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REVIEW ARTICLE

Evolution of antiemetic studies for radiation-induced nausea and vomiting within an outpatient palliative radiotherapy clinic

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Abstract

Purpose Radiation-induced nausea and vomiting (RINV) is a common side effect of radiotherapy and can affect up to 50–80% of patients, potentially causing detrimental effects to physical health, clinical efficacy, and patient quality of life. Antiemetic drugs act on receptors involved in the emesis pathway to block the uptake of neurotransmitters and inhibit stimulation of vomiting centers in the brain to prevent and treat RINV. The most commonly prescribed antiemetics for RINV are 5-hydroxytryptamine receptor antagonists (5-HT3 RA). Guidelines describing the optimal management of RINV are produced by the Multinational Association for Supportive Care in Cancer, the European Society of Medical Oncology, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network. This review will present findings from research on antiemetic management for RINV conducted at our center.

Methods A selective review of research conducted in a palliative outpatient radiotherapy clinic relating to antiemetic management for RINV was performed.

Results Several studies investigating the efficacy of different routes of administration, new antiemetic drug types, and novel combinations of antiemetics have been tested at our clinic to elucidate which approach provides the best response. These include studies on the use of ondansetron rapidly dissolving film, palonosetron, and the addition of a neurokinin-1 receptor antagonist to traditional 5-HT3 RA regimens.

Conclusions These studies provide a framework for future research and could potentially inform changes to future guidelines to include the use of these novel regimens and techniques.

Keywords Nausea and vomiting · Antiemetics · Pre-existing emesis · Cancer center

Background

Depending on the site of irradiation, radiation-induced nausea and vomiting (RINV) can affect up to 50–80% of patients as a result of radiotherapy (RT) [1, 2]. RINV may cause nutritional deficiency, weight loss, electrolyte imbalance, and dehydration and could compromise overall survival through treatment delay, termination, or decreased compliance with oncological treatments [3, 4]. The detrimental effects of RINV on quality of life (QOL) are often inadequately addressed, with one European survey finding that the degree of symptom control was often suboptimal and health practitioners underestimated the effect chemotherapy-induced nausea and vomiting (CINV) and RINV had on patient's daily lives, particularly for mild and moderate nausea and vomiting [5]. The negative outcomes associated with RINV establish the need for improved prevention, commonly accomplished through treatment with antiemetics. Antiemetics are medications prescribed for prophylaxis of nausea and vomiting or for use as a rescue treatment once symptoms develop. RINV can occur within 24 h of treatment (acute phase) or within 2–10 days after treatment completion (delayed phase) [6]. The level of emetogenic risk between various RT regimens

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depends on the location of irradiation, dose per fraction, total dose, radiation field size, radiation technique, and concurrent chemotherapy [2]. The Multinational Association for Supportive Care in Cancer (MASCC), the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) have written standardized, antiemetic guidelines for the treatment of RINV based on the emetic risk of RT regimens [7–9]. Table 1 displays the risk categories used by the guidelines to make antiemetic recommendations for RT delivered to various regions of the body.

Antiemetic use

Antiemetics commonly used in clinical practice have evolved as research in RINV and CINV management has revealed superior antiemetic regimens. Historically, metoclopramide, a mixed dopamine receptor antagonist (DRA), and 5-hydroxytryptamine (serotonin) receptor subtype 3 antagonists (5-HT3 RA) were the most commonly used antiemetics. Although metoclopramide is still administered, it carries a risk of sedation and extrapyramidal sensations [3, 10]. Currently, the most frequently recommended antiemetic in standardized guidelines is the 5-HT3 RA as it has the largest body of literature promoting its use for RINV with demonstrated positive results from studies with ondansetron and granisetron [1, 3, 10–13]. Other antiemetics such as dexamethasone (DEX) and neurokinin 1 receptor antagonists (NK-1 RA) have also proven beneficial in RINV treatment but are not as well substantiated within the literature [14–17]. Palonosetron, a second generation 5-HT3 RA, has recently been a research focus due to its marked positive results in a CINV setting for reduction of emetic episodes, particularly in the delayed phase [18]. This has been attributed to the drug's increased binding affinity and longer half-life [18]. The present review aims to investigate the evolution of antiemetic studies for RINV performed in an outpatient palliative radiotherapy clinic at the Odette Cancer Centre and to explore future possibilities for antiemetic use in patients experiencing RINV.

Pathophysiology of RINV

In 1953, Borison and Wang confirmed the existence of a vomiting center (VC) in the brain, which is a collection of neurons in the medulla oblongata that can be affected by several neurotransmitters, including serotonin (5-HT), dopamine, histamine, acetylcholine, and substance-P [19–21]. Various antiemetics prescribed to treat nausea and vomiting induced by cancer treatment act as receptor antagonists to block uptake of these neurotransmitters, thereby preventing excess stimulation of the vomiting center [19–21]. Table 2 shows the classes of common antiemetic drugs, often grouped according to the neurotransmitter receptors they act upon. The primary neurotransmitters responsible for the induction of nausea and vomiting are serotonin and substance-P [22]. Enterochromaffin (EC) cells are responsible for detecting toxic stimuli in the gut and its vasculature [23]. Although the mechanism is not entirely understood, active metabolites of radiation can cause direct damage to EC cells, possibly via generation of free radicals, resulting in the release of serotonin from EC cells which stimulate the vagus nerve via 5-HT3 receptors [23, 24]. These afferent signals travel to the nucleus tractus solitarius (NTS) in the brain via the vagus nerve, arriving at the chemotherapy trigger zone (CTZ) in the area postrema [23, 25]. The CTZ is responsible for transmitting most of the emetogenic stimuli to the VC. These signals activate reflexes in the gut to regulate secretion of digestive enzymes and peristalsis, causing local effects such as smooth muscle relaxation, vasodilation, and secretion of water and electrolytes [26].

Current guidelines

As RINV is believed to have a similar pathophysiology as chemotherapy-induced nausea and vomiting (CINV), the development of therapeutic approaches for these phenomena is similar. A summary of treatment recommendations according to emetogenicity risk group for CINV and RINV from MASCC/ESMO, ASCO, and NCCN is shown in Table 3. Treatment of moderate and high-risk RINV for the acute and delayed phase consists of a 5-HT3 RA and dexamethasone either alone or in combination [7–9]. For low and minimal-risk RINV, a single agent antiemetic of either a 5-HT3 RA, DRA, or dexamethasone is recommended in the acute phase for prophylaxis or rescue therapy [7–9]. A survey of international practice patterns in RINV management demonstrated that 5-HT3 RAs were the most commonly prescribed antiemetics [27]. However, despite the use of a 5-HT3 RA in the prophylaxis of RINV, the control rate of RINV can still be further improved in patients receiving multiple fraction (MF) RT to the upper abdomen and total body irradiation (TBI) where complete control of nausea can be as low as 9% and 26.7%, respectively, and complete control of vomiting can be as low as 12% and 13.3%, respectively [11, 12].

In CINV management, patients receiving highly emetogenic chemotherapy (HEC) are recommended prophylaxis in the acute phase with a regimen consisting of a 5-HT3 RA and dexamethasone, plus either olanzapine, an NK-1 RA, or both [7–9]. For HEC prophylaxis in the delayed phase, the guidelines recommend regimens with various combinations of NK-1RAs, dexamethasone, and olanzapine [7–9]. Patients receiving moderately emetogenic chemotherapy (MEC) are recommended prophylaxis in the acute phase with a regimen consisting of a 5-HT3 RA and dexamethasone with or without the addition of an NK-1 RA or olanzapine. For the delayed

Table 1 Emetogenic risk classification for RINV regimens

Risk level	Risk of emetic event (%)	Site of radiation
High	> 90	Total body irradiation
Moderate	30–90	Upper abdomen, craniospinal
Low	10–30	Cranium, head and neck, thorax, pelvis
Minimal	< 10	Extremities, breast

phase, a one or two-drug regimen with the same drugs mentioned above is recommended [7–9]. A study by Gilmore et al. ($n = 1295$) found that the incidence of no CINV was significantly higher in the guideline-consistent CINV prophylaxis cohort when compared with the guideline-inconsistent CINV prophylaxis group (53.4% vs. 43.8%; $p = 0.001$) [28]. Although it has been suggested that adherence to guidelines produces superior outcomes for patients, a study on international patterns of practice for prescription of RINV antiemetics revealed that just 54% of physician respondents were aware the guidelines existed, and risk estimates and management strategies varied significantly, especially for low- and moderate-risk RT regimens [27].

Methods

A selective review of research pertaining to antiemetic use for RINV management was performed for all studies conducted in the Rapid Response Radiotherapy Program (RRRP) of the Odette Cancer Centre. The RRRP is a palliative outpatient radiotherapy clinic that delivers radiation treatment to advanced cancer patients with the aim of alleviating symptoms from painful bone metastases to improve their QOL. Eligible study participants were recruited from this clinic and consented to participate in studies investigating RINV management with novel antiemetics or new combinations of traditional antiemetic regimens.

Table 2 Drug classes

Class	Drug
1st generation 5-HT3 RA	Ondansetron, granisetron, *metoclopramide
2nd generation 5-HT3 RA	Palonosetron
NK-1 RA	Aprepitant, netupitant, fosaprepitant
Steroid	Dexamethasone, prednisone, prednisolone
DRA	Haloperidol, *metoclopramide, scopolamine
Benzodiazepine	Lorazepam, alprazolam
Cannabinoid	Dronabinol, nabilone

NK-1 RA, neurokinin 1 receptor antagonist; *5-HT3 RA*, 5-hydroxytryptamine receptor antagonist; *DRA*, dopamine receptor antagonist

*Metoclopramide is a mixed DRA and 5-HT3 RA

Results

Efficacy of ondansetron in RINV

An initial study in 2012 at the Rapid Response Radiotherapy Program by Dennis et al. ($n = 32$) documented the incidence and timing of RINV with the use of prophylactic, oral ondansetron in patients receiving single fraction (SF) or MF palliative radiation for bone metastases in moderate- or low-risk emetogenic regions [6]. RT was delivered to the upper abdomen between the vertebral levels of T11-L3 inclusive in the moderately emetogenic group and to the pelvis in the low emetogenic group [6]. RINV was experienced by patients in the SF and MF groups, with rates of complete prophylaxis being lower in the delayed phase for both nausea and vomiting [6]. The incidence of nausea was higher than emesis in the moderately emetogenic SF group (19–44% vs. 0–25%), moderately emetogenic MF group (0–43% vs. 0–29%) and low emetogenic SF group (25–50% vs. 0–29%) [6].

A study by Wong et al. ($n = 30$) investigated the efficacy of an ondansetron rapidly dissolving film (RDF) which was determined to be bioequivalent to ondansetron disintegrating tablets, allowing its use for the same indications as traditional ondansetron tablets. This study found that the overall control for nausea and for vomiting was improved with use of the ondansetron RDF [13]. In this study, complete control was defined as no emetic episodes or no increase of emetic episodes (if pre-existing emesis was present) and no use of rescue antiemetic medication during and after RT. Partial control was defined as an increase of two or fewer emetic episodes from baseline and no use of rescue antiemetic medication during or after RT. Overall control (OC) was defined as the sum of complete and partial control. In the acute phase, OC of nausea and vomiting was found in 88% and 93% of patients ($n = 26$), respectively and in 73% and 75% of patients in the delayed phase, respectively [13]. This study also included a smaller subgroup of patients ($n = 4$) with pre-existing emesis who were treated with ondansetron as secondary prophylaxis to reduce the number of emetic episodes or prevent an increase in emetic episodes [13]. In this group, 100% of patients achieved OC for nausea and vomiting during the acute phase [13]. However, in the delayed phase only 50% had OC for both nausea and vomiting [13]. Patients also completed a six-question self-reported drug administration survey gauging the patient experience of the ondansetron RDF. Of the 26 patients that completed the survey, 22 (84.6%) would choose to use the RDF formulation again over tablets [13].

Efficacy of palonosetron in RINV

A systematic review and meta-analysis by Popovic et al. investigated the use of palonosetron in CINV regimens. This study examined 16 randomized controlled trials (RCT) to

Table 3 Antiemetic regimens recommended by MASCC/ESMO, ASCO, and NCCN for treatment of CINV and RINV

Emetogenicity		CINV			RINV		
		NCCN	ASCO	MASCC/ESMO	NCCN	ASCO	MASCC/ESMO
High	Acute	NK-1RA + 5-HT3 RA + DEX Olanzapine + palonosetron + DEX Olanzapine + NK-1RA + 5-HT3 + DEX	NK-1RA + 5-HT3 RA + DEX + olanzapine	NK-1RA + 5-HT3 RA + DEX	5-HT3 RA + DEX 5-HT3 RA	5-HT3 RA + DEX	5-HT3 RA + DEX
	Delayed	NK-1RA + DEX Olanzapine Olanzapine + NK-1 RA + DEX	DEX + olanzapine Olanzapine	NK-1RA + DEX NK-1RA	None	5-HT3 RA ± DEX	5-HT3 RA ± DEX
Moderate	Acute	5-HT3 RA + DEX + NK-1RA 5-HT3 RA + DEX Olanzapine + palonosetron + DEX	NK-1RA + 5-HT3 RA + DEX 5-HT3 RA + DEX	2nd Gen 5-HT3 RA + DEX	5-HT3 RA + DEX 5-HT3 RA	5-HT3 RA ± DEX	5-HT3 RA ± DEX
	Delayed	5-HT3 RA/DEX Olanzapine Aprepitant ± DEX	DEX	DEX/None	None	5-HT3 RA ± DEX	5-HT3 RA ± DEX
Low	Acute	DEX/metoclopramide/5-HT3 RA/prochlorperazine	5-HT3 RA/DEX	DEX/5-HT3 RA/DRA	No routine use	No routine use	DEX/DRA/5-HT3 RA/no routine use
	Delayed	No routine use	No routine use	No routine use	No routine use	No routine use	No routine use
Minimal	Acute	No routine use	No routine use	No routine use	No routine use	No routine use	No routine use
	Delayed	No routine use	No routine use	No routine use	No routine use	No routine use	No routine use
Adjunct		Lorazepam H2 RA PPI	Lorazepam	N/A	N/A	N/A	N/A
Breakthrough or Rescue	Acute	Add an additional agent from a different drug class 5-HT3 RA NK-1 RA Steroid: DEX DRA: haloperidol, metoclopramide, scopolamine Phenothiazine: prochlorperazine, promethazine Benzodiazepine: lorazepam Atypical antipsychotic: olanzapine Cannabinoid: dronabinol, nabilone	Add an additional agent from a different drug class 5-HT3 RA NK-1 RA Steroid DRA Atypical antipsychotic: olanzapine Lorazepam/alprazolam Cannabinoid: dronabinol, nabilone	Add an additional agent from a different drug class 5-HT3 RA NK-1 RA Steroid DRA Atypical antipsychotic: olanzapine Benzodiazepine	Add an additional agent from a different drug class 5-HT3 RA NK-1 RA Steroid: DEX DRA: haloperidol, metoclopramide, scopolamine Phenothiazine: prochlorperazine, promethazine Benzodiazepine: lorazepam Atypical antipsychotic: olanzapine Cannabinoid: dronabinol, nabilone	Add an additional agent from a different drug class 5-HT3 RA Steroid: DEX DRA	Add an additional agent from a different drug class 5-HT3 RA Steroid: DEX DRA

/, or; *DEX*, dexamethasone; *NK1 RA*, neurokinin 1 receptor antagonist; *5-HT3 RA*, 5-hydroxytryptamine receptor antagonist; *2nd Gen*, second generation; *DRA*, dopamine receptor antagonist; *PPI*, proton pump inhibitors; *H2 RA*, H2 histamine receptor antagonist

analyze 2896 patients randomized to palonosetron and 3187 patients randomized to other 5-HT3 RAs [18]. Primary endpoints for this study included complete response (CR; defined as no emetic episodes and no use of rescue medication), complete control (CC; defined as no emetic episodes, no use of rescue medication, and no more than mild nausea), no emesis, no nausea, and no use of rescue medications [18]. Through examination of overall efficacy in acute and delayed phases with odds ratios (OR) and confidence intervals (CI), palonosetron was statistically superior to other 5-HT3 RAs in rates of CR (OR = 1.54, 95% CI 1.34–1.77), CC (OR = 1.54, 95% CI 1.31–1.81), no emesis (OR = 1.54, 95% CI 1.32–1.80), no nausea (OR = 1.51, 95% CI 1.20–1.88), and no use of rescue medications (OR = 1.53, 95% CI 1.11–20.13) [18]. Side effects such as constipation, headache, and diarrhea were similar between palonosetron and other 5-HT3 RAs [18]. Palonosetron was found to be safer with regard to dizziness (OR = 2.15, 95% CI 1.05–4.41) and mean QTc interval increase after treatment ($p = 0.002$), although only three RCTs reported this measure [18]. This study concluded that for CINV, palonosetron was safer and more efficacious than other 5-HT3 RAs.

The success of palonosetron in the CINV setting, particularly for treatment in the delayed phase where rates of control have been historically lower, prompted our group to evaluate the efficacy of oral palonosetron 0.5 mg administered every other day during RT to low to moderate emetogenic risk areas for RINV prophylaxis [29]. Patients were followed from the day of RT to 10 days after completion of RT [29]. Palonosetron was able to achieve complete control of vomiting in 93.3% in the acute phase and 93.2% in the delayed phase [29]. Complete control of nausea was 74.7% in the acute phase and 74.0% in the delayed phase [29]. The side effects of RINV prophylaxis included mild headache in 12.7% of patients and mild or moderate constipation in 70.4% of patients during the study period [29]. Another study conducted by our group to assess the efficacy of palonosetron in controlling RINV in patients with pre-existing emesis found that control was higher in the acute phase for nausea with complete prophylaxis achieved in 42.9% of patients while complete prophylaxis was achieved in 71.4% for vomiting [30]. In the delayed phase, complete prophylaxis for nausea and vomiting was only achieved in 7.7% and 53.8%, respectively [30]. A decrease in antiemetic use, or episodes of nausea and/or vomiting from baseline was achieved in 42.9% and 21.4% for acute nausea and vomiting, respectively, and 42.9% and 15.4% for delayed nausea and vomiting, respectively [30].

Efficacy of NK-1 RAs with 5-HT3 regimens

A case report by Rowbottom et al. described a patient undergoing moderately emetogenic lumbar spine irradiation and experienced severe nausea and vomiting with prophylactic, oral ondansetron. The patient was switched to oral granisetron and aprepitant and for the remainder of RT, after which only mild nausea and no further episodes of emesis were reported [31]. This demonstrated the addition of aprepitant to traditional 5-HT3 RA regimens may be beneficial for patients, prompting further study of this combination.

A prospective pilot study by Dennis et al. ($n = 19$) tested the efficacy of a combined regimen of granisetron and aprepitant prophylaxis in moderately emetogenic RT for thoracolumbar bone metastases given in single or multiple fractions [32]. Control was defined as no episodes of vomiting and/or nausea and no use of rescue therapy for the duration of the study. Control rates for acute nausea and vomiting were both 100% and reduced to 62% and 85% for delayed nausea and vomiting, respectively for SF patients ($n = 13$) [32]. For patients receiving MF RT ($n = 6$), the control rates were both 67% for acute nausea and vomiting, and 83% for delayed nausea and vomiting [32]. No grade 3 or 4 toxicities related to the study intervention were observed, indicating that this regimen was safe for RINV management in patients receiving moderately emetogenic RT [32].

Discussion

Studies at the Odette Cancer Centre have demonstrated the efficacy of two different routes of administration of ondansetron for management of RINV. Potential improvements in the complete control of nausea and vomiting with palonosetron were indicated, particularly in the delayed phase. Also, the role of the addition of an NK-1 RA such as aprepitant to traditional 5-HT3 RAs could have the potential to improve outcomes for patients experiencing RINV. Studies conducted at the Odette Cancer Centre investigated the efficacy of ondansetron for RINV management. The study by Dennis et al. demonstrated that despite prophylaxis with ondansetron, incidence rates for RINV for SF and MF RT to moderate and low emetogenic regions were substantial, supporting the need for improved antiemetic treatment [6]. Potential methods to improve traditional 5-HT3 RA antiemetic regimens will be discussed below. In addition, this study highlighted the importance of delayed RINV management as both the SF and MF moderately emetogenic groups and the SF low-risk group experienced significant rates of nausea and vomiting throughout RT and up to 10 days following RT completion [6]. The 2015 study by Wong et al. found ondansetron RDF was safe, efficacious, and easy to use, according to patient reports [10]. This alternative route of administration is particularly important for palliative patients with comorbidities such as dysphagia or pre-existing nausea and vomiting that make swallowing tablets difficult.

The Ganesh et al. studies conducted at our center are the first to address the use of palonosetron in a radiation-only

setting with promising results. However, in the chemoradiation setting, several studies have been conducted that show a benefit for RINV and CINV prevention with the use of palonosetron. Ruhlmann et al. demonstrated that in patients using prophylactic palonosetron and prednisolone to prevent nausea and vomiting while receiving chemoradiation, 57% had complete control of emesis [33]. However, patients free from nausea deteriorated from 42% at first cycle to only 23% after 5 cycles and at least 50% of patients used rescue antiemetic treatment at least once during the 5 cycles [33]. Affronti et al. demonstrated that a weekly dose of palonosetron in patients with malignant glioma receiving chemoradiation was safe and tolerable [34].

One limitation from the studies conducted at our center is that they were all conducted in low and moderately emetogenic risk regions. This is due to the nature of the study population which consisted of patients undergoing palliative RT to symptomatic bone metastases. Therefore, patients undergoing high-risk TBI could not be included in our studies. Although the presented results may not be generalizable to those receiving RT with high emetic risk, our results have provided new evidence to support the use of palonosetron for RINV prophylaxis in patients who receive low and moderate emetic RT. Despite this demonstrated benefit with the use of palonosetron, current RINV guidelines by MASCC/ESMO, ASCO, and NCCN do not recommend palonosetron for any risk level. Further evidence is needed to confirm the benefit of palonosetron in different RINV risk regimens and to determine the optimal timing and dosage.

Although the role of NK-1 RAs in the management of CINV is well established, the use of NK-1 RAs in RINV has not been thoroughly studied. The case report by Rowbottom et al. provides preliminary evidence for improved symptom control in RINV-only settings with the addition of NK-1 RAs to traditional 5-HT3 RA regimens [31]. Recent publications on the use of NK-1 RAs in the chemoradiation setting will be discussed below.

Most studies have small sample sizes of patients solely receiving RT to moderate- or high-risk regions or receiving concurrent chemotherapy and radiation. A prospective, observational study conducted in Germany compared a regimen consisting of aprepitant, a 5-HT3 RA (ondansetron or tropisetron), and dexamethasone, with a control regimen consisting of only a 5-HT3 RA and dexamethasone in patients receiving chemoradiation with cisplatin for a heterogeneous group of cancers [16]. Complete response (CR) was achieved in 75.9% and 64.5% for cycles 1 and 2 for the experimental group and 60.7% and 54.2% for the control group, respectively [16]. A 15.2% absolute difference was reached in cycle 1; however, this was not statistically significant ($p < 0.2$) [16]. This study indicated that the addition of an NK-1 RA is effective for patients receiving chemoradiation, and therefore, may demonstrate utility for radiation alone.

A randomized controlled trial by Emami et al. divided 40 patients with pathologically indicated abdominal malignancies into an ondansetron-alone group or ondansetron with aprepitant for the prevention of RINV while undergoing RT to the abdominopelvic region [35]. Patients treated with ondansetron only experienced a higher frequency and grade of RINV than the group treated simultaneously by aprepitant and ondansetron (OR = 21.2; $p < 0.01$), demonstrating the superiority of a combination of ondansetron and aprepitant in this study [35]. In an observational study with patients receiving RT to the upper abdomen with concurrent radio-sensitizing chemotherapy, oral ondansetron and aprepitant were administered every Monday, Wednesday, and Friday throughout the course of RT [36]. This regimen demonstrated effective control of RINV with CR in 58% of patients, control of vomiting in 73% (95% CI 59.0–84.4%), and no use of rescue medication during the treatment period in 71% (95% CI 56.9–82.9%) [36]. However, this study did not demonstrate the superiority of ondansetron with the addition of aprepitant in comparison with ondansetron monotherapy as dosed in this trial. These studies suggest possible clinical utility for the addition of an NK-1 RA to traditional 5-HT3 RA regimens in RINV prophylaxis.

In the GAND-emesis study, cervical cancer patients who were receiving MF RT with weekly cisplatin were administered intravenous palonosetron and oral dexamethasone with random assignment to receive fosaprepitant intravenously or a saline placebo in combination before cisplatin administration [17]. Complete control at 5 weeks was demonstrated in 65.7% of patients in the fosaprepitant group compared with 48.7% in the placebo group [17]. There was a significantly lower cumulative risk of emesis in the experimental group (subhazard ratio 0.58 (95% CI 0.39–0.87); $p = 0.008$) [17].

In another study, locally advanced head and neck cancer and esophageal cancer patients receiving MF RT concurrent with HEC were randomized to receive olanzapine, palonosetron, and dexamethasone (OPD) or fosaprepitant, palonosetron, and dexamethasone (FPD) [16]. The OPD and FPD regimens had similar complete response rates [16]. CR for acute and delayed phase was 88% and 76% for the OPD regimen and 84% and 74% for the FPD regimen, respectively [16]. Nausea in the delayed and overall period was significantly better using the OPD regimen compared with the FPD regimen, 71% vs 40% for delayed nausea and 71% vs 40% overall (both $p < 0.01$) [16]. Additionally, a study by Matsuda et al. noted that 76.2% of malignant glioma patients treated with chemoradiation and given aprepitant, palonosetron, and dexamethasone as prophylaxis could sustain a CR during the treatment period [15]. Overall, the available evidence in chemoradiation patients suggests that NK-1RAs, with or without olanzapine, may increase the control rates of RINV without compromising safety. The benefits of using new, higher-cost drugs as part of RINV prophylaxis should be balanced with efficiency of resource allocation in cancer centers.

Conclusion

This review summarized a series of antiemetic studies done at a single, specialized cancer program to highlight several emerging therapies for RINV management. These include the addition of NK1-RAs such as aprepitant to traditional regimens of 5-HT3 RAs and dexamethasone in moderate-risk regions. Additionally, the clinical utility of palonosetron for patients receiving moderately or low emetogenic risk radiotherapy regimens was indicated for use in the delayed phase in particular. Future research into the optimal management for patients with pre-existing nausea and vomiting is suggested, as preliminary studies conducted at our center have indicated prophylactic antiemetic treatment can result in superior management of nausea and emesis. Future discussions surrounding antiemetic guidelines for RINV should consider the use of these emerging therapies. Improving the treatment of RINV has the potential to enhance patient outcomes and QOL as well as reduce unscheduled medical consultation visits, emergency attendances, and hospital admissions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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