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SPECIAL ARTICLE

2016 updated MASCC/ESMO consensus recommendations: prevention of radiotherapy-induced nausea and vomiting

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Abstract
Purpose Radiotherapy-induced nausea and vomiting (RINV) are distressing symptoms. Evidence-based guidelines should facilitate the prescription of the best possible antiemetic prophylaxis. As part of the MASCC/ESMO Antiemetic Guidelines Update 2016, a thorough review of the literature concerning RINV since the 2009 update was required.
Methods A systematic review of the literature including data published from June 2009 to May 2015 was performed. Committee VII (RINV) under the MASCC/ESMO Antiemetic Guidelines Update Committee assessed the literature.
Results The searches yielded 926 records, 906 records were excluded, leaving 20 records for full text assessment, and 18 publications were finally included. The only fully published randomized studies in prevention of RINV were two negative studies in acupuncture and green tea, respectively. No data to support new recommendations for antiemetic prophylaxis in RINV was available. However, based on expert opinions, the committee agreed on changes in emetic risk level for certain sites of irradiation.
Conclusions The serotonin receptor antagonists are still the corner stone in antiemetic prophylaxis of nausea and vomiting induced by high and moderate emetic risk radiotherapy. The studies available since the last update did not change recommendations for antiemetic prophylaxis. The emetogenicity of craniospinal radiotherapy was reclassified from low to moderate emetic level along with some other minor changes. In the future, RINV prophylaxis in single fraction, multiple fraction, and in concomitant chemo-radiotherapy still need to be explored with regard to the different classes and combinations of antiemetic drugs.

Keywords Antiemetics · Guideline · Nausea · Radiotherapy · Vomiting

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Introduction

Approximately 50 % of patients with a cancer diagnosis receive radiotherapy either as curative or as palliative treatment [1]. For patients receiving curative radiotherapy, it is critical that they receive the treatment as scheduled as tumor control may be compromised if overall treatment time is prolonged. Nausea and vomiting may lead to interruptions or delays of radiotherapy due to patient refusal, dehydration, and electrolyte disturbances; hence, optimal antiemetic prophylaxis is crucial. In the palliative setting, higher doses per fraction can result in acute nausea and vomiting which is unacceptable as

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the treatment is administered in the hope of relieving symptoms and optimizing quality of life [2].

Radiotherapy-induced nausea and vomiting (RINV) are under-treated, as demonstrated in several observational studies, with few patients receiving antiemetics as prophylaxis [3–5]. Antiemetic practice guidelines offer health care providers a tool to administer effective antiemetic drugs according to the evidence available, and societies as the Multinational Association of Supportive Care in Cancer (MASCC), European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), as well as the National Comprehensive Cancer Network (NCCN) provide such guidelines.

The last MASCC/ESMO Antiemetic Guidelines Update Consensus Conference was held in 2009, and on June 28, 2015 the MASCC/ESMO Antiemetic Guidelines committees gathered to update the guidelines at a consensus meeting in Copenhagen, Denmark. The present article discusses the literature available since the last update in 2009 [6], and presents the updated antiemetic guideline for RINV, which is also available at www.mascc.org/antiemetic-guidelines.

Literature review and methods

The systematic review of the literature included data published from June 2009 to May 2015. Medline and Cochrane databases were explored using search terms for antiemetic treatment (5-HT_3 receptor antagonists, NK_1 receptor antagonists, dopamine receptor antagonists, and corticosteroids), nausea, emesis, vomiting, radiotherapy, RINV, concomitant chemotherapy, and risk factors. All titles and abstracts of the references from the search were screened by two members of the committee. Abstracts were excluded if the studies were not focused on nausea and vomiting experienced by patients receiving radiotherapy or combined chemo-radiotherapy, if they covered pediatric patients, or if they were written in a language other than English.

The members of the MASCC/ESMO Antiemetic Guidelines Committee VII (RINV) assessed the remaining literature, and three teleconferences with discussions and conclusions preceeded the final proposal for the RINV guideline update, which was presented at the MASCC/ESMO Antiemetic Guidelines Consensus Conference in Copenhagen, Denmark, June 28, 2015.

Results

The search yielded 926 records, 906 records were excluded, leaving 20 records for full text assessment, and 18 publications were finally included (Fig. 1). Four studies were classified as reviews [6–9]; one study was a meta-analysis [10];

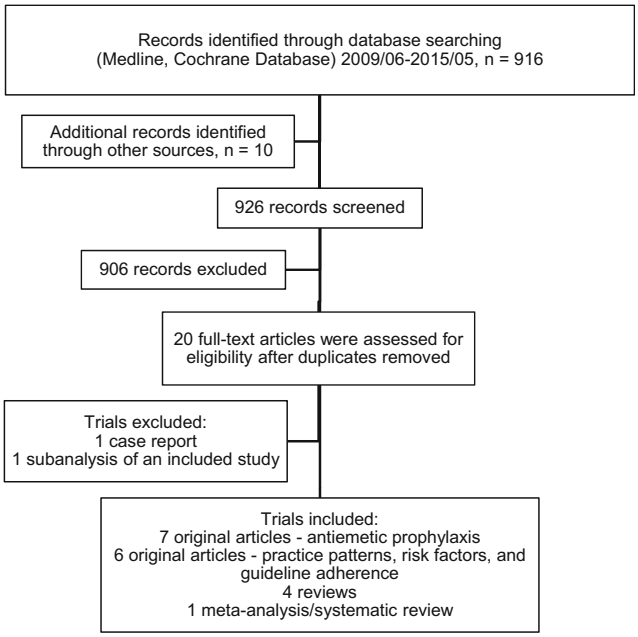

Fig. 1 Flow chart of search strategy and study selection

seven studies were clinical efficacy studies [11–18]; and six studies (five prospective studies and one retrospective study) concerned risk factors, practice patterns, and guideline adherence [2, 5, 19–22]. The studies are reviewed and discussed below.

Risk classification

The emetic risk of radiotherapy is divided into four risk levels; high, moderate, low, and minimal (Table 1). The risk levels depend on the site of radiation and do not take into account radiation dose, fractionation, or technique, or other proposed risk factors. The risk classification is mainly based on incidence of emesis in clinical studies and expert opinions. Two observational studies by the Italian Group for Antiemetic Research in Radiotherapy (IGAAR), identified that irradiated site (upper abdomen), field size >400 cm^2, and concomitant chemotherapy, are independent risk factors for development of RINV [4, 5].

For the development of chemotherapy-induced nausea and vomiting (CINV), several patient-related risk factors have been identified, including female gender, younger age, history of nausea/emesis, anxiety, and non-habitual alcohol intake [23, 24]. In RINV, only previous treatment with chemotherapy has been identified as a patient-related risk factor [4, 5]. As proposed at the last guideline update, a scoring system including patient-related risk factors would be useful in order to individualize the antiemetic prophylaxis [6, 9]. However, the model has not been prospectively validated.

Radiotherapy planning systems provide dosimetry data that should be explored with respect to the risk of RINV. The radiation dose and volume of small bowel is likely a measure

Table 1 Radiotherapy emetic risk levels and MASCC/ESMO antiemetic guidelines update 2016

Emetic risk level	Area of treatment	Antiemetic recommendation	MASCC evidence (level of confidence/level of consensus)	ESMO evidence (level of evidence/grade of recommendation)
High	Total body irradiation	Prophylaxis with a 5-HT_3-RA + DEX	High/high (for the addition of DEX: moderate/high)	II /B (for the addition of DEX: III/C)
Moderate	Upper abdomen, craniospinal	Prophylaxis with a 5-HT_3-RA + optional DEX	High/high (for the addition of DEX: moderate/high)	II/A (for the addition of DEX: II/B)
Low	Cranium	Prophylaxis or rescue with DEX	Low/high	IV/D
	Head and neck, thorax region, pelvis	Prophylaxis or rescue with DEX, a dopamine RA, or a 5-HT_3-RA	Low/high	IV/D
Minimal	Extremities, breast	Rescue with DEX, a dopamine RA, or a 5-HT_3-RA	Low/high	IV/D
Concomitant CRT	In concomitant radiochemotherapy, the antiemetic prophylaxis is according to the chemotherapy-related antiemetic guidelines of the corresponding risk category, unless the risk of emesis is higher with radiotherapy than chemotherapy		Low/high	IV/D

5-HT_3-RA 5-HT_3-receptor antagonist, *CT* chemotherapy, *CRT* chemo-radiotherapy, *DEX* dexamethasone, *RT* radiotherapy

that could be used to predict RINV, and radiation dose to the medulla oblongata and brain stem including the essential parts of the central emetic pathway is also thought to be predictive. The latter has been explored in small hypothesis-generating studies. One study prospectively analyzed the association between RINV and dosimetry for the dorsal vagal complex, and the vestibules in 49 patients receiving intensity-modulated radiation therapy (IMRT) for nasopharyngeal carcinoma [21]. Antiemetic prophylaxis was not permitted. Nausea was reported by 14 patients, and vomiting was reported by eight patients. On multivariate analysis only V40 (the volume receiving 40 Gy) to the combined vestibules of ≥80 % was predictive of radiotherapy-induced nausea. Few patients had nausea when V40 was less than 80 %. No predictor of radiotherapy-induced vomiting was found.

A retrospective study aimed at defining organs at risk (OARs) and potential constraints for those OARs in the interest of reducing RINV [20]. Data from 91 patients receiving IMRT for squamous cell carcinoma of the head and neck, already enrolled on a longitudinal patient reported outcome assessment study, was extracted from a database and analyzed. On univariate assessment, associations were found between any nausea and/or vomiting and dorsal vagal complex <29.6 Gy; mean brainstem <36 Gy; area postrema V24 < 76 %; whole brain V16 < 5 %; and nucleus solitarius V20 < 99 %. After multivariate analysis, only area postrema V24 < 76 % retained significance.

These two studies, aiming to bring dosimetric predictors into clinical use, add importantly to the literature. However, the limited validity of symptom reporting, the sample size, and for the latter study the retrospective nature of symptom assessment, do not provide sufficient evidence to influence guidelines.

Antiemetic efficacy studies in radiotherapy

Since the 2009 update, no randomized, controlled antiemetic studies in RINV have been published. The studies available were previously covered in the 2009 update, and in summary, the studies evaluated efficacy of dopamine RAs, 5-HT_3 RAs, and corticosteroid as RINV prophylaxis in patients receiving multiple fraction or single fraction radiotherapy to sites mainly including the upper abdomen. In conclusion, prophylaxis with 5-HT_3 RAs was superior to dopamine RAs or placebo [25–31], and one study suggested that adding corticosteroid to a 5-HT3 RA further improves efficacy over multiple fractions [32]. Furthermore, prophylaxis with a 5-HT_3 RA was superior to rescue medication with a 5-HT_3 RA [33]. In total body irradiation (TBI), small studies demonstrated that prophylaxis with a 5-HT_3 RA was superior to placebo [34], 5-HT_3 RA plus corticosteroid was superior to corticosteroid alone [35, 36], and comparison between two different 5-HT_3 RAs (ondansetron and granisetron) showed no difference [37].

In 2010, a systematic review and meta-analysis evaluated prophylaxis with 5-HT_3 RAs in single or multiple fraction radiotherapy [10]. The analysis included studies comparing ondansetron, dolasetron, tropisetron, or granisetron to placebo, metoclopramide, prochlorperazine, or chlorpromazine. Nine studies were included in the analysis, and different sites of irradiation (abdominal, lower half body, lumbar spine, pelvis, or gynecologic areas) were represented. Managing the heterogeneity in primary endpoints, antiemetic schedules,

and radiotherapy regimens, the authors concluded that 5-HT_3 RAs are superior to placebo or dopamine RAs in prevention of emesis during radiotherapy. The evidence is less concrete for the control of nausea, and the dose and duration of prophylaxis with a 5-HT_3 RA remain unclear, as well as comparison between different 5-HT_3 RAs, and evaluation of newer drugs such as palonosetron are unsettled areas of investigation. Thus, the analysis does not change existing guideline recommendations.

The use of an NK_1 RA as prophylaxis in moderate emetogenic radiotherapy for thoracolumbar bone metastases without concomitant chemotherapy was explored in a two-arm non-randomized pilot study (n = 19) [11]. In arm 1 (8 Gy as a single-fraction), patients (n = 13) received aprepitant 125 mg and granisetron 2 mg on the day of radiotherapy followed by aprepitant 80 mg the following 2 days. In arm 2 (20 Gy in five fractions), patients (n = 6) received aprepitant 125 mg on the first day of radiotherapy, aprepitant 80 mg on days 3 and 5, and granisetron 2 mg on every day of radiotherapy. Compared to historical data, the authors conclude that symptom control rates of the 5-HT_3 RA and NK_1 RA combination is superior to a 5-HT_3 RA alone, but larger scale studies are warranted.

Non-pharmacologic treatment of RINV

Two randomized double-blind trials dealing with alternative treatment of RINV have been published since that last update. In the first study, 215 patients with a cancer diagnosis submitted to radiotherapy to the abdomen or pelvis (field size ≥800 cm^3, total dose ≥25 Gy) were randomly assigned to acupuncture (verum acupuncture, n = 109) or placebo (sham acupuncture, n = 106) [13]. The acupuncture (verum or sham) was carried out for 30 min three times per week for the first 2 weeks, followed by twice per week for the remaining radiotherapy period. In the verum acupuncture and the sham acupuncture group, 70 and 62 % experienced nausea at least once during the radiotherapy period. Vomiting was experienced by 25 and 28 % for the verum and the sham acupuncture groups, respectively. However, 95 % percent in the verum acupuncture group and 96 % in the sham acupuncture group believed that the treatment had been effective against nausea. None of the results were statistically significant.

The other study was a small study (n = 42) evaluating the efficacy of green tea on gastrointestinal symptoms (diarrhea, nausea, and vomiting) induced by abdominal or pelvic radiotherapy (dose ≥50 Gy) [12]. Patients were randomly assigned to receive a green tea tablet 450 mg (n = 21) or placebo (n = 21) for 5 weeks. Diarrhea, nausea, and vomiting were assessed weekly. There was a statistically significant difference in frequency of reported diarrhea between the two groups in favor of green tea ($p < 0.002$), whereas there was no difference between groups with respect to nausea and vomiting, and green tea cannot be considered a substance with antiemetic effect.

Hence, the two studies in alternative treatment here summarized are not applicable for inclusion in the antiemetic guideline recommendations for RINV.

Breakthrough RINV

As discussed in the previous guideline update, several studies in high and moderate emetic risk radiotherapy have suggested that 5-HT_3 RAs are effective as antiemetic treatment of established nausea and vomiting, and as mentioned above prophylaxis with a 5-HT_3 RA is superior to rescue treatment with a 5-HT_3 RA [33]. The best rescue medication in low and minimal emetic risk radiotherapy still remains to be explored.

Patients treated with moderate emetic risk radiotherapy should receive prophylaxis with a 5-HT_3 RA and optional corticosteroid [6]. There is no evidence for rescue antiemetic treatment during ongoing prophylaxis with a 5-HT_3 RA. A case report describes the potential benefit adding an NK_1 RA to a 5-HT_3 RA as treatment for breakthrough nausea and vomiting induced by radiation (30 Gy in ten fractions) for lumbar spine metastases in a patient receiving prophylaxis with a 5-HT_3 RA [16].

Duration of antiemetic prophylaxis

A systematic review focused on timing and duration of the prophylaxis of RINV with 5-HT_3 RAs. Antiemetic prophylaxis studies (n = 25) in high, moderate, and low emetic risk level radiotherapy were reviewed [7]. Response rates for nausea and vomiting were recorded, but formal statistical comparisons between duration of the prophylaxis and response rates could not be made due to the heterogeneity of the studies (e.g., reported endpoints, emetic risks, fractionation). Superior control rates for nausea and vomiting were found for extended duration prophylaxis compared with the equal duration prophylaxis in high emetogenic single fraction radiotherapy. In moderate and low emetic risk single fraction radiotherapy, shortened prophylaxis was inferior to cohorts using extended or equal duration prophylaxis. However, the study did not provide evidence for guideline recommendations, and the duration of prophylaxis still remains unclear.

Antiemetic efficacy studies in chemo-radiotherapy

During the recent years, antiemetic studies in concomitant chemo-radiotherapy have been published, but without sufficient evidence to change guideline recommendations. The guidelines state that patients treated with concomitant chemo-radiotherapy should receive antiemetic prophylaxis according to the guidelines for the chemotherapy. If the risk level of the radiotherapy is higher than that for the

concomitant chemotherapy, then the risk level of the radiotherapy is determining the antiemetic prophylaxis.

Patients treated with multiple fraction radiotherapy are, depending on the site of the radiation field, continuously submitted to emetic stimulus. If treated with concomitant weekly cisplatin, then the patients receive weekly prophylaxis for acute and delayed emesis according to high emetic risk chemotherapy.

A pilot study prospectively assessed the antiemetic efficacy of palonosetron and prednisolone during fractionated radiotherapy and weekly cisplatin 40 mg/m^2 in patients (n = 48) treated for gynecological cancer [17]. Palonosetron was administered weekly before cisplatin (day 1), and prednisolone was given days 1 to 4. Complete response (CR; no emesis and no use of rescue medication) during the first 24 h (0–24 h) post cisplatin was 87 %, and CR 0–120 h was 71 %. The sustained no emesis, i.e., cumulative probability of patients completing 5 weeks of treatment without emesis, was 57 %. No nausea 0–120 h was 42 %, and only 23 % of patients completed 5 weeks of treatment with no nausea, and one half of patients used rescue therapy. The authors conclude that palonosetron plus prednisolone seem to be an insufficient prophylaxis in this setting, and a randomized, placebo-controlled phase III study comparing palonosetron, dexamethasone, and fosaprepitant to palonosetron, dexamethasone, and placebo was planned. The results of the GAND-emesis study have recently been published and demonstrated a significantly lower cumulative risk of emesis in the fosaprepitant group compared with the placebo group (subhazard ratio 0·58 [95 % CI 0·39–0·87]; p = 0·008) [38]. However, the data was published after the current update and will therefore be part of a future update.

A prospective observational study (n = 59) compared the antiemetic efficacy of aprepitant, a 5-HT$_3$ RA (ondansetron or tropisetron), and dexamethasone (n = 31) versus a 5-HT$_3$ RA (ondansetron or tropisetron) and dexamethasone [14]. Patients (head and neck, lung, esophageal, or cervical cancer) received fractionated radiotherapy and either weekly cisplatin 40 mg/m^2 or 5 days (20–25 mg/m^2 daily) cisplatin. The standard aprepitant regimen 125 mg day 1 and 80 mg days 2–3 was given to the patients receiving weekly cisplatin, while patients receiving daily cisplatin received 125 mg day 1 and 80 mg days 2–7. CR 0–120 h was achieved by 75.9 % for the aprepitant group, and 60.7 % for the control group, respectively. Despite the heterogeneous and unbalanced study population, and the fact that the primary endpoint was not obtained, the authors concluded that the study adds to the hypothesis that the addition of an NK$_1$ RA to a 5-HT$_3$ RA and a corticosteroid will improve RINV prophylaxis in patients receiving fractionated radiotherapy and concomitant low dose cisplatin.

Two abstracts on efficacy of olanzapine in concurrent chemo-radiotherapy presented in 2014 and 2015, respectively, should be mentioned. The first study, still not available as full paper which hamper the evaluation, reports a small randomized study in patients with head and neck, cervical, or esophageal cancer (n = 60) [15]. Antiemetic prophylaxis was given as palonosetron and dexamethasone (n = 30), or palonosetron, dexamethasone, and olanzapine (n = 30). Emesis in the delayed phase (days 2–5 post chemotherapy) was observed in 3.3 and 27 % for the olanzapine and the control regimen, respectively. Nausea was less severe in olanzapine-treated patients.

The second abstract to note, published as full paper after the consensus conference but with no impact on the decisions made, reports a randomized, double-blind trial comparing efficacy of olanzapine and fosaprepitant during the 5 days following fractionated radiotherapy and concomitant cisplatin >70 mg/m^2 in patients (n = 101) with head and neck or esophageal cancer [18]. Patients had received 2 weeks of radiotherapy before randomization. On day 1, the olanzapine group (n = 51) received olanzapine 10 mg, and the fosaprepitant group (n = 50) received fosaprepitant 150 mg, and all patients additionally received palonosetron and dexamethasone. Olanzapine 10 mg was administered to the first group on days 2–4, and the second group received dexamethasone 4 mg twice daily on days 2 and 3. There was no difference with respect to the primary endpoint (complete response 0–120 h; 76 and 74 % for the olanzapine and the fosaprepitant group, respectively (p > 0.05)), but fewer patients in the olanzapine group had nausea during the overall period compared with the fosaprepitant group. Patients had significantly more drowsiness on day 2 in the olanzapine group compared to the fosaprepitant group, otherwise the treatments were well tolerated.

Although these two studies present several shortcomings, including that they only observe symptoms over the first 5 days, and as such evaluate CINV rather than RINV, the results add to the still increasing amount of evidence of antiemetic efficacy of olanzapine.

Guideline adherence

In a small prospective study in patients receiving fractionated radiotherapy, with or without concomitant chemotherapy, to abdominal/pelvic regions (n = 48), it was demonstrated that even if 72.9 % of patients received antiemetic treatment, nausea and emesis were still frequently observed (nausea reported by 80.0 and 85.7 %, and emesis by 35.0 and 67.9 % of patients receiving combined chemo-radiotherapy or radiotherapy alone, respectively) [22].

Guideline dissemination and implementation in clinical practice is difficult. In a large web-based survey, oncologists (n = 1022) from 12 countries assessed the risk of nausea and vomiting in different settings of radiotherapy [19]. In general, there was a low awareness (<50 % of respondents) of antiemetic guidelines, risk classification was difficult for low and

moderate emetic risk radiotherapy, and antiemetic prophylaxis was under-utilized for moderate risk radiotherapy.

Guideline recommendation update

Based on the previous MASCC/ESMO Antiemetic Guidelines Update 2009 and a thorough up to date literature search, a new proposal for MASCC/ESMO Antiemetic Guidelines in radiotherapy was presented and discussed at the Guidelines Update meeting held in Copenhagen, June 28, 2015.

Mainly based on expert opinions, the following changes of the risk classification for the 2016 update were proposed. (1) Total nodal irradiation was previously classified as high emetic risk, but as this radiotherapy field technique is no longer in use, it was decided to be excluded. (2) In the moderate emetic risk level, half body irradiation (HBI) and upper body irradiation (UBI) were also excluded. Both HBI and UBI include the upper abdomen, and as it is the irradiation of the upper abdomen that gives the moderate risk of RINV, it would be sufficient just to mention upper abdomen. (3) Craniospinal irradiation was in the low emetic risk level previously. No randomized antiemetic studies in craniospinal radiotherapy are available, but the risk of RINV in craniospinal radiotherapy is unlikely to be less than for large field vertebral irradiation for which data from randomized trials has demonstrated that prophylaxis with a 5-HT_3 RA is superior compared to prophylaxis with a dopamine RA or placebo [26, 29]. Therefore, it was decided to move craniospinal radiation up in the moderate risk category. (4) Lower thorax region is in the low emetic risk level. In the IGARR 2010 study, the risk of nausea and/or vomiting was 31 % for patients receiving thorax radiotherapy (n = 126) and no distinction between upper and lower region was made [5]. Thus, it was decided to remove the word "lower." (5) Finally, the percentages following the four emetic risk levels (previously: high risk >90 %, moderate risk 90–60 %, low risk 30–60 %, and minimal risk <30 %) were omitted as evidence for this subdivison with percentages is lacking.

The recommendation of antiemetic prophylaxis or rescue treatment during radiotherapy was changed according to the following. (1) Previously, the recommendation for the low emetic risk level (cranium, head and neck, thorax region, and pelvis) included prophylaxis or rescue with a 5-HT_3-RA. Due to the very heterogenous sites of irradiation in the low risk group, the limited number of studies including these sites and mainly addressing efficacy of 5-HT_3-RAs [26, 33], it was decided that the guideline should not be restricted to recommend a 5-HT_3-RA, but the choice could also be dexamethasone or a dopamine RA. (2) In clinical practice, the antiemetic treatment of choice in cranial irradiation would be a corticosteroid (due to the edema), and therefore, this was included in the guideline. (3) For minimal risk, and again based on expert opinion, it was decided not to restrict the recommendation to a dopamine RA or a 5-HT_3-RA, but also to include dexamethasone. The recommendations are summarized in Table 1.

Conclusion

Despite the advances in development of antiemetic treatment, the goal of RINV prophylaxis for all patients receiving radiotherapy is still not achieved. In radiotherapy, antiemetics are most often prescribed as treatment for established nausea and vomiting rather than prophylaxis, as radiation oncologists underestimate the risk of RINV [8]. This antiemetic guideline update should help physicians to prescribe the most effective antiemetic RINV prophylaxis.

Future studies should investigate the significance of patient- and treatment-related risk factors in order to individualize antiemetic prophylaxis. The duration of prophylaxis remains to be clarified both for single and multiple fraction radiotherapy. The NK_1 receptor antagonists have been investigated in randomized trials in concomitant chemo-radiotherapy, but in radiotherapy alone, the role of the NK_1 receptor antagonists in combination with other antiemetic drugs for the prevention of RINV in different treatment settings still needs to be established.

Compliance with ethical standards

Conflict of interest CR reports honoraria from Swedish Orphan Biovitrum. FJ reports honoraria from MSD Merck and Helsinn and as advisory consultant for Tesaro. KJ reports as advisory consultant for Merck, Helsinn, and Tesaro. AM reports funding from MSD Merck and Acacia Pharma and as advisory consultant for MSD Merck, Helsinn Healthcare, Tesaro, and Norgine. PF reports as advisory consultant for Merck, Riemser, and Tesaro. KD, EM, and FR declare no competing interests.

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