Editor's note:
"Palliative Radiotherapy Column" features articles emphasizing the critical role of radiotherapy in palliative care. Chairs to the columns are Dr. Edward L.W. Chow from Odette Cancer Centre, Sunnybrook Health Sciences Centre in Toronto and Dr. Stephen Lutz from Blanchard Valley Regional Cancer Center in Findlay, gathering a group of promising researchers in the field to make it an excellent column. The column includes original research manuscripts and timely review articles and perspectives relating to palliative radiotherapy, editorials and commentaries on recently published trials and studies.

Palliative Radiotherapy Column (Review Article)

Latest advances in the management of radiation-induced pain flare, nausea and vomiting

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Contributions: (I) Conception and design: N Chiu, E Chow; (II) Administrative support: N Pulenzas; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Palliative radiotherapy (RT) is an effective treatment for symptomatic bone metastases. However, pain flare, nausea and vomiting are common adverse effects associated with this treatment. The management of pain flare and radiation-induced nausea and vomiting (RINV) are important endpoints in palliative care. Our report documents the incidence, clinical importance, and advances in the management of these two adverse-effects. We recommend that antiemetic prophylaxis be given based on emetic risk category as outlined in the American Society of Clinical Oncology (ASCO) guidelines. Newer antiemetics investigated in the chemotherapy setting should also be studied in the radiation setting. As there are no guidelines for the use of pain flare prophylaxis at present, further research in this area is needed.

Keywords: Antiemetics; nausea; pain flare; radiation; vomiting

Submitted Jul 07, 2015. Accepted for publication Aug 07, 2015.
doi: 10.3978/j.issn.2224-5820.2015.08.01
View this article at: http://dx.doi.org/10.3978/j.issn.2224-5820.2015.08.01

Introduction

Palliative radiotherapy (RT) has been well-established as an effective treatment for symptomatic bone metastases (1). In this patient population, response rates often approach 60% (2). Nevertheless, palliative RT is associated with several treatment-related side-effects including pain flare, defined as a temporary worsening in pain (3,4). In addition, RT has shown to lead to radiation-induced nausea and

vomiting (RINV) (5). The management of pain flare and RINV are important objectives in supportive care. Recent developments have been investigated to add to the currently available management options (6,7). The purpose of the current review is to provide a background on pain flare and RINV, as well as to discuss the novel advances in their management.

Pain flare

Pain flare can be defined in one of two ways: (I) as an a priori 2-point increase in worst pain score [0–10] when compared to baseline with no decrease in analgesic intake; or (II) as a 25% increase in analgesic intake with no decrease in worst pain score. In addition, to distinguish between pain flare and progression of pain, a practical proviso should require pain score and analgesic intake to return to baseline after the flare (8). Several studies have reported the incidence of pain flare in patients treated with palliative RT to painful bone metastases (2,3,6,7,9-13).

The incidence of pain flare following palliative RT for symptomatic bone metastases was reported in a study of 111 patients from three different cancer centers in Canada (2). The overall incidence of pain flare was 40% during RT and within 10 days following the completion of RT. Of the patients treated with a single 8 Gy, pain flare incidence was 39%, which was comparable to the 41% of patients who sustained pain flare following multiple fraction radiation. The majority of pain flares occurred within days 1–5 during the 10-day follow-up period, with only 20% of pain flares occurring through days 6–10. As more than 1/3 of patients experienced pain flare, health care professionals should be aware of this phenomenon and treat patients accordingly.

Hird *et al*. conducted a questionnaire interview of 13 patients with pain flare. The authors found that pain flare interfered with patients' daily activities and general functioning (9). Patients also experienced anxiety and worry regarding the success of the treatment. When pain flare occurred, 85% of patients preferred prophylaxis for the management of pain flare rather than an increase in analgesic use, which is associated with adverse events such as dry mouth, drowsiness and constipation (9).

Dexamethasone has been shown to be feasible as a prophylactic agent against pain flare. Two pilot studies, including a phase II study by Hird *et al*., investigated the use of dexamethasone before treatment for prophylaxis (6,7). The first study included 33 patients who were prescribed 8 mg of dexamethasone before RT and reported that only one patient experienced pain flare in the first 2 days of follow-up (7). In the second phase II study by Hird *et al*., 62 patients were prescribed 8 mg of dexamethasone just before receiving a single 8 Gy of palliative RT and for 3 consecutive days afterwards (6). Of the 41 patients evaluable, overall incidence of pain flare was 22% with 55% of these flares occurring on day 5. After the completion of RT, the absence of pain flare for days 1–5 was 83% and 95% for days 6–10. The authors concluded that dexamethasone is effective in the prophylaxis of radiation-induced pain flare after palliative RT for bone metastases and recommended that randomized studies should be done to confirm this finding.

Yousef and El-Mashad randomized 120 patients with bone metastases treated with 30 Gy in 10 fractions to a 24-hour infusion of methylprednisone (5 mg/kg) the day before RT or normal saline infusion. Four patients (6.6%) in the steroid arm and 12 patients (20%) in the placebo arm experienced pain flare ($P<0.05$). The mean duration of the pain flare was 1.25 and 3.75 days, respectively (14). The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) SC23 study is a phase III, double-blind study of dexamethasone *vs*. placebo in the prophylaxis of pain flare following palliative RT for bone metastases (Chow E, NCT01248585, unpublished data). Patients treated with a single 8 Gy were randomized to receive either 8 mg dexamethasone or placebo for 5 days. The accrual has been completed and we await the analysis of the results.

Radiation-induced nausea and vomiting (RINV)

RINV was first described in 1953 as an acute syndrome by Brown (15) and further explained as such by Danjoux *et al*. in 1979 (16). As RINV was initially defined as an acute syndrome, relatively few trials have reported the presence of delayed or prolonged emesis (17). Recognizing this, Presutti *et al*. published a study in 2010 that sought to report the pattern of nausea and vomiting in patients in the moderate risk group receiving prophylaxis with a 5-HT_3 receptor antagonist while undergoing palliative RT for painful bone metastases (17). They defined the acute phase as the beginning of RT up until 24 hours after completion of RT, and the delayed phase as 24 hours after the completion of RT up to 10 days following RT. From the acute to delayed phase, complete control of nausea was observed to decline from 54% to 46% in the single-fraction group and from 67% to 50% in the multiple-fraction group. In addition, complete control of vomiting declined from 92% to 62% in the single-fraction group and from 67% to 50% in the

Table 1 Rates of CP in patients prescribed ondansetron [Dennis *et al.* (20)]

Treatment group	Adverse effect	Rate of CP (%)
Moderate-risk single fraction, acute phase	Nausea	56
	Vomiting	69
Moderate-risk single fraction, delayed phase	Nausea	31
	Vomiting	44
Moderate-risk multiple fraction, acute phase	Nausea	71
	Vomiting	57
Moderate-risk multiple fraction, delayed phase	Nausea	43
	Vomiting	57
Low-risk single fraction, acute phase	Nausea	50
	Vomiting	100
Low-risk single fraction, delayed phase	Nausea	43
	Vomiting	57
Low-risk multiple fraction, acute phase	Nausea	100
	Vomiting	100
Low-risk multiple fraction, delayed phase	Nausea	100
	Vomiting	100

CP, complete prophylaxis.

Table 2 Emetic risk categories of radiation based on ASCO guidelines (21)

Emetic risk [% *]	Irradiated area
High [>90]	√ Total body irradiation
	√ Total nodal irradiation
Moderate [60–90]	√ Upper abdominal irradiation,
	√ Hemi-body irradiation
	√ Upper body irradiation (UBI)
Low [30–60]	√ Cranium
	√ Craniospinal
	√ Head and neck
	√ Lower thorax region
	√ Pelvis
Minimal [<30]	√ Breast and extremities

*, risk of emesis without antiemetic prophylaxis. ASCO, the American Society of Clinical Oncology.

multiple-fraction group. The authors noted that RINV may occur up to 10 days post-RT.

The clinical significance of the delayed phase has been further illustrated in several studies. In a study demonstrating the prevalence of RINV in the delayed phase, Dennis *et al.* prefaced their paper by noting that if deprived of prophylactic treatment, approximately 50–80% of patients undergoing RT would experience symptoms of nausea and vomiting (18). However, Dennis *et al.* showed that even with the aid of prophylaxis, RINV continues to be common among patients undergoing palliative RT for bone metastases (18). In a study designed to investigate the incidence and timing of RINV in bone metastases patients receiving prophylaxis with a 5-HT_3 receptor antagonist, Dennis *et al.* prescribed ondansetron to 59 patients and had them document episodes of nausea and vomiting in daily dairies before and during RT, and up until 10 days after completion of RT. To determine the incidence and timing of nausea and vomiting, rates of complete prophylaxis (CP), defined as no nausea or vomiting events and no rescue medication (19), were calculated for the acute and delayed phases. These CP rates are summarized in *Table 1*. Despite prophylaxis with 5-HT_3 receptor antagonists, RINV was common, especially in the delayed phase.

RINV is among the most common adverse effects of RT and is often the first clear sign of radiation toxicity (5). Despite its clinically important effect of potentially decreasing compliance with treatment (21), RINV continues to be underestimated by radiation oncologists (22).

The Multinational Association for Supportive Care in Cancer (MASCC) and the European Society for Medical Oncology (ESMO) have formulated guidelines for categorizing the risk of emesis due to RT (23). These guidelines have been endorsed by the American Society of Clinical Oncology (ASCO) and are divided into four categories (23). *Table 2* summarizes the emetic risk categories of radiation.

Serotonin (5-hydroxytryptamine; 5-HT) 5-HT_3 receptor antagonists are the first class of antiemetic drug designed specifically to prevent against radiation-induced emesis (RIE) (24). 5-HT_3 receptor antagonists inhibit emesis through the action of 5-HT. Specifically, they block the site of 5-HT_3 receptors on the vagus nerve in the gastrointestinal tract as well as in the section of the brain dedicated to emesis (19). The effectiveness of 5-HT_3 receptor antagonists in treating RINV has been well established (25). However, prior to a randomized trial published in 2006 by Wong *et al.* (25), the role of dexamethasone alone or in combination with 5-HT_3 receptor antagonists was not well-defined. Co-ordinated by the NCIC CTG, Wong *et al.* (25) conducted a placebo-controlled randomized trial of 211 patients to assess the efficacy of prophylactic dexamethasone for the control

of RIE when added to ondansetron during days 1–5 of fractionated RT. The study tested whether ondansetron and dexamethasone could provide superior control of RIE over ondansetron alone during the prophylactic period, and whether the combination could provide sustained control of RIE during subsequent fractions of RT. They found a trend for improved complete control of nausea in the dexamethasone arm during the prophylactic period (50% *vs.* 38%; P=0.06). In addition, patients treated with dexamethasone had statistically significant benefit in terms of complete control of emesis (23% *vs.* 12%; P=0.02) and had a lower average nausea score (0.28 *vs.* 0.39, P=0.03) during the overall study period. Dexamethasone is a potentially useful addition to the 5-HT_3 receptor antagonists in the RT setting.

In their recent practice guideline update for antiemetics published in 2011, ASCO acknowledged the findings of Wong *et al.* (25) and accordingly recommended that patients be offered a short course of dexamethasone during fractions 1–5 as the optimal prophylaxis option for nausea and vomiting caused by moderate emetic risk RT (23). A summary of their full recommendations for antiemetic dosing by radiation risk category is found in *Table 3*.

With the acknowledgement of 5-HT_3 receptor antagonists as effective antiemetics in the prophylaxis of RINV, further studies have been undertaken to examine the comparative efficacy of specific 5-HT_3 receptor antagonists as well as their efficacy when used in combination with aprepitant, a substance P neurokinin 1 receptor antagonist (NK1-RA). Specifically, in a paper published in 2014, Dennis *et al.* completed a pilot study to evaluate, for the first time, the efficacy of a combination of aprepitant and granisetron (a 5-HT_3 receptor antagonist) in patients suffering from RINV after receiving moderately-emetogenic RT for thoracolumbar bone metastases (20). This combination had been shown to be effective in the setting of chemotherapy-induced nausea and vomiting (CINV) (26-29), however, prior to Dennis *et al.*'s study; no published studies had assessed the efficacy of this combination in a RINV setting (20). In their two-armed, nonrandomized prospective pilot study, Dennis *et al.* found control rates for single-fraction patients (n=13) to be 100% for acute nausea, 62% for delayed nausea, 100% for acute vomiting and retching, and 85% for delayed vomiting and retching. In addition, 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. The combination of aprepitant and granisetron produced symptom control rates that were numerically superior to those observed in well-matched historical control patients receiving prophylaxis with a 5-HT_3 receptor antagonist alone.

Further evidence has since favored the use of aprepitant in combination with granisetron. A case report published by Rowbottom *et al.* also described the efficacy of aprepitant prescribed in conjunction with granisetron for a patient who had failed ondansetron in the prophylaxis of RINV (30). In this case, a 47-year-old female patient with extensive bone metastases to the spine from breast cancer was initially prescribed ondansetron as an antiemetic after RT. After unsuccessful prophylaxis in which she experienced severe nausea and emesis, the patient was switched to a course of granisetron and aprepitant. This treatment proved efficacious, and the patient completed the remainder of her radiation treatment with no further emesis and minimal nausea.

Even though some 5-HT_3 receptor antagonists, such as ondansetron, have mainly been prescribed in the form of oral pills (31), patients in the palliative setting may suffer from co-morbidities such as dysphagia that can make it difficult to administer pills orally. As such, rapidly dissolving film (RDF) formulations have been created, and ondansetron has been produced as a dissolvable film formulation (Ondissolve). Wong *et al.* conducted a prospective pilot trial to investigate the efficacy of Ondissolve in patients receiving emetogenic radiation (32). The 30 patients in the study were categorized into primary or secondary prophylaxis groups, with primary prophylaxis patients not having pre-existing emetic episodes. In the primary prophylaxis group, the overall control rates during the acute phase for nausea and vomiting were 89% and 93%, respectively; in contrast, the control rates were 73% and 75% for nausea and vomiting in the delayed phase, respectively. In the secondary prophylaxis group the overall control rates for both nausea and vomiting were 100% for the acute phase, and 50% for the delayed phase. The authors concluded that Ondissolve is effective in the prophylaxis of RINV. Randomized trial of ondansetron *vs.* Ondissolve may be needed as control rates were higher than numerical values historically reported for ondansetron.

Popovic *et al.* sought to compare, through meta-analysis in the chemotherapy setting, the efficacy of palonosetron compared with other 5-HT_3 receptor antagonists (33). Palonosetron is a new generation 5-HT_3 receptor antagonist characterized by a longer plasma elimination half-life (about 40 *vs.* 5.7 hours for the half-

Table 3 Antiemetic dosing based on radiation risk category (ASCO) (21)

Risk category	Drug/dose	Schedule
High emetic risk		
5-HT_3 receptor antagonist	Granisetron[a] √ 2 mg oral dose √ 1 mg or 0.01 mg/kg IV Ondansetron[a] √ 8 mg oral dose 2×/day √ 8 mg or 0.15 mg/kg IV Palonosetron[b] √ 0.50 mg oral dose √ 0.25 mg IV Dolasetron √ 100 mg oral Tropisetron √ 5 mg oral or IV	Administer 5-HT_3 receptor antagonist before each fraction throughout RT and continue for at least 24 hours after completion of RT
Corticosteroid	Dexamethasone √ 4 mg oral or IV	Before fractions 1–5
Moderate emetic risk		
5-HT_3 receptor antagonist	Any of the above listed agents can be acceptably used (preferred options[a])	5-HT_3 antagonist before each fraction throughout RT
Corticosteroid	Dexamethasone √ 4 mg IV or oral	Before fractions 1–5
Low emetic risk		
5-HT_3 receptor antagonist	Any of the above listed agents can be acceptably used (preferred options[a])	5-HT_3 can be used either as rescue or prophylaxis. If used as rescue, then prophylactic therapy should be given until the end of RT
Minimal emetic risk		
5-HT_3 receptor antagonist	Any of the above listed agents can be acceptably used (preferred options[a])	Either class should be given to patients as rescue therapy. Prophylactic therapy should be given until the end of RT if rescue is used
Dopamine receptor antagonist	Metoclopramide √ 20 mg oral Prochlorperazine √ 10 oral or IV	

The MASCC Update Committee suggests that dosing every 2nd or 3rd day may be appropriate for this agent. [a], preferred agents; [b], no data currently available on appropriate dosing frequency with palonosetron. RT, palliative radiotherapy; MASCC, the Multinational Association for Supportive Care in Cancer.

life of ondansetron) and highly-selective binding affinity to the 5-HT_3 receptor (33). Of the 16 randomized controlled trials identified, 2,896 patients were randomized to palonosetron and 3,187 were randomized to other 5-HT_3 receptor antagonists for the prophylaxis of CINV. They found palonosetron to be consistently statistically superior in measures of complete response, complete control, no emesis, no nausea, and sometimes in no rescue medication. Palonosetron was also found to be statistically significantly safer in dizziness and mean QTc interval change.

Palonosetron is safer and more efficacious than other 5-HT_3 receptor antagonists (33). A phase II prospective study of palonosetron in the prophylaxis/rescue of RINV is ongoing in Canada (Chow E, NCT02388750, unpublished data).

The use of a granisetron transdermal delivery system (GTDS) patch in the CINV population with moderately or highly emetogenic multi-day chemotherapy has been proven effective (34). A GTDS patch is an 8×6 cm clear plastic-backed patch with an adhesive layer containing 34.3 mg of granisetron (34). GTDS provides continuous delivery of granisetron over a period of 7 days, and provides similar exposure to an oral dose of 2 mg a day (35). As such, it enables a convenient option for sustaining antiemetic administration throughout a multi-day chemotherapy regimen and may also be beneficial in a radiation setting. In their double-blind, phase III, non-inferiority study, Boccia *et al*. (34) compared the efficacy and tolerability of the GTDS to daily oral granisetron. A total of 582 patients were studied, and complete control was achieved by 60% of patients in the GTDS group, and 65% in the oral granisetron group; as such, the GTDS displayed non-inferiority to oral granisetron. Investigation of the efficacy of a GTDS patch in the radiation setting may yield similar findings.

Another finding from chemotherapy-based prophylaxis studies that might be interesting to investigate in a radiation setting was described by Grote *et al*. (36) in a phase II, open-label study. They investigated the safety and efficacy of palonosetron given in conjunction with dexamethasone and aprepitant in the prophylaxis of CINV. Of the 58 patients evaluable, 88% had a complete response in the acute phase, and 78% in the delayed phase. Moreover, greater than 90% of patients during all time intervals had no emetic episodes, leading the authors to conclude that this particular regimen to be a safe and highly efficacious course of prophylaxis for CINV. Few patients were found to have adverse events considered by the investigators to be related to study medication, however, the most common events were constipation (21% of patients), diarrhea (17%), fatigue (16%), insomnia (14%), and thrombocytopenia (10%) (36). Given the similar underlying mechanism of RINV and CINV, this combination of palonosetron, dexamethasone, and aprepitant may also be efficacious in a radiation setting and should be further investigated.

Finally, a novel oral fixed dose combination of a new NK1-RA called netupitant plus palonosetron (NEPA) has been shown to provide superior prophylaxis of CINV when compared with palonosteron alone (37,38). A randomized phase III published by Aapro *et al*. evaluating the safety and efficacy of NEPA compared the efficacy of a single oral dose of NEPA *vs*. a single oral dose of palonosetron alone (38). In a population of 1,455 patients receiving chemotherapy, the authors discovered that the percentage of patients with complete response in the delayed phase was significantly higher in the NEPA group when compared with the palonosetron group (76.9% *vs*. 69.5%; P=0.001). In addition, the percentages of patients with complete response in the overall (0–120 hours) and acute phases (0–24 hours) were also significantly higher in the NEPA group: 74.3% *vs*. 66.6% (P=0.001) and 88.4% *vs*. 85.0% (P=0.047) respectively. As all patients also received a dose of dexamethasone, Aapro *et al*. concluded that NEPA plus dexamethasone were superior to palonosetron plus dexamethasone in preventing CINV. Again, whether or not this finding can be reproduced in a RINV population would be an interesting study objective to achieve.

Conclusions

The phenomena of pain flare, nausea and vomiting after RT, are important considerations for health care professionals involved in the supportive treatment of patients undergoing palliative RT. The current report sought to provide a background on developments in the area of these two adverse-effects, and to provide an update on recent advances in the field. We recommend that antiemetic prophylaxis be given based on emetic risk category as outlined in the ASCO guidelines. In dealing with RINV, we recommend that further research place greater attention on different prophylactic treatments investigated in chemotherapy studies, and to reproduce such studies in a radiation setting in order to assess whether similar findings might apply. At present, there are no guidelines for the use of pain flare prophylaxis. Further research in this area is needed.

Acknowledgements

We thank the generous support of Bratty Family Fund, Michael and Karyn Goldstein Cancer Research Fund, Joey and Mary Furfari Cancer Research Fund, Pulenzas Cancer Research Fund, Joseph and Silvana Melara Cancer Research Fund, and Ofelia Cancer Research Fund.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Chiu N, Chiu L, Popovic M, DeAngelis C, Pasetka M, Lutz S, Zhang N, Marta GN, Mendez LC, Lechner B, Pulenzas N, Milakovic M, Chow R, Chow E. Latest advances in the management of radiation-induced pain flare, nausea and vomiting. Ann Palliat Med 2016;5(1):50-57. doi: 10.3978/j.issn.2224-5820.2015.08.01

