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The pattern of emesis following high-dose cyclophosphamide and the anti-emetic efficacy of ondansetron

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Two randomized, double-blind placebo-controlled ondansetron dose ranging studies in patients receiving high-dose cyclophosphamide (with or without doxorubicin) were completed in the US. These studies enable the pattern of emesis and nausea for 3 days following high-dose cyclophosphamide to be described and give some insight into the mechanisms of emesis which may be operating. Nausea and vomiting induced by cyclophosphamide-based chemotherapy has a long latency of onset (8–13 h) and continues for at least 3 days. These findings are of particular importance as many of these patients receive chemotherapy as outpatients and emphasize the need for appropriate anti-emetic prophylaxis for patients at home. Ondansetron was extremely effective over this time in the control of emesis and nausea. These results suggest that high-dose cyclophosphamide-induced emesis over days 1–3 is largely mediated via 5-hydroxytryptamine (5-HT) and 5-HT_3 receptors.

Key words: Cyclophosphamide, emesis, mechanisms, ondansetron.

Introduction

Nausea and vomiting following chemotherapy are considered by patients as the worst aspects of their treatment.[1] If not adequately controlled with anti-emetics these symptoms can lead to a loss of appetite, metabolic disturbances, deterioration of physical and mental condition as well as the possible rejection of potentially beneficial treatment.[2] Cytotoxic drugs vary in their emetogenicity. Cisplatin is generally regarded as the most emetogenic agent. However, many other 'non-cisplatin' antineoplastic drugs such as high-dose cyclophosphamide induce severe emesis and the combinations of drugs used often increase the emetogenicity of the chemotherapy.

The introduction of the highly selective 5-HT_3 receptor antagonists, such as ondansetron, has been a major advance in the control of chemotherapy and radiotherapy induced emesis and nausea. This advance has helped our understanding of the pathophysiology of chemotherapy-induced emesis, i.e. the importance of 5-hydroxytryptamine (5-HT) and 5-HT_3 receptors in the vomiting reflex. However, our understanding of the mechanisms involved in the emetic reflex is not complete. Important information can be obtained from studying the time-course of emesis following different cytotoxic agents and the efficacy of specific receptor antagonists such as ondansetron. For example, it is known that following high-dose cisplatin chemotherapy the majority of emesis occurs over the first 6 h. During this time ondansetron is highly effective.[3,4] These data strongly suggest that 5-HT acting at 5-HT_3 receptors on the vagus nerve in the gastrointestinal tract and/or the central vomiting system is largely responsible for this initial phase of emesis. Indeed, this pattern of emesis correlates with the urinary excretion of the main metabolite of 5-HT, 5-hydroxyindolacetic acid (5-HIAA).[5–7] After the initial phase of emesis following cisplatin there is a later phase of emesis called cisplatin-induced delayed emesis which is most severe 48–72 h following cisplatin.[8] The effect of 5-HT_3 receptor antagonists during this delayed period following cisplatin remains to be fully established.[9]

The pattern of emesis seen with cyclophosphamide based therapy is somewhat different in that the acute phase of emesis begins later than that of cisplatin but this acute emesis phase can last for a number of days (prolonged emesis). In addition there is no second phase of delayed emesis as seen with cisplatin.

Two large, placebo-controlled dose ranging studies looking at the use of orally administered ondansetron in the control of cyclophosphamide (with or without doxorubicin) induced emesis over 3 days were completed in the US.[10,11] These studies were conducted as at the time no oral compound had been approved by the FDA as efficacious in the prevention of emesis associated with cyclophosphamide or doxorubicin. Additionally, few studies evaluating the effectiveness of phenothiazines, ster-

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oids and cannabinoid compounds have used homogenous chemotherapy populations, a double-blind design or conventional efficacy end-points, thus limiting the value of the results.[12–14] Furthermore, some anti-emetic studies have shown a significant placebo response, with 22–47% of placebo-treated patients reporting no emetic episodes.[15–17] Based on this lack of valid data from clinical trials, a placebo arm was thought to be required in these clinical trials to validate the study model and to fully evaluate the efficacy of ondansetron in this group of patients. Because of the ethical concerns of a placebo arm in such trials, approved doses of oral prochlorperazine were provided as rescue therapy. Additionally, the protocols did not restrict the withdrawal of any patients from the studies, thereby allowing investigators to withdraw patients at any time. All patients gave written informed consent, and the protocols were reviewed and approved by the institutional review board of each participating center.

These placebo-controlled studies[10,11] enable the time course of emesis in patients given cyclophosphamide (with and without doxorubicin) over 3 days to be described and give some insight into the emetic mechanisms operating over this period. There are data to show that cyclophosphamide has a longer latency to emesis compared with cisplatin.[18] However, few studies have described the pattern of emesis following high-dose cyclophosphamide over 3 days. This is of particular importance as the majority of these patients are treated as outpatients and significant emesis and/or nausea at home may adversely affect patients' quality of life. Indeed, the extent of nausea and vomiting at home may not be fully appreciated by clinicians.

Patients and methods

The studies were multicenter, randomized, double-blind, dose comparison trials, comparing orally administered ondansetron, 1,4 and 8 mg three times a day for 3 days with placebo. All patients were chemotherapy naive having their first cycle of cyclophosphamide ($\geq$450 mg/m^2)-based chemotherapy. Because of the more emetogenic nature of doxorubicin compared with methotrexate, patients were stratified as to whether the cyclophosphamide regimen contained doxorubicin ($\geq$35 mg/m^2) or methotrexate ($\geq$30 mg/m^2). All patients were at least 18 years of age. Women of childbearing potential were required to have a negative pregnancy test prior to entry. Concomitant administration of cisplatin, carboplatin, dacarbazine, nitrogen mustard, procarbazine or ifosfamide rendered the patient ineligible. The use of any anti-emetic during the 24 h prior to study initiation also excluded the patient. Ondansetron was the only anti-emetic administered during the 3 day study period. Patients received the study drug or placebo drug 30 min prior to the administration of chemotherapy and 4 and 8 h following chemotherapy on day 1 and three divided doses on study days 2 and 3. All patients were given 10 mg prochlorperazine capsules for rescue. The study drug was discontinued at rescue.

The primary efficacy variable was the number of emetic episodes (vomits and/or retches). A complete response was defined as no emetic episodes during the 3 day study period. A major response was defined as one to two emetic episodes over the 3 day study period and a minor response was defined as three to five emetic episodes. Patients experiencing more than five emetic episodes or those who were withdrawn because of the severity of nausea and vomiting or adverse events were deemed treatment failures.

Secondary efficacy variables were severity of nausea and food intake. Patients assessed their own nausea. A 100 mm visual analog scale was used. A score of 0 mm represented 'no nausea' and a score of 100 mm indicated 'nausea as bad as it could be'. A four-point scale was used to evaluate food intake. An adverse event was defined as any untoward medical occurrence or an exacerbation of a pre-existing medical condition.

Results

Six hundred and seventy-three cancer patients were enrolled in both studies. Six hundred and fifteen patients were evaluable for efficacy. Three hundred and forty-five patients received doxorubicin ($\geq$ 35 mg/m,^{2}) in addition to cyclophosphamide; 308 of these patients were evaluable for efficacy. Breast cancer was the most common malignancy and represented 76% of the total population. The ondansetron 8 mg arm provided optimal control of nausea and emesis; the dose comparison results are reported elsewhere.[10,11] Results from the placebo and optimal 8 mg ondansetron arms are reported in this review.

Pattern of emesis (patients given placebo)

Significant nausea and vomiting was experienced by approximately 80–90% of placebo patients over

days 1–3. The addition of doxorubicin to cyclophosphamide induced more emesis (Figure 1).

Time to onset of emesis

In patients given placebo, the time to onset of emesis was similar in the two studies. The mean time to emesis in patients who experienced at least one emetic episode was approximately 10.5 h. There was little difference in the time to onset of emesis in patients given cyclophosphamide $\geq 600\ mg/m^2$ and patients given a lower dose of cyclophosphamide ($<600\ mg/m^2$). However, patients who also received doxorubicin had a more rapid onset of emesis with a mean time to onset of emesis of 8–8.5 h compared with 12–13 h for patients not given doxorubicin (Table 1).

Duration of emesis

Significant nausea and emesis occurred in patients given placebo for at least 3 days (Figures 2 and 3).

Efficacy of ondansetron

Ondansetron was significantly superior to placebo over the 3 day study period ($p \leq 0.001$ emesis; $p \leq 0.05$ nausea) (Figures 1 and 2). Ondansetron improved anti-emetic control to the same extent in patients who did and did not receive doxorubicin. Over the 3 day study period only 11% of placebo patients in the doxorubicin group experienced no emetic episodes compared with 61% of the 8 mg ondansetron group. Similarly, in patients who did not receive doxorubicin, anti-emetic control was increased from 21% with placebo to 71% with ondansetron (Figure 1). Importantly, the efficacy of ondansetron over the 3 days of the study is not due to the response to ondansetron on day 1 alone. Logistic regression analysis to account for a number of prognostic factors, including the response on day 1, shows that ondansetron is superior to placebo over days 2/3 (Figure 3). Patients given ondansetron also benefited from a superior food intake on study days 2 and 3 compared with the placebo group.

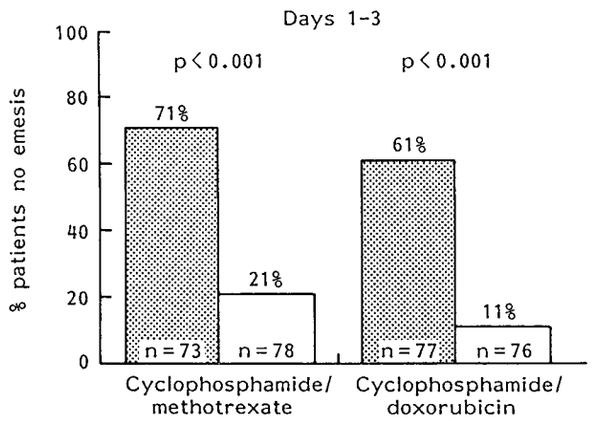

Figure 1. Ondansetron (▨) versus placebo (□) in the control of cyclophosphamide-induced emesis.

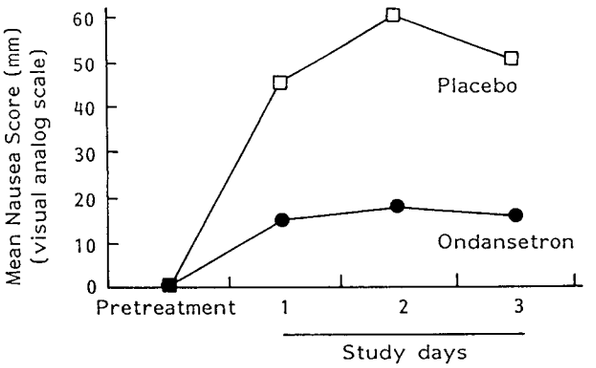

Figure 2. The time course of nausea following high-dose cyclophosphamide-based chemotherapy and the efficacy of ondansetron.

Table 1. Mean time (h) to onset of emesis in patients with at least one emetic episode

	Study 1	Study 2
All chemotherapies	10.5	10.53
Low-dose cyclophosphamide ($<600\ mg/m^2$)	10.41	10.54
High-dose cyclophosphamide ($\geq 600\ mg/m^2$)	10.66	10.52
Non-doxorubicin patients	13.02	12.26
Doxorubicin patients	8.09	8.23

Adverse events

Side effects due to ondansetron were infrequent. Neurologic (headache, tiredness and dizziness) and gastrointestinal (constipation, diarrhoea, flatulence, abdominal pain, stomach cramps and xerostomia) symptoms were most common. No extrapyramidal reactions were observed.

Discussion

It is known that nausea and emesis associated with antineoplastic therapy is of variable intensity and duration, and dependent on the agent, dose and additional drugs used. Information on the patterns of emesis induced by different antineoplastic agents can give a valuable insight into the mechanisms of emesis and consequently the most effective therapeutic interventions. Cisplatin is known to be the most emetogenic agent, which invariably induces severe emesis within 1–3 h following administration. During this time ondansetron is extremely effective.[3,4] These data strongly suggest that 5-HT and 5-HT_3 receptors are important in mediating emesis over this period.

These placebo-controlled ondansetron dose ranging studies enabled the time course of nausea and emesis over 3 days following high-dose cyclophosphamide to be described. Significant nausea and emesis was observed in more than 70% of all patients in both studies who received placebo. Following cyclophosphamide there was a long latency to emesis (approximately 10.5 h) and emesis and nausea continued for at least 3 days (Figure 4), which suggests that a 3 day regimen of anti-emetic therapy may be warranted.

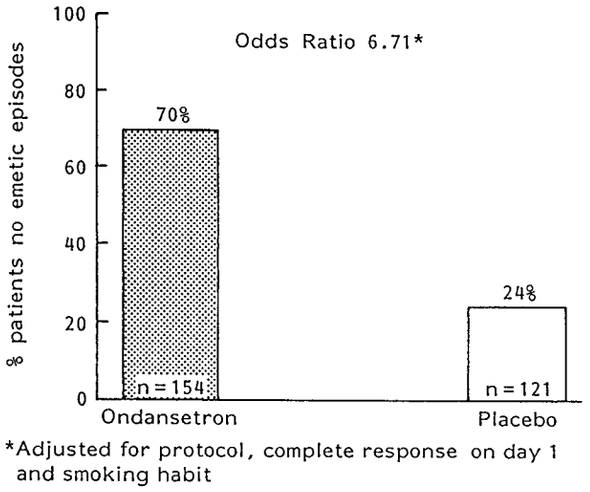

Figure 3. Ondansetron versus placebo for the control of emesis over days 2/3 following cyclophosphamide.

The reasons for the longer latency to emesis after cyclophosphamide compared with cisplatin are unknown. Although following cisplatin there is some delay before the onset of emesis (peak levels are present in plasma within minutes of an i.v. dose). The longer delay following cyclophosphamide suggests that secondary mechanisms need to be activated to induce emesis such as its conversion to active metabolites. However, peak levels of active metabolites are present within 2 h of dosing.[19]

The pattern of emesis following high-dose cyclophosphamide differs from the time course of emesis induced by cisplatin where there is intense emesis during the first 6 h,[3,4] followed by a delayed phase of emesis which is most severe 48–72 h following cisplatin,[8] i.e. cyclophosphamide induces a more prolonged pattern of emesis (Figure 4). Ondansetron is extremely effective in the control of emesis and nausea over days 1–3 following high-dose cyclophosphamide with or without doxorubicin. These findings are in agreement with previous studies which have compared ondansetron with other anti-emetics over days 1–3/5 following non-cisplatin chemotherapy. Indeed, a meta-analysis of three similar studies showed that ondansetron was superior to metoclopramide.[20] This suggests that 5-HT acting at 5-HT_3 receptors on the vagus nerve in the gastrointestinal tract and/or in the brainstem vomiting system play a significant role in the prolonged pattern of emesis following high-dose cyclophosphamide.

Interestingly, there is little or no elevation of urinary 5-HIAA (the main metabolite of 5-HT) in patients given high-dose cyclophosphamide.[6] Following high-dose cisplatin chemotherapy the urinary concentrations of 5-HIAA correlate with the initial phase of severe emesis.[5–7] This may be because cyclophosphamide induces less 5-HT release

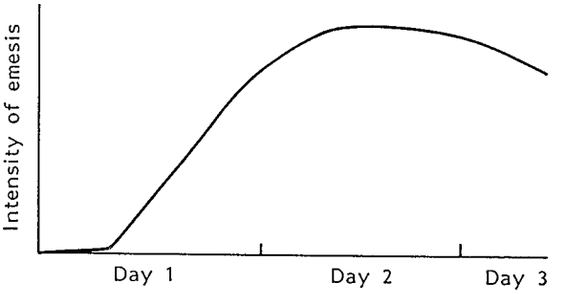

Figure 4. The pattern of emesis and nausea following high-dose cyclophosphamide chemotherapy.

from enterochromaffin cells compared with cisplatin which may account for the less severe emesis produced by cyclophosphamide. Moreover, 5-HT is readily taken up into platelets and may not be excreted into the urine. Alternatively, the relative importance of central nervous system versus peripheral nervous system 5-HT_3 receptors may be different for different cytotoxic drugs. Interestingly in this context, it has recently been shown that urinary 5-HIAA concentrations are not elevated during the delayed phase of cisplatin induced emesis.[7]

Although 5-HT and 5-HT_3 receptors play a significant role in mediating emesis following cancer chemotherapy, there are still patients who suffer nausea and vomiting despite the use of 5-HT_3 receptor antagonists. This suggests that additional emetic mechanisms may also be involved. Indeed, the addition of dexamethasone to ondansetron has been shown to significantly enhance efficacy.[21,22] However, the anti-emetic mechanism of action of dexamethasone is unknown. The use of other combinations of anti-emetics may enhance efficacy even further and provide valuable information relating to the mechanisms of the emetic response.

The late onset of nausea and emesis following high-dose cyclophosphamide and the high incidence on days 2/3 is particularly important for this group of patients who often receive chemotherapy on an outpatient basis. These results therefore emphasize the need for adequate anti-emetic protection for patients when they are at home, to maintain their nutritional status and their quality of life.

Conclusions

Cyclophosphamide induces nausea and emesis for at least 3 days following administration. Over this time ondansetron is a highly effective anti-emetic indicating that 5-HT and 5-HT_3 receptors underlie the main emetic mechanism over days 1–3.

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