A randomized, double-blind, multicentre study comparing daily 2 and 5 mg of tropisetron for the control of nausea and vomiting induced by low-dose cisplatin- or non-cisplatin-containing chemotherapy

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Summary

Background: This study compares efficacy, safety and tolerability of 2 and 5 mg tropisetron in prevention of nausea and vomiting induced by low-dose cisplatin- or non-cisplatin-containing chemotherapy.

Patients and methods: 152 chemotherapy-naive cancer patients were randomized in a double-blind manner to receive 2 or 5 mg tropisetron intravenously day 1 and orally days 2-6. Primary efficacy criteria were control of acute (day 1) and delayed (days 2-6) vomiting and nausea. Secondary efficacy criteria included overall control (days 1-6) and control of vomiting and nausea by chemotherapy regimen. Safety and tolerability were evaluated clinically, biochemically and by the patient's diary. Only the first cycle was evaluated.

Results: 124 of the 144 intention-to-treat patients were evaluable. There was a better total control (no events) of acute vomiting in the 5 mg (73%) than in the 2 mg group (55%, P = 0.02). Total control (< 15 minutes) of acute nausea was obtained in 70% of the 5 mg group and in 51% of the 2 mg (P = 0.03). No differences were observed for total control of delayed nausea or vomiting and for the overall outcome of nausea. Less vomiting (days 1-6) occurred in the 5 mg than in the 2 mg group. Efficacy rates ranged widely between chemotherapy regimens, independent of the tropisetron dose groups. There occurred more headache in the 5-mg group (P < 0.05).

Conclusions: Once daily 5 mg tropisetron is superior to 2 mg for prevention of acute vomiting and nausea induced by low-dose cisplatin- or non-cisplatin chemotherapy regimens, but causes more headache.

Key words: chemotherapy, dose-finding, nausea, tropisetron, vomiting

Introduction

Nausea and vomiting are among the most common and distressing side effects of cancer chemotherapy [1, 2]. The introduction of the 5-hydroxytryptamine (5-HT3) receptor antagonists as antiemetic treatment gave an improvement in prevention of chemotherapy-induced nausea and vomiting but coincides with side effects, such as headache and constipation [3]. Tropisetron, one of the 5-HT3 antagonists, is recommended at a 5-mg daily dose, to be given intravenously (i.v.) prior to the chemotherapy on day 1 and orally thereafter. This dose is based on dose finding studies with high-dose cisplatin-based chemotherapy [4-6]. However, no formal dose finding study with tropisetron has been performed for low-dose (<40 mg/m²) cisplatin- or non-cisplatin-containing emetogenic chemotherapy regimens. The present study has been performed to investigate whether the low dose 2 mg of tropisetron is equally effective as the standard used daily dose of 5 mg for the prevention of emesis of low-dose cisplatin- or non-cisplatin-containing emetogenic chemotherapy.

Patients and methods

Study design

The study was designed as a prospective, multicentre, controlled, double-blind, randomized, parallel group trial.

Patient eligibility

Chemotherapy-naive patients between 18 and 75 years old were eligible if they were to receive at least one cycle of an emetogenic chemotherapy regimen for confirmed malignant disease, other than head and neck cancer. This chemotherapy had to be based on either monotherapy or combination regimens containing high-dose cyclophosphamide (>400 mg/m² i.v.), ifosfamide (>2.5 g/m² i.v.), doxo-
rubin (> 50 mg/m² i.v.) or carboplatin (> 400 mg/m² i.v. as mono-
therapy or > 300 mg/m² i.v. in combination regimens), administered
during one to a maximum of five days or cisplatin < 40 mg/m² i.v.
per day, given for a maximum of five consecutive days. Local radio-
therapy was only allowed if given prior to the chemotherapy. Pa-
tients with severe hepatic, renal or cardiac insufficiency were ex-
cluded, as were patients with uncontrolled infection, insufficiently
controlled hypertension, drug or alcohol abuse, hypersensitivity
reaction or drug allergy as well as clinical evidence of malignancy
involving the central nervous system. Patients were also ineligible if
they suffered from nausea or vomiting unrelated to chemotherapy.
Concomitant treatment with drugs, which might affect emesis, was
not permitted. The protocol was approved by the local ethics com-
mittee at each centre, and all patients gave informed consent.

Safety assessments

Safety assessments consisted of a physical examination, vital signs
and laboratory evaluations prior to treatment and at study end, as
were adverse events and comments stated by the patients in the
patient diaries. Vital signs parameters measured were weight, blood
pressure and radial pulse. A systolic blood pressure > 170 mm Hg, a
diastolic blood pressure > 100 mm Hg or a radial pulse > 120 beats
per minute were classified as abnormal.

Before treatment and at study end, laboratory evaluation was
performed, and included hemoglobin, leucocyte and platelet counts,
creatinine and liver enzyme tests. Values out of the clinically rel-
evant ranges were classified as abnormal. For hematological param-
eters hemoglobin < 100 g/l, leucocytes < 2.8 X 10⁹/1 or platelets < 75
X 10⁹/1 were considered abnormal. Adverse events and comments
made by the patients were also summarized.

Results

Between May 1993 and September 1994, 152 patients
were randomized. Eight were withdrawn because of
ineligibility before the start of the study, and con-
sequently could not be included in the final analysis.
Reasons elucidated for ineligibility before treatment
were postponement of chemotherapy (n = 1), with-
drawal of informed consent (n = 1), pharmacist mis-
take (n = 1), ineligibility was found out after the study
medication had been prepared already (n = 3), not
using study medication (n = 1) and erroneous co-
administration of standard antiemetic treatment (n = 1).
The remaining 144 patients constituted the
intention-to-treat (ITT) population. In addition, 20 pa-
patients had a major protocol violation such as an insuffi-
cient chemotherapy regimen (n = 7), previous chem-
otherapy (n = 1) or co-administration of high-dose
glucocorticoids (n = 12). Therefore, the efficacy anal-
ysis population consisted of 124 patients. Primary effi-
cacy analyses were carried out on all 144 patients in the
ITT population as well as on all 124 patients in the effi-
cacy analysis population. Safety evaluations were per-
formed for all patients who received study medication.

Patient characteristics

The baseline characteristics of the two groups are shown in Table 1. There were no significant differences
between the groups. More women than men entered
into the study since many of the chemotherapy regi-
mecam were specially targeted to treat breast cancer and gynecological tumors. The male patients mostly re-
cieved chemotherapy for lung cancer. The main coex-
tent conditions were hypertension (n = 19), insomnia
(n = 7), anxiety, depression and nervousness (n = 5),
chronic obstructive pulmonary disease (n = 6) and
constipation (n = 6). Most patients who received con-
comitant medication for coexistent diseases at entry
continued their medication unaltered during the study.
However, new medication was started sometimes,
mainly for reasons of supportive care, such as pain
relief or sleeping disorders. In addition, in 30 patients
various antiemetic rescue treatments were given (18 in
the 2-mg group and 14 in the 5-mg group; NS).

The chemotherapy regimens are listed in Table 2.
The chemotherapy regimens were converted into total
daily doses and regimens were classified as cis- or
carboplatin-based, cyclophosphamide-based or anthra-
cycline-based. A regimen was defined as cyclophos-
phamide-based if the dose cyclophosphamide exceed-
ed a total amount of 1000 mg, or if the total cyclophos-
phamide dose was <1000 mg and no anthracyclines
were used, or the cyclophosphamide dose was equal to
1000 mg but the dose of epirubicin was <90 mg or the
dose of doxorubicin was ≤75 mg. Any regimen con-
taining ifosfamide was categorized as ‘other’. All regi-
mens not already classified and containing doxorubicin/
epirubicin were then classified as anthracycline-
minimal. All patients received chemotherapy on day 1
and between 12% and 34% of the patients also re-
ceived chemotherapy on each of days 2–5.

Efficacy evaluation

Figure 1 shows the proportion of patients with total
and major control of vomiting of each of days 1 to 6 per
treatment arm. In the ITT population total control of
acute vomiting (day 1) was achieved in 55% of the
2-mg group and 73% in the 5-mg group (P = 0.02). In
the 2-mg group 12% of patients had minor control of
acute vomiting and 19% had a treatment failure. In
contrast, only 1% of the patients in the 5-mg group had
minor control and 13% a treatment failure. Also for
total plus major control there was a better control at 5
mg than at 2 mg (P = 0.02). The results of the efficacy
analysis population were quite similar to those of the
ITT population, the differences between the treatment
groups were significant (P = 0.03 for total and P = 0.02
for total plus major control of acute vomiting).

Figure 2 shows the percentage of patients with total
and major control of nausea of each of days 1 to 6.
Total control of acute nausea was obtained in 51% in
the 2-mg group and in 70% in the 5-mg group (P = 0.03).
Total or major control of acute nausea was achieved in
77% in the 2-mg group and in 91% in the
5-mg group (P = 0.004). The results of the efficacy
analysis population were quite similar to those of the
ITT population, the differences between the 2- and
5-mg groups were significant (P = 0.03 for total control
and P = 0.003 for total or major control of acute nau-
sea).

The total control of delayed vomiting (days 2 to 6
combined) in the ITT population was not significant
different at 2 mg (51%) and 5 mg (69%) group. For the
efficacy analysis population these figures were 51% and
64%, respectively (NS).

The total control of delayed nausea (days 2 to 6
combined) in the ITT population and the efficacy anal-
ysis population did also not significantly differ between
do the groups. (ITT population 42% at 2 mg and 56% at
5 mg, in the efficacy analysis population these amounts
were 35% and 49%, respectively).

The overall outcome of vomiting (days 1–6 com-
bined) in the ITT population was 35% total control in
the 2-mg group and 59% in the 5-mg group (P = 0.007).
Also for the efficacy analysis population total control of
vomiting during all 6 days was worse in the
2-mg group (33%) than in the 5-mg group (54%; P = 0.03).

### Table 1. Baseline characteristics for ITT-population.

<table>
<thead>
<tr>
<th>No. of patients entered</th>
<th>2 mg</th>
<th>5 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>74</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>27 (36%)</td>
<td>31 (44%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>54</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>69</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Mean height (cm)</td>
<td>169</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>No. of patients with</td>
<td>42 (58%)</td>
<td>35 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Co-existent disease</td>
<td>47 (64%)</td>
<td>39 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>62 (84%)</td>
<td>59 (64%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>2 mg</th>
<th>5 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer (female)</td>
<td>29 (30%)</td>
<td>21 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Genitourinary tract cancer</td>
<td>16 (22%)</td>
<td>19 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>15 (20%)</td>
<td>13 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>6 (8%)</td>
<td>9 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrointestinal tract cancer</td>
<td>4 (5%)</td>
<td>4 (6%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2. Chemotherapy regimens for ITT-population.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>2 mg</th>
<th>5 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin-based</td>
<td>5 (7%)</td>
<td>8 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Carboplatin-based</td>
<td>6 (8%)</td>
<td>10 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cyclophosphamide-based</td>
<td>29 (39%)</td>
<td>30 (43%)</td>
<td>NS</td>
</tr>
<tr>
<td>Anthracycline-based</td>
<td>11 (15%)</td>
<td>7 (10%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy on</th>
<th>2 mg</th>
<th>5 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>16 (22%)</td>
<td>18 (26%)</td>
<td>NS</td>
</tr>
<tr>
<td>Day 3</td>
<td>25 (34%)</td>
<td>24 (34%)</td>
<td>NS</td>
</tr>
<tr>
<td>Day 4</td>
<td>9 (12%)</td>
<td>12 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Day 5</td>
<td>18 (24%)</td>
<td>19 (27%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
The overall outcome of total control of nausea (days 1–6 combined) in the ITT population did not differ between the groups (35% at 2 mg, 51% at 5 mg; NS). Also for the efficacy analysis patients the control of nausea during all 6 days of the chemotherapy course was not significantly different between the treatment arms.

In all chemotherapy regimens, except the cisplatin-based, the 5-mg group was superior in control of acute vomiting. In all chemotherapy regimens except the carboplatin-based, the efficacy of the 5-mg dose exceeded the 2-mg dose in control of acute nausea. Furthermore the efficacy rates ranged rather widely between the chemotherapy regimens, independent of the tropisetron dose given.

Safety evaluation

An overview of the adverse events is presented in Table 3. Of the 210 adverse events, 155 were recorded by 92 patients in the patient diaries. No patient discontinued the tropisetron treatment because of an adverse event. Eight percent of the adverse events were attributed by the investigator to the antiemetic treatment, the remaining adverse events were assigned to the cancer or the sequelae of the chemotherapy. The most frequently reported adverse event by the patients was headache, mentioned by 37 (26%) patients; 12 (16%) of the 2-mg group and 25 (36%) of the 5-mg group ($P < 0.05$). Furthermore, a total of 21 (15%) patients recorded constipation, eight (11%) patients of the 2-mg group and 13 (19%) patients of the 5-mg group (NS). However, six patients had constipation entered as co-existent condition at entry, two in the 2-mg group and four in the 5-mg group. Two of these six patients had a recurrence during the study.

There were seven serious adverse events, according to the investigator not related to tropisetron, namely pneumothorax/catheter complication ($n = 1$), agranulocytosis ($n = 1$), fatal pneumonia ($n = 1$), lung embolism ($n = 1$), death due to rapid disease progression ($n = 1$), thrombosis of a subclavian vein ($n = 1$) and paralytic ileus due to underlying cancer ($n = 1$).

The physical examination revealed no adverse

<table>
<thead>
<tr>
<th>Tropisetron dose</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg ($n = 74$)</td>
<td>5 mg ($n = 70$)</td>
</tr>
<tr>
<td>No of patients reporting adverse events</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>43 (58%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Rigors</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
Control of nausea

![Control of nausea chart](image)

Figure 2. Proportion of ITT-patients with total and major control of nausea on each of days 1–6.

Discussion

Management of chemotherapy-induced nausea and vomiting has improved since the availability of 5-HT₃ receptor antagonists, such as ondansetron, granisetron and tropisetron. Tropisetron is a 5-HT₃ antagonist and is also a weak antagonist for 5-HT₄ receptors [4]. It is administered once daily, which can be an advantage in a nauseated and vomiting patient. Tropisetron is administered orally, with a short i.v. infusion or with a slow i.v. injection, the recommended dose is 5 mg once daily [4, 5]. However, the lower limit of efficacy of tropisetron is unknown. The present dose-finding study shows that 5 mg tropisetron daily was more effective in the major control of acute nausea and vomiting than 2 mg.

In the present study, no significant difference between both treatment arms towards delayed nausea and vomiting was observed. This is in accordance with previous studies, since the role of serotonin antagonists alone in control of delayed nausea and vomiting has its limitations [10]. When ondansetron was compared with high-dose metoclopramide in patients treated with cisplatin (50–100 mg/m² i.v.), no difference was obtained in the control of delayed vomiting, and metoclopramide was even superior in the control of delayed nausea. Patients preferred ondansetron, probably because of the lower frequency of side effects and the better control of acute nausea and vomiting [11, 12]. The combination of tropisetron with dexamethasone provides a better protection for delayed vomiting and nausea then tropisetron alone [13–15]. This has also been observed for ondansetron and granisetron [16–18].

The efficacy rates of tropisetron varied considerably between the various chemotherapy regimens. It is not clear whether this is the result of the chemotherapy treatment alone or whether also the small patient numbers within some chemotherapy subgroups have contributed.

In the present study more side effects were observed in the 5-mg dose group, especially headache and constipation. These are known side effects of all 5-HT₃ antagonists [3]. In a comparative study of a single dose ondansetron, tropisetron or granisetron in the prevention of acute vomiting, no differences in prevalence of headache were obtained between the three study drugs [19]. Previously published data from a meta-analysis of tropisetron administered at 5 mg daily, showed that 27% of patients treated with this antiemetic drug reported headache, and 14% constipation [5]. In the current study the frequencies of these side effects in the 5-mg group are slightly higher, 36% for headache and 19% for constipation, whereas in the 2-mg group these figures are lower, 16% and 11%, respectively, suggesting a dose-response.

In conclusion, daily 5 mg tropisetron is more effec-
tive than daily 2 mg in the prevention of acute vomiting and nausea induced by low-dose cisplatin or non-cisplatin containing chemotherapy. In addition, the 5-mg dose was more effective than the 2-mg regimen for overall control of vomiting. Notwithstanding the fact that tropisetron can be given safely, a daily dose of 5 mg tropisetron causes side effects, especially constipation and headache. In patients with these side effects co-medication with laxatives and/or analgetics should be considered. In patients with insufficient control of nausea and vomiting, tropisetron should be combined with another antiemetic drug.

Acknowledgement

Study medication was supplied by Sandoz, Basle, Switzerland.

References


Received 21 December 1995; accepted 10 April 1996.

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