Radiotherapy Induced Nausea and Vomiting (RINV)
Perrugia Antiemetic Consensus Conference 2004

Petra Feyer, Prof Dr med, E.Maranzano, A.Molassiotis, R.Clark-Snow, F.Roila, F.Olver, Warr

Objectives

1. Presentation consensus guidelines RINV Perugia 2004
2. To learn differences in emetogenic risk of different radiotherapy methods
3. Influencing factors on RINV
4. Prevention of RINV
5. Contribution of 5-HT3-antagonists
6. Evidence based guidelines in RINV

As many as 40-80% of patients undergoing radiotherapy (RT) will experience nausea and/or vomiting depending on the site of irradiation (Danjoux 1979, Feyer 1996, The Italian Group 1999). 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 (Franzen 1996). Furthermore uncontrolled nausea and vomiting may result in patients delaying or refusing further radiotherapy (Laszlo 1983).

Nausea and vomiting are often underestimated by radiation oncologists (The Italian Group 1999, Feyer 2003, Goldsmith 2003).

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-HT3-receptor antagonists with or without a steroid for prophylaxis in moderately and highly emetogenic treatment (MASCC, ASCO, ASHP, NCCN).

The new proposed guidelines summarize an update 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 risk including high – moderate – low – minimal emetogenic risk. They offer guidance to prescribing physicians for effective antiemetic therapies in radiotherapy induced nausea and vomiting.

Background

The published observational trials on radiotherapy-induced nausea and vomiting (RINV) evidenced that the overall cumulative incidence of vomiting and nausea occurred in about one-third of patients undergoing radiotherapy. It was also evidenced the attitude of radiation oncologists in prescribing antiemetic drugs as a rescue, with a large range of doses and schedules, and that 5-HT3 antagonists rather than other antiemetics are generally used (Feyer 1996, The Italian Group 1999, Feyer 2003, Goldsmith 2003).

Patients submitted to total body irradiation (TBI), half body irradiation (HBI) or abdominal radiotherapy were at major risk of nausea and vomiting. Few randomized controlled clinical trials have evaluated the efficacy of various antiemetic drugs in preventing RINV. The trials published have shown that dopamine receptor antagonists were effective in only about 50% of patients, whereas 5-hydroxytryptamine (5-HT3) antagonists were more effective up to 80% (Aas 1997, Bey 1996, Lewis 2002, Spitzer 2000).

Current practice guidelines for RINV

The current MASCC and ASCO as well as ASHP and NCCN practice guidelines for the use of antiemetics in radiotherapy are quiet different, both when classifying radiation emetogenic risk categories, and giving indications for the use of antiemetic drugs (The Italian Group 1995, Kirkbridge 2000, ASHP 1998, NCCN 2001, Tonini 2003).

This diversity of recommendations reflects the limited amount of a high level of evidence (i.e., few randomised controlled trials and few number of patients entered in each trial). The following differences are the most important.

1) The ASCO guidelines classified only TBI at high risk, whereas MASCC,NCCN and ASHP guidelines added to this group upper abdomen resp. abdominal bath, HBI and TBI.
2) Moderate risk categories were quite different: thorax and pelvis were classified as at low risk by ASCO and at moderate risk by MASCC guidelines.
3) Two therapeutic attitudes are suggested: prophylaxis, giving the antiemetic drug(s) before each radiotherapy fraction, or rescue, on an as-needed basis therapy beginning as soon as symptoms (usually nausea) develop. If for high risk levels (5-HT3 antagonists) and low risk levels (no prophylaxis) the antiemetics suggested by the guidelines are similar, for patients at moderate risk level there are clear differences because MASCC and NCCN suggests prophylaxis or rescue treatment with 5-HT3 antagonists eventually associated with dexamethasone, whereas ASCO suggests only prophylaxis with dopamine receptor agonist or 5-HT3 antagonists without dexamethasone. 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 there is given the same nausea and vomiting treatment as that given for chemotherapy related nausea and vomiting (NCCN 2001).

**Trials**

There are three randomised controlled trials (RCT) in patients with fractionated radiotherapy (Priestmann 1987, Sokol 1986, Ungerleider 1984) and one RCT with single fraction radiotherapy (Lucraft 1982) investigating the efficacy of non-5-HT 3 antagonists in radiotherapy of the upper abdomen. There was no difference among the various used compounds and the antiemetic efficacy was limited.

The only double blind RCT on Corticosteroids suggests that the use of dexamethasone resulted in a significantly better control of RINV than placebo (Kirkbride 2000). There are a number of trials on 5-HT-3 antagonists for patients treated with total body or upper abdomen irradiation (Tramer 1998). The 5-HT-3-antagonists gave a significantly greater protection from 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 (Le Bourgeois 1999).

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 including high – moderate – low – minimal emetogenic risk. The new guidelines are shown in table 1.

**References**

18. Spitzer TR, Friedman CJ, Bushnell W, Frankel SR, Raschko J: Double-blind, randomised, 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 Transp 2000; 26:2003-210
20. ASHP. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm 1998; 56: 729-764

Tab.1: Radiotherapy-induced emesis: Radiation emetic risk levels and new MASCC and ASCO guidelines.

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Irradiated area</th>
<th>Antiemetic Guidelines</th>
<th>MASCC Evidence (level of scientific confidence/level of consensus)</th>
<th>ASCO Evidence (type of evidence/grade of recommendation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Total body irradiation</td>
<td>Prophylaxis with 5-HT3 antagonists + dexamethasone</td>
<td>1- High/High</td>
<td>1- II/B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2- Moderate/High</td>
<td>2- III/ C</td>
</tr>
<tr>
<td>Moderate</td>
<td>Upper abdomen</td>
<td>Prophylaxis with 5-HT3 antagonists</td>
<td>High/High</td>
<td>II/A</td>
</tr>
<tr>
<td>Low</td>
<td>1- Lower thorax region and Pelvis</td>
<td>Prophylaxis or rescue with 5-HT3 antagonists</td>
<td>1- Moderate/High</td>
<td>1- III/B</td>
</tr>
<tr>
<td></td>
<td>2- Cranium (radiosurgery) and Craniospinal</td>
<td></td>
<td>2- Low/High</td>
<td>2- IV/D</td>
</tr>
<tr>
<td>Minimal</td>
<td>Head and neck, Extremities</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>