A Comparison of Oral Ondansetron and Intravenous Granisetron for the Prevention of Nausea and Emesis Associated with Cisplatin-Based Chemotherapy

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ABSTRACT

Purpose: To compare the efficacy and safety of oral ondansetron with i.v. granisetron each given as a single dose prior to administration of highly emetogenic cisplatin chemotherapy.

Patients and Methods: Chemotherapy-naive patients with histologically confirmed malignancies were randomized to receive a single 24 mg ondansetron hydrochloride tablet plus a 50 ml i.v. infusion of normal saline, or a single 10 µg/kg (50 ml) i.v. infusion of granisetron plus a placebo tablet in this multicenter, double-blind, parallel-group trial. Study drug was administered 30 min prior to a single i.v. infusion of cisplatin (50-75 mg/m²), given over a period of ≤ three h. Concurrent administration of corticosteroids was not allowed. Efficacy measurements included the number of emetic episodes, need for rescue medication, and patient assessments of nausea and appetite. Complete response (CR) was defined as no emetic episodes, rescue, or withdrawal; major response was defined as one or two episodes. Safety was evaluated by monitoring adverse events and changes in laboratory parameters.

Results: A total of 371 patients entered the study and received study drug, of whom 184 received ondansetron and 187 received granisetron. For all parameters tested, a single 24 mg oral ondansetron tablet was at least as effective as i.v. granisetron. CR was achieved in 58% of ondansetron-treated patients and 51% of granisetron-treated patients (95% confidence interval on the difference: -4% to 17%). Subjective assessments revealed no difference with regard to complete control of nausea, appetite, or satisfaction with antiemetic therapy. Both drugs were well tolerated; the most common adverse event was headache.

Conclusion: A single 24 mg oral dose of ondansetron is at least as safe and effective as a single i.v. infusion of 10 µg/kg of granisetron in preventing nausea and vomiting induced by highly emetogenic cisplatin chemotherapy.

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INTRODUCTION

Highly emetogenic chemotherapeutic agents, including cisplatin, are widely used in treating malignant disease. Nausea and vomiting are the most frequently occurring side effects of therapy with these agents. Although the extent of nausea and vomiting varies by chemotherapeutic regimen,
more than 90% of patients who receive ≥ 50 mg/m² of cisplatin will vomit during the first 24 h after administration unless they receive effective prophylactic antiemetic therapy [1]. Failure to control these sequelae negatively affects patients’ quality of life and may result in reluctance to continue potentially beneficial treatment [2, 3].

Physiologically, serotonin and 5-HT3 receptors play key roles in the induction of nausea and vomiting by chemotherapeutic agents [4-7]. Ondansetron is a selective 5-HT3 receptor antagonist highly effective in controlling nausea and vomiting in a variety of clinical situations. Additionally, numerous studies investigating the use of ondansetron and granisetron, another 5-HT3 receptor antagonist, have shown that when delivered intravenously both drugs are safe and highly effective in preventing nausea and vomiting induced by moderately high or highly emetogenic chemotherapy [4, 8-15]. Studies have also been conducted which demonstrate similar efficacy results with oral granisetron 2 mg and i.v. ondansetron 32 mg in patients receiving moderately to highly emetogenic chemotherapy [16, 17]. Although oral ondansetron at doses of 8 mg TID and 8 mg BID has been proven effective for use in moderately emetogenic chemotherapy, the optimal oral ondansetron dose and regimen for patients receiving highly emetogenic chemotherapy has not been clearly defined.

A single oral dose of ondansetron 24 mg was chosen for investigation in this study. It was theorized that having the most ondansetron available to interact with the 5-HT3 receptors at the time of maximal release of serotonin, 2 to 6 h following cisplatin administration [8], would provide the greatest antiemetic efficacy. Beck et al. [18] demonstrated that a single 32 mg i.v. dose of ondansetron prior to the administration of cisplatin was as effective as, if not superior to, the continuous infusion and intermittent dosing regimens used in earlier studies. Using this same logic, the approved 1994 oral dosing regimen of ondansetron (8 mg TID) effective in moderately emetogenic chemotherapy regimens was combined into a single oral dose (24 mg) to be administered prior to a cisplatin-based chemotherapy regimen.

This study was designed to compare the antiemetic efficacy and safety of ondansetron administered as a single 24 mg tablet with a single infusion of granisetron 10 µg/kg in patients receiving highly emetogenic cisplatin chemotherapy (cisplatin 50-75 mg/m²). Although numerous reports in the literature state that the use of dexamethasone adds to the efficacy of the 5-HT3 receptor antagonists, corticosteroids (including dexamethasone) were excluded from the study in order to demonstrate the antiemetic activity of a single oral dose of ondansetron and a single i.v. dose of granisetron in patients receiving highly emetogenic cancer chemotherapy.

**Patients and Methods**

**Patient Selection**

Two identically designed multicenter, randomized, double-blind, parallel-group studies were conducted. Chemotherapy-naive male or female patients, age 12 years or older, with histologically confirmed malignancy, scheduled to receive cisplatin 50-75 mg/m² administered intravenously over a period of ≤ 3 h were eligible to participate. Females were eligible if surgically sterilized, post-menopausal, or pre-menopausal with a negative pregnancy test. Patients were excluded from the trial if they had a Karnofsky performance status of <60%; had received an investigational drug within the previous 30 days (or were scheduled to receive an investigational drug during the study); were scheduled to receive any additional highly emetogenic chemotherapeutic agents; had chronic nausea and/or vomiting, or experienced retching, vomiting, or uncontrolled nausea within 24 h prior to administration of the study drug. Medications with antiemetic properties were not allowed within 24 h prior to or during the study period. Patients could not undergo radiation therapy to the abdomen or pelvis within 48 h prior to or during the study period. The protocol was reviewed and approved by the Institutional Review Board at each study site and written informed consent obtained from each patient prior to the performance of any study-related procedures.

**Chemotherapy**

Eligible patients were to receive cisplatin at a dose of 50-75 mg/m² administered over a period of ≤ three h as a single i.v. infusion. The protocol was amended after study initiation to allow use of carboplatin at a dose of >200 mg/m² in place of cisplatin. Co-administration of other chemotherapeutic agents was permitted at the discretion of the investigator, with the exception of cyclophosphamide at a dose of ≥500 mg/m², nitrogen mustard, dacarbazine (DTIC), procarbazine, carmustine, and ifosfamide.

**Antiemetic Treatment**

Patients were randomized (1:1) in a double-blind fashion to receive either a single 24 mg ondansetron hydrochloride tablet (Zofran®, Glaxo Wellcome Inc.; Research Triangle Park, NC) and a 50 ml i.v. infusion of normal saline, or a single 10 µg/kg (50 ml) i.v. infusion of granisetron (Kytril®, SmithKline Beecham Pharmaceuticals; Philadelphia, PA) and a placebo tablet. The co-administration of corticosteroids, including dexamethasone, was not permitted. The administration of rescue antiemetic therapy was allowed at the discretion of the investigator if emetic symptoms were not controlled by the study drug.
Assessment of Antiemetic Efficacy and Safety

Efficacy data were collected for each patient for 24 h after the start of cisplatin administration. The primary efficacy variable was the number of patients with no emetic episodes who completed the trial without rescue medication (complete response [CR]). An emetic episode was defined as a single vomit or retch, or any number of continuous vomits and/or retches (i.e., two or more vomits and/or retches occurring within one minute of each other). Secondary efficacy parameters included the number of patients with therapeutic failures (i.e., more than five emetic episodes over the 24-h study period, the need for rescue therapy due to the severity of nausea or vomiting, or withdrawal from the study due to lack of efficacy); the number of patients with CR or major response (defined as one to two emetic episodes); time to first emetic episode, and withdrawal or rescue.

Subjective measures of efficacy included patient assessment of nausea, appetite, and satisfaction with antiemetic therapy. Patient assessment of nausea was performed using an 11-point linear numerical scale ranging from 0 (no nausea) to 10 (nausea as bad as it could be). Appetite was assessed using a 4-point scale categorized as “as usual,” “better than usual,” “worse than usual,” and “not assessable” (i.e., unable to take anything by mouth). Patient satisfaction with antiemetic therapy was rated using a 5-point scale ranging from 1 (very satisfied) to 5 (very dissatisfied).

Safety evaluations were based on reports of adverse events (defined as any untoward medical occurrence) and laboratory data. Adverse events were monitored from the time of study drug administration up to 24.5 h post-administration. Adverse events considered by investigators to be potentially related to study drug were documented for up to eight days after study drug administration. Laboratory studies monitoring hematological parameters and blood chemistries including liver function tests were performed within seven days of the start of study drug administration and within eight days following the end of study drug administration. Any laboratory test results out of the normal range which were judged to be potentially drug related or clinically relevant were repeated and followed until return to normal or explained to the satisfaction of the investigator.

Statistical Methods

As the two studies were identical, data were combined and analyzed as a single trial. The planned sample size of 364 patients was sufficient to detect a 15% difference between groups at the nominal, two-sided, 0.05 level of significance and 80% power. The safety population consisted of all patients who received at least one dose of study medication. The intent-to-treat population comprised all patients in the safety population who received cisplatin or carboplatin chemotherapy and was used for all study endpoints.

The primary efficacy analysis compared the number of patients in each treatment group who experienced a CR during the post-treatment period. Patients who reported more than five emetic episodes, who were rescued with additional medications, or who were withdrawn due to lack of efficacy were assigned the same arbitrarily high value for the number of emetic episodes (i.e., >5) to designate therapeutic failure. The number of patients in each group with a complete or major response was also compared. These efficacy endpoints were analyzed using Mantel-Haenszel tests controlling for study site differences, with a 95% confidence interval for the difference in response rates between treatments computed using a large sample normal. Time to treatment failure (first emetic episode, rescue, or withdrawal) was assessed using Kaplan-Meier methods, and treatment groups were compared using log-rank tests. Nausea and appetite assessments were analyzed with overall scores compared between treatment groups using Mantel-Haenszel methods. Patient assessments of nausea, appetite, and patient satisfaction with antiemetic therapy made after a patient was withdrawn or rescued and any missing observations after a patient was withdrawn or rescued were replaced by the worst possible score (i.e., nausea = 10, appetite = worse than normal, patient satisfaction = very dissatisfied).

RESULTS

Patient Disposition

A total of 371 patients entered the study and received study drug at 37 centers across the United States. Of these patients, 184 were randomized to ondansetron and 187 were randomized to granisetron.

Patient Characteristics

Treatment groups were similar with regard to demographic characteristics (Table 1). The majority of patients were Caucasian (88% in the ondansetron group and 92% in the granisetron group). One patient in the granisetron group received carboplatin in place of cisplatin. Other cytotoxic agents were used in combination with cisplatin, including etoposide (49% in the ondansetron group and 47% in the granisetron group) and 5-fluorouracil (14% in the ondansetron group and 11% in the granisetron group). Combination chemotherapy regimens were similar between treatment groups. Lung cancer was the most common malignancy in both groups (Table 1).

Efficacy

Treatment response data are presented in Table 2. CR (no emetic episodes, rescue or withdrawal) was achieved in 58%
of ondansetron-treated patients and 51% of granisetron-treated patients (95% confidence interval on the difference: -4% to 17%). The difference between the two treatment groups was not statistically significant. CR rates for both treatment groups showed that females were less likely to respond to antiemetic treatment than were males. In the ondansetron group, 46% of females versus 67% of males were CRs; in the granisetron group, 41% of females versus 59% of males were CRs. Therapeutic failure occurred in 27% of ondansetron-treated patients and in 35% of granisetron-treated patients. Similarly, 27% of ondansetron-treated patients and 34% of granisetron-treated patients received rescue medication. The proportion of patients experiencing CR plus major response was not statistically different between groups, occurring in 68% of ondansetron-treated patients and 61% of granisetron-treated patients (Table 2). No statistically significant differences existed between treatment groups for time to treatment failure. Of those subjects who did fail treatment, few did so within the first 3 h; most did so between 6 and 24 h after the start of chemotherapy.

### Patient Assessments

Subjective patient responses regarding antiemetic efficacy were similar in both treatment groups and are listed in Table 3. Nausea assessments were not significantly different between treatment groups at any time point. The greatest difference between groups was noted at the 24-h assessment, when 10% more patients in the ondansetron group relative to the granisetron group reported no nausea (56% versus 46%, respectively). More ondansetron-treated patients (43%) completed the study without nausea, rescue, or withdrawal compared with granisetron-treated patients (35%), but this difference was not statistically significant. Post-treatment appetite assessments were not statistically significantly different between treatment groups (Table 3). No statistically significant difference existed between treatment groups with regard to the number of patients who were satisfied with therapy. At 24 h 88% of patients in the ondansetron group were either “very satisfied” or “somewhat satisfied” with their therapy compared with 83% of the patients in the granisetron group.

### Safety Assessments

All 371 patients who received study drug were included in the safety analyses. Adverse events reported during the study were similar between the two treatment groups. Twenty-four percent (24%) of patients in the ondansetron group and 28% of the patients in the granisetron group experienced one or more adverse events. The most common event was headache, reported in 7% of ondansetron-treated patients and 12% of granisetron-treated patients. Other events were nausea, vomiting, and diarrhea, each reported by less than 10% of patients in both treatment groups.
adverse events, including diarrhea, constipation, malaise/fatigue, and fever, were similar between treatment groups and occurred in fewer than 5% of patients in either treatment group (Table 4). The only adverse event occurring in 5% or more patients in either treatment group that was considered to be potentially drug related was headache (7% in the ondansetron group and 9% in the granisetron group). Analyses of pre-treatment and post-treatment laboratory values revealed similar changes between treatment groups in hematologic and clinical chemistry parameters, including hepatic enzymes. The majority of the transitions in laboratory values were within the normal range of the laboratory parameters evaluated and none of the changes were considered by investigators to be clinically significant.

**DISCUSSION**

Recent changes in oncology practice and shifts in health care delivery have resulted in more patients being treated with highly emetogenic chemotherapeutic agents, including cisplatin, on an outpatient basis [19]. Consequently, oncology health care providers are forced to identify new and effective ways to provide high-quality patient care while containing costs. These changes pose unique challenges for the management of chemotherapy-associated symptoms such as nausea and vomiting. Single dose, oral antiemetic therapy that is proven safe and effective for highly emetogenic chemotherapy could provide a more convenient dosing regimen, improve antiemetic therapy compliance, reduce time of hospitalization or time spent in an outpatient treatment facility, and reduce administration costs.

Many significant improvements have been made in the past 10 years in the efficacy, safety, and ease of administration of antiemetic therapy used to control chemotherapy-induced nausea and vomiting. Serotonin receptor antagonists have been shown to be safe and effective, with corticosteroids reported to increase the rate of antiemetic control over that obtained with a 5-HT₃ receptor antagonist alone [10, 19-22]. As a result, 5-HT₃ antagonists in combination with corticosteroids are now the standard of care for moderately to highly emetogenic chemotherapy [23, 24]. However, in the current study co-administration of dexamethasone was not allowed so that the antiemetic efficacy of oral ondansetron 24 mg alone could be determined.

Complete control of acute cisplatin-induced emesis in this study was achieved by 58% of patients who received oral ondansetron 24 mg as a single prophylactic antiemetic agent.

A recent study by Krazakowski et al. [25] evaluated single dose regimens of oral ondansetron 24 mg and i.v. ondansetron 8 mg in patients receiving cisplatin ≥50 mg/m² (median dose 75 mg/m²). Dexamethasone, 12 mg oral or 20 mg i.v., was included in the antiemetic treatment regimens. Complete control of emesis was obtained by 85% of patients in the oral group and 83% of patients in the i.v. group. No nausea was reported by 70% of patients in the oral group and 68% in the i.v. group. The results of this study support the use of a single 24 mg oral dose of ondansetron in patients receiving highly-emetogenic cisplatin chemotherapy and provide additional data on the additive antiemetic benefit of dexamethasone.

The present study demonstrates that a single 24 mg oral dose of ondansetron is as safe and effective in preventing nausea and vomiting induced by highly emetogenic cisplatin chemotherapy as a single i.v. infusion of 10 µg/kg of granisetron. An effective oral agent for highly emetogenic cisplatin chemotherapy offers improvements over i.v. therapy in terms of greater ease of administration, less time required by health care personnel, and reduction in overall health care expenses [26]. Furthermore, the use of oral antiemetics was approved by Medicare as part of the Balanced Budget Act of 1997 [27]. In order for a given oral antiemetic to be reimbursable by Medicare, the therapy must be: A) approved by the Food and Drug Administration for use in preventing nausea

<table>
<thead>
<tr>
<th>Table 4. Safety</th>
<th>Ondansetron 24 mg po (n = 184)</th>
<th>Granisetron 10 µg/kg i.v. (n = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of patients with any adverse event</td>
<td>44 (24%)</td>
<td>52 (28%)</td>
</tr>
<tr>
<td><strong>Most common events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13 (7%)</td>
<td>23 (12%)</td>
</tr>
<tr>
<td>Malaise/fatigue</td>
<td>5 (3%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (3%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (&lt;1%)</td>
<td>4 (2%)</td>
</tr>
</tbody>
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and vomiting associated with emetogenic chemotherapy; B) used as full replacement for the i.v. antiemetic that would have otherwise been administered at the time of chemotherapy; C) administered by the treating physician or in accordance with a written order from the physician as part of a cancer chemotherapy regimen, and D) administered with that particular chemotherapy regimen (i.e., initiated within 2 h of administration of chemotherapy and continued for no longer than 48 h from that time). Depending on the specifics of each clinical case, oral ondansetron potentially fulfills all of these criteria.

**CONCLUSION**

In conclusion, oral ondansetron 24 mg, when given as a single prophylactic dose prior to highly emetogenic cisplatin chemotherapy, is as safe and effective as i.v. granisetron. Oral ondansetron 24 mg provides the clinician a convenient dosing alternative and demonstrates a continuation of the proven efficacy and safety profile of ondansetron.

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