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Original Paper

Nausea and Vomiting in Fractionated Radiotherapy: a Prospective On-demand Trial of Tropisetron Rescue for Non-responders to Metoclopramide

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A prospective trial was performed to better assess the risk of nausea and vomiting and the rescue value of tropisetron (TRO), a 5-HT_3 receptor antagonist, in 88 patients undergoing fractionated radiotherapy to the abdomen or to large supradiaphragmatic fields and failing a first anti-emetic trial with metoclopramide (MET). Nausea was graded 0 (absent), 1 (mild), 2 (moderate) and 3 (severe). Nausea requiring anti-emetics (≥ grade 2) was present in 64% of the patients. MET was able to control nausea (≤ grade 1) in 26 of 58 patients (45%) who developed ≥ grade 2 nausea during radiation treatment (2 patients vomiting without nausea included). 34 patients required TRO, and 31 experienced immediate relief. However, nausea (≥ grade 2) recurred in 7 patients from 1 to 3 weeks after starting TRO. Sex, age, field type and field size (cm^2) did not influence the incidence and severity of nausea and vomiting. Only 24/88 patients vomited after starting radiotherapy. MET helped to eliminate emesis in one third of these patients. TRO helped to control vomiting in 73% of the salvaged patients. Constipation was observed in 8 patients on TRO and was a reason to stop the medication in 4 cases.

Key words: anti-emetics, nausea, radiotherapy, tropisetron, 5-HT_3 receptor antagonists
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INTRODUCTION

APPROXIMATELY 50% of patients subjected to a course of fractionated radiotherapy of the upper abdomen or treated to large volumes (e.g. mantle, inverted Y, or hockey stick fields) develop nausea and vomiting [1]. Metoclopramide (MET) has proved its usefulness in half of these patients [1]. Although MET can be associated with sedation and/or extrapyramidal side-effects, there is considerable experience in the use of this relatively inexpensive medication. The 5-HT_3 receptor antagonists have shown an unmatched efficacy in patients undergoing chemotherapy [2, 3], whole-body irradiation [4], and single high-dose radiation to the upper abdomen [5]. Radiation may induce nausea and vomiting by triggering the same serotonin receptors of the gut wall as chemotherapy. Thus, 5-HT_3 receptor antagonists should also be effective anti-emetics in fractionated radiotherapy. Two preliminary, non-controlled studies addressing this issue have already been published [6, 7]. Although these studies included a reduced number of patients, all of them receiving upfront 5-HT_3 receptor antagonists, a success rate of 80% in preventing nausea and vomiting was observed.

In our study, the potential role and efficacy of the 5-HT_3 receptor antagonists against radiation-induced nausea and vomiting were tested with tropisetron (TRO) (Navoban, Sandoz Wander-Pharma Ltd, Bern, Switzerland). The choice of TRO was mainly based on availability of an oral presentation and prescription simplicity assuring compliance (i.e. a single 5-mg capsule a day). It is not a controlled randomised study but a prospective "on-demand" rescue trial. Patients at risk for nausea and vomiting did not receive upfront medication when starting radiotherapy. MET was first prescribed if needed. Patients who continued to experience nausea or vomiting while on MET were rescued with TRO. We assumed that this simple trial would

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help us to better assess the overall risk of nausea and vomiting, and to define those patients potentially benefiting from TRO.

PATIENTS AND METHODS

From October 1992 to June 1994, 88 patients from the University Hospitals of Geneva and Lausanne agreed to participate in this study. Patients at high risk for nausea and vomiting during standard fractionated radiotherapy were included: upper abdominal, large abdominal and large supradiaphragmatic ("mantle") fields. All patients were treated with single daily fractions, 5 days a week, and 1.5–2 Gy/fraction. Patients undergoing total or hemi-body irradiation were excluded. Patients receiving abdominal irradiation for bone metastasis or painful soft tissue lesions were also excluded to avoid the confounding effect of morphine and other analgesics in the development and control of nausea and emesis. Simultaneous steroids or chemotherapy, however, were not considered reasons for exclusion. 9 patients received concomitant 5-fluorouracil (5-FU) during radiotherapy, 1 patient received simultaneous cisplatin, and 1 patient was treated with alternating radiotherapy and cyclophosphamide doxorubicin. 3 patients received simultaneous steroids and 1 patient interferon.

A daily status check was performed and a few questions concerning the nausea intensity and duration, the daily number of emetic episodes and the potential side-effects of the antiemetics were answered by the patients in the presence of a nurse or a physician. Nausea was graded 0 (absent), 1 (mild, spontaneous relief, normal intake, not requiring medication), 2 (moderate, decreased intake, requiring medication), and 3 (severe, continuous, no significant intake, requiring medication). Vomiting was graded according to the number of daily episodes. No upfront treatment was given. Patients who developed nausea (i.e. $\geq$ grade 2) and/or emesis within at least a 24-h period after the start of radiotherapy were given the usual recommended dose of MET in its oral presentation (10 mg, three times a day, orally) for the remainder of the treatment. However, if after a 24–48-h trial of MET (or any time thereafter) nausea ($\geq$ grade 2) or vomiting persisted (or recurred) the patients were given TRO (5 mg, once a day, orally) for the remainder of the radiotherapy period.

The median age was 46 years (range 8–83). There were 64 males and 24 females. The treated sites and field types are presented in Table 1. Treatments were almost always delivered with a set of two AP/PA parallel and opposed fields. Field sizes were calculated by multiplying the two X and Y field dimensions (cm^2), not taking into account the block-related shielded surfaces. The median field size surface was 466.5 cm^2 (range 70–1400).

Table 1. Irradiated fields and sites

Field/site	Number of patients
Upper abdominal	
Para-aortic	12
Stomach	9
Pancreas	5
Hepatobiliary	4
Others	4
Large abdominal	
"Hockey stick"	21
Pelvic-para-aortic/"inverted Y"	12
Whole abdomen	7
"Mantle"	14
Total	88

The incidence and severity of spontaneous nausea and vomiting, and the efficacy of MET or TRO in controlling them is reported. Chi-square and two tailed Fisher's exact tests were used to examine the influence of variables such as sex, age, site and field size on the incidence of nausea and vomiting. The potential influence of the severity of nausea (i.e. grade 2 versus grade 3) and of the time interval to nausea from the start of radiotherapy in response to MET and to TRO was also analysed. Side-effects and compliance are also presented.

RESULTS

Table 2 shows the incidence of nausea (grade 0–3) after starting radiotherapy. No nausea (grade 0) or mild nausea (grade 1, not requiring medication) was observed in 32 cases (36%) during the surveillance period. 56 patients required anti-emetics because of the onset of grade 2–3 nausea. MET was first prescribed to the former 56 patients and to 2 additional patients with grade 1 nausea who vomited. MET was sufficient to control nausea (i.e. $\leq$ grade 1) in 26/58 (45%) patients treated. The remaining 32 patients with continuous $\geq$ grade 2 nausea and 2 additional patients vomiting but with only mild nausea under MET were offered TRO. In this group, 31/34 patients (91%) had immediate relief ($\leq$ grade 1 nausea). However, 7 patients presented a recurrence of $\geq$ grade 2 nausea from 6 to 25 days after starting TRO. Figure 1 displays the prevalence of grade 2–3 nausea versus time after starting TRO. Despite the small number of patients at risk for nausea 3 weeks after starting the TRO trial, a time-dependent increase in the proportion of patients with nausea was observed. A total of 24/34 patients (71%) had a definite improvement with $\leq$ grade 1 nausea while on TRO. However, among those 24 responders, 4 who stopped the medication because of side-effects (while on radiation) presented a recurrence of significant nausea shortly after.

Neither sex, nor age, nor field size influenced the incidence or severity of nausea ($\leq$ grade 1 versus $\geq$ grade 2). Table 3 presents the demand of anti-emetics by treated site or field type. We were able to find in each site a similar proportion of anti-emetic-free patients. Furthermore, a similar proportion of patients in each site either never needed anti-emetics or were successfully relieved ($\leq$ grade 1 nausea) with MET: 21/34 (62%) upper abdominal, 25/40 (62%) large abdominal and 8/14 (57%) mantle fields.

Almost half of the patients (17/36) with grade 2 but only one quarter (5/20) with grade 3 nausea at presentation were successfully treated with MET. This difference was not statistically significant; hence, a relation between severity of nausea and likelihood of responding to MET could not be clearly demonstrated. The response to MET was also analysed as a function of the relation between the time interval between the start of radiotherapy and the onset of $\geq$ grade 2 nausea or emesis. Fourteen of 24 (58%) MET responders, but 30/34 (88%) MET failures presented with spontaneous nausea/vomiting during the first 5 days of radiotherapy ($P = 0.021$). Thus, an early onset of radiation-induced nausea and/or vomiting suggests a poorer response to MET.

There were no significant differences in the incidence and severity of nausea between patients receiving or not receiving simultaneous or alternating radiochemotherapy or steroids. 6 patients never complained of nausea or were controlled with MET, whereas 9 patients required TRO. Nausea ($\geq$ grade 2)

Table 2. Nausea: incidence and severity (worst day)

Score	Number of patients (%) At onset	On MET	On TRO
Grade 0 (absent)	21 (24)	18 (31)	11 (32)
Grade 1 (mild)	11 (12)	8 (14)	13 (38)
Grade 2 (moderate)	36 (41)	18 (31)	5 (15)
Grade 3 (severe)	20 (23)	14 (24)	5 (15)
Total (at risk)	88	58*	34†

* 56 patients with ≥ grade 2 nausea and 2 patients vomiting but without nausea at onset. † 32 patients with ≥ grade 2 nausea and 2 patients vomiting but without nausea on MET.

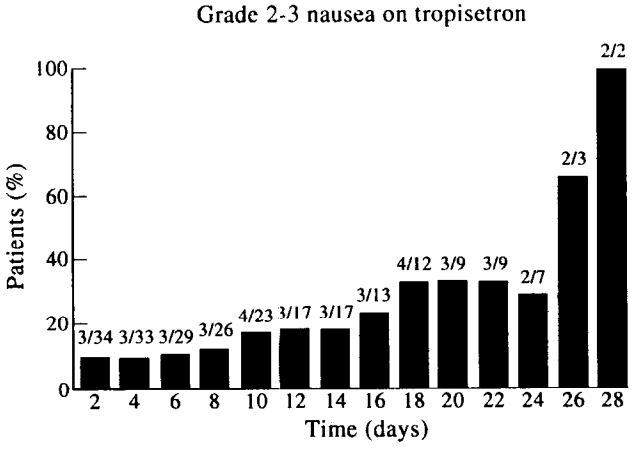

Figure 1. Daily proportion of patients on TRO with grade 2–3 nausea. Figures above the columns represent the ratios between the patients with nausea and the total patients at risk for a specific 2-day time interval.

recurred in 5 patients on TRO (all of them treated with 5-FU and radiotherapy).

Unlike nausea, vomiting was a rather infrequent event. Table 4 presents the proportion of patients vomiting while on surveillance, on MET and on TRO, respectively. Only 24 vomited at least once a day after starting radiotherapy. MET was helpful in eliminating the emetic episodes in one third of these patients (i.e. 8/24). The remaining 16 MET failures and 6 patients with ≥ grade 2 nausea who vomited for the first time while on MET entered the TRO trial. The overall effect of TRO on vomiting was a complete remission in 16/22 (73%) patients and a stabilisation (one daily emetic episode) in the remaining 6 patients. As mentioned above, 4 patients discontinued TRO because of side-effects and 3 restarted vomiting.

Two extrapyramidal MET-related events were observed in 2 patients, respectively. One patient presented with dysarthria, the other with facial dyskinetic movements. An additional patient complained of dizziness while on MET. Constipation was observed in 8 patients on TRO. Four days was the median time to constipation (range 2–20). Migraine episodes were also observed in 3 additional patients on TRO, 2 of whom were already known as chronic migraine patients.

The above-mentioned TRO-related constipation was the reason to stop the medication in 4 patients despite a satisfactory control of nausea and vomiting. The absence of anti-emetic benefit was the reason to discontinue the medication in five TRO failures. An additional patient stopped TRO after 10 days because of an acute radiation-induced oesophagitis and was switched to MET in suppository form.

DISCUSSION

Because of patient subjectivity, nausea is a difficult end-point to score. It is doubtful whether mild (grade 1) nausea need be considered a problem requiring medical attention. In our grading system we deliberately decided not to offer anti-emetics to these patients and attributed the same significance to grade 1 as to grade 0. In fact, the difference between grade 1 and grade 2 nausea was frequently based on the patient's demand for medical relief. The distinction between grade 2 and grade 3 was sometimes difficult to establish. There is, however, a good correlation in this study between severe nausea (occurring in 23% of

Table 3. Nausea and vomiting: need for anti-emetics (MET or TRO) versus treated site

Site	Number of patients No anti-emetics	on anti-emetics	Total
Upper abdominal			
Para-aortics	5	7	12
Stomach/pancreas/hepatobiliary/others	6	16	22
Large abdominal			
"Hockey stick"	9	12	21
Pelvic-para-aortic/"inverted Y"	4	8	12
Whole abdomen	2	5	7
"Mantle"	6	8	14

Table 4. Vomiting: incidence and severity (worst day)

Daily episodes	Number of patients (%) At onset	On MET	On TRO
0	64 (73)	8 (27)	16 (73)
1	12 (14)	16 (53)	6 (27)
2	7 (8)	4 (13)	0
≥3	5 (6)	2 (7)	0
Total (at risk)	88	30*	22†

* 24 patients with one or more vomit episodes and 6 patients without vomiting but with ≥ grade 2 nausea at onset. † 22 patients with one or more vomit episodes on MET.

patients) and any vomiting (occurring in 28% of patients) at onset which would tend to validate this grading system.

TRO proved to be very effective in the majority of patients failing the MET trial. This efficacy was specially marked during the first days on TRO. However, a time-dependent nausea recurrence was suggested by our data. This could reflect either a weakening of the anti-emetic effect over time or a non-admitted lack of compliance. The median total duration of radiotherapy for the patients who eventually received TRO was rather short (26 days). The surveillance period and the MET trial additionally shortened the time interval at risk for nausea and vomiting while on TRO (median 12 days). Thus, although one should be cautious with conclusions reached with small numbers of patients, the possibility of a loss of efficacy over time should be kept in mind, especially for long radiotherapy treatments. Sorbe and colleagues [6] also observed an increase of nausea from start to end of radiotherapy in a group of 20 patients undergoing abdominal irradiation for ovarian cancer and receiving upfront TRO.

Nutritional problems with weight loss, electrolyte disturbances and deteriorated quality of life have been mentioned as the potential results of continuous severe vomiting during long irradiation periods using abdominal fields. In our study, a large majority of patients never vomited and only 6% of the patients presented three or more daily (worst day) emetic episodes. Thus, serious medical problems from vomiting are rather exceptional during abdominal irradiation. Fortunately, with the sequential use of MET and TRO, vomiting was controlled in all but 6 (7%) patients who presented only one daily (worst day) episode.

It has been suggested that the constipating effect of 5-HT_3 receptor antagonists can help to control the diarrhoea commonly associated with abdominal irradiation. In our study, no patient undergoing abdominal irradiation suffered diarrhoea after TRO. 8 patients complained, however, of an excessive bowel movement reduction. A similar situation was reported by Henriksson and colleagues with ondansetron, who reported 11/33 cases of mild constipation [7]. Unlike their patients who were easily treated with lactulose, 4 of our patients stopped the anti-emetic medication because of this side-effect.

In summary, while moderate to severe nausea was present in almost two thirds of patients undergoing upper abdominal or large field (abdominal or "mantle") irradiation, less than one third vomited. No patient- or radiotherapy-related factors were found to be predictive in the incidence and severity of nausea and vomiting. TRO shows a remarkable rescue potential for patients failing MET. The TRO anti-emetic efficacy, however, may diminish over long treatment periods. Although TRO seems to reduce radiation-induced diarrhoea it may lead to constipation. Avoidance of TRO on weekends and the use of laxatives for constipated patients can be helpful in relieving this problem. To avoid overtreating patients who may never need anti-emetics, future trials in patients treated by radiotherapy should be confined to those patients actually requiring treatment for nausea and vomiting.

1. Priestman TJ, Priestman SG. An initial evaluation of nabilone in the control of radiotherapy induced nausea and vomiting. *Clin Radiol* 1984, **35**, 265–266.
2. Marty M, Pouillart P, Scholl S, *et al.* Comparison of the 5-hydroxytryptamine 3 (serotonin) antagonist ondansetron (GR38032F) with high dose metoclopramide in the control of cisplatin induced emesis. *N Engl J Med* 1990, **322**, 816–821.
3. Sagar SM. The current role of anti-emetic drugs in oncology: a recent revolution in patient symptom control. *Cancer Treat Rev* 1991, **18**, 95–135.
4. Drakos P, Or R, Nagler A, Cass Y. Anti-emetic efficacy and tolerability of tropisetron in patients conditioned with high dose chemoradiotherapy pre-bone marrow transplantation. *Eur J Cancer* 1993, **29A** (suppl. 6), S207.
5. Priestman TJ, Roberts JL, Lucraft H. Results of a randomized double-blind comparative study of ondansetron and metoclopramide in the prevention of nausea and vomiting following high-dose upper abdominal irradiation. *Clin Oncol* 1990, **2**, 71–75.
6. Sorbe B, Berglind AM, de Bruijn K. Tropisetron, a new 5-HT3 receptor antagonist, in the prevention of radiation-induced emesis. *Radiother Oncol* 1992, **23**, 131–132.
7. Henriksson R, Lomberg H, Israelson G, *et al.* The effect of ondansetron on radiation-induced emesis and diarrhoea. *Acta Oncol* 1992, **31**, 767–769.