*Acta Oncologica* Vol. 32, No. 4, pp. 413–415, 1993

# COMPARISON OF ONDANSETRON WITH CUSTOMARY TREATMENT IN THE PROPHYLAXIS OF NAUSEA AND EMESIS INDUCED BY NON-CISPLATIN CONTAINING CHEMOTHERAPY

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**One hundred cancer patients receiving non-cisplatin containing chemotherapy were entered in a prospective study in which the efficacy of ondansetron was compared with standard antiemetic treatments in the prophylaxis of nausea and emesis. During the first 24 h, 77% of patients on ondansetron reported complete control of emesis compared with 56% of those on customary treatments ($p = 0.03$). However, no statistically significant difference was observed between ondansetron and customary treatments in control of delayed emesis on days 2–5. Nor was any statistically significant difference seen between ondansetron and customary treatments in preventing acute or delayed nausea.**

Cancer patients are distressed by nausea and vomiting more than by any other side-effect of chemotherapy (1). The exact mechanism of chemotherapy-induced emesis is still partly unclarified. Recent research has emphasized the importance of serotonin receptors in controlling emesis. Cytotoxic agents are thought to release serotonin from the enterochromaffin cells in the upper gastrointestinal tract (2). Serotonin may activate the vomiting reflex via 5-$HT_3$-receptors located on vagal afferent nerves or in the area postrema (3, 4). Ondansetron (GR 38032F) is a highly selective 5-$HT_3$-receptor antagonist with demonstrated antiemetic activity in patients receiving cisplatin (5, 6). Addition of dexamethasone to ondansetron results in an even better antiemetic control than achieved by ondansetron alone (7). Ondansetron is also effective in the treatment of emesis induced by non-cisplatin containing chemotherapy regimens (8). However, comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy showed no significant difference in complete and major control of acute or delayed emesis (9). In fact, dexamethasone was even more effective than ondansetron in the control of delayed nausea (9). Metoclopramide is frequently used at low or intermediate doses in the prophylaxis of emesis induced by non-cisplatin containing chemotherapy. To improve antiemetic efficacy, metoclopramide is often combined with corticosteroids and benzodiazepines. We have completed an open, randomized, multicentre study to compare ondansetron with standard antiemetic treatments in each centre for the prevention of nausea and vomiting induced by non-cisplatin containing chemotherapy regimens.

Received 3 September 1992.
Accepted 16 March 1993.
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## Material and Methods

Eligible patients were at least 18 years old, had not received previous cancer chemotherapy and were designated to receive non-cisplatin containing chemotherapy regimens. Exclusion criteria were vomiting or use of antiemetic drugs within 24 h prior to chemotherapy, gastrointestinal obstruction, central nervous system metastases, severe concurrent illness other than neoplasia, use of corticosteroids unless as part of the chemotherapy regimen, and use of benzodiazepines, except when given for night seda-

**Table 1**

*Patient characteristics and the chemotherapy administered*

| | Treatment group | |
|---|---|---|
| | Ondansetron | Customary treatment |
| No. of patients | 52 | 48 |
| Males/females | 15/37 | 7/41 |
| Median age (yr) | 52.4 | 54.1 |
| Age range | 21–76 | 25–70 |
| Type of cancer (No. of patients) | | |
| Breast | 16 | 19 |
| Lymphoma | 16 | 9 |
| Gynaecological | 12 | 8 |
| Gastrointestinal | 3 | 5 |
| Other | 5 | 7 |
| Chemotherapy | | |
| Cyclophosphamide plus anthracycline | 20 | 18 |
| CMF | 9 | 10 |
| Carboplatin-containing | 11 | 11 |
| DTIC-containing | 7 | 2 |
| Anthracycline-containing | 3 | 4 |
| Other | 2 | 3 |

tion. Routine haematology and liver function tests were made before the study. Written informed consent was obtained from all of the patients and the study was approved by the institutional ethical committees of each participating centre. One hundred patients were enrolled into the study. Characteristics of the patients are given in Table 1.

The patients were entered consecutively and were randomly assigned to receive either ondansetron or the centre's customary treatment for the non-cisplatin chemotherapy regimen being used. Ondansetron was received either as an 8 mg slow intravenous injection immediately before chemotherapy or as an 8 mg tablet 1–2 h before chemotherapy. Ondansetron was continued 8 mg tds on an outpatient basis for 3 days or, if symptoms persisted, to the end of day 5. Antiemetics used in the customary treatment group were chosen by each participating centre. Customary treatments given before chemotherapy are shown in Table 2. Following the loading dose, the majority of patients received metoclopramide, 10 mg 8-hourly orally or 20 mg 8-hourly per rectum, for 2–5 days.

An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches by definition each emetic episode had to be separated by the absence of vomiting or retching for at least one minute. The antiemetic response was graded according to the number of emetic episodes within 24 h: complete response 0, major control 1–2, minor response 3–5, and failure 5 episodes. Nausea was assessed by the patients as none, mild, moderate or severe. Patients reporting no nausea were regarded as a success. Patients completed diary cards daily for 5 days, recording the number of vomits and retches, grade of nausea and the number of antiemetic tablets taken.

**Table 2**

*Antiemetics given before chemotherapy in the customary treatment group*

| Antiemetics | No. of patients |
|---|---|
| Metoclopramide 20–100 mg i.v.<br>Dexamethasone 10–20 mg i.v.<br>Lorazepam 1–2 mg p.o. | 18 |
| Metoclopramide 20–50 mg i.v.<br>Lorazepam 1 mg p.o. | 16 |
| Levomepromazine 10 mg p.o. | 10 |
| Metoclopramide 20 mg i.v. | 4 |

The differences in group means and the differences between the groups were analysed by Student's t-test and Mantel-Haenszel $\chi^2$-test when applicable.

## Results

There were more males in the ondansetron group than in the customary treatment group. However, the difference was not statistically significant. There was no statistically significant difference between the mean ages. DTIC-containing chemotherapy regimens were overrepresented in the ondansetron group (7 against 2). The response to antiemetic treatment, as indicated by the number of emetic episodes, is shown in Table 3. Ondansetron was superior to customary treatment in the complete control of emesis during the first 24 h (77% vs. 56%; $p = 0.03$). Forty-six (88%) patients in the ondansetron treatment group and 41 (77%) patients in the customary treatment group achieved

**Table 3**

*Number of patients reporting each grade of control of emesis by ondansetron and customary treatment*

| | Grade of control of emesis | | | |
|---|---|---|---|---|
| | Complete 0 | Major 1–2 | Minor 3–5 | Failure >5 |
| First 24 h | | | | |
| ondansetron (n = 52) | 40 | 6 | 1 | 5 |
| customary treatment (n = 48) | 27 | 10 | 6 | 5 |
| Second 24 h | | | | |
| ondansetron | 43 | 2 | 2 | 5 |
| customary treatment | 33 | 9 | 4 | 2 |
| Third 24 h | | | | |
| ondansetron | 42 | 3 | 2 | 5 |
| customary treatment | 37 | 7 | 3 | 1 |
| Fourth 24 h | | | | |
| ondansetron | 45 | 3 | 1 | 3 |
| custromary treatment | 43 | 4 | 1 | 0 |
| Fifth 24 h | | | | |
| ondansetron | 49 | 2 | 0 | 1 |
| customary treatment | 44 | 3 | 1 | 0 |

**Table 4**

*Number (%) of patients reporting nausea on each day*

| | Treatment group | |
|---|---|---|
| | Ondansetron n = 52 | Customary treatment n = 48 |
| First 24 h | 22 (48) | 27 (56) |
| Second 24 h | 22 (48) | 28 (58) |
| Third 24 h | 19 (37) | 22 (46) |
| Fourth 24 h | 10 (19) | 14 (29) |
| Fifth 24 h | 8 (15) | 9 (19) |

complete or major control during the first 24 h. The difference was not statistically significant ($p = 0.13$). Nor was there any statistically significant difference between the ondansetron treatment group and the customary treatment group in delayed emesis on days 2–5.

Control of nausea is reported in Table 4. There was no statistically significant difference between the ondansetron treatment group and the customary treatment group in control of acute or delayed nausea. Three female patients from the ondansetron treatment group experienced severe vomiting and were given rescue antiemetic treatment while ondansetron was stopped. However, rescue medication was not given during the first 72 h and patients were included in the final analysis. Spontaneously reported adverse events were uncommon in both treatment groups. In the ondansetron treatment group two patients complained of headache, one patient experienced upper abdominal pain and another two patients complained of obstipation. In the customary treatment group two patients reported headache and four patients complained of sedation. Extrapyramidal side-effects were not reported. In this study a poor response to antiemetic therapy was not related to any specific chemotherapy regimen.

## Discussion

Ondansetron has been demonstrated to be at least as effective as high-dose metoclopramide in preventing cisplatin-induced emesis (5). Particular improvement in the prophylaxis of emesis has been shown during the first 24 h after the administration of cisplatin (5, 6). 5-$HT_3$-receptor antagonists show no tendency to cause sedation or extrapyramidal effects seen with antidopaminergic agents. These properties of 5-$HT_3$-antagonists offer a remarkable advantage in the treatment of cisplatin-induced emesis. The role of 5-$HT_3$-antagonists in the prophylaxis of emesis, induced by moderately emetogenic non-cisplatin containing regimens, is not as clear. Efficacy of 5-$HT_3$-antagonists with these less emetogenic treatments is good. However, usually a good control of emesis is achieved already with standard antiemetics. Jones et al. (9) showed dexamethasone to be even more effective than ondansetron in control of delayed nausea.

In the present study there was a statistically significant advantage for ondansetron over standard antiemetic treatments in the complete control of emesis during the first 24 h. On the other hand, there were no statistically significant differences in control of delayed emesis or in control of nausea. Side-effects were rare and mild in both treatment groups. The cost on ondansetron is high compared to conventional antiemetic treatments. The use of ondansetron as a first-line therapy in patients receiving moderately emetogenic chemotherapy may be justified during the first 24 h. However, in our study ondansetron did not produce any advantage over the standard antiemetics on delayed emsis or nausea. It may be useful to investigate the outcome of using ondansetron during first 24 h and switching over to standard antiemetics from day 2 and onwards.

In the present study the patients graded the nausea experienced into no nausea, mild nausea, moderate nausea, and severe nausea. This, of course, is an entirely subjective grading and is a potential confounder in the analysis of the results, as well as in comparing the results with other studies. In order to simplify the analysis we graded the nausea reported by the patients into two categories: no nausea or nausea at any grade. We feel that this simple grading could be recommendable for further studies, so that in this respect the studies would be comparable.

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