Original Contribution

Prevalence of Delayed Nausea and/or Vomiting in Patients Treated With Oxaliplatin-Based Regimens for Colorectal Cancer

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Abstract

Purpose: To measure the prevalence of nausea and vomiting 2 to 5 days after oxaliplatin-based chemotherapy.

Patients and Methods: Sixty-four patients (55% men; 44% women) enrolled onto this cross-sectional study. Fifty-three (83%) had colon cancer and received oxaliplatin biweekly. Eleven (17%) had rectal cancer and received oxaliplatin weekly. We collected data on 23 patients for the first cycle and on 41 patients for the first two cycles, for a total of 105 cycles. Nausea and vomiting was graded using Common Toxicity Criteria. Patients maintained a 7-day postinfusion diary of nausea and vomiting and antiemetic use.

Results: All patients received antiemetics and steroids on day 1 of each cycle. For patients with data collected for both cycles, the occurrence of nausea was the same during cycles one and two. Thirty-nine percent used rescue antiemetics in cycle one, and 34% did so in cycle two. Sixty-eight percent of men reported no nausea in cycle one compared with 33% of women; for cycle two, these figures were 67% and 36%, respectively. Eighty-nine percent of patients reported no vomiting in cycle one, and 85% did so in cycle two. Seven patients (11%) had a history of motion sickness; 13 of 28 women (46%) reported history of pregnancy-induced morning sickness. Palonosetron slightly but significantly reduced the occurrence of nausea. Female sex and history of chemotherapy were significant risk factors for nausea.

Conclusion: Delayed nausea associated with oxaliplatin was well controlled and evenly divided between grades 1 and 2; vomiting was rare. Factors associated with nausea were intrinsic to the patient and mostly unrelated to the antiemetics used. Sex and previous experience with emesis should be considered for efficient antiemetic management.

Introduction

Delayed nausea and vomiting (days 2 to 5 postchemotherapy) are common adverse effects of platinum-based chemotherapy regimens. Oxaliplatin (Eloxatin; sanofi-aventis, Bridgewater, NJ) has been approved for use with fluorouracil (FU) and leucovorin in previously treated patients with advanced colorectal cancer.[1] It is also used in various regimens in clinical trials, including one current trial using FOLFOX7 (infusional FU, leucovorin, and oxaliplatin), a regimen that features higher doses (130 mg/m^2) than used in the past. Although delayed nausea and vomiting has not been conclusively associated with the use of oxaliplatin, a moderately emetogenic antineoplastic agent,[2] thus far, it is possible or even probable that as more patients are treated with oxaliplatin, an emetogenic profile might emerge, as it has with the other organoplatinums.

Antiemetics can be divided into four groups: dopamine receptor antagonists, corticosteroids, serotonin receptor antagonists (5-HT$_3$ RAs), and neurokinin-1 receptor antagonists (NK$_1$ RAs). Cannabinoids are used as the fourth or fifth choice in some countries, whereas their use is illegal in others.[3]

According to American Society of Clinical Oncology (ASCO) guidelines, a three-drug combination of 5-HT$_3$ RAs, dexamethasone, and aprepitant (NK$_1$ RAs) is recommended before chemotherapy of high emetic risk, and only 5-HT$_3$ RAs with dexamethasone is recommended for moderately emetogenic chemotherapy. Aprepitant is added for those receiving anthracyclines and cyclophosphamide.[2] There are reports of the addition of aprepitant to an antiemetic regimen of ondansetron and dexamethasone resulting in significantly better prevention of chemotherapy-induced nausea and vomiting (CINV) than ondansetron and dexamethasone alone in patients receiving moderately emetogenic chemotherapy.[4]

However, even with the current standard regimen of antiemetics, there is residual nausea and/or vomiting in a significant percentage of patients treated for cancer. It was unknown whether patients receiving oxaliplatin for treatment of colorectal cancer experience delayed nausea and vomiting despite treatment with standard antiemetic drugs.

The initial purpose of this study was to measure the prevalence of residual delayed nausea and vomiting in this population to determine whether future studies of an additional antiemetic such as an NK$_1$ RA—aprepitant (Emend; Merck, Whitehouse Station, NJ [sponsor of this study])—was warranted. However, during the course of the study, standards of care at our institution changed, and it became increasingly common for patients treated with oxaliplatin to receive aprepitant in addition to other antiemetics. Thus, a natural experiment was created, allowing us to compare the experience of patients who received a three-drug regimen containing aprepitant with that of patients who received a two-drug antiemetic regimen of dexamethasone plus one of the 5-HT$_3$ RAs. Because the popu-

Table 1. Patient Demographic and Diagnostic Characteristics

Characteristic	Patients No.	Patients %
Sex		
Male	35	54.7
Female	28	43.8
Transgendered	1	1.6
Total	64	100.0
Age, years		
20-39	2	3.1
40-49	7	10.9
50-59	18	28.1
60-69	23	35.9
≥ 70	14	21.9
Total	64	100.0
Mean	60.9	
Median	62.0	
Mode	62.0	
SD	11.1	
Diagnosis		
Colon	53	82.8
Rectal	11	17.2
Total	64	100.0
Stage		
0	24	37.5
2	3	4.7
3	20	31.3
4	17	26.6
Total	64	100.0
Dose, mg		
65	10	15.6
85	53	82.8
100	1	1.6
Total	64	100.0
Nausea		
Present	31	48.4
Absent	33	51.6
Total	64	100.0
Rating scale		
Mean	0.76	
Median	0.0	
Mode	0.0	
SD	0.86	
Vomiting		
Present	8	12.5
Absent	56	87.5
Total	64	100.0
Rating scale		
Mean	0.16	
Median	0.0	
Mode	0.0	
SD	0.48	
Antinausea drug regimen		
Standard two drug	50	78.1
Three drug (standard plus aprepitant)	14	21.9
Total	64	100.0

Abbreviation: SD, standard deviation.

lation was diverse in terms of cancer stage, dose of oxaliplatin, and specific antiemetic regimen used, the number of patients in each group was small. The primary objective of this study was to assess the prevalence of delayed nausea and vomiting during the first and/or second chemotherapy cycle in patients treated with oxaliplatin for colorectal cancer who were receiving standard antiemetic medication.

Patients and Methods

This was a convenience sample of patients who agreed to participate and were able to complete quality-of-life forms in English or Spanish. Almost all patients were being treated with FOLFOX regimens every 14 days for colon cancer or weekly oxaliplatin plus continuous-infusion FU for rectal cancer. Potential patients were approached at the time of their first infusion of oxaliplatin in the cancer centers at Beth Israel and Roosevelt Hospitals (New York, NY) from June 2005 through November 2008. Consent was obtained by the research team at Continuum Cancer Centers of New York. It was estimated that 100 patient/cycles would provide adequate power to the study.

As listed in Table 1, 64 patients (55% men; 44% women; one transgender patient) signed institutional review board–approved informed consent and were enrolled on day 1 of cycle one. Fifty-three patients (83%) had colon cancer; 52 received 85 mg/kg of oxaliplatin, and one received 100 mg/kg. Eleven patients (17%) had rectal cancer; 10 received 65 mg/kg of oxaliplatin, and one received 85 mg/kg. Age ranged from 29 to 84 years, with 64% between ages 50 and 69 years. Data were collected on the first chemotherapy cycle for 23 patients and the first and second cycles for 41 patients, for a total of 105 cycles. Baseline demographic data were collected by medical record review and interviews. Delayed nausea and vomiting were defined as occurring on days 2 through 5 after oxaliplatin infusion. The maximum grade of delayed nausea and vomiting for each cycle was assessed by the Common Toxicity Criteria.[5] The Functional Living Index–Emesis was obtained at baseline in person or by telephone 5 to 7 days after infusion. Inclusion criteria were: ability to sign informed consent, ability to maintain diary and complete standardized quality-of-life questionnaires in English or Spanish, and receiving FOLFOX7/modified FOLFOX6 regimens for treatment of colorectal cancer. Patients

who were younger than 18 years of age, had received aprepitant in the preceding 90 days, or had clinical or radiologic evidence of brain metastasis were excluded from the study. Statistical analysis was performed using SAS 9.13 (SAS Institute, Cary, NC).

Results

Among 41 patients for whom data were collected on both the first and second cycles, the occurrence of delayed nausea was the same during both cycles more than 75% of the time (75.7%). There was a high correlation between the nausea rating in cycles one and two (Kendall's T = 0.68; $P < .001$). Almost 40% of patients (39.1%) received rescue antiemetics (prochlorperazine, metoclopramide, or lorazepam) in cycle one and 34.1% in cycle two; more than 60% of patients never received rescue antiemetics. In cycle one, men experienced no delayed nausea 68% of the time, compared with 33% of the time for women. The figures for cycle two were 67% and 36%, respectively. In cycle one, 89% of patients reported no vomiting, and 85% reported no vomiting in cycle two.

At baseline, seven patients (11%) reported a history of motion sickness. History of pregnancy-related morning sickness

Table 2. Factors Associated With Frequency and Severity of Nausea in Cycle 1

	Present		Absent			Rating				
Factor	**No.**	**%**	**No.**	**%**	**Significance**	**Mean**	**Median**	**Mode**	**SD**	**Signficance***
Sex					$\chi^2 = 5.6$; $P = .0178$†					Test statistic = 1,053.0; $P < .001$†‡
Male	12	34.29	23	65.71		0.38	0.00	0.00	0.60	
Female	18	64.29	10	35.71		1.19	2.00	2.00	0.92	
Transgendered	1	100.0	0	0.0		2.00	2.00	2.00	—	
Total	31		33			0.76	0.0	0.0	0.86	
History of motion sickness					.7039§					Test statistic = 250.5; $P = .5473$‖
Yes	4	57.14	3	42.86		1.00	1.00	0.0	1.00	
No	27	47.37	30	52.63		0.73	0.0	0.0	0.85.	
Total	31		33			0.76	0.0	0.0	0.86	
History of morning sickness					1.000§					Test statistic = 181.00‡; $P = .7505$‖
Yes	8	61.54	5	38.46		1.23	2.00	2.00	1.01	
No	9	64.29	5	35.71		1.15	1.00	2.00	0.90	
Missing	1	100.0	0	0.0						
Total	18		10							
History of chemotherapy					.0245§					Test statistic = 364.5; $P = .0108$‖
Yes	7	87.50	1	12.50		1.50	2.00	2.00	0.76	
No	24	42.86	32	57.14		0.65	0.0	0.0	0.83	
Total	31		33			0.76	0.0	0.0	0.86	
Nausea with prior chemotherapy					1.000§					Test statistic = 11.0; $P = .4643$‖
Yes	4	80.00	1	20.00		1.60	2.00	2.00	0.89	
No	3	100.00	0	0.0		1.33	1.00	1.00	0.58	
Total	7		1							
Any prior nausea					$\chi^2 = 2.2$; $P = .1361$					Test statistic = 889.5; $P = .0098$‖
Yes	14	60.87	9	39.13		1.17	2.0	2.0	0.98	
No	17	41.46	24	58.54		0.51	0.0	0.0	0.68	
Total	31		33							
Antinausea regimen					$\chi^2 = 0.3$; $P = .85$					Test statistic = 379.5; $P = .61$‖
Standard 5-HT_3 inhibitor regimen	25	49.0	26	51.0		0.80	0.0	0.0	0.89	
Standard plus aprepitant	6	46.2	7	53.9		0.62	0.0	0.0	0.77	
Total	31		33							
Regimen including palonosetron					$\chi^2 = 4.04$; $P = .04$					Test statistic = 832.0; $P = .09$‖
No	20	60.6	13	39.4		0.94	1.0	0.0	0.88	
Yes	11	35.5	20	64.5		0.57	0.0	0.0	0.82	
Total	31		33							

Abbreviations: 5-HT_3, serotonin; SD, standard deviation.
* Wilcoxon rank sums.
† Transgendered dropped from significance testing.
‡ Exact probability, one sided.
§ Fisher's exact test, two sided.
‖ Exact probability, two sided.

Table 3. Antiemetic Regimens, Single Agent or in Combination

5-HT_3 Combination	Single 5-HT_3	5-HT_3 + Aprepitant	5-HT_3 + 5-HT_3	5-HT_3 + 5-HT_3 + Aprepitant	Total Use
Palonosetron (Aloxi; Helsinn Healthcare, Lugano, Switzerland)	28	2	1, dolasetron	0	31
Ondansetron (Zofran; GlaxoSmithKline, London, United Kingdom)	3	2	2, granisetron	3, granisetron	10
Granisetron (Kytril; Genentech, South San Francisco, CA)	4	6	2, ondansetron; 2, dolasetron	3, ondansetron	17
Dolasetron (Anzemet; sanofi-aventis, Bridgewater, NJ)	9	0	2, granisetron; 1, palonosetron	0	12
Aprepitant (Emend; Merck, Whitehouse Station, NJ)	10	—	0	3, granisetron and ondansetron	13
Unknown 5-HT_3	2	0	0	0	2

Abbreviation: 5-HT_3, serotonin.

was reported by 13 (46%) of the 28 women. All patients received antiemetics and steroids on day 1 of each cycle. During cycle one, 78% of patients received 5-HT_3 inhibitors in combination with steroids (ie, two-drug regimen), 22% received steroids plus 5-HT_3 plus an oral NK_1 RA (ie, three-drug regimen), and none received an NK_1 RA alone.

We examined a number of factors (sex; use of two- *v* three-drug regimen; specific antiemetic used; history of morning sickness, motion sickness, or nausea associated with previous chemotherapy) to assess whether they were associated with increased frequency and severity of nausea in the first cycle of chemotherapy (Table 2). Female sex and history of prior chemotherapy were associated with the presence of nausea and increased severity of nausea, whereas history of any type nausea was associated with increased severity only. Those patients who received palonosetron, as compared with patients who received any other antiemetic regimen, were significantly ($P = .04$) less likely to experience nausea in cycle one. There was no difference in the prevalence of nausea in cycle one between those who received aprepitant and those who did not. However, there was a wide variety of antiemetic regimens received by the patients in this study (Table 3), and the number of patients in any given group was too small to achieve a high degree of significance.

Discussion

The optimal prevention and treatment of CINV remains a major challenge of modern cancer treatment. Those most at risk include younger female patients and those with a history of motion sickness[6] and pregnancy-related morning sickness. CINV can be broadly categorized by onset latency, previous patient experience with CINV, and relationship to antiemetic treatment. Delayed CINV commences more than 24 hours after treatment and can persist for as long as 6 to 7 days. Failure of prophylaxis during the first 24 hours after chemotherapy is highly predictive for delayed emesis during the same cycle.[7]

The patient's experience of nausea and vomiting may have a significant effect on outcomes, because it may lead to reduced adherence, which in turn may compromise the effectiveness of therapy.[8] Beyond these important practical concerns, nausea and vomiting are also of theoretic interest. These adverse effects seem not to be completely determined by the nature of the drugs that the patient is receiving; among patients with breast cancer, nausea and vomiting vary as much within a single regimen as they do across regimens.[9,10] Not only do patients receiving the same regimen display different adverse effect patterns, but the same patient often responds to the same drugs differently from one cycle to the next. Thus, individual difference factors and/or situational factors seem to influence patient reactions to chemotherapy; this is particularly likely to be the case with anticipatory nausea.

Anticipatory/conditioned emesis occurs in patients who have had poor control of vomiting with prior chemotherapy. A history of motion sickness has been thought to predispose patients to anticipatory emesis. Currently, ASCO does not recommend any changes from original guidelines for prevention. However, it does recommend behavioral therapy with systematic desensitization for treatment. The optimal antiemetic regimen should be used with the initial chemotherapy dose rather than waiting to assess the patient's emetic response to a more minimal regimen. Because of their amnestic and antianxiety effects, alprazolam and lorazepam have been used to treat and prevent anticipatory symptoms. Although lorazepam and alprazolam are recommended, to our knowledge, there have been no prospective trials to establish their effectiveness in this setting.[2]

The predictive power of motion sickness is also independent of the effects of pretreatment anxiety, taste during injection, and age.[11] In two studies, Morrow[12,13] reports that anticipatory nausea is especially prevalent among patients with a susceptibility to motion sickness. In the second of these studies, motion sickness was also found to be a significant predictor of posttreatment nausea and vomiting; those patients with a history of motion sickness reported more frequent, severe, and long-lasting episodes of nausea and vomiting than did their matched controls.

In a study by Shih et al,[14] history of chemotherapy-induced nausea was a significant risk factor influencing both acute and delayed nausea. A history of motion sickness was also a significant risk factor that influenced delayed vomiting. Choice of antiemetic was not a factor in preventing delayed nausea or vomiting, a finding confirmed by our study.

Physicians and nurses have markedly underestimated the incidence of delayed nausea and emesis after both highly eme-

togenic and moderately emetogenic chemotherapy.[15] We tried to overcome this issue by accessing the patient's experience directly, using a patient diary and the Functional Living Index–Emesis. However, our study had its own limitations. The study population was a convenience sample; we could include only English- or Spanish-speaking patients; and there was potential for bias, because the patients self-reported CINV.

Our original intent was to assess the need for more rigorous antiemetic prophylaxis, but the prevalence of CINV was not high enough to warrant that. A randomized study enrolling only those patients receiving chemotherapy who are at high risk (because of female sex and/or history of nausea and vomiting) could assess the effectiveness of aprepitant in this special population.

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