



# Aprepitant and granisetron for the prophylaxis of radiotherapy-induced nausea and vomiting after moderately emetogenic radiotherapy for bone metastases: a prospective pilot study

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## ABSTRACT

### Purpose

We evaluated the novel combination of aprepitant and granisetron for the prophylaxis of radiotherapy-induced nausea and vomiting (RINV) among patients receiving moderately-emetogenic radiotherapy for thoracolumbar bone metastases.

### Methods

In this single-centre two-arm nonrandomized prospective pilot study, patients undergoing single-fraction radiotherapy (8 Gy) received aprepitant 125 mg and granisetron 2 mg on the day of radiotherapy and aprepitant 80 mg on each of the first 2 days after the day of radiotherapy. Patients undergoing multiple-fraction radiotherapy (20 Gy in 5 fractions) received aprepitant 125 mg on day 1 of radiotherapy, aprepitant 80 mg on days 3 and 5 of radiotherapy, and granisetron 2 mg on every day of radiotherapy. Symptoms and total medication intake were recorded daily during the acute phase (day 1 of radiotherapy until the first day after the last day of radiotherapy), and the delayed phase (days 2–10 after the last day of radiotherapy). Control of vomiting, retching, and nausea was defined as no symptoms and no use of rescue medication.

### Results

Control rates for single-fraction patients ( $n = 13$ ) were 100% for acute nausea, 62% for delayed nausea, 100% for acute vomiting and retching, and 85% for delayed vomiting and retching. Control rates for multiple-fraction patients ( $n = 6$ ) were 67% for acute nausea, 83% for delayed nausea, 67% for acute vomiting and retching, and 83% for delayed vomiting and retching. No grade 3 or 4 toxicities attributable to the study intervention were observed.

## Conclusions

The combination of aprepitant and granisetron was safe and efficacious for the prophylaxis of RINV after both single- and multiple-fraction moderately emetogenic radiotherapy for thoracolumbar bone metastases. Our results require confirmation in a larger population.

## KEY WORDS

Antiemetic, aprepitant, granisetron, nausea, vomiting, radiotherapy

## 1. INTRODUCTION

Previously, we reported the results of a prospective cohort study demonstrating that, despite prophylaxis with a 5-HT<sub>3</sub> receptor antagonist (5-HT<sub>3</sub>RA) as recommended in international antiemetic guidelines<sup>1,2</sup>, radiotherapy-induced nausea and vomiting (RINV) was common in patients receiving moderately emetogenic radiotherapy alone for thoracolumbar bone metastases<sup>3</sup>. From the time of radiotherapy commencement until 10 days after radiotherapy completion, only 31% and 43% of patients receiving single- and multiple-fraction radiotherapy respectively were free of nausea, and only 44% and 43% were free of vomiting.

Aprepitant is a substance P neurokinin 1 receptor antagonist that, when combined with a 5-HT<sub>3</sub>RA and dexamethasone, improves control of acute and delayed vomiting after highly and moderately emetogenic chemotherapy<sup>4–7</sup>. No published studies have described an evaluation of aprepitant for the prophylaxis of nausea and vomiting after radiotherapy alone, although the mechanisms underlying chemotherapy-induced nausea and vomiting (CINV) and RINV are believed to be similar<sup>8,9</sup>.

In the present pilot study, we evaluated the novel combination of aprepitant and granisetron (a 5-HT<sub>3</sub>RA) for the prophylaxis of RINV in patients

receiving moderately emetogenic radiotherapy for thoracolumbar bone metastases. We hypothesized that the combination would provide symptom control rates superior to those in our historical control data from patients receiving prophylaxis with a 5-HT<sub>3</sub>RA alone.

## 2. METHODS

For this single-centre two-arm nonrandomized prospective cohort pilot study, the authors alone collected, managed, and analyzed the data. The research ethics board of the host centre approved the study protocol. Health Canada approved the study. Participants gave written informed consent.

### 2.1 Patients

Patients were eligible if their score on the Karnofsky performance status scale was 40 or greater and if they were scheduled to receive moderately emetogenic radiotherapy to a dose of either 8 Gy in 1 fraction or 20 Gy in 5 fractions for bone metastases from a solid primary tumour. Radiotherapy was considered moderately emetogenic if it was delivered using a posterior field, with or without an anterior field, and if it included an area of at least 80 cm<sup>2</sup> (calculated from a posterior or an anterior beam's eye view) between the superior border of the 11th thoracic vertebral body and the inferior border of the 3rd lumbar vertebral body. This radiotherapy target definition is consistent with definitions found in phase III randomized trials of RINV from the NCIC Clinical Trials Group<sup>10,11</sup> and is considered moderately emetogenic in international antiemetic guidelines<sup>1,2</sup>. Patients were ineligible if they had received highly or moderately emetogenic chemotherapy or cranial radiotherapy during the 7 days before the day of radiotherapy commencement; if they had experienced nausea, retching, or vomiting during the 24 hours before the hour of radiotherapy commencement; if they were scheduled to receive chemotherapy or cranial radiotherapy during the 10 days after the day of radiotherapy completion; or if they were taking corticosteroids or other antiemetics.

### 2.2 Treatments

All radiotherapy treatments were planned using computed tomography simulation. Parallel-opposed anterior and posterior field plans were prescribed to midplane, and direct posterior field plans were prescribed to the mid vertebral body as recommended in palliative radiotherapy expert guidelines<sup>12</sup>. Patients receiving 8 Gy in 1 fraction could attend on any given working day. Patients receiving 20 Gy in 5 fractions attended on consecutive days. Patients in the 8 Gy arm received oral aprepitant 125 mg and oral granisetron 2 mg at least 1 hour before radiotherapy and

aprepitant 80 mg in the morning on each of the first 2 days after the day of radiotherapy. Patients in the 20 Gy arm received oral aprepitant 125 mg and oral granisetron 2 mg at least 1 hour before treatment on the first day of radiotherapy, oral aprepitant 80 mg in the morning on days 3 and 5 of radiotherapy, and oral granisetron 2 mg in the morning on days 2–5 of radiotherapy.

### 2.3 Symptom Assessments

During the hour before each patient's first radiotherapy treatment, research assistants recorded baseline medication intake and verified that the patient had not experienced nausea, retching, or vomiting in the preceding 24 hours. Patients subsequently recorded their symptoms and medication intake in daily diaries until the end of day 10 after the last day of radiotherapy. For the 8 Gy group, all diary data were collected over the telephone. For the 20 Gy group, diary data were collected in person on days 2–5 of radiotherapy treatment and over the telephone afterwards. Diary data recorded on weekends or holidays were collected on the subsequent working day. When symptom or medication intake data were not complete, research assistants prompted patients to recall the necessary information at the time of collection. "Nausea" was defined as the feeling that one might vomit. "Vomiting" was defined as the bringing up of stomach contents. "Retching" was defined as the attempt to bring up stomach contents without actually bringing anything up. Patients rated the severity of their nausea, vomiting, and retching respectively as none, mild, moderate, or severe. This rating system had not previously been specifically validated, but it duplicated the system used in a previous trial of RINV by the NCIC Clinical Trials Group<sup>11</sup>.

### 2.4 Quality-of-Life Assessments

Quality of life (QOL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the Functional Living Index–Emesis (FLIE). Both tools were completed at baseline and at days 5 and 10 after the last day of radiotherapy, and those data were collected together with the symptom data.

The EORTC QLQ-C30 is a 30-item questionnaire designed to assess the QOL of patients with cancer<sup>13</sup>. It contains 5 multi-item functional scales (physical, role, cognitive, emotional, and social), 3 multi-item symptom scales (fatigue, pain, and nausea and vomiting), a multi-item global health and QOL scale, single-item symptom measures (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), and a measure of the perceived financial impact of the disease and its treatment. The EORTC QLQ-C30 has been widely validated and has been used in earlier phase III trials of RINV<sup>10,11</sup>.

The FLIE is an 18-item questionnaire designed to assess the impact of CINV on daily living function in patients<sup>14</sup>. It contains 9 items for nausea and 9 for vomiting. Each item is graded by the patient using a Likert scale with possible scores ranging from 1 to 7. The total FLIE score can range from 18 to 126, with lower scores indicating a more negative impact of nausea and vomiting. We are not aware of the FLIE having been used in trials of RINV, but it has been extensively used in earlier trials of CINV and has good face validity for patients at risk of RINV.

## 2.5 Endpoints and Statistical Analyses

The co-primary endpoints were the percentages of patients with control of vomiting and retching during the acute, delayed, and combined phases of treatment. "Control" was defined as no symptom and no use of rescue antiemetics. The acute phase was the period inclusive of day 1 of radiotherapy until day 1 after the last day of radiotherapy. For the 8 Gy arm, the day of radiotherapy was considered both the first and the last day. The delayed phase was the period inclusive of days 2–10 after the last day of radiotherapy. The combined phase was the acute and delayed phases combined.

Secondary endpoints were the percentages of patients with control of nausea during the acute, delayed, and combined phases; the percentages of patients with control of nausea and vomiting and of retching during the acute, delayed, and combined phases; the percentages of patients with nausea, vomiting, and retching on each study day; toxicity as measured by the *Common Terminology Criteria for Adverse Events* (version 4.0)<sup>15</sup>; and the EORTC QLQ-C30 and FLIE QOL ratings at baseline and at days 5 and 10 after the last day of radiotherapy. With respect to the FLIE, patients were asked to rate the impact of nausea and vomiting during the 3 days preceding their baseline assessment (the period of interest in the original FLIE instrument); however, on day 5 after the end of radiotherapy, they were asked to rate the impact of nausea and vomiting since radiotherapy completion, and on day 10 after the end of radiotherapy, they were asked to rate the impact of nausea and vomiting since the day 5 assessment.

Descriptive statistics are used to summarize demographic and symptom data. Sample mean imputation with a population standard deviation (SD) correction for augmented observations<sup>16</sup> is used to control for missing QOL forms.

## 3. RESULTS

Between January 2011 and October 2012, the study enrolled 19 patients (8 men, 11 women; 13 in the 8 Gy arm, 6 in the 20 Gy arm). Median age in the group was 70 years (range: 33–89 years), and median score on the Karnofsky performance status

scale was 60 (range: 50–80). All patients received their radiotherapy as planned; 18 were treated with opposed anterior and posterior beams, and 1 with a posterior beam alone. All patients received their study medications as planned. Complete diary data for symptoms and medication intake were collected for all patients. No grade 3 or 4 toxicities attributable to radiotherapy or the study medications were recorded. Table 1 summarizes the characteristics of the study group.

### 3.1 Symptom Control Rates

With respect to the co-primary endpoints, 100% of the patients in the 8 Gy arm had control of vomiting and retching during the acute phase, and 85% had control during both the delayed and the combined phases. Of patients in the 20 Gy arm, 67% had control of vomiting and retching during the acute phase, 83% had control during the delayed phase, and 67% had control during the combined phase. Notably, patient 4 in the 20 Gy arm was inadvertently given an antiemetic while admitted to hospital, not in response to new symptoms. Table 2 summarizes symptom control rates in the study arms. Figures 1 and 2 present individual patient symptoms and rescue antiemetic intake events for the 8 Gy and 20 Gy arms respectively.

Concerning the secondary endpoints, 100% of patients in the 8 Gy arm had control of nausea and 100% had control of nausea and vomiting and retching during the acute phase; 62% and 62% had control during the delayed phase; and 62% and 62% had control during the combined phase (Table 2). Among patients in the 20 Gy arm, 67% had control of nausea and 67% had control of nausea and vomiting and retching during the acute phase; 83% and 83% had control during the delayed phase; and 67% and 67% had control during the combined phase (Table 2).

In the 8 Gy arm, the incidence of nausea on a given day ranged from a minimum of 0% of patients on the day of radiotherapy and on day 1 after the day of radiotherapy to a maximum of 23% on day 8 after the day of radiotherapy. The incidence of vomiting or retching, or both, ranged from a minimum of 0% on the day of radiotherapy and on days 1–5 and day 7 after the day of radiotherapy to a maximum of 8% on days 6–8 and day 10 after the day of radiotherapy (Figure 3). In the 20 Gy arm, the incidence of nausea on a given day ranged from a minimum of 0% of patients on days 7–9 after the last day of radiotherapy to a maximum of 17% on all other days. The incidence of vomiting or retching, or both, ranged from a minimum of 0% on the first day of radiotherapy and days 1–5 and days 7–10 after the last day of radiotherapy to a maximum of 17% on day 4 of radiotherapy and day 6 after the last day of radiotherapy (Figure 4). Of the 15 days during which nausea events were experienced by 5

patients in the 8 Gy arm, 10 were described as mild and 5 as moderate; of the 5 moderate days, 4 were experienced by patient 9 (Figure 1). Of the 12 days during which nausea events were experienced by 1 patient in the 20 Gy arm, 5 days were described as mild, 4 as moderate, and 3 as severe (Figure 2).

### 3.2 QOL Scores

All QOL forms but 3 were completed. The exceptions were the assessment of 1 patient in the 8 Gy arm on day 10 after radiotherapy completion, and the assessments of 1 patient in the 20 Gy arm on days 5 and 10 after radiotherapy completion. The mean

(population SD) EORTC QLQ-C30 scores on the physical functioning scale for the 8 Gy arm at baseline and at 5 and 10 days after radiotherapy completion were, respectively, 47.4 (30.9), 44.1 (34.8), and 35.5 (23.1). The corresponding scores for the 20 Gy arm were 54.5 (20.9), 50.7 (23.8), and 50.6 (26.4). The scores on the global QOL scale for the 8 Gy arm at the same time points were 42.9 (21.6), 30.1 (22.1), and 32.6 (18.5). The corresponding scores for the 20 Gy arm were 55.5 (19), 61.68 (25), and 58.34 (20.1).

The baseline FLIE score for all patients was the maximum (126), because none had experienced symptoms before radiotherapy. Of the 3 patients in the 8 Gy arm who had experienced any or a combination of nausea,

TABLE I Characteristics of the study patients

Study arm	Pt ID	Age (years)	Sex	Primary cancer	KPS score	Radiotherapy fields	Vertebral levels irradiated
<i>8 Gy in 1 fraction</i>							
	13	89	Male	Prostate	60	Anterior and posterior	T11–S5
	12	40	Female	Breast	50	Anterior and posterior	T8–T12
	11	70	Male	Lung	60	Anterior and posterior	L1–L3
	10	87	Male	Prostate	70	Anterior and posterior	T8–L1
	9	79	Male	Prostate	60	Anterior and posterior	T11–L3
	8	33	Female	Breast	60	Anterior and posterior	T12–L6 <sup>a</sup>
	7	64	Female	Lung	80	Anterior and posterior	L1–S3
	6	82	Female	Unknown	60	Anterior and posterior	L1–L4
	5	83	Male	Prostate	50	Posterior	T10–L3
	4	72	Male	Unknown	80	Anterior and posterior	T11–L4
	3	70	Male	Kidney	50	Anterior and posterior	T11–L4
	2	70	Female	Lung	60	Anterior and posterior	T7–L3
	1	81	Female	Breast	50	Anterior and posterior	T9–L3
<i>20 Gy in 5 fractions</i>							
	6	73	Female	Breast	70	Anterior and posterior	T11–L2
	5	74	Male	Liver	80	Anterior and posterior	T11–L1
	4	45	Female	Breast	70	Anterior and posterior	T10–L3
	3	64	Female	Lung	60	Anterior and posterior	T9–T12, L3–L5
	2	56	Female	Breast	70	Anterior and posterior	T9–T12
	1	68	Female	Breast	60	Anterior and posterior	T10–L2

<sup>a</sup> Anatomic variant.

Pt = patient; KPS = Karnofsky performance status.

TABLE II Patients with control<sup>a</sup> of nausea and of vomiting and retching

Study arm	Control by treatment phase (%)								
	Nausea			Vomiting and retching			Nausea, vomiting, and retching		
	Acute	Delayed	Combined	Acute	Delayed	Combined	Acute	Delayed	Combined
8 Gy in 1 fraction	100	62	62	100	85	85	100	62	62
20 Gy in 5 fractions	67	83	67	67	83	67	67	83	67

<sup>a</sup> Symptom absent, and no use of antiemetics.



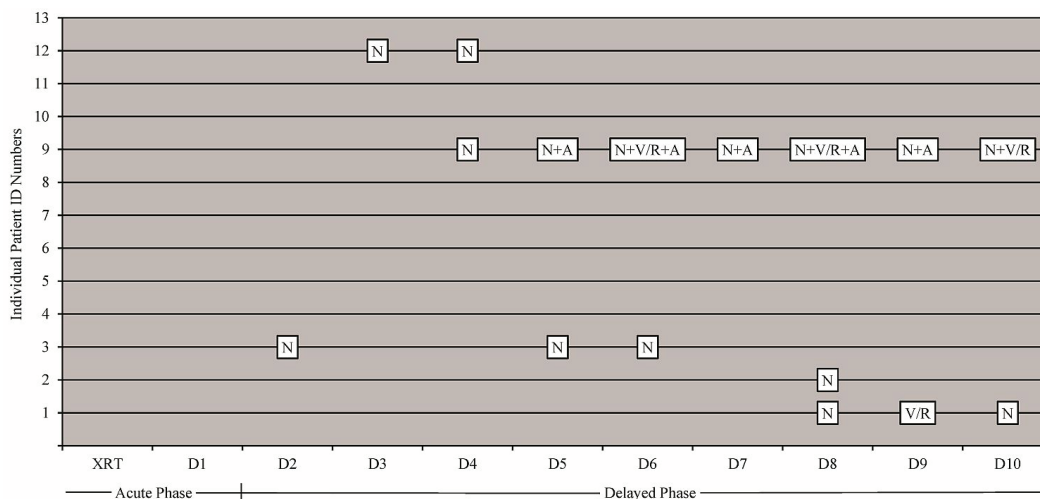


FIGURE 1 Patient symptom and rescue antiemetic intake events for the 8 Gy in 1 fraction arm, from the day of radiotherapy (XRT) until day 10 after the day of radiotherapy (D1 ... D10). Each patient is represented by a single horizontal line. N = nausea; A = use of rescue antiemetic; V/R = vomiting or retching, or both.

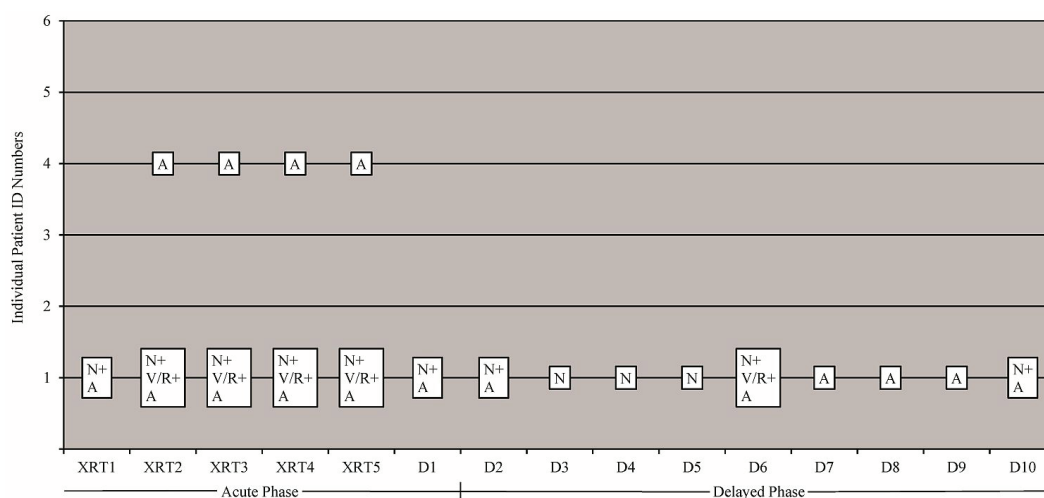


FIGURE 2 Patient symptom and rescue antiemetic intake events for the 20 Gy in 5 fractions arm, from the first day of radiotherapy (XRT1), through the end of radiotherapy (XRT5), until day 10 after the last day of radiotherapy (D1 ... D10). Each patient is represented by a single horizontal line. N = nausea; A = use of rescue antiemetic; V/R = vomiting or retching, or both.

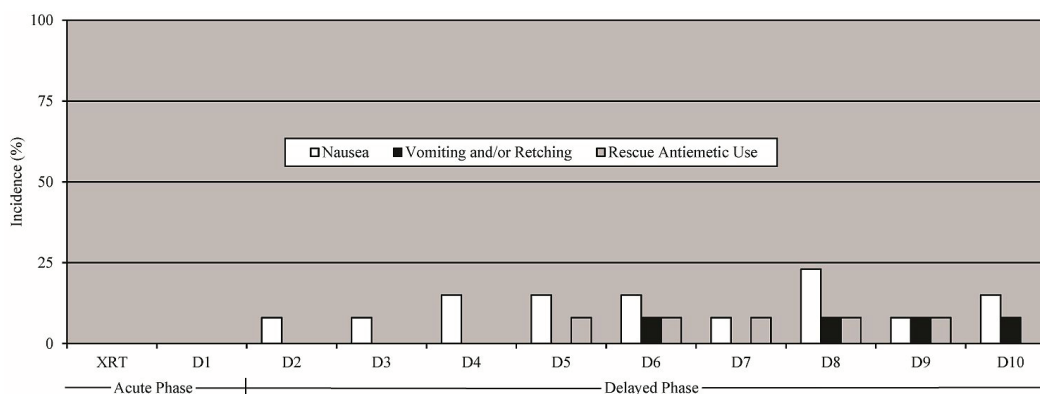


FIGURE 3 Daily incidence rates of nausea, vomiting or retching (or both), and rescue antiemetic use in the 8 Gy in 1 fraction arm. XRT = day of radiotherapy; D1 ... D10 = the 10 days after the day of radiotherapy.

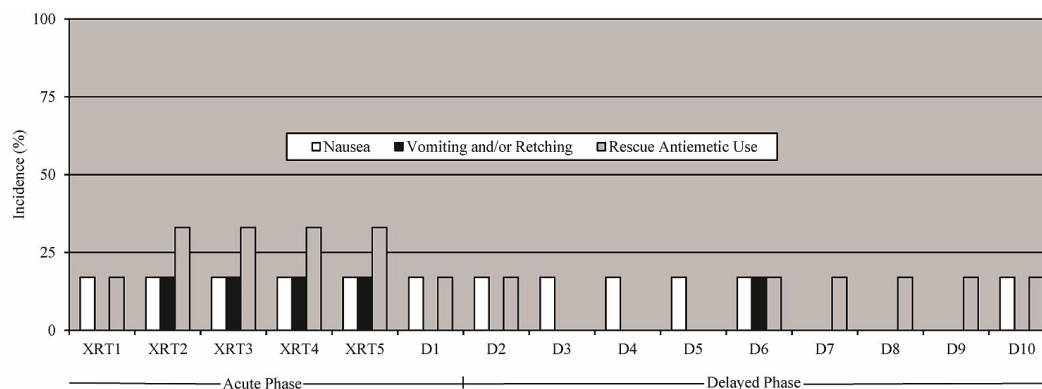


FIGURE 4 Daily incidence rates of nausea, vomiting or retching (or both), and rescue antiemetic use in the 20 Gy in 5 fractions arm. XRT1 ... XRT5 = days of radiotherapy; D1 ... D10 = the 10 days after the last day of radiotherapy.

vomiting, and retching before the QOL assessment on day 5 after radiotherapy completion, the mean FLIE score on day 5 was 105 (SD: 20). Of the 4 patients in the 8 Gy arm who had experienced any or a combination of nausea, vomiting, and retching between the time of the day 5 and 10 assessments, the mean day 10 FLIE score was 108 (SD: 32.2). The FLIE score for the 1 patient in the 20 Gy arm who had experienced nausea before the day 5 assessment was 110 on day 5. The same patient had experienced some combination of nausea and vomiting or retching between the day 5 and day 10 QOL assessments and had a day 10 score of 107.

#### 4. DISCUSSION

To our knowledge, this is the first published report on the use of aprepitant alone or in combination with other antiemetics for the prophylaxis of RINV. Compared with historical control patients receiving prophylaxis with a 5-HT<sub>3</sub>RA alone for identically-defined moderately emetogenic radiotherapy for thoracolumbar bone metastases<sup>3</sup>, patients receiving the combination of aprepitant and granisetron experienced numerically superior control rates both for nausea and for vomiting or retching. Further evaluation of this novel form of RINV prophylaxis in a larger phase II study is warranted. Our high rates of completion for the EORTC QLQ-C30 and FLIE forms also make us hopeful that the effect of symptoms on quality of life can also be determined in the future.

In a conference abstract, Blackstock and colleagues<sup>17</sup> previously reported on a cohort patients receiving aprepitant, a 5-HT<sub>3</sub>RA, and dexamethasone for the prophylaxis of nausea and vomiting secondary to concurrent radiotherapy and chemotherapy for locally advanced or resected pancreatic cancer. That report is the only one of the use of prophylactic aprepitant for patients undergoing radiotherapy that we could identify, but unlike our cohort, that study's patients were also all receiving concurrent chemotherapy, such that the study intervention was aimed at preventing not only RINV, but CINV as well.

At baseline, 3 of 15 patients reported nausea, compared with 4 of 15 after 1 week of treatment and 2 of 13 at the time of treatment completion. However, neither the cumulative symptom incidence rates for all patients nor the proportions of patients receiving rescue antiemetics at the time of individual symptom assessments were reported.

The role of serotonin in the production of RINV is well supported by clinical and translational data<sup>8,9,18</sup>. However, it is unlikely that all RINV is mediated through the 5-HT<sub>3</sub> system because of the reduced efficacy of 5-HT<sub>3</sub>RA for preventing symptoms beyond the early stages of an extended radiotherapy course<sup>11,19–21</sup>. If multiple mechanisms indeed underlie RINV as they are suspected of underlying CINV, then the added benefit of neurokinin 1 receptor antagonists observed in the CINV literature could be relevant to the RINV setting as well. Our data support further testing of that hypothesis.

The antiemetic clinical practice guidelines from both the Multinational Association of Supportive Care in Cancer and the American Society of Clinical Oncology recommend that patients receiving moderately emetogenic radiotherapy be administered prophylaxis with a 5-HT<sub>3</sub>RA, with or without a short course of dexamethasone<sup>1,2</sup>. That recommendation is supported by a separate meta-analysis of nine randomized trials evaluating 5-HT<sub>3</sub>RA for RINV prophylaxis, which estimated that, compared with metoclopramide and placebo, 5-HT<sub>3</sub>RA provide superior control of emesis (relative risk vs. metoclopramide: 0.27; 95% confidence interval: 0.15 to 0.47; relative risk vs. placebo: 0.7; 95% confidence interval: 0.57 to 0.86)<sup>22</sup>. The benefit of 5-HT<sub>3</sub>RA for preventing nausea was, however, less pronounced, which make our high control rates notable. In the present study and in our reference pilot work<sup>3</sup>, we chose not to add dexamethasone to a 5-HT<sub>3</sub>RA because the inclusion of that option in the Multinational Association of Supportive Care in Cancer and American Society of Clinical Oncology guidelines stemmed from a single randomized

trial<sup>11</sup> that enrolled patients receiving radiation therapy of a different duration and dose per fraction than our patients received. Moving forward, we also hope to establish an option for “add-on” therapy that will allow patients to avoid the potential toxicities of corticosteroids.

Of specific relevance to our study, a separate systematic review summarized the per-patient cumulative symptom incidence data that were reported from studies of both randomized and nonrandomized cohorts receiving 5-HT<sub>3</sub>RAs for RINV prophylaxis after moderately emetogenic radiotherapy<sup>23</sup>. Control rates for nausea ranged from 54% to 100% after single-fraction radiotherapy and from 20% to 100% after multiple-fraction radiotherapy. The corresponding control rates for vomiting ranged from 58% to 100% and from 58% to 100%. However, most of the cumulative symptom incidence data from the studies were reported only for the first 24 hours after radiotherapy commencement and the definitions of control varied, so that a true picture of the cumulative symptom burden borne by patients throughout the entire duration of their treatment is lacking.

By comparison, we report all symptom and rescue antiemetic events that our patients experienced until 10 days after radiotherapy completion. Interestingly, despite that extended time at risk for events, the cumulative symptom control rates compared very favourably to the truncated rates from the systematic review<sup>23</sup> and to the rates from our previous study examining 5-HT<sub>3</sub>RA prophylaxis alone<sup>3</sup>. Patients within the 8 Gy arm were particularly well protected during the acute phase; no symptom or rescue antiemetic events were reported. That observation is notable for a number of reasons: Historically, nausea has been considered more difficult to control than vomiting<sup>24</sup>. Compared with conventional radiation doses of 1.8–2.0 Gy, high single doses such as 8 Gy are believed to increase the risk of RINV. In addition, our patients were all taking opioids, which themselves frequently induce symptoms. Further, if patient 4 in the multiple-fraction arm had not inadvertently been administered an antiemetic and had continued to be asymptomatic (no symptom events were recorded during any stage), the control rates for nausea and for vomiting or retching in that arm would have improved by an additional 17%.

Because aprepitant was not, in earlier antiemetic trials, administered to patients undergoing multiple-fraction radiotherapy alone, we made the pragmatic decision to administer that agent on days 1, 3, and 5 of multiple-fraction radiotherapy in the hope that it would be active longer than it might have been if given on the first 3 days. Our dosing schedule also conveniently allowed us to use the same drug supply for both arms and to complete each patient's antiemetic therapy by the end of radiotherapy.

## 5. CONCLUSIONS

The combination of aprepitant and granisetron was safe and efficacious for the prophylaxis of moderately emetogenic radiotherapy for thoracolumbar bone metastases. The regimen produced symptom control rates that were numerically superior to those observed in well-matched historical control patients receiving prophylaxis with a 5-HT<sub>3</sub>RA alone. Further evaluation of this novel form of RINV prophylaxis in a larger phase II study is warranted.

## 6. ACKNOWLEDGMENTS

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## 7. CONFLICT OF INTEREST DISCLOSURES

The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Canada or its affiliates and related companies. MP has received honoraria for consultant activities from Merck, Eisai, Amgen, Hoffman–La Roche, Novartis, and Lundbeck.

## 8. REFERENCES

1. Feyer PC, Maranzano E, Molassiotis A, *et al.* Radiotherapy-induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: update 2009. *Support Care Cancer* 2011;19(suppl 1):S5–14.
2. Basch E, Prestrud AA, Hesketh PJ, *et al.* Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2011;29:4189–98. [Erratum in: *J Clin Oncol* 2014;32:2117]
3. Dennis K, Nguyen J, Presutti R, *et al.* Prophylaxis of radiotherapy-induced nausea and vomiting in the palliative treatment of bone metastases. *Support Care Cancer* 2012;20:1673–8.
4. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, *et al.* on behalf of the Aprepitant Protocol 054 Study Group. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003;97:3090–8.
5. Gralla RJ, de Wit R, Herrstedt J, *et al.* Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5HT<sub>3</sub> antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of combined data from two phase III randomized clinical trials. *Cancer* 2005;104:864–8.
6. Hesketh PJ, Grunberg SM, Gralla RJ, *et al.* on behalf of the Aprepitant Protocol 052 Study Group. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving

- high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003;21:4112–19.
7. Warr DG, Hesketh PJ, Gralla RJ, *et al.* Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol* 2005;23:2822–30. [Erratum in: *J Clin Oncol* 2005;23:5851]
  8. Feyer PC, Stewart AL, Titlbach OJ. Aetiology and prevention of emesis induced by radiotherapy. *Support Care Cancer* 1998;6:253–60.
  9. Wong RKS. Nausea and vomiting induced by radiotherapy [chapter 38]. In: Merrick J, ed. *Alternative Medicine Yearbook 2010*. Hauppauge, NY: Nova Science Publishers; 2011: 333–43.
  10. Kirkbride P, Bezjak A, Pater J, *et al.* Dexamethasone for the prophylaxis of radiation-induced emesis: a National Cancer Institute of Canada Clinical Trials Group phase III study. *J Clin Oncol* 2000;18:1960–6.
  11. Wong RKS, Paul N, Ding K, *et al.* on behalf of the National Cancer Institute of Canada Clinical Trials Group (sc19). 5-Hydroxytryptamine-3 receptor antagonist with or without short-course dexamethasone in the prophylaxis of radiation induced emesis: a placebo-controlled randomized trial of the National Cancer Institute of Canada Clinical Trials Group (sc19). *J Clin Oncol* 2006;24:3458–64.
  12. Chow E, Hoskin P, Mitera G, *et al.* Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Int J Radiat Oncol Biol Phys* 2012;82:1730–7.
  13. Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
  14. Lindley CM, Hirsch JD, O'Neill CV, *et al.* Quality of life consequences of chemotherapy-induced emesis. *Qual Life Res* 1992;1:331–40.
  15. United States, Department of Health and Human Services, National Institutes of Health, National Cancer Institute (NCI). *Common Terminology Criteria for Adverse Events (CTCAE)*. Ver. 4.0. Bethesda, MD: NCI; 2009. [Available online at: [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf); cited April 1, 2013]
  16. Fayers PM, Machin D. Missing data. In: Fayers PM, Machin D, eds. *Quality of Life: The Assessment, Analysis and Interpretation of Patient-Reported Outcomes*. 2nd ed. Chichester, UK: John Wiley and Sons; 2007: 355–84.
  17. Blackstock A, Ayala D, Squire S, *et al.* A reduction in chemoradiation induced nausea and vomiting (CRINV) with prophylactic aprepitant/5HT-3/dexamethasone therapy during upper abdominal chemoradiation [abstract]. *Int J Radiat Oncol Biol Phys* 2009;75:S520.
  18. Scarantino CW, Ornitz RD, Hoffman LG, Anderson RF Jr. On the mechanism of radiation-induced emesis: the role of serotonin. *Int J Radiat Oncol Biol Phys* 1994;30:825–30.
  19. Franzen L, Nyman J, Hagberg H, *et al.* A randomised placebo controlled study with ondansetron in patients undergoing fractionated radiotherapy. *Ann Oncol* 1996;7:587–92.
  20. Lanciano R, Sherman DM, Michalski J, Preston AJ, Yocom K, Friedman C. The efficacy and safety of once-daily Kytril (granisetron hydrochloride) tablets in the prophylaxis of nausea and emesis following fractionated upper abdominal radiotherapy. *Cancer Invest* 2001;19:763–72.
  21. Maisano R, Pergolizzi S, Settineri N. Escalating dose of oral ondansetron in the prevention of radiation induced emesis. *Anticancer Res* 1998;18:2011–14.
  22. Salvo N, Doble B, Khan L, *et al.* Prophylaxis of radiation-induced nausea and vomiting using 5-hydroxytryptamine-3 serotonin receptor antagonists: a systematic review of randomized trials. *Int J Radiat Oncol Biol Phys* 2012;82:408–17.
  23. Dennis K, Makhani L, Maranzano E, *et al.* Timing and duration of 5-HT<sub>3</sub> receptor antagonist therapy for the prophylaxis of radiotherapy-induced nausea and vomiting: a systematic review of randomized and non-randomized studies. *J Radiat Oncol* 2013;2:271–84.
  24. Olver I, Molassiotis A, Aapro M, Herrstedt J, Grunberg S, Morrow G. Antiemetic research: future directions. *Support Care Cancer* 2011;19(suppl 1):S49–55.

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