

Radiation-Induced Nausea and Vomiting

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Key Words

Radiation, nausea, emesis, anti-emetics

Abstract

Radiation-induced nausea and vomiting is a common problem for cancer patients. The emetogenic potential of radiation depends greatly on the location of the radiation field, the size of the radiation field, and the fractionation scheme. Radiation fields can be categorized as having high, moderate, low, or minimal emetogenic risk, and treatment differs accordingly. The National Comprehensive Cancer Network, the Multinational Association of Supportive Care in Cancer, and the American Society of Clinical Oncology publish clinical practice guidelines addressing the issue of radiation-induced nausea and vomiting. This article reviews the treatment recommendations for each category of radiation-induced nausea and vomiting from these national and international guideline committees and provides the rationale for these recommendations. (*JNCCN* 2007;5:60–65)

Radiation therapy is capable of inducing nausea and vomiting (NV) in many patients and an estimated 40% to 80% of patients may experience this problem. The syndrome termed *radiation sickness* was described many years ago as consisting of a latent period, followed by NV for a period of approximately 6 hours, and then gradual relief.¹ However, the acute problem may last up to 24 hours. The severity of NV is typically determined by the area of the body being irradiated. Total body irradiation (TBI) is probably the worst offender, followed by the upper abdomen. The larger the volume being irradiated, the larger the treatment fraction; and the higher the total dose delivered, the higher the chance that patients will develop NV.

The Italian Group for Antiemetic Research in Radiotherapy reported a prospective observational multi-

center trial designed to assess the incidence, pattern, and prognostic factors associated with radiation-induced emesis.² Multifactorial analysis of the 914 patients enrolled and evaluated showed that the only significant patient-related risk factor for NV was previous experience with chemotherapy, which increased the emetogenic severity. Two radiotherapy-related factors were significant: the irradiated site and the field size. Upper abdominal radiation was the worst site, although no patients with TBI were included in this study. Patients undergoing radiation to a field larger than 400 cm² experienced earlier and more severe NV.

The gastrointestinal tract (specifically the small intestine) contains rapidly dividing cells that are particularly sensitive to radiation. Radiation-induced emesis damages the enterochromaffin cells of the gastrointestinal mucosa, causing serotonin to be released.³ Serotonin binds to receptors on the vagal afferent nerves that send stimuli to the area postrema, which houses the vomiting center of the brain. The serotonin pathway is also integral to the mechanism of NV associated with the delivery of emetogenic chemotherapy.

Many patients and physicians do not believe that radiation causes the same level of emetogenicity as chemotherapy. However, radiation can cause a prolonged effect for days after completion of total fractionation, and the dramatically increasing delivery of concurrent chemoradiation compounds the problem each individual modality can cause. Clinical guidelines for antiemetic therapy have been developed to help clinicians understand appropriate standard care to prevent NV in patients undergoing emetogenic therapy. Although these guidelines typically emphasize the treatment of chemotherapy-induced NV, they all contain a subsection on the control of radiation-related problems.

Clinical Guidelines for Antiemetic Therapy

Clinical guidelines for antiemetic therapy have been developed by several groups. Three of the most widely circulated

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guidelines are from the National Comprehensive Cancer Network (NCCN), most recently updated in 2006;⁴ the Multinational Association of Supportive Care in Cancer (MASCC), updated in September 2005;⁵ and the American Society of Clinical Oncology (ASCO), recently updated in May 2006.⁶ In a fashion similar to the design of the guidelines for chemotherapy emetogenicity, the ASCO and MASCC guidelines characterize radiation-therapy emetogenicity as high, moderate, low, or minimal, and recommend treatment accordingly. NCCN simply specifies the type of radiation being delivered (i.e., total body, upper abdomen, chemoradiation, or “other sites”) and recommends treatment accordingly.

Highly Emetogenic Radiation: TBI

TBI may be used as part of a conditioning regimen before bone marrow transplant. When chemotherapy is administered concurrently, the specific incidence of emetogenicity contributed by the radiation is somewhat difficult to quantitate. However, NV occurs nearly universally in these patients. Because single-dose TBI consists of a larger fraction than when it is delivered in several fractions over several days, it is therefore more emetogenic. The recommendations for preventing NV in this situation are summarized below.

NCCN

Patients receiving whole body radiation therapy have a high likelihood of developing NV because of the high daily fractional dose of radiotherapy, the total dose, and the amount of irradiated tissue. TBI may be treated with either ondansetron (8 mg 2 or 3 times a day) or granisetron (2 mg PO or 3 mg IV qd). The dose of ondansetron is a category 2A recommendation (uniform NCCN consensus based on lower-level evidence, including clinical experience). The dose of granisetron is a category 2B recommendation (nonuniform NCCN consensus, but no major disagreement, based on lower-level evidence, including clinical experience) because this dose of granisetron is higher than the dose typically administered. Dexamethasone (2 mg PO 3 times a day) may be added to either ondansetron or granisetron. This pretreatment regimen should be given for every day of radiation.

A supporting trial for granisetron was conducted in France involving 36 patients with TBI for leukemia, multiple myeloma, or lymphoma.⁷ Granisetron was

administered 30 to 45 minutes before TBI either as a 3-mg intravenous bolus or a 3-mg 24-hour intravenous infusion. Half of these patients experienced no nausea or vomiting, and no difference was seen among those treated with the bolus and those treated with continuous infusion.

A randomized trial was conducted to compare oral granisetron and oral ondansetron in preventing NV in patients undergoing hyperfractionated TBI.⁸ In this study, 34 patients received either granisetron 2 mg by mouth 1 hour before the first dose of radiation, or ondansetron, 8 mg, 1.5 hours before each fraction. Each arm was compared with a historical control group of 90 patients who had undergone TBI without a 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist. Over 4 days, complete control (no emesis or need for rescue medication) was experienced by 28% of patients in the granisetron group, 27% of those in the ondansetron group, and 0% of the historical controls.

MASCC

TBI is classified as highly emetogenic. The guideline recommends that patients receive a 5-HT₃ antagonist plus dexamethasone. The MASCC level of confidence was moderate, and the level of consensus was high. The criterion for consensus was 75% or greater agreement among the panelists.

ASCO

The ASCO committee recommends administering a 5-HT₃ serotonin receptor antagonist with or without a corticosteroid before each fraction and for at least 24 hours afterwards. The 2006 Update Committee did not designate a preferred 5-HT₃ antagonist. While considering the newest serotonin antagonist to be approved for chemotherapy-induced NV, palonosetron, the committee determined that although palonosetron showed some increased control of NV compared with ondansetron and dolasetron in large randomized trials for patients undergoing highly or moderately emetogenic chemotherapy, the primary end point of the registration trials was noninferiority.⁹⁻¹¹ Although the end point was met, the trials were not specifically designed to show superiority of palonosetron compared with the other 5-HT₃ antagonists.

The 2 agents most recently approved for highly emetogenic chemotherapy are palonosetron (a long-acting 5-HT₃ receptor inhibitor) and aprepitant (a natural killer [NK]-1 receptor inhibitor). A natural question is whether either of these agents would have

improved activity against radiation-induced NV. Currently, no studies have been published using either agent for this indication.

Summary

Reasonable agreement exists among the 3 guidelines regarding TBI, which represents high emetogenic risk. A daily serotonin antagonist should be used preventatively. MASCC also recommends concurrent use of dexamethasone, whereas NCCN and ASCO suggest that dexamethasone may be used at the discretion of the treating physician.

Moderately Emetogenic Radiation: Upper Abdominal Radiation

Radiation of the upper abdomen is classified as moderately emetogenic in the MASCC and ASCO guidelines. Although it is not officially classified by NCCN, the recommended therapy suggests that that panel also considers it moderately emetogenic. A 50% to 80% incidence of NV was reported in those undergoing fractionated radiation of the upper abdomen, and an 80% incidence is seen in those treated with single-dose radiation.²

NCCN

Radiation to the upper abdomen may be treated with ondansetron (8 mg PO 2 or 3 times a day), dexamethasone (2 mg PO 3 times a day), or granisetron (2 mg PO qd). The pretreatment should be given each day before the dose of radiation.

A randomized trial was conducted comparing oral ondansetron, 8 mg orally twice a day, with placebo in 111 patients undergoing 10 or more daily fractions of radiotherapy that included the abdomen.¹² Of patients given ondansetron, 67% experienced complete control of emesis compared with 45% of patients given placebo ($P < .05$).

A trial conducted by the National Cancer Institute of Canada Clinical Trials Group provides rationale for using dexamethasone to prevent radiation-induced NV.¹³ In this trial, 154 patients who underwent fractionated radiation to the upper abdomen (at least 20 Gy and at least 5 fractions) were randomized to receive either dexamethasone, 2 mg orally 3 times a day, or placebo. Complete protection from NV was experienced by 70% of patients treated with dexamethasone compared with 49% of those treated with placebo ($P = .025$). Interestingly, a quality-of-life assessment

using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire did not show that reducing NV had an overall effect on global quality of life.

The efficacy of once-daily granisetron at a dose of 2 mg orally was compared with placebo in 260 patients undergoing fractionated upper abdominal radiotherapy.¹⁴ Treatment comparisons were made at 24 hours, 10 days, and 20 days. Patients treated with granisetron experienced superior time to first emesis and first nausea, and more were emesis-free (78% vs. 42%) and nausea-free (30% vs. 17%) compared with those treated with placebo.

MASCC

Upper abdominal radiation is considered moderately emetogenic. MASCC recommends that these patients be treated with a 5-HT₃ antagonist. The level of confidence and consensus for this recommendation is high.

ASCO

Upper abdominal radiation is considered to confer a moderate risk for NV. The committee recommended a 5-HT₃ receptor antagonist before each fraction. In the recent update, the committee mentioned that preventative treatment is better than as-needed intervention for this group, and that 5-HT₃ receptor antagonists are more effective than metoclopramide or phenothiazines.

A major difference between the ASCO guidelines and the NCCN and MASCC guidelines is the inclusion in the moderate-risk group of pelvic, mantle, craniospinal radiation, and cranial radiosurgery. Therefore, the ASCO committee generally recommends that a 5-HT₃ antagonist be used for this group; however, they suggest that a dopamine receptor antagonist, such as metoclopramide, may be more appropriate for some patients, such as those undergoing craniospinal radiotherapy or radiotherapy to the lower half of the body, which has somewhat less risk for emesis.

Summary

The guidelines differ somewhat in what constitutes moderately emetogenic radiation therapy. All agree that radiation to the upper abdomen falls into this category. ASCO also includes the possibility of pelvic, mantle, craniospinal radiation, and cranial radiotherapy. All committees agree that a serotonin antagonist should be used daily, although the NCCN also considers dexamethasone to be another option for treatment.

Low–Emetic-Risk Radiation: Lower Thorax, Pelvis, Cranium, and Craniospinal

Some differences in this category exist between the sets of guidelines. NCCN and MASCC agree on the recommendations for treatment, whereas ASCO takes a slightly more aggressive approach. ASCO's categorization of the level of emetogenicity for these other sites of radiation also has less clarity and more overlap.

NCCN

The NCCN panel did not create a specific category called “low risk”; however, it did create a category called “Radiation–Other Sites,” which presumably includes patients undergoing radiation to the lower thorax, pelvis, cranium, and craniospinal field. No primary prophylaxis is recommended, but 8 mg of ondansetron by mouth 2 or 3 times a day should be given if the patient experiences breakthrough nausea.

MASCC

Patients undergoing radiation of low emetic risk should receive rescue with a 5-HT₃ antagonist. The level of confidence for this recommendation was low, but the level of consensus was high. If patients undergoing radiation of low emetic risk develop NV and must be rescued, they should receive prophylaxis with a 5-HT₃ antagonist on a daily basis for the remainder of treatment. For this reason, the MASCC level of confidence was moderate, with a high level of consensus.

ASCO

ASCO's own guideline contains some overlap, because cranial radiosurgery and craniospinal irradiation are included in both moderate– and low–emetic-risk categories. However, the recommendation for treatment is the same: a 5-HT₃ antagonist before each fraction. This is a major difference between the NCCN and MASCC guidelines (summarized above), which recommend giving no prophylaxis and simply rescuing the patients who experience NV.

Summary

Radiation to the lower thorax, pelvis, cranium, and craniospinal field are included in the low-risk level. NCCN and MASCC recommend that these patients be treated without antiemetics, and rescued with a serotonin antagonist if emesis occurs. Once rescued, the patient should continue to undergo prophylactic treatment for the remaining days of radiotherapy.

ASCO's recommendations differ in that they recommend daily prophylactic serotonin antagonist treatment for this group.

Minimal Emetic Risk

NCCN

This category would be included in the “Radiation–Other Sites” recommendation in the NCCN algorithm. Therefore, both categories of low and minimal risk apparently fall into this grouping. No preventive treatment is recommended initially. If the patient needs a rescue antiemetic, 8 mg of ondansetron 2 or 3 times a day is recommended and then should be continued for the remainder of daily radiation.

MASCC

The MASCC committee determined that radiation of the head and neck, extremities, cranium, and breast are included in this category. These patients would not be treated prophylactically and, if they should require rescue for nausea or vomiting, should be treated with a dopamine antagonist or a 5-HT₃ antagonist. The committee's level of confidence was low, but consensus was high.

ASCO

The same radiation fields are included in ASCO's list of low–emetic-risk radiation fields: head and neck, extremities, cranium, and breast. The committee estimates that the incidence of emesis in this patient group is less than 30%. These patients should be treated on an “as needed” basis with a dopamine or serotonin antagonist. If rescue medication is started, then it should be continued daily for each remaining radiation treatment day.

Summary

Examples of radiation fields that have a low risk for inducing NV include the head and neck, extremities, cranium, and breast. All committees agree that no prophylaxis is needed. If patients eventually require rescue medication, then a serotonin antagonist or a dopamine antagonist could be used.

Conclusions

Radiation therapy is capable of inducing NV, depending on the area of the body being radiated, size of the field, and fractionation scheme. Clinical treatment

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Table 1 Clinical Guidelines for Radiation-Induced Nausea and Vomiting

Emetogenicity	Radiation Therapy Fields	NCCN	MASCC	ASCO
High	Total body irradiation	Serotonin antagonist +/- dexamethasone	Serotonin antagonist + dexamethasone	Serotonin antagonist +/- dexamethasone
Moderate	Upper abdomen	Serotonin antagonist or dexamethasone	Serotonin antagonist	Serotonin antagonist
Low	Lower thorax, pelvis, cranium, craniospinal	No prophylaxis; rescue with serotonin antagonist	No prophylaxis; rescue with serotonin antagonist	Serotonin antagonist
Minimal	Head and neck, extremities, cranium, breast	No prophylaxis; rescue with serotonin antagonist	No prophylaxis; rescue with serotonin antagonist or dopamine antagonist	No prophylaxis; rescue with serotonin antagonist or dopamine antagonist

guidelines have been written to help guide clinicians appropriately treat patients undergoing radiation (Table 1). Although the sets of guidelines have some minor differences, several overriding principles can clearly guide experts in getting patients through radiation as comfortably as possible:

- High risk for emesis: TBI. These patients should be treated with a serotonin antagonist and dexamethasone. Treatment should continue daily throughout radiation.
- Moderate risk for emesis: upper abdominal radiation. These patients should be treated with a serotonin antagonist; the NCCN guidelines recommend dexamethasone as another possibility.
- Low risk for emesis: lower thorax, pelvis, cranium, craniospinal radiation. Patients can be treated without prophylaxis, and just rescued with a serotonin antagonist if they become symptomatic (NCCN and MASCC), or they can receive prophylaxis daily with a serotonin antagonist.
- Minimal risk for emesis: head and neck, extremities, cranium, and breast. No prophylactic treatment is recommended. These patients can be treated on an “as needed” basis with a serotonin antagonist.
- Ondansetron or granisetron are the serotonin antagonists typically used, because these agents are utilized in most supporting trials. Palonosetron has not been formally tested for patients with radiation-induced NV. However, for chemotherapy-induced NV, all of the serotonin antagonists are considered equivalent.
- Aprepitant has not been formally tested for patients with radiation-induced NV.

Symptom management is an extremely important aspect of the care of cancer patients, and aggressive support of patients undergoing radiotherapy is essential. Preventing NV is one of the key ways clinicians can help patients through a difficult treatment.

References

1. Danjoux CE, Rider WD, Fitzpatrick PJ. The acute radiation syndrome. A memorial to William Michael Court-Brown. *Clin Radiol* 1979;30:581–584.
2. The Italian Group for Antiemetic Research in Radiotherapy. Radiation-induced emesis: a prospective observational multicenter Italian trial. *Int J Radiat Oncol Bio Phys* 1999;44:619–625.
3. Horiot JC. Prophylaxis versus treatment: is there a better way to manage radiotherapy-induced nausea and vomiting? *Int J Radiat Oncol Biol Phys* 2004;15:1018–1025.
4. Ettinger DS, Bierman PJ, Bradbury B, et al. The NCCN antiemesis clinical practice guidelines in oncology, version 2, 2006. Available at: http://www.nccn.org/physician_gls/index.html. Accessed November 2, 2006.
5. Multinational Association of Supportive Care in Cancer. Antiemetic Guideline Consensus. Available at: http://www.mascc.org/ktml2/images/uploads/Resource_centers/MASCC_Guidelines_Update_9_05.pdf. Accessed November 2, 2006.
6. American Society of Clinical Oncology, Kris MG, Hesketh PJ, et al. American Society of Clinical Oncology guidelines for antiemetics in oncology: update 2006. *J Clin Oncol* 2006;24:2932–2947.
7. Belkacemi Y, Orsahin M, Pene F, et al. Total body irradiation prior to bone marrow transplantation: efficacy and safety of granisetron in the prophylaxis and control of radiation-induced emesis. *Int J Radiat Oncol Biol Phys* 1996;36:77–82.
8. Spitzer TR, Friedman CJ, Bushnell W, et al. Double-blind, randomized, parallel-group study on the efficacy and safety of oral granisetron and oral ondansetron in the prophylaxis of nausea and vomiting in patients receiving hyperfractionated total body irradiation. *Bone Marrow Transplant* 2000;26:203–210.
9. Gralla R, Lichinitser M, Van Der Veegt S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a

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- double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. [Ann Oncol 2003;14:1570–1577.](#)
10. Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT₃ receptor antagonist: results of a phase III, single-dose trial versus dolasetron. [Cancer 2003;98:2473–2482.](#)
 11. Aapro M, Grunberg S, Manikhas G, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. [Ann Oncol 2006;17:1441–1449.](#)
 12. Franzen L, Nyman J, Hagberg H, et al. A randomised placebo controlled study with ondansetron in patients undergoing fractionated radiotherapy. [Ann Oncol 1996;7:587–592.](#)
 13. Kirkbride P, Bezjak A, Pater J, et al. Dexamethasone for the prophylaxis of radiation induced emesis: a National Cancer Institute of Canada Clinical Trials Group phase III study. [J Clin Oncol 2000;18:1960–1966.](#)
 14. Lanciano R, Sherman DM, Michalski J, et al. The efficacy and safety of once-daily kytril (granisetron hydrochloride) tablets in the prophylaxis of nausea and emesis following fractionated upper abdominal radiotherapy. [Cancer Invest 2001;19:763–772.](#)