Efficacy of Ondansetron Against Nausea and Vomiting Caused by Dacarbazine-Containing Chemotherapy

Sewa S. Legha, M.D., Cynthia Hodges, R.N., and Sigrid Ring, R.N.

Background and Methods. **The antiemetic activity of ondansetron (Zofran, Glaxo Pharmaceuticals, Research Triangle Park, NC) was evaluated in 25 patients with recurrent melanoma who were treated sequentially with dacarbazine (DTIC), vinblastine, and cisplatin. The antiemetic regimen included ondansetron alone in 11 patients; ondansetron plus lorazepam (Ativan, Wyeth-Ayerst, Philadelphia, PA) in 9 patients; and ondansetron plus lorazepam plus metoclopramide (Reglan, A. H. Robins Co., Richmond, VA) in 5 patients. Twenty-one patients had no prior exposure to chemotherapy, whereas 4 patients had previously received the same chemotherapy regimen and had severe vomiting despite administration of standard antiemetics.**

Results. **The antiemetic efficacy of ondansetron was impressive. Administration of a single dose of 10 mg resulted in complete control of nausea and vomiting in 22 patients, and the remaining 3 patients had only mild vomiting.**

Conclusions. **Ondansetron is highly effective in controlling the nausea and vomiting caused by dacarbazine.** *Cancer* **1992; 70:2018–2020.**

Key words: ondansetron, antiemetics, dacarbazine, melanoma, chemotherapy.

Ondansetron (Zofran, Glaxo Pharmaceuticals, Research Triangle Park, NC) is a novel antiemetic agent with a unique mechanism of action, being an antagonist of serotonin that has been incriminated as a mediator of emesis that results from cytotoxic agents.[1] It has been marketed recently in the United States for use against the severe nausea and vomiting induced by cisplatin therapy.

The recommended dose schedule is 0.15 mg/kg intravenously before administration of cisplatin, and administration of ondansetron is repeated at 4 and 8 hours afterward. Used in this dose schedule, ondansetron can completely control the nausea and vomiting caused by cisplatin therapy in 40%–60% of patients, with an additional 20%–30% of patients having partial control of nausea and vomiting.[1–3]

In several prospective randomized trials, the efficacy of ondansetron was clearly superior to that of metoclopramide, which was the best antiemetic agent before ondansetron became available.[2,4–6] Besides providing superior control of nausea and vomiting, ondansetron therapy is not associated with neuromuscular side effects, which frequently accompany the use of metoclopramide. Furthermore, metoclopramide therapy requires coadministration of lorazepam (Ativan, Wyeth-Ayerst, Philadelphia, PA) or diphenhydramine hydrochloride (Benadryl, Parke-Davis, Morris Plains, NJ) for prophylaxis against neurologic side effects and consequently results in significant sedation and amnesia, which compromise the quality of life in patients receiving these drugs. In most trials reported to date, ondansetron has been tested against cisplatin-containing chemotherapy regimens, often in combination with other drugs such as 5-fluorouracil, vinblastine, or etoposide. Other chemotherapy regimens in which ondansetron has been evaluated and found efficacious include combinations of cyclophosphamide, doxorubicin, and 5-fluorouracil or methotrexate, as in the two popular regimens of FAC or CMF used to treat breast cancer.[5] Ondansetron also has been evaluated on a limited basis as an antiemetic for ifosfamide and carboplatin, with satisfactory results.

Besides cisplatin, dacarbazine (DTIC) is the most emetic agent used to treat cancer. The nausea and vomiting induced by DTIC are generally acute in onset and very intense, although these symptoms generally are short-lived, lasting no more than 4–6 hours after drug administration. The best currently available antiemetic agents—such as metoclopramide (Reglan, A. H. Robins Co., Richmond, VA), dexamethasone, and lorazepam, used alone or in combination—have not been effective

From the Department of Medical Oncology, Division of Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

Address for reprints: Sewa S. Legha, M.D., Department of Medical Oncology, Division of Medicine, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 77, Houston, TX 77030.

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in most patients in controlling the nausea and vomiting caused by DTIC.[7] Furthermore, DTIC commonly is used in combination with cisplatin, as in the treatment of melanoma, or with doxorubicin, as in the treatment of sarcomas and Hodgkin disease, which further exacerbates the nausea and vomiting.

This article reports the evaluation of ondansetron as an antiemetic agent in patients with malignant melanoma treated with a triple-drug regimen of cisplatin, vinblastine, and DTIC used sequentially.

Patients and Methods

Twenty-five patients with recurrent melanoma were treated with cisplatin, vinblastine, and DTIC and received ondansetron as an antiemetic agent. The chemotherapy regimen included DTIC, 800 mg/m^2 given over 2 hours on day 1; cisplatin, 20 mg/m^2/day intravenously on days 2–5; and vinblastine, 1.6 mg/m^2 intravenously on days 1–5. The courses of chemotherapy were repeated at 3-week intervals.

Ondansetron was evaluated in a step-wise manner, initially as a replacement for metoclopramide in combination with dexamethasone and lorazepam. Patients received a fixed dose of ondansetron, 10 mg intravenously, preceding chemotherapy along with lorazepam, 1.5 mg intravenously, and dexamethasone, 10 mg intravenously. Only a single dose of ondansetron was given to most of the patients who received chemotherapy in the outpatient clinic. The patients admitted to the hospital could receive repeat doses at 8-hour intervals if needed.

After the first five patients treated with this regimen experienced complete control of nausea and vomiting, the next group of nine patients were treated with a combination of ondansetron and lorazepam, without dexamethasone. Because we were impressed with the antiemetic efficacy of ondansetron in these patients, the third group of 11 patients were treated with ondansetron alone. Patients who had nausea or vomiting while receiving ondansetron alone could receive other antiemetic agents, which were added subsequently to ondansetron with the next course of chemotherapy. Patients were asked to keep records of episodes of nausea or vomiting after they left the outpatient clinic and were given a prescription for an oral antiemetic regimen of lorazepam plus diphenhydramine hydrochloride plus haloperidol to be used at home if needed. Patients also were asked to keep a daily record of side effects attributable to antiemetic therapy and were checked by one of the investigators on a daily basis during the 5 days of chemotherapy.

The general characteristics of patients participating in this study are outlined in Table 1. Twenty-one of the 25 patients were chemotherapy naive, and 4 did not have satisfactory control of nausea and vomiting with our standard antiemetic regimen of metoclopramide, lorazepam, and dexamethasone for the cisplatin, vinblastine, and DTIC regimen. Because the major focus of our study was assessment of the efficacy of ondansetron against DTIC, there was the option of using rescue and alternative antiemetics during cisplatin administration (days 2–5), and the data collection was less stringent.

Results

The data from all 25 patients in this study are evaluable for the DTIC phase of the study, which was completed within 24 hours. During this phase, 22 patients had no nausea or vomiting, for a complete response rate of 88%. The remaining three patients had one or two episodes of vomiting, resulting in 100% major control of nausea and vomiting with the use of ondansetron. Complete control was achieved in 5 of 5 patients receiving ondansetron in combination with lorazepam and dexamethasone, 8 of 9 patients receiving ondansetron plus lorazepam, and in 9 of 11 patients treated with ondansetron alone. Based on the excellent control of emesis with ondansetron alone, 24 of these 25 patients received their second and subsequent courses of cisplatin, vinblastine, and DTIC with ondansetron alone. A single patient required addition of dexamethasone because of significant nausea and vomiting with ondansetron alone. All four patients who had not responded to prior antiemetics experienced complete control of vomiting with ondansetron.

Control of nausea and vomiting was excellent for the first 2–3 days of this chemotherapeutic regimen, although a significant number of patients had some vomiting on the fourth or fifth day of cisplatin treatment. Consequently, dexamethasone was added in approximately one-third of the patients for subsequent courses on days 2–5 of their chemotherapy. The efficacy of ondansetron was well maintained during subsequent courses of chemotherapy. The tolerance of ondansetron therapy was excellent. The only side effects of note were headache in three patients and constipation in two patients.

Table 1. Patient Characteristics

No. of patients	25
Median age in yr (range)	41 (18–72)
Sex	
Male	17
Female	8
No prior chemotherapy	21
Prior chemotherapy	4
No. of patients treated with	
Ondansetron alone	11
Ondansetron + lorazepam	9
Ondansetron + lorazepam + metoclopramide	5

Discussion

The antiemetic efficacy of ondansetron in preventing nausea and vomiting caused by DTIC was impressive, resulting in complete control in more than 80% of the patients. Our prior experience with the best available combination of antiemetics, including metoclopramide and dexamethasone, provided complete protection in less than 20% of the patients receiving DTIC, which makes DTIC the most distressful emetic agent.[7] Besides its high efficacy, ondansetron provided prolonged protection; a single daily dose of 10 mg provided adequate control in all patients after DTIC administration and in most patients receiving cisplatin on subsequent days. Because there is a wide range of doses over which ondansetron is effective as an antiemetic,[8] we elected to use a round dose of 10 mg instead of the exact calculated dose based on the recommended dose of 0.15 mg/kg.

In view of the prolonged protection experienced by our patients, we believe that the recommendation for repeat administration at 4-hour intervals may be unnecessary. This is further reinforced by some of the previously reported studies in which an interval of 8 hours between doses appeared to provide as good a protection from nausea as 4- or 6-hour intervals.[3,9,10] Although the exact duration of antiemetic effects from ondansetron is yet to be determined, recent evaluation of another serotonin antagonist, granisetron, has shown protection from nausea and vomiting lasting as long as 12 hours after single-dose administration.[11] These data indicate that longer intervals between doses of ondansetron should be investigated to make this drug more cost-effective in comparison with other antiemetic agents commonly used.

Because the antiemetic protection from the triple combination of metoclopramide, dexamethasone, and lorazepam was unsatisfactory, we initially used ondansetron in combination with dexamethasone and lorazepam. Subsequently, we were able to eliminate dexamethasone and lorazepam without compromising the efficacy of ondansetron, which alone provided excellent protection from DTIC-induced nausea and vomiting. The addition of other drugs is still necessary when using ondansetron in the treatment of nausea and vomiting caused by high-dose cisplatin, in which case addition of dexamethasone clearly enhanced its antiemetic effect such that nearly 90% of the patients experienced complete protection compared with approximately 60% of patients receiving ondansetron alone.[12] These data suggest that ondansetron can be used as a single agent for the first course of chemotherapy with a provision for the addition of dexamethasone for second and subsequent courses of treatment in patients who do not achieve complete control of nausea and vomiting with ondansetron alone.

We believe that the availability of ondansetron is a major advance in the antiemetic therapy for patients with cancer and makes it possible to use chemotherapy without the resultant nausea and vomiting in more than 90% of patients. Furthermore, patients now can receive their chemotherapy while staying fully alert and functional and without having to "sleep through" it to avoid the nausea and vomiting that generally occurred with previously available antiemetic agents.

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