1], the dexamethasone dose was higher than recommended practice and most patients received cisplatin at only 50 mg/m^2.

Table 4 Patients receiving aprepitant for secondary prophylaxis (N=35) during cycle 3

	Va		Vd			Na		Nd	
	N	%	*N*	%		*N*	%	*N*	%
Complete response	35	100.0	27	77.1	None	35	100.0	25	71.4
Major response	0	0.0	5	14.3	Mild	0	0.0	7	20.0
Minor response	0	0.0	2	5.7	Moderate	0	0.0	3	8.6
Failure	0	0.0	1	2.9	Severe	0	0.0	0	0.0

Va acute vomiting, *Vd* delayed vomiting, *Na* acute nausea, *Nd* delayed nausea

Third, we asked patients to record their symptoms daily during the days after discharge, and this may be a source of bias. In addition, there were six patients in the current study who were refractory to aprepitant, and the role of anticipatory nausea and vomiting (ANV) was not considered [13]. Although ANV can be prevented with adequate primary antiemetics, it is difficult to distinguish ANV from other causes of CINV.

In conclusion, our study showed that primary antiemetic prophylaxis with 5-HT3 antagonists plus dexamethasone provided more than 80% complete protection against cisplatin-induced emesis. Addition of aprepitant as secondary antiemetic prophylaxis in subsequent cycles provided adequate emesis protection in patients who failed primary prophylaxis. This study provides evidence that using aprepitant as secondary prophylaxis for cancer patients with cisplatin-induced emesis is feasible and cost-effective.

Conflict of interest The authors declare that they have no competing interests and no financial relationship with other organizations sponsoring this research. All authors have nothing to disclose. We have full control of all primary data and agree to allow the journal to review these data if requested.

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