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REVIEW ARTICLE

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Radiotherapy-induced nausea and vomiting (RINV): antiemetic guidelines

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Abstract As many as 40–80% of patients undergoing radiotherapy (RT) will experience nausea and/or vomiting, depending on the site of irradiation. Fractionated RT may involve up to 40 fractions over a 6–8 weeks period, and prolonged symptoms of nausea and vomiting could affect quality of life. Furthermore, uncontrolled nausea and vomiting may result in patients delaying or refusing further radiotherapy. Nausea and vomiting are often underestimated by radiation oncologists. Incidence and severity of nausea and vomiting depend on RT-related factors (single and total dose, fractionation, irradiated volume, radiotherapy techniques) and patient-related factors (gender, general health of the patient, age, concurrent or recent chemotherapy, psychological state, tumor stage). Current antiemetic guidelines prescribe the emetogenicity of radiotherapy regimens and recommend the use of 5-HT_3 antagonists with or without a steroid for prophylaxis in moderately and highly emetogenic treatment (MASCC, ASCO, ASHP, NCCN). The new proposed guidelines summarise the updated data from the literature and take into consideration the existing guidelines. According to the irradiated area (the most frequently studied risk factor), the proposed guidelines are divided into four levels of emetogenic risk: high, moderate, low and minimal. They offer guidance to prescribing physicians for effective antiemetic therapies in RINV.

Keywords Radiotherapy-induced nausea and vomiting · Risk factors · 5-HT-$_3$ antagonists · Guidelines

Introduction

Published observational trials on radiotherapy-induced nausea and vomiting (RINV) highlight that the overall cumulative incidence of vomiting and nausea is about one third of patients undergoing radiotherapy. Also highlighted was the attitude of radiation oncologists in prescribing antiemetic drugs as a rescue, with a large range of doses and schedules, and that 5-hydroxytryptamine (5-HT_3) antagonists rather than other antiemetics were generally being used [7, 6, 9, 35].

Patients submitted to total body irradiation (TBI), half body irradiation (HBI) or abdominal radiotherapy are at major risk of nausea and vomiting. Few randomised

controlled clinical trials have evaluated the efficacy of various antiemetic drugs in preventing RINV. Published trials have shown that dopamine receptor antagonists were effective in only about 50% of patients whereas 5-HT_3 antagonists were more effective in up to 80% of patients [24, 33].

Current practice guidelines for RINV

Current MASCC, ASCO, ASHP and NCCN practice guidelines for the use of antiemetics in radiotherapy are quite different when classifying radiation emetogenic risk categories and giving indications for the use of antiemetic drugs [3, 13, 22, 34, 37]. This diversity of recommendations reflects the limited amount of high-level evidence available to date [i.e. few randomised controlled trials (RCTs) and small number of patients entered in each trial]. The following differences are the most important:

1. ASCO guidelines classified only TBI at high risk, whereas MASCC, NCCN and ASHP guidelines added to this group abdominal bath and HBI
2. Moderate-risk categories were quite different: thorax and pelvis were classified as low risk by ASCO and at moderate risk by MASCC
3. Two therapeutic attitudes are suggested: prophylaxis, giving the antiemetic drug(s) before each radiotherapy fraction; or rescue, on an as-needed basis beginning as soon as symptoms (usually nausea) develop. For high-risk levels (5-HT_3 antagonists) and low-risk levels (no prophylaxis), the antiemetics suggested by the guidelines are similar while for patients at moderate-risk level, there are clear differences in the guidelines; MASCC suggests prophylaxis or rescue with 5-HT_3 antagonists eventually associated with dexamethasone (DEX) whereas ASCO suggests only prophylaxis with dopamine receptor antagonists or 5-HT_3 antagonists without DEX. No recommendations are given in the ASHP guidelines for moderate emetogenic risk.

Only the NCCN guidelines discuss the combination of radiotherapy and chemotherapy. The combination increases the chance of nausea and vomiting. The antiemetic treatment is determined by the chance of vomiting occurring with the chemotherapy and not the radiation therapy. So the same nausea and vomiting antiemetic treatment is given for patients receiving a combination of radiotherapy and chemotherapy as that given for chemotherapy-related nausea and vomiting [22].

Observational trials

The incidence and management of RINV have been evaluated in some observational studies [7, 6, 9, 35]. The first survey showed that although approximately one third of radiotherapy patients experienced nausea and vomiting, the vast majority (85%) were not prescribed antiemetics [1]. Another study, from the Italian Group for Antiemetic Research in Radiotherapy (IGARR) [33], reinforced the tendency of radiation oncologists in not prescribing antiemetics. In fact, only a minority (14%) of patients received an antiemetic drug, and the prescriptions were more often symptomatic rather than prophylactic (9 and 5%, respectively). More often, a 5-HT_3 antagonist was prescribed by the oral route and at a wide variety of doses and schedules. The IGARR study provided evidence that the overall cumulative incidence of vomiting and nausea was about 40% of patients undergoing radiotherapy and that the irradiated site and radiation field size (>400 cm^2) were significant radiotherapy-related risk factors whereas previous chemotherapy was the only patient-related factor. Age, gender and alcohol consumption did not result as significant prognostic factors. Considering irradiated site and emetogenic risk, upper-abdomen irradiation resulted as the "most emetogenic" regimen. Unfortunately, RINV was not evaluable in patients submitted to TBI or HBI due to the small number of patients who received these therapies during the survey [35].

A European survey on 200 radiation oncologists from France, Italy, Germany, Spain and the UK suggested that 5-HT_3 antagonists are under-used in patients receiving radiotherapy. Only 52% of patients who received highly emetogenic radiotherapy (radiotherapy site: gastrointestinal or abdominal) actually received a 5-HT_3 antagonist. There are also differences in the prescribing procedure between the evaluated countries [7]. A 5-HT_3 antagonist was more frequently prescribed if the patient received radiation with chemotherapy than in radiotherapy alone (46 versus 33%). Similar results are demonstrated by Goldsmith [9] with data from the United States.

Randomised clinical trials

Few small randomised clinical trials have evaluated the efficacy of various antiemetic drugs in preventing RINV. Generally, patients entering these trials are those submitted to TBI, HBI or upper-abdomen irradiation because of the higher risk of developing nausea and/or vomiting.

Prophylaxis with non-5-HT_3 antagonists

Three randomised trials on RINV in patients treated with fractionated radiotherapy to the abdomen and thorax were published before the introduction of 5-HT_3 antagonists. In the first study, 39 patients were randomised to receive oral metoclopramide or nabilone. In the second, 89 patients were treated with oral metoclopramide, prochlorperazine or placebo, and in the third, 11 patients received

tetrahydrocannabinol or prochlorperazine [24, 29, 39]. Only one randomised study has been carried out with 43 patients submitted to single-fraction palliative radiotherapy to the thoracic and/or lumbar spine. In this study, chlorpromazine was compared with two different doses of levonantradol [18]. All these studies enrolled a small number of patients (median 46) and showed no difference among the various compounds determining a limited antiemetic efficacy (complete protection of vomiting in only about 50% of cases).

Prophylaxis with 5-HT_3 antagonists

In the last decade, the 5-HT_3 antagonists have been used more extensively in clinical practice to treat RINV. Tables 1 and 2 show randomised trials with 5-HT_3 antagonist or corticosteroids in patients submitted to radiotherapy with single or fractionated regimens. Different compounds and a wide range of doses and schedules have been used. One interesting trial evaluated the efficacy of an escalating dose of oral ondansetron (OND) in the prevention of emesis induced by fractionated radiotherapy. The dose-adapted regimen of OND was effective and showed the possibility to reduce costs without compromising the activity [19]. Antiemetics were generally started 1–2 h before radiotherapy and usually continued until the end of irradiation when a fractionated regimen of dose was adopted. The oral route was prevalent (70%). The seven published trials regarding patients submitted to upper-abdomen irradiation showed that 5-HT_3 antagonists achieved significantly greater protection for RINV than metoclopramide, phenothiazines or placebo (Table 1; [1, 4, 8, 15, 17, 25, 26]). Also, in patients treated with TBI or HBI, 5-HT_3 antagonists gave a significantly better protection for RINV than placebo or conventional antiemetics (Table 2; [23, 30, 31, 32, 36]).

Furthermore, Spitzer [31] showed in his randomised trial that granisetron (GRAN) and OND are equally effective in controlling emesis during TBI [31]. One further trial confirmed that a 5-HT_3 antagonist (GRAN) achieved a significantly greater protection for RINV than placebo in patients undergoing fractionated upper-abdomen irradiation [15]. That trial compared 1 mg of oral GRAN bid versus 2 mg of the same drug once a day in patients submitted to fractionated radiotherapy to abdomino-pelvic area and showed no significant differences between the two modalities in controlling RINV [17]. Further reports support the efficacy of 5-HT_3 antagonists in RINV [12, 14].

Side effects were evaluated and compared by Goodin [10]. The side-effect profile is particularly important in certain subgroups of patients, including pediatric patients, the elderly and those suffering from comorbid conditions, such as cardiovascular disease and renal or hepatic impairment. Clinicians are encouraged to evaluate patients on an individual basis when choosing which 5-HT_3 an-

Table 1 Randomized clinical trials with 5-hydroxytryptamine antagonists or steroids in patients submitted to upper abdomen irradiation. *OND* ondansetron, *MTC* metoclopramide, *DOL* dolasetron, *PCP* prochlorperazine, *p.o.* orally, *i.v.* intravenously

Author, publication year (no. of patients)	Radiotherapy regimen	Antiemetic randomization	Percent of complete response	Results
Priestman, 1990 (82)	8–10 Gy single fraction	OND 8 mg×3/day p.o. for 5 days	97%	OND better than MTC
		MTC 10 mg×3/day p.o. for 5 days	46%	
Priestman, 1993 (135)	1.8 Gy/day for at least 5 fractions	OND 8 mg×3/day p.o.	61%	OND better than PCP (for vomiting)
		PCP 10 mg×3/day p.o.	35%	
Bey, 1996 (50)	At least 6 Gy single fraction	DOL 0.3 mg/kg i.v.	100%[a]	DOL better than placebo
		DOL 0.6 mg/kg i.v.	93%[a]	
		DOL 1.2 mg/kg i.v.	83%[a]	
		placebo	54%[a]	
Franzen, 1996 (111)	At least 1.7 Gy/day for $\geq$ 10 fractions	OND 8 mg×2/day p.o.	67%	OND better than placebo
		placebo	45%	
Aass, 1997 (23)	2 Gy/day to 30 Gy in 15 fractions	TRO 5 mg/day p.o.	91%	TRO better than MTC
		MTC 10 mg×3/day p.o.	50%	
Lanciano, 2001 (260)	10–30 fractions (1.8–3 Gy/fraction)	GRAN 2 mg/day	57.5%	GRAN better than placebo
		placebo	42%	
Lewis, 2002 (40) (available only as an Abstract)	1.5–2Gy/day to a total dose of 25–50.4 Gy	GRAN 2 mg/day (once a day)	Not reported	Once a day better than bid (nausea)
		GRAN 2 mg/day (bid)		
Kirkbridge, 2000 (154)	At least 5 fractions to minimum total dose of 20 Gy	DEX 2 mg×3/day p.o. for 5–7 days	70%	DEX better than placebo
		Placebo	49%	

[a] Complete plus major response

Table 2 Randomized clinical trials with 5-hydroxytriptamine antagonists in patients submitted to total-body irradiation (TBI) and half-body irradiation (HBI). *OND* ondansetron, *GRAN* granisetron, *MTC* metoclopramide, *LOR* lorazepam, *CLP* chlorpromazine, *DEX* dexamethasone, *p.o.* orally, i.v. intravenously

Author, publication year (no. of patients)	Radiotherapy regimen	Antiemetic randomization	Percent of complete response	Results
Tiley, 1992 (20)	10.5 Gy TBI single fraction	OND 8 mg i.v. placebo	90%[a] 50%[a]	OND better than placebo
Spitzer, 1994 (20)	1.2 Gy×3/day TBI 11 fractions to a total dose of 13.2 Gy	OND 8 mg×3/day p.o. Placebo	50% 0%	OND better than placebo
Prentice, 1995 (30)	7.5 Gy TBI single fraction	GRAN 3 mg i.v. versus MTC 20 mg i.v. plus DEX 6 mg/m^2 i.v. plus LOR 2 mg i.v.	53% 13%	GRAN better than MTC+DEX+LOR
Huang X, 1995 (116) (Abstract only; article in Chinese)	7–7.7 Gy TBI single fraction	OND 8 mg (i.v.?) plus DEX 10 mg (i.v.?) versus paspertin 10 mg plus DEX 10 mg (i.v.?)	84% 20%	OND+DEX better than paspertin+DEX
Sykes, 1997 (66)	8–12.5 Gy HBI single fraction	OND 8 mg×2 p.o. versus CLP 25 mg×3 p.o. plus DEX 6 mg×3 p.o.	94% 34%	OND better than CLP+DEX
Spitzer, 2000 (34)	1.2 Gy×3/day TBI 11 fractions to a total dose of 13.2 Gy	OND 8 mg×3/day p.o. versus GRAN 2 mg×1/day p.o.	47% 61%	No difference

[a] All patients received intravenous dexamethasone (8 mg) and phenobarbitone (60 mg/m^2)

tagonist to prescribe. Headache and/or constipation were the most common adverse events registered with the use of 5-HT$_3$ antagonists [23, 25, 26, 30]. Sometimes, rather than causing constipation, 5-HT$_3$ antagonists reduced the frequency of diarrhoea, a troublesome side effect due to acute radiation enteric toxicity [6, 8].

Prophylaxis with corticosteroids

In chemotherapy-induced emesis, corticosteroids (above all DEX) are also suggested as single agents for the prevention of delayed emesis or in combination with a 5-HT$_3$ antagonist for patients receiving highly emetogenic chemotherapy [34, 33]. Their widespread availability, low cost, and benefit make corticosteroids very interesting antiemetic drugs. To date in radiotherapy, no prospective randomised studies have been published evaluating the addition of corticosteroids to the 5-HT$_3$ antagonist in comparison to the 5-HT$_3$ antagonist alone [28]. Regarding the use of DEX as a single agent for the prophylaxis of RINV, a double-blind study has recently been published [13]. Patients enrolled received fractionated radiotherapy to the upper abdomen and oral DEX (2 mg×3/day) or placebo only in the first week of radiotherapy even though the courses lasted up to 6 weeks (Table 1). Complete protection from RINV was significantly better in the DEX group with acceptable side effects but with no overall positive effect on global quality of life. Considering that the majority of emetic episodes occurred early in the treatment, it is possible that prophylactic antiemetics may not be necessary for a full course of radiotherapy but only for the first week [13]. More studies evaluating the efficacy of steroids compared to 5-HT$_3$ antagonists or in combination with them may answer these questions.

Rescue

The role of antiemetics given on an as-needed basis has been investigated in two randomised trials [16, 20]. In the first one [16], 455 patients who developed emesis and/or moderate/severe nausea after receiving fractionated radiotherapy to sites located between thorax and pelvis were randomised to receive one of the following treatments: two placebo orally disintegrating tablets (odt); one 8-mg OND odt and one placebo odt (OND 8 mg group); two 8 mg OND odt (OND 16 mg group). The study showed that OND was clinically superior to placebo independent of the OND dose prescribed. Both OND 8 mg and 16 mg doses increased treatment success over the 12 h after treatment compared with placebo (53 and 56% respectively compared with 41% for placebo). Statistically significant differences were observed between OND 8 mg and placebo (p=0.026) and between OND 16 mg and placebo (p=0.008). There was no significant difference between the two doses of OND. Considering that (a) routine prophylactic antiemetic treatment is generally not prescribed from radiation oncologists in the clinical practice, and that (b) prophylaxis is not always appropriate for patients who are receiving radiotherapy, LeBourgeois et al. [16] conclusions are that there is a need for an ef-

fective symptomatic antiemetic treatment. This trial showed that OND odt (8 mg) given as a rescue treatment can control emesis and nausea effectively in radiotherapy patients who have established symptoms [16].

The IGARR [33] recently closed a double-blind randomised clinical trial in patients undergoing fractionated radiotherapy to the upper abdomen comparing prophylactic OND plus DEX versus placebo and, if sickness was registered, a cross-over rescue treatment. Of the 400 patients planned as the sample size to reach in three consecutive years, only 155 patients entered the trial (of which 153 were evaluable). Comparing OND plus DEX prophylaxis with placebo, vomiting was registered in 30 and 40% and nausea in 57 and 67% of cases, respectively. The 10% of major control in the group treated with OND plus DEX was not statistically significant. Examining rescue treatment, the placebo given to the group of patients who developed vomiting in spite of the prophylaxis with OND plus DEX was effective in 24% of cases whereas when vomiting was not controlled with placebo given as a prophylactic drug, the rescue with OND plus DEX was effective in 64% of cases. Thus, when a rescue treatment was used, OND plus DEX was significantly more effective than placebo in controlling vomiting (64 versus 24%, p=0.003). On the contrary, nausea was controlled in 56% of cases in both rescue treatment groups. In conclusion, this study showed that (a) in clinical practice, radiation oncologists generally under-value the problem of nausea and vomiting in radiotherapy and do not participate in trials about RINV; and (b) antiemetic rescue treatment seems to be as effective as prophylaxis provided it is administered when the first symptom(s) appear(s). It should be further explored if this timeline on administration of rescue antiemetics can be applicable in the clinical practice [20].

Two open pilot studies evaluated the use of rescue treatment using a 5-HT_3 antagonist in patients failing to achieve relief with common antiemetics [21, 27]. In the first study, four patients who had RINV after prophylaxis with prochlorperazine and metoclopramide received rescue treatment with OND. All patients achieved complete protection from vomiting [27]. In the second, 34 patients experiencing RINV during fractionated radiotherapy to the abdomen were treated with tropisetron, which controlled vomiting in 73% of cases [21]. The potential role of 5-HT_3 antagonists as rescue medication has been suggested in all these reports.

Evaluating the best antiemetic strategy in RINV

In order to achieve an optimal treatment strategy to prevent nausea and/or vomiting, it could be useful to develop a risk-adjusted treatment for RINV. Therefore, the individual risk of the patient to develop nausea and/or vomiting should be taken into consideration as well as the emetogenicity of the radiotherapeutic regimen and any simultaneous administration of chemotherapy.

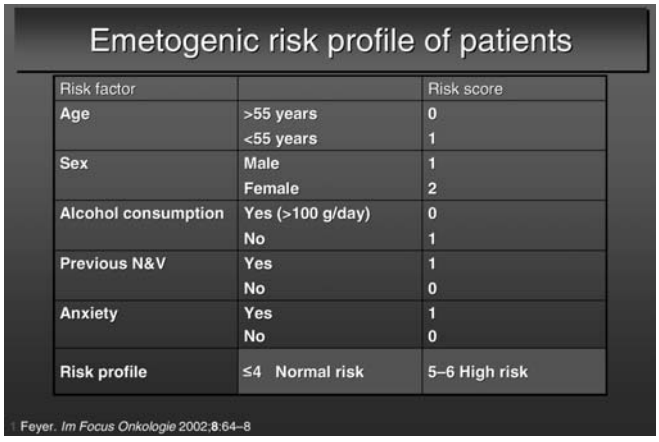

Fig. 1 Individual risk factors according to patient-related emetogenic risk factors [33].

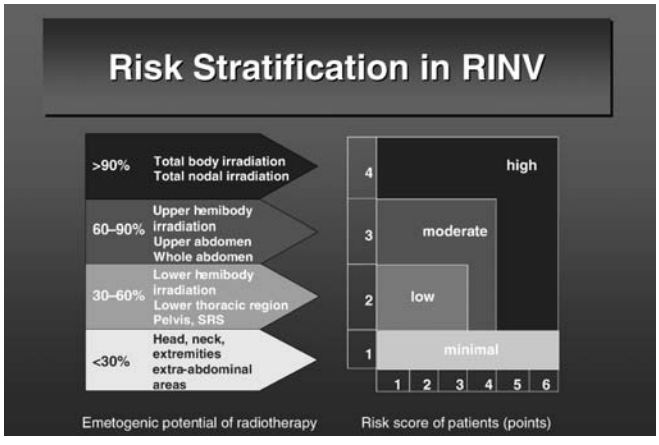

Fig. 2 Risk evaluation of emetogenic potential [33].

Patient factors are known to influence the risk of emesis in cancer patients. For example, previous chemotherapy-induced emesis is a significant prognostic factor for developing RINV (IGARR [33]). Individual risk profiles according to patient-related emetogenic risk factors are age, gender, alcohol consumption, previous experience of nausea and vomiting and anxiety (Fig. 1). The emetogenic potential of radiotherapy is divided into high, moderate, low and minimal, as is the emetogenicity of cytotoxic drugs. Using this tool, it is possible to develop a risk-adjusted treatment for RINV (Fig. 2).

Conclusions

After the last MASCC Consensus Conference in 1997, new data on RINV suggested a need to update the existing guidelines. Therefore, an Antiemetic Consensus Conference Perugia 2004 was held. Data from the literature were evaluated, and relevant data with evidence of levels I and

Table 3 Radiotherapy-induced emesis: Radiation emetic risk levels and new MASCC and ASCO guidelines

Risk level	Irradiated area	Antiemetic guidelines	MASCC evidence (level of scientific confidence/ level of consensus)	ASCO evidence (type of evidence/grade of recommendation)
High	Total body irradiation	1: Prophylaxis with 5-HT_3 antagonists	1- High/High	1: II/B
		2: +dexamethasone	2- Moderate/High	2: III/C
Moderate	Upper abdomen	Prophylaxis with 5-HT_3 antagonists	High/High	II/A
Low	1: Lower thorax region and pelvis	Prophylaxis or rescue with 5-HT_3 antagonists	1- Moderate/High	1: III/B
	2: Cranium (radiosurgery) and craniospinal		2- Low/High	2: IV/D
Minimal	Head and neck, extremities, cranium and breast	Rescue with dopamine receptor antagonists or 5-HT_3 antagonists	Low/High	IV/D

II were included. These provided the basis for the new proposed guidelines discussed by the experts and described below.

There are three RCTs in patients with fractionated radiotherapy [24, 29, 39] and one with single-fraction radiotherapy [18] investigating the efficacy of non-5-HT_3 antagonists in radiotherapy of the upper abdomen. There was no difference among the various compounds used, and the antiemetic efficacy was limited. The only double-blind RCT on corticosteroids suggested that the use of DEX resulted in a significantly better control of RINV than did placebo [13]. There are a number of trials with 5-HT-$_3$ antagonists for patients treated with total-body or upper-abdomen irradiation [38]. The 5-HT_3 antagonists gave a significantly greater protection from radiotherapy-induced emesis (RIE) than placebo or non-5-HT_3 antagonists.

The limited research on rescue therapy in RINV suggest that 5-HT_3 antagonists are clinically superior to placebo [16]. There is additional need to investigate the importance of the individual risk factors of the patient, the incidence of delayed nausea and vomiting and the duration of antiemetic treatment as well as the duration of the effect of the antiemetic treatment.

According to the irradiated area (the most frequently studied risk factor), the guidelines are divided into four levels of risk: high, moderate, low and minimal emetogenic risk of the radiotherapy. The new guidelines are shown in Table 3.

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