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Original Research Article

A prospective cohort study of patient-reported vomiting, retching, nausea and antiemetic use during neoadjuvant long-course radiation therapy and concurrent 5-fluorouracil-based chemotherapy for rectal adenocarcinoma

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ABSTRACT

Background and purpose: Antiemetic guidelines suggest daily prophylaxis with a serotonin$_3$ receptor antagonist (5-HT$_3$RA) as an option for patients receiving long-course neoadjuvant radiation therapy and concurrent 5-fluorouracil-based chemotherapy for rectal cancer, despite the risks that 5-HT$_3$RA-induced constipation may pose. We explored the incidence of patient-reported vomiting, retching, nausea and antiemetic intake among patients in this setting to determine if these risks are justified.

Materials and methods: We carried out a single-centre non-randomised prospective cohort study of adult patients receiving long-course neoadjuvant radiation therapy and concurrent 5-fluorouracil-based chemotherapy for rectal adenocarcinoma. Patients recorded symptoms and medication intake daily until 7 days following treatment completion.

Results: From 33 evaluable patients, we collected 1407 days of patient-reported data. Vomiting was reported by 7 patients (21%), retching by 5(15%) and nausea by 21(64%). No patients were administered prophylactic antiemetics. The median number of days with vomiting was 2, and the cumulative number of days for all affected patients was 22 (1.6% of 1407 evaluable days). There were no differences in PTV or small bowel loop V15Gy, V45Gy and V50Gy volumes between patients that did and did not vomit.

Conclusions: The cumulative incidence of days with vomiting was only 1.6%. 5-HT$_3$RA prophylaxis during long-course neoadjuvant treatment seems unnecessary.

Introduction

A standard treatment for locally-advanced rectal adenocarcinoma (i.e., T3-4 or N+) is neoadjuvant long-course pelvic radiation therapy (RT) with concurrent 5-fluorouracil (5-FU)-based chemotherapy, followed by surgery approximately six to eight weeks later [1]. Neoadjuvant RT and chemotherapy reduce the risk of locoregional recurrence compared to adjuvant RT and chemotherapy, but this long-term gain in tumor control comes at the cost of having an often symptomatic tumor remain in situ throughout treatment. Tumors narrow the rectal lumen, putting patients at risk of bleeding, pain and obstruction. Patients are taught to modify their diet and take medications to reduce the risk of constipation and to monitor for symptoms suggesting worsening obstruction.

Nausea and vomiting induced by RT and chemotherapy are common among patients receiving anticancer therapies. International antiemetic guidelines [2–5] estimate that pelvic RT subjects patients to a 30–60% risk of vomiting, while 5-FU-based chemotherapy poses a 10–30% risk. For pelvic RT, these guidelines recommend using a serotonin$_3$ receptor antagonist (5-HT$_3$RA, e.g. ondansetron) as either prophylactic therapy given prior to and throughout RT to prevent vomiting, or as rescue therapy given only after vomiting occurs and then for the remainder of RT.

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We have two main concerns with these recommendations as they apply to neoadjuvant treatment for rectal adenocarcinoma. The first is that the incidence of vomiting in this setting has not been well described and the 30–60% estimate might be inflated. Phase III trials that helped define the role of long course neoadjuvant treatment did not report rates of vomiting [1,6], and anecdotally oncologists generally do not prescribe prophylactic antiemetics in this setting. The largest prospective radiotherapy-induced nausea and vomiting (RINV) observational studies to date cumulatively followed 501 patients receiving pelvic RT [7,8]. Within the two studies respectively, 17% and 10% of these patients reported vomiting at some point during RT. However, pelvic RT was directed towards a heterogeneous group of primary and metastatic tumors involving the rectum, bladder, prostate, uterus, vagina and bone. Also missing from those and most other antiemetic studies is the cumulative incidence of vomiting. Whether a patient receiving weeks of RT is likely to vomit daily or just once is important to determine whether daily prophylactic, or rescue as necessary antiemetics are most appropriate, especially when antiemetics have potential side effects themselves.

Our second concern is 5-HT_3RA-induced constipation, a well-known side effect that can occur soon after administration. Constipation can worsen symptoms and increase the risk of obstruction among patients with rectal adenocarcinoma. The risk could be high if patients receive prophylactic 5-HT_3RA therapy daily for weeks as suggested as an option in the guidelines. Because the cumulative incidence of vomiting in this setting is unknown, whether such a risk is warranted is an open question.

To address our concerns, we carried out a prospective cohort study to investigate the incidence of vomiting, retching, nausea and antiemetic use among patients receiving neoadjuvant long-course pelvic RT and concurrent 5-FU-based chemotherapy for rectal adenocarcinoma. We hypothesised that the incidence of vomiting is lower than the 30–60% antiemetic clinical practice guideline estimate.

Materials and methods

This was a single-centre non-randomised prospective cohort study carried out at the Odette Cancer Centre, Sunnybrook Heath Sciences Centre, Toronto, Canada. The Sunnybrook research ethics board approved the study protocol. Patients gave written informed consent. Research assistants collected all patient-reported data. Enrolment was limited to a four-month period and the entire study duration to a six-month period that was pre-determined by research assistant availability.

Patients were eligible if they: were $\geq$18 years old, understood English alone or with an interpreter, had a Karnofsky Performance Status Scale rating of $\geq$40, and were scheduled to receive neoadjuvant long-course pelvic RT with concurrent 5-FU-based chemotherapy for a histologically-proven adenocarcinoma of the rectum. Patients were ineligible if they: had received prior RT to the abdomen or pelvis (prior superficial RT for cutaneous malignancies was permitted), had received or were scheduled to receive cranial RT during the period from seven days prior to- and seven days following the days of on-study pelvic RT inclusive, or if they were scheduled to receive chemotherapy during the seven days following the last day of on-study RT.

The specific RT, chemotherapy and antiemetic treatment plans were left to the discretion of the treating oncologists, but many features of those plans were similar and defined according to institutional protocol as follows: RT was planned using non-contrast-enhanced computed tomography simulation with patients positioned prone on a belly board with a full bladder. Patients received 50.4 Gy in 28 daily fractions, delivered with 6-18MV photons via either conventional three-dimensional conformal or intensity-modulated radiation therapy (IMRT). Target volumes were consistent with those within international contouring guidelines [9,10]. The gross tumor volume (GTV) included all frank disease identified on imaging, clinical- and endoscopic examination. The clinical target volume (CTV) provided a minimum margin of 10 mm around the GTV, included the mesorectum, the peri-rectal, pre-sacral, and internal iliac nodal regions, but excluded uninvolved natural barriers to spread. The planning target volume (PTV) was a 10 mm expansion around the CTV. For dose volume histogram (DVH) analysis, small bowel loops were contoured to 1 cm above the superior aspect of the PTV. 5-FU-based chemotherapy was either oral capecitabine (825 mg/m^2 twice daily) administered on days of RT or infusional 5-FU (225 mg/m2 daily) administered throughout the entire course of RT.

The following demographic, clinical and RT variables were collected, which include those purported to modulate a patient's risk of developing RINV [2–3,7–8,11]: age, gender, stage, anxiety disorder (yes or no), average daily alcohol consumption (less or more than 100 g), previous RT or chemotherapy, previous nausea and vomiting with RT or chemotherapy, RT total dose and dose per fraction, PTV volume (in cc), and the volume of the small bowel loops (in cc) that received 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 Gy. We were chiefly interested in the volumes receiving 15, 45 and 50 Gy (V15Gy, V45Gy, V50Gy) due to their visibility in other publications related to RT-induced gastrointestinal toxicity [12–13] and their relevance to typical RT prescription doses for adenocarcinoma of the rectum.

Vomiting was defined as the bringing up of stomach contents through the mouth. Retching was defined as the attempt to bring up stomach contents through the mouth without actually doing so. Nausea was defined as the feeling that one might vomit. An antiemetic was defined as any medication taken to prevent or treat vomiting, retching or nausea. A prophylactic antiemetic was one taken prior to treatment in order to prevent symptoms. A rescue antiemetic was one taken to treat symptoms after they developed. Patients documented their symptoms and antiemetic use daily on paper diary forms during the entire study period. Diary form data was verified and recorded daily by research assistants; in-person on days of RT and over telephone on days of RT when in-person collections were not possible or on days following RT completion. Data recorded on weekends and holidays was collected on the next working day. When data was incomplete patients were prompted at the time of collection to recall if possible the missing symptom or anti-emetic data.

Events were categorised according to whether they occurred within the during-RT period (the time interval from the time of RT commencement until the last day of RT inclusive), the after-RT period (the time interval from the first to seventh days following the last day of RT inclusive) or the entire study period (the during- and after-RT periods combined).

The co-primary endpoints were the percentages of patients that reported vomiting within the entire study-, during-RT-, and after-RT periods respectively. The secondary endpoints were the percentages of patients that reported: retching, vomiting and/or retching, nausea, and antiemetic use respectively during all periods, the cumulative incidence of days with-, and the number of days until the first episode of those events during the entire study period.

Descriptive statistics summarised baseline and outcomes data. Independent samples *t*-tests (two-tailed, 0.05 significance level) compared the PTV, small bowel loop V15Gy, V45Gy and V50Gy between patients that did and did not report vomiting respectively. Although we knew the entire study duration would be limited to a 6-month period because of research assistant availability, we performed some power calculations to help set expectations for interpreting our results with respect to the primary endpoint of

vomiting within the entire study period. If we assumed that the true rate of vomiting from the literature was 30% (the low end of the guideline risk estimate range of 30–60%), using one proportional power analysis with a one-sided binomial hypothesis test with a target significance level of 0.05, if we enrolled 20 patients, we would have power values of 0.68, 0.4 and 0.21 to detect differences in the vomiting rate of 20%, 15% and 10% respectively. If we enrolled 40 patients, we would have power values of 0.9, 0.61 and 0.29 to detect differences of 20%, 15% and 10% respectively.

Results

The study was open from May to October 2012. Thirty-four patients enrolled and 33 were evaluable; a single patient withdrew after enrolling and prior to RT. Characteristics of the 33 evaluable patients and their treatments are shown in Table 1. Two patients were prescribed 45 Gy in 25 fractions to reduce the dose to the small bowel. One patient discontinued RT after 45 Gy due to high ileostomy output and hyponatremia requiring admission. One patient discontinued RT after 41.4 Gy due to diarrhea, nausea, vomiting and CT-confirmed pelvic and upper abdominal enteritis requiring admission. One patient was prescribed 40 Gy in 20 fractions.

In total, 1407 evaluable days of patient-reported symptom- and antiemetic use diary data were collected (89% of a potential total of 1575 days). Eighty-five percent of patients had at least one day with missing data (median days missing = 4, range 1–20).

Table 1
Demographics and clinical characteristics of 33 evaluable patients.5-FU = 5-fluourouracil, CINV = chemotherapy-induced nausea and vomiting, CT = chemotherapy, Gy = Gray, RINV = radiation therapy-induced nausea and vomiting, RT = radiation therapy.

		n	(%)
Age (in years)	Median 60, Range 25–87		
Gender	Male	21	(64)
	Female	12	(36)
Stage	I	1	(3)
	III	32	(97)
Prior toxicities	Prior RT	1	(3)
	Prior RINV	0	(0)
	Prior CT	3	(9)
	Prior CINV	1	(3)
Daily alcohol intake	≤100 g	33	(100)
Anxiety disorder	Yes	2	(6)
	No	31	(94)
RT duration (in days)	Median 41, Range 32–51		
RT prescribed	50.4 Gy in 28 fractions	30	(91)
	45 Gy in 25 fractions	2	(6)
	40 Gy in 20 fractions	1	(3)
RT received	50.4 Gy in 28 fractions	28	(85)
	45 Gy in 25 fractions	3	(9)
	41.4 Gy in 23 fractions	1	(3)
	40 Gy in 20 fractions	1	(3)
CT prescribed	Capecitabine	32	(97)
	Infusional 5-FU	1	(3)
CT received	Capecitabine	31	(94)
	Infusional 5-FU	1	(3)
	None	1	(3)

Concerning the co-primary endpoints, 7 of 33 patients (21%) reported vomiting within the entire study period (95% CI [7–35]): 6 patients (18%) within the during-RT period and 1 patient (3%) within the after-RT period (Table 2).

Concerning the secondary endpoints, most events were reported within the during RT period. Nausea was the most common and earliest-reported event (Tables 2 and 3). The median number of days with vomiting was two, and the cumulative number of days for all seven affected patients was 22 (1.6% of the 1407 total evaluable days for all 33 patients). A single patient was responsible for nine (41%) of these days (Fig. 1). Fig. 2 shows the percentage of patients that reported vomiting and retching and nausea daily as a function of patients at risk within the during-RT period.

The mean PTV, mean small bowel V15Gy, V45Gy and V50Gy were similar in patients that did and did not report vomiting (Table 4). Interestingly, the patient that reported the most days with vomiting (Fig. 1) had the second highest V15Gy (394 cc) and the highest V45Gy (161 cc) and V50Gy (81 cc) values amongst the seven patients that reported vomiting.

No patients received prophylactic antiemetics prior to RT initiation. All antiemetics were taken as single agent rescue therapy in response to symptoms except those for one patient who did not initially have symptoms, but began taking them as prophylaxis after RT commencement for a total of 22 days. Of the 11 patients who reported taking antiemetics, 3 took prochlorperazine and dimenhydrinate, 3 took an unspecified agent, 2 took ondansetron, 1 took prochlorperazine and ondansetron, 1 took prochlorperazine and 1 took metoclopramide.

Discussion

This is the first prospective study of which we are aware to chiefly focus on prospectively-gathered patient-reported vomiting, retching, nausea and antiemetic data among patients receiving neoadjuvant long-course pelvic RT with concurrent 5-FU-based chemotherapy for rectal cancer. Our patients received standard neoadjuvant treatment in this setting, making our results widely applicable and relevant. The per-patient incidence of vomiting (21%) was numerically lower than the estimated rates in antiemetic guidelines (30–60%). If we assumed the true rate of vomiting from the literature was 30%, using one proportion power analysis with a one-sided binomial hypothesis test and a target significance level of 0.05, with our sample size of 33 patients we had a low power of 0.28 to detect a real difference in the vomiting rate between the 30% literature estimate and our observed 21% rate. A sample size of 149 patients would have been required to detect a real difference with a minimal power of 0.8.

Although our sample size was underpowered to detect a true difference, the cumulative incidence of days with vomiting over the entire study period was very low (1.6% of all evaluable days). In our opinion, from the point of view of a practitioner deciding between prophylactic or rescue therapy, this cumulative incidence data is clinically different from the 30–60% estimate. Our results suggest that weeks of prophylaxis with a 5-HT_3RA prior to every fraction of RT is unnecessary. Also, given the potential exacerbation

Table 2
Patients reporting symptom events within the during RT-, after RT- and entire study periods. RT = radiation therapy.

	Vomiting n (%)	Retching n (%)	Vomiting and/or retching n (%)	Nausea n (%)	Antiemetic Use n (%)
During RT period	6 (18)	5 (15)	8 (24)	21 (64)	11 (33)
After RT period	1 (3)	0	1 (3)	7 (21)	2 (6)
Entire study period	7 (21)	5 (15)	9 (27)	21 (64)	11 (33)

Table 3
Symptom event frequencies reported within the entire study period.

	Vomiting (n = 7)	Retching (n = 5)	Vomiting and/or Retching (n = 9)	Nausea (n = 21)	Antiemetic Use (n = 11)
Days with events per affected patient [median(range)]	2 (1–9)	2 (1–3)	2 (1–11)	5 (1–36)	3 (1–23)
Days to first event per affected patient [median(range)]	20 (2–43)	24 (6–35)	19 (2–43)	7 (1–37)	20 (2–29)
Cumulative days with events for all affected patients (% of 1407 evaluable days)	22 (1.6)	10 (0.7)	29 (2.1)	210 (14.2)	94 (6.7)

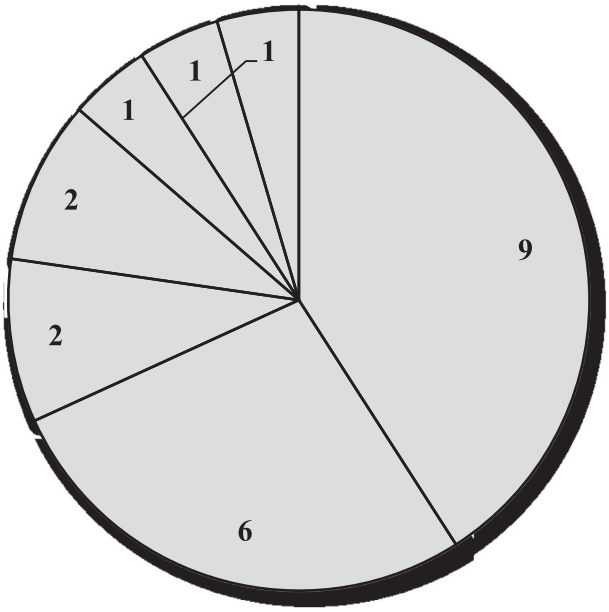

Fig. 1. The number of days that each of the 7 affected patients reported vomiting during the entire study period. Each segment represents an individual patient's days.

of symptoms related to the primary tumor and ongoing RT-induced proctitis, as well as the risk of obstruction that 5-HT_3RA-induced constipation poses to patients in this setting, we believe a recommendation for rescue therapy as necessary within the guidelines would be both sufficient and safe.

The Radiation Oncology Institute stated that identifying best practices for the management of radiation toxicity and issues in cancer survivorship is one of its six research priorities [14], and the ASCO antiemetic guideline specifically highlighted patients suffering from RINV as a special and understudied population [4]. Further, the National Cancer Institute has made the measurement of patient-reported symptoms within clinical trials a priority for future research [15].

Few other studies have prospectively documented symptom outcomes reported by patients undergoing RT and chemotherapy for rectal adenocarcinoma. Randomised trials evaluating these treatments typically reported simple group rates of any grade 3 or 4 non-specific gastrointestinal toxicities, but this type of data does not provide oncologists and patients with an understanding of the timing and frequency of symptoms. In a single-institution report, Chen and colleagues documented symptoms reported weekly by 54 patients like ours, and found that diarrhea, urgency, pain, cramping, mucus discharge and tenesmus were common. Vomiting and nausea were not measured however [12]. Other similar studies gathered data before and after RT from 42 patients [16] and weekly during RT from 12 patients [17], but the timing of RT in relation to surgery was not standardised and the symptom measurement tools did not focus on vomiting and nausea specifically.

Nausea was the most common symptom patients reported in our study. This symptom impacts daily functioning to a greater degree than does vomiting, and although the two are related, they are distinct phenomena. Indeed, most antiemetic regimens for RINV and CINV have demonstrated less effective control for nausea compared to vomiting [18]. Vomiting is an all-or-none symptom well suited to measurement in clinical trials. In contrast, nausea is deeply subjective with variability in frequency, severity and

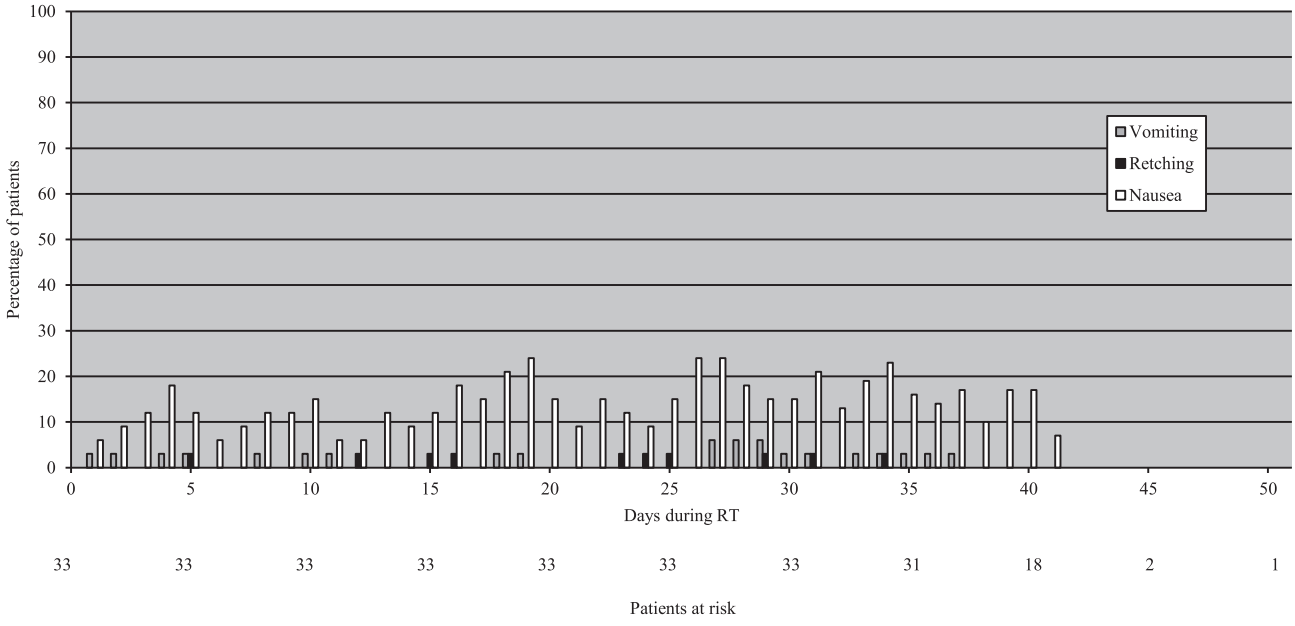

Fig. 2. Percentage of patients reporting vomiting and retching and nausea per day within the during-RT period. RT = radiation therapy.

Table 4
Dosimetric data for patients that did and did not report vomiting during the entire study period. Gy = Gray, PTV = planning target volume, SD = standard deviation, V15Gy = volume receiving 15 Gy, V45Gy = volume receiving 45 Gy, V50Gy = volume receiving 50 Gy.

Volume	Patients reporting vomiting (n = 7)	Patients not reporting vomiting (n = 26)	p value
PTV [mean cc (SD)]	1201 (277)	1495 (470)	0.20
Small bowel V15Gy [mean cc (SD)]	216 (173)	157 (136)	0.34
Small bowel V45Gy [mean cc (SD)]	29 (59)	38 (51)	0.68
Small bowel V50Gy [mean cc (SD)]	13 (30)	20 (28)	0.56

duration. These complicating factors have slowed attempts at study and more progress is needed.

It is believed that the small bowel plays an important role in the production of vomiting, retching and nausea induced by RT [19] but translational work attempting to delineate the mechanisms underlying these symptoms is severely underrepresented. One reason for this is that more observational studies such as ours are needed to first identify patient groups at high risk for symptoms. It is unlikely that expensive and laborious translational work will be funded without proof of a reliable, well suited source of patients to study. Although the volumes of the small bowel receiving 15 Gy and 45 Gy have been suggested as important predictors of gastrointestinal toxicity [12,13], in our study there did not seem to be an apparent relationship with these parameters and the incidence of vomiting. However, both our small sample size and low event rates limit interpretations of these data. This is an important area of study; having dosimetric variables predictive of vomiting, retching and nausea would meaningfully inform future updates of antiemetic guidelines, and allow practitioners to proactively make decisions about prescribing prophylactic or rescue as necessary antiemetics at the time of RT planning, prior to patients commencing RT. Indeed, recent studies involving patients receiving IMRT for cancers of the head and neck have reported brainstem and vestibular dosimetric values that may increase a patient's risk of RINV. Unlike our study that involved daily patient-reported assessments, however, symptom data from these studies was collected retrospectively [20], or was physician-rated [21].

We had missing data from 11% of all potential study days for the cohort, but missing data is common among studies in supportive care due to patient attrition. Given that daily rather than weekly or monthly assessments were made and our data completion levels are respectable, we feel our conclusions are likely to be valid. If one conservatively assumed that vomiting took place during every day of missing data for all patients, the total number of days with vomiting would rise to 190 and still only represent 12% of the 1575 total potential days; considerably lower than the 30–60% guideline risk estimates. RT was delivered in a single phase. However, pelvic RT for rectal cancer is sometimes delivered in two phases, the first over many weeks to a large volume such as that used in our study, and a second over the final few days to a smaller volume [1]. It might be that the incidence of symptoms would be even less with this approach.

In conclusion, our novel cohort study of patients undergoing standard long-course neoadjuvant RT and chemotherapy for rectal adenocarcinoma demonstrated that the per-patient incidence of vomiting (21%) was numerically lower than that estimated in antiemetic guidelines (30–60%). We also demonstrated the value of collecting patient-reported symptom data daily; the very low cumulative incidence of days with vomiting (1.6% of 1407 evaluable days) conveys a dramatically different message than the per-patient incidence. Our results suggest that 5-HT_3RA prophylaxis throughout RT is unnecessary.

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Conflict of interest statement

We declare no financial or personal relationships with other people or organisations that could inappropriately influence (bias) our work.

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