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Comparison of oral itasetron with oral ondansetron: results of a double-blind, active-controlled phase II study in chemotherapy-naive patients receiving moderately emetogenic chemotherapy

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Itasetron hydrochloride is a new 5-hydroxytryptamine$_3$ (5-HT$_3$) antagonist. Experimental investigations show that orally it is rapidly absorbed (about 90 min), is highly bioavailable (greater than 90%), has a long half-life (about 12 h) and is more potent (about 10 times) in animal models than ondansetron, currently standard therapy for the prophylactic control of chemotherapy induced nausea and vomiting. This paper describes the results of a study designed to assess the efficacy and tolerability of five (0.5, 1, 2, 4 and 8 mg) twice-daily doses of itasetron hydrochloride, in comparison with 8 mg b.i.d. ondansetron. Assessments were made in patients ($n = 104$) with histologically confirmed cancer (excluding head and neck tumors) and about to receive their first course of moderately emetogenic chemotherapy. Itasetron hydrochloride demonstrated comparable efficacy to ondansetron; no statistically significant between-group differences were observed in the primary (complete response rate) or secondary (nausea and delayed emesis) efficacy criteria. Adverse events were similar in type and incidence across all treatment groups, and were those expected for this therapeutic class. The tolerability of itasetron hydrochloride was assessed as 'very good' or 'rather good' by 81% of patients and 89% of physicians. In conclusion, itasetron hydrochloride is effective and well tolerated in patients receiving moderately emetogenic chemotherapy. Oral doses of 1 mg b.i.d. or above will be used in further clinical studies.

Key words: Chemotherapy, efficacy, emesis, itasetron, ondansetron, safety.

The following co-investigators participated in this study: Professor Fauser, University of Freiburg; Dr Schoenborn, University of Berlin—Rudolf Virchow; Professor Scheulen, University of Essen; Professor Brecht, University of Bonn; Professor Opri, University of Berlin; Dr Schroeder, University of Frankfurt/M; Dr Beck, University of Mainz; Professor Meerpohl, St-Vincentius-Hospital Karlsruhe; Professor Dietl, University of Tübingen; Dr Moebus, University of Ulm.

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Introduction

Of all the side effects of anti-cancer chemotherapy, nausea and vomiting are perceived by patients as amongst the worst.[1] Inadequate management of these symptoms can not only affect the quality of life of these patients, but can lead to poor compliance to further potentially curative treatment.[2,3]

The onset of nausea and vomiting is variable in intensity and duration depending on the chemotherapy regimen employed.[4,5] Strongly emetogenic agents such as cisplatin usually provoke an early (3 h after chemotherapy) and intensive response which subsequently fades into a milder form of nausea and vomiting that may last several days.[6–8] The response to cyclophosphamide-based chemotherapy is less intense.[9,10] Emesis starts after a latency of approximately 10 h and little emetic activity is observed 24–36 h after chemotherapy.[11] These differences are thought to be due to a multiplicity of mechanisms that are involved in triggering the emetic response.

Emesis occurring during the first 24 h after cytotoxic treatment is generally classed as acute in onset. The importance of achieving maximal control of acute emesis at the patient's first cycle is highlighted by studies showing that incomplete protection predisposes to further emetic problems.[12] Failure to achieve adequate acute control increases the risk of delayed emesis manifesting 24 h or more after chemotherapy.[8,13] Furthermore, inadequate control of acute emesis can act as a conditioning stimulus leading to development of anticipatory symptoms at subsequent cycles.[14,15] Thus, effective prophylactic treatment of acute emesis at the initial cytotoxic cycle is critical to the success of chemotherapy.

The discovery that acute emesis induced by

moderate and severely emetogenic chemotherapy could be prevented or greatly reduced by selective 5-hydroxytryptamine$_3$ (5-HT$_3$) antagonists has been important in the palliative care of cancer patients undergoing chemotherapy.[16–21]

Of the currently available 5-HT$_3$ antagonists, ondansetron is considered to be the 'standard therapy'. When given as monotherapy it protects about 45–70% of patients from acute onset of nausea and vomiting, depending on the chemotherapy given.[22] However, failure to control emesis after chemotherapy can still occur in about 30% of patients receiving highly emetogenic chemotherapies (e.g. 50 mg/m^2 cisplatin or greater) and in about 25% of patients receiving moderately emetogenic chemotherapy.[23,24] Indeed, about 20% of patients receiving cisplatin regimens require ondansetron to be given in combination with agents such as dexamethasone in order to provide adequate anti-emetic protection.[25] Moreover, treatment with ondansetron is associated with headache and constipation that occur in about 20 and 7% of patients, respectively.[22] Notably, ECG changes, tachycardia and cardiac deaths have been reported during ondansetron treatment.[26]

Itasetron hydrochloride is a new 5-HT$_3$ antagonist currently in development. Animal models of emesis show that it is at least twice as potent as ondansetron when administered i.v. and about 10 times more potent when administered orally.[27] Clinical pharmacokinetic studies also highlight a number of interesting differences. Compared with ondansetron, ita- setron hydrochloride is highly bioavailable (above 90% versus approximately 55%), has a longer half-life of elimination (approximately 12 h versus approximately 3 h) and does not undergo extensive hepatic biotransformation before elimination (BI data on file).[22,28,29] The major pathway of elimination of itasetron hydrochloride is renal excretion (60% or higher in the form of the unchanged compound, BI data on file).

In volunteer studies, single oral administration of itasetron hydrochloride was well tolerated at doses between 0.5 and 60 mg, the highest dose tested (BI data on file). In patients undergoing high-dose cisplatin chemotherapy, single i.v. doses between 35 and 280 μg/kg body weight (equivalent to approximately 3 and 18 mg/patient) were effective in preventing emesis and also well tolerated (BI data on file). A lower dose of 17 μg/kg body weight (corresponding to about 1 mg per patient) was found to be not effective in this trial.

On the basis of these preliminary investigations, the following dose concentrations of itasetron hydrochloride were selected for investigation: 0.5, 1, 2, 4 and 8 mg. These were to be administered twice daily, for three consecutive days, to chemotherapy-naive patients. This patient population was selected to avoid any prior conditioning (anticipatory emesis and nausea) and to reduce variability in the emetogenic potential of the population.

The aim of the study was to investigate the efficacy and tolerability of oral itasetron hydrochloride and to define the therapeutic dose range for the prophylactic control of acute emesis in cancer patients receiving moderately emetogenic chemotherapy. The results were evaluated by double-blind, randomized comparison with ondansetron 8 mg b.i.d. An active control was used on ethical grounds because of the proven efficacy of this class of agent in preventing acute onset of nausea and vomiting. The dose and dosing regimen of ondansetron was the label recommendation in Europe for the indication. The label recommendation (8 mg t.i.d.) in the USA at the time of the trial was not used because a clinical trial of 309 patients receiving moderately emetogenic chemotherapy found that ondansetron 8 mg b.i.d. was as effective as 8 mg t.i.d.[30] In 1995, 8 mg b.i.d. became the recommended regimen in the USA.

Patients and methods

Study design

This was a multicenter ($n = 11$), double-blind, actively controlled and randomized, parallel-group study. The study was designed as a dose-escalation trial with at least 16 patients per dose level treated with itasetron hydrochloride and four patients treated with ondansetron. The study protocol received ethical committee approval and was conducted in accordance with the recommendations of the 18th World Medical Assembly, Helsinki (1964), and 29th (Japan, 1975) and 35th (Hong Kong, 1989) World Medical Assembly revisions. The study was performed in accordance of the EC-GCP Note for Guidance and the requirements of the German Drug Law (AMG). All patients gave written informed consent.

Patients

Patients with histologically confirmed cancer (other than head and neck tumors) were enrolled to allow a minimum of 20 patients in each treatment group.

Patient numbers were allocated according to a telephone randomization procedure. No sample size estimations based on response rates could be performed because this was the first phase II trial of itasetron hydrochloride in this patient population.

All patients were about to undergo their first course of chemotherapy with one of the following cytotoxic agents (alone or in combination with less emetogenic cytotoxic agents): cyclophosphamide (500 mg/m^2 or greater) in combination with other cytotoxic drugs, ifosfamide (2 mg/m^2 or greater) alone, doxorubicin alone (40 mg/m^2 or greater) or in combination (25 mg/m^2 or greater) with other cytotoxic drugs, epirubicin alone (75 mg/m^2 or greater) or in combination (50 mg/m^2 or greater) with other cytotoxic drugs.

Patients were excluded from the trial on the basis of criteria related to their state of health. These included a Karnofsky performance score below 60%, concomitant serious cardiovascular or cerebrovascular diseases, clinically relevant prolongation of PQ interval or QRS complex, antiarrhythmic therapy, liver cirrhosis, active peptic ulcer disease, leucocyte and platelet counts below 3500 and 100 000/mm^3, respectively, serum creatinine above 1.5 mg/100 ml and serum bilirubin above 2.0 mg/100 ml, and transferases above 50 U/l. Other exclusion criteria included pregnancy or any possible causes of interferences with emesis such as drug intake, radiation therapy and history of drug or alcohol abuse.

Treatment

Patients were randomized to receive twice-daily, oral doses of 0.5 ($n = 16$), 1 ($n = 17$), 2 ($n = 18$), 4 ($n = 17$) or 8 mg ($n = 6$) of itasetron hydrochloride or 8 mg b.i.d. ondansetron ($n = 20$). The patients were randomized per dose level of itasetron hydrochloride. The first dosing group was 1 mg b.i.d. itasetron hydrochloride (or ondansetron 8 mg b.i.d.). Subsequently, the dose of itasetron hydrochloride was doubled in the next dosing group (2 mg b.i.d. itasetron hydrochloride or ondansetron 8 mg b.i.d.). Before each increase in the dose of itasetron hydrochloride, an assessment of tolerability was made, without compromising the study blinding. Itasetron hydrochloride 0.5 mg b.i.d. (or ondansetron 8 mg b.i.d.) was included as the last of the dosing groups because of the efficacy seen (without comprising the study blind) in the 1 mg b.i.d. itasetron hydrochloride dosing group. All treatments were administered 1.5 h before chemotherapy and at 12 h intervals thereafter for three consecutive days.

The chronological succession of dosing in the trial meant that account had to be made of time-related occasion differences between treatment groups. In order to control for this variable, patients receiving ondansetron were assigned to each itasetron hydrochloride treatment group in a double-blind and randomized fashion.

Anti-emetic 'rescue' therapy could be administered to patients having at least three distinct emetic episodes (more than 5 min apart) within 24 h or if the intensity of nausea and/or emesis required immediate anti-emetic therapy. Patients receiving such therapy were considered to be treatment failures in the efficacy analysis, but were included in the evaluation of safety.

Concomitant therapy was allowed provided patients were receiving a constant dosage and were stabilized on the medication prior to the commencement of the study. In the case of an intercurrent disease, the potential for drug interactions was assessed and prescribed medication documented. Any drug with the potential to influence emesis was forbidden for the full study period.

Efficacy evaluation

The primary endpoint of this study was to determine the efficacy of itasetron hydrochloride as an anti-emetic agent. The primary measure was defined as the number of patients in each group who achieved a complete response (i.e. no emetic episode) to treatment within the first 24 h after starting chemotherapy (acute emesis). An emetic episode was defined as a single vomit or retch or continuous vomits or retches. Episodes were, by definition, separated by the absence of vomiting or retching for at least 5 min.

Secondary endpoints were to determine the delayed emetic response, time to onset of first nausea and vomiting, patient's statement of the intensity of nausea, and patient's and physician's global assessments of efficacy and tolerability. The delayed emetic response was evaluated by recording the number of patients achieving a complete response in the 24–72 h following treatment. Patient diaries were used to record the number of emetic episodes for each 24 h interval after the start of chemotherapy. The response categories, per 24 h period, were defined as follows: complete response, no emetic episodes; major response, one to two emetic episodes; minor response, three to five emetic episodes; treatment failure, more than five emetic episodes or patient received 'rescue' therapy. The time from the start of

chemotherapy to the onset of the first emetic episode and/or first nausea was also recorded, and each patient graded feelings of nausea per 24 h period for the duration of treatment as: none, no nausea; mild, no interference with normal daily life; moderate, interference with normal daily life; severe, confined to bed due to nausea. Both the patients' and the physicians' assessment (very good, rather good, rather bad or very bad) of the efficacy of itasetron hydrochloride and ondansetron was made at the end of the trial.

Safety evaluations

Adverse events were recorded and classified as mild, moderate or severe, and the causal relationship between the study medication and the adverse event was defined. Routine laboratory analyses, including haematology tests, blood chemistry and urinalysis, were performed at a screening visit and in the post-treatment period. A 12-lead ECG was also performed during the screening period as well as post-treatment.

At the end of the trial, patients and physicians assessed the tolerability of the treatments on a scale of very good, rather good, rather bad or very bad.

Statistical analyses

No sample size predictions could be made as the trial was the first phase II study of chemotherapy naive patients receiving moderately emetogenic regimens. Confidence intervals for complete responder rates were calculated according to Pearson–Clopper.[31] Fisher's exact test was used for pairwise comparisons of doses of itasetron hydrochloride. Secondary efficacy and laboratory safety parameters were evaluated using the Kruskal–Wallis test.

Results

Patient demographics and disposition

A total of 104 patients (aged between 20 and 74 years) were enrolled in the trial. Table 1 shows the patient demographics and baseline characteristics. A total of seven patients withdrew from the trial; five due to lack of efficacy of the study drug, one due to an adverse event and one patient did not comply with the protocol.

Patients were randomized to treatment with twice-daily itasetron hydrochloride (0.5, 1, 2, 4 or 8 mg) or twice-daily ondansetron (8 mg). The patient group treated with 0.5 mg b.i.d. itasetron hydrochloride showed differences in patient distribution and chemotherapy treatment in comparison with the other treatment groups. The number of women, and hence breast cancer patients, was lower than in the other treatment groups and more patients had a Karnofsky performance score of 80–90%. One patient received cyclophosphamide, methotrexate and fluorouracil (CMF) while eight out of 16 received cyclophosphamide/doxorubicin. In the other treatment groups eight to 11 patients received CMF and one to five patients received cyclophosphamide/doxorubicin.

Efficacy

There were no fundamental differences between the per protocol analysis and the intention-to-treat analysis. Data are therefore presented according to the per protocol analysis.

Ninety-nine patients were included in the analysis of acute emesis which is presented in Figure 1. No statistically significant between-group differences were indicated for the primary efficacy parameter, complete response rate. Highest complete response rates were for the 1 and 8 mg b.i.d. itasetron hydrochloride treatment groups. The complete response rates observed were 88%. The complete response rate for patients given ondansetron 8 mg b.i.d. was 65%. There were seven treatment failures over all treatment groups; four patients in the 0.5 mg b.i.d. itasetron hydrochloride group, two in the 2 mg b.i.d. itasetron hydrochloride group and one patient receiving 8 mg b.i.d. ondansetron.

Over all treatment groups, 29 patients experienced emesis or were administered 'rescue' therapy. In this population, the range of time-to-onset of emesis was 3 h 45 min to 68 h 34 min. There was no clear indication of a dose–response relationship from the calculated time-to-onset of emesis or 'rescue' therapy in these patients. However, there was a trend for patients receiving 1 mg b.i.d. itasetron hydrochloride to have the longest time to first emesis (21 h 00 min). Notably, this was approximately twice the duration (9 h 30 min) of patients given ondansetron (Figure 2).

The efficacy of itasetron hydrochloride compared with ondansetron in delayed emesis was evaluated in 97 patients. Figure 3 presents the response to treatment on the worst day of day 2 (24–48 h after chemotherapy) and day 3 (48–72 h after chemo-

Table 1. Patient demographics and baseline characteristics

	Itasetron hydrochloride (mg b.i.d.)					Ondansetron (mg b.i.d.)
	0.5	1	2	4	8	8
Patient age range (years)	25–73	33–69	27–74	29–65	30–70	23–74
Height (cm)	157–186	150–187	158–175	156–172	150–197	152–188
Weight (kg)	48–100	40–90	54–93	54–98	51–92	50–100
Sex						
female	9	12	15	14	11	17
male	7	4	2	0	5	3
Chemotherapy regimen						
CMF	1	10	8	9	10	11
CD (+ others)	8	3	2	1	4	5
C (+ others)	5	1	2	1	2	3
CE (+ others)	2	1	4	3	0	1
E	0	1	1	0	0	0
Cancer diagnosis						
Hodgkin's disease	1	1	1	0	1	3
acute lymphoblastic leukaemia	2	0	0	0	0	0
malignant neoplasm of the bone/ articular cartilage	0	1	0	0	0	0
breast cancer	3	11	13	12	10	13
malignant neoplasm of the lymph nodes	0	1	0	0	1	0
malignant neoplasm of the testis	0	0	1	0	0	0
malignant neoplasm of the liver	0	1	0	0	0	0
multiple myeloma	3	0	1	1	1	0
other malignant neoplasm of the lymph/histiocytes	7	1	1	1	3	4

CMF = cyclophosphamide, methotrexate, fluorouracil; CD = cyclophosphamide, doxorubicin; C = cyclophosphamide; CE = cyclophosphamide, epirubicin; E = epirubicin.

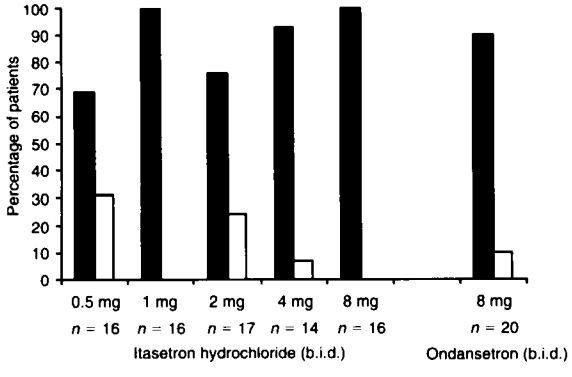

Figure 1. Acute emesis: response to treatment 24 h after chemotherapy. ■, Complete or major response. □, Minor response or treatment failure.

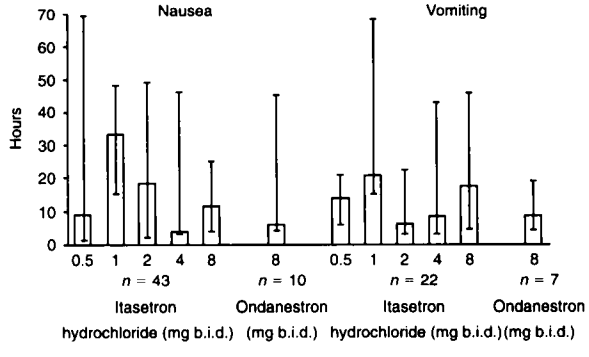

Figure 2. Median time to onset of nausea and vomiting.

therapy). A complete response (i.e. no emesis in the 3 days following chemotherapy) or major response (i.e. one to two emetic episodes) was observed in 80% (0.5 mg), 100% (1 mg), 82% (2 mg), 95% (4 mg) and 100% (8 mg) of patients in the itasetron hydrochloride dosage groups, and in 95% of patients receiving 8 mg ondansetron. Similar to the results for acute emesis, no significant differences were observed between the treatment groups.

Ninety-eight patients were included in the evaluation of nausea. Figure 4 presents the intensity of nausea recorded by patients over the whole trial

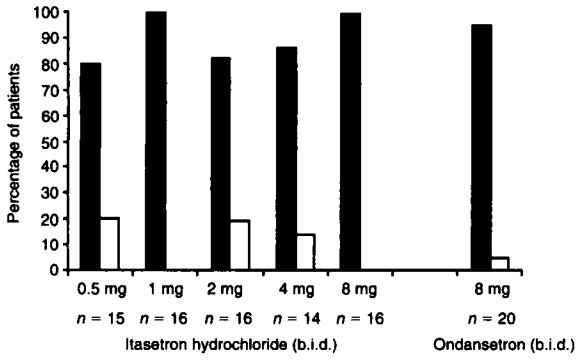

Figure 3. Delayed emesis: response to treatment on the worst of days 2 and 3. ■, Complete or major response. □, Minor response or treatment failure.

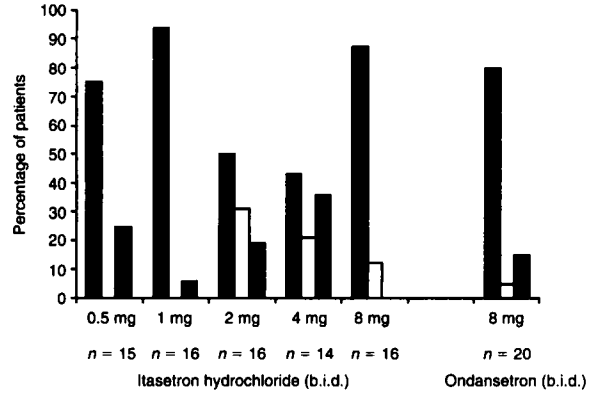

Figure 4. Patients' assessment of the intensity of nausea during the study period. ■, No nausea or mild nausea. □, Moderate nausea. ■, Severe nausea or rescue therapy.

period. Across all treatment groups, between 43 and 94% of patients had no experience of nausea or only mild nausea that did not interfere with their normal daily life. Similar results were observed on each single observation day. No clear dose–response relationship between treatment and the intensity or time-to-onset of nausea was observed either over the study period or after a single observation period. Of the patients receiving itasetron hydrochloride, those given 1 mg b.i.d. had the lowest intensity of nausea (94% reporting no or mild nausea). Eighty percent of patients receiving ondansetron experienced no or mild nausea. Between 0 and 36% of patients reported severe nausea or were administered 'rescue' therapy. However, there was a trend for patients receiving 1 mg b.i.d. itasetron hydrochloride to have the longest time-to-onset of nausea (median time 33 h 45 min) (Figure 2).

The physicians' and patients' assessment of global efficacy of the study medications was similar. Physicians assessed that 75% (0.5 mg), 100% (1 mg), 65% (2 mg), 64% (4 mg) and 100% (8 mg) of patients receiving itasetron hydrochloride, and 85% of patients receiving ondansetron had a 'very good' or 'rather good' response.

Safety and tolerability

All patients ($n = 104$) were included in the safety analysis. Table 2 shows the most common adverse events which occurred on day 1 and in the post-treatment period or worsened after the screening visit. The type and incidence of adverse events were similar across all treatment groups. In addition, no dose relationship in the patients receiving itasetron hydrochloride was evident. The most common adverse events were headache and constipation, experienced by 25 and 18%, respectively, of all patients. Most adverse events were mild or moderate in severity, and none were considered to be serious and/or definitively related to the study drug.

The majority of both physicians (89%) and patients (81%) considered tolerability to the study

Table 2. Most common (incidence 5% or greater) adverse events[a]

	Itasetron hydrochloride (mg b.i.d.)					Ondansetron (mg b.i.d.)	Total
	0.5	1	2	4	8	8	
Number of patients	16	17	18	17	16	20	104
Headache	6	6	6	4	1	3	26
Constipation	4	3	1	6	2	3	19
Fatigue	0	2	4	0	4	4	14
Anorexia	1	1	2	1	2	4	11
Dry mouth	2	0	0	3	2	0	7
Abdominal pain	0	0	1	2	0	2	5

[a]Values presented as number of patients reporting an adverse event.

medication (itasetron hydrochloride or ondansetron) as either 'very good' or 'rather good'. According to physicians, only 12 (12%) patients warranted a 'rather bad' or 'very bad' assessment across all treatment groups. Patients' and physicians' assessment were closely correlated.

No clinically relevant changes or differences between groups in laboratory variables, ECG, vital signs or physical examinations were evident.

Discussion

Chemotherapy based on cyclophosphamide and anthracycline combinations induces nausea and vomiting which may persist for several days in approximately 80% of patients.[32] It is estimated that without antiemetic prophylactic treatment between 10 and 15% of patients may delay or stop anti-cancer treatment because of problems with severe emesis.[33] As these combination therapies are often given on an outpatient basis, effective and safe control of nausea and vomiting is essential in order to maintain patients' quality of life and, importantly, compliance to these potentially curative therapies.

Ondansetron is considered to be 'standard therapy' for the prevention of acute nausea and vomiting caused by anti-cancer drugs. Therefore, the recommended oral dose of 8 mg b.i.d. ondansetron was used as the active control and comparator for evaluating the efficacy and tolerability of five escalating twice-daily, oral doses of itasetron hydrochloride. The doses of itasetron hydrochloride selected for investigation were 0.5, 1, 2, 4 and 8 mg b.i.d. These doses were selected on the basis of the results of preliminary investigations of the tolerability of itasetron hydrochloride in volunteers (BI data on file).

The results demonstrate that doses of 1 mg b.i.d. or above itasetron hydrochloride are effective in preventing acute emesis induced by moderately emetogenic chemotherapy. There were no statistically significant differences in the primary (complete response rate) or secondary (nausea and delayed emesis) efficacy criteria between the itasetron hydrochloride treatment groups or the patient groups receiving ondansetron. Indeed, the range of complete and major response rates (69–100%) in this study are not only similar to ondansetron, but to the reported response rates for granisetron, tropisetron and dolasetron.[34–38]

Concerning the dose–response relationship, a 'plateau effect' was evident. This seems to be a typical class effect. For the majority of endpoints, 1 mg b.i.d. itasetron hydrochloride produced the best numerical response. Thus, the maximally effective dose of 1 mg b.i.d. itasetron hydrochloride is lower than the approved and recommended dose of 8 mg b.i.d. ondansetron. This supports pre-clinical data indicating that orally administered itasetron hydrochloride is approximately 10 times more potent than oral ondansetron.[27] Interestingly, experimental studies also show that itasetron hydrochloride is more potent when given orally, compared with i.v. administration. The underlying reason for this difference is not clear, but the pharmacokinetic characteristics of orally administered itasetron hydrochloride, which include rapid absorption (maximum plasma concentrations about 90 min), high bioavailability (above 90%), low metabolic biotransformation (above 60% eliminated unchanged) and long half-life (approximately 12 h), are probably contributory factors (BI data on file).[29]

The pharmokinetic characteristics of oral itasetron hydrochloride may also provide clinical benefit in terms of the duration of anti-emetic protection. There is tendency for patients receiving the 1 mg b.i.d. dose to have longer times to onset of vomiting (median time 21 h 00 min) and onset of nausea (median time 33 h 45 min), compared with ondansetron (9 h 30 min and 6 h 45 min, respectively). These differences were not tested statistically owing to the limited patient numbers in this study, but clearly further clinical studies involving larger patient numbers are warranted.

The least effective dose of itasetron hydrochloride was 0.5 mg b.i.d. However, analysis of demographic and baseline characteristics highlighted three main differences from the other treatment groups, all of which may have affected the efficacy response. Firstly, fewer patients were female. Gender is a prognostic factor for vomiting. Females tend to vomit more than males, and suffer a larger number of vomiting episodes, duration and intensity of nausea and vomiting.[39–44] Secondly, the chemotherapy given to patients in this group had greater emetogenic potential. Eight out of 16 patients received cyclophosphamide in combination with doxorubicin; only one received a CMF scheme (the principal chemotherapy of the other treatment groups). Finally, a 'center effect' cannot be discounted as 13 out of 16 patients were enrolled from one center.

All doses of itasetron hydrochloride were well tolerated. The type and incidence of adverse events were similar across all treatment groups and are those typically reported for other 5-HT_3 antagonists.[22,45,46] Notably, all doses of itasetron hydrochloride were free of the ECG and cardiac changes

(e.g. prolongation of QTc, class I and II anti-arrhythmic activity) reported for other 5-HT_3 antagonists. These include ondansetron,[26] granisetron,[47] tropisetron[48] and, recently, dolasetron.[49] This is important clinically for two reasons. Firstly, anti-emetic therapy should not add to the potential cardiotoxicity imposed by anti-cancer therapy. Secondly, much chemotherapy and therefore anti-emetic therapy is given on an outpatient basis where the support of the hospital is lacking.

In conclusion, these findings confirm that itasetron hydrochloride is an effective and well tolerated prophylactic anti-emetic agent in patients receiving moderately emetogenic chemotherapy. Twice-daily oral doses of 1 mg b.i.d. or above provide comparable anti-emetic efficacy to 8 mg b.i.d. ondansetron. The maximally effective dose in this study was 1 mg b.i.d. However, the wide emetogenic potential of chemotherapeutic agents classified as moderate may indicate the use of a higher dose of itasetron hydrochloride despite the typical 'plateau effect' which is common to this therapeutic class.

References

1. Coates A, Abraham S, Kaye SB, *et al.* On the receiving end—patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol* 1983; **19**: 203–8.
2. Parliament MB, Danjoux CE, Clayton T. Is cancer treatment toxicity accurately reported? *Int J Radiat Oncol Biol Phys* 1985; **11**: 603–8.
3. Triozzi PL, Laszlo J. Optimum management of nausea and vomiting in cancer chemotherapy. *Drugs* 1987; **34**: 136–9.
4. Laszlo J, Lucas VS Jr. Emesis as a critical problem in chemotherapy (editorial). *N Engl J Med* 1981; **305**: 948–9.
5. Laszlo J, *et al.* Nausea and vomiting as major complications of cancer chemotherapy. *Drugs* 1983; **25** (suppl 1): 1–7.
6. Marty M, Pouillart P, Scholl P, *et al.* Comparison of the 5-hydroxtryptamine (serotonin) antagonist ondansetron (GR 38032 F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990; **322**: 816–21.
7. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Finn AL. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. *N Engl J Med* 1990; **322**: 810.
8. Kris MG, Gralla RJ, Clark RA, *et al.* Incidence course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. *J Clin Oncol* 1985; **3**: 1379–84.
9. Gralla RJ, Tyson LB, Kris MG, *et al.* The management of chemotherapy-induced nausea and vomiting. *Med Clin North Am* 1987; **71**: 289–301.
10. Craig JB, Powell BL. Review: the management of nausea and vomiting in clinical oncology. *Am J Med Sci* 1983; **293**: 34–44.
11. Fetting JH, Grochow LB, Felstein MF, *et al.* The course of nausea and vomiting after high dose cyclophosphamide. *Cancer Treat Rep* 1982; **66**: 1487–93.
12. Roila F, Tonaton M, Basurto C, *et al.* Protection from nausea and vomiting in cisplatin-treated patients: high-dose metoclopramide combined with methylprednisolonge versus metoclopramide combined with dexamethasone and diphenhydramine: a study of the italian oncology group for clinical research. *J Clin Oncol* 1989; **7**: 1693–700.
13. Roila F, Boschetti E, Tonato M, *et al.* Predictive factors of delayed emesis in cisplatin-treated patients and antiemetic activity and tolerability of metoclopramide or dexamethasone. *Am J Clin Oncol* 1991; **14**: 238–42.
14. Morrow GR. Prevalence and correlates of anticipatory nausea and vomiting in chemotherapy patients. *J Natl Cancer Inst* 1982; **68**: 585–8.
15. Smyth JF. The problem of emesis induced by cancer chemotherapy. *Clinician* 1988; **6**: 2–12.
16. Fozard JR, Mobarok Ali ATM. Blockade of neuronal tryptamine receptors by metoclopramide. *Eur J Pharmacol* 1978; **49**: 109–12.
17. Miner WD, Sanger GJ. Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. *Br J Pharmacol* 1986; **88**: 497–9.
18. Kilpatrick GJ, Jones BJ, Tyers MB. Identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding. *Nature* 1987; **330**: 746–8.
19. Costall B, Domeney AM, Gunning SJ. GR38032F: a potent and novel inhibitor of cisplatin-induced (abstract). *Br J Pharmacol* 1987; **90**: 90.
20. Stables R, Andrews PL, Bailey HE, *et al.* Anti-emetic properties of the 5-HT_3 antagonist, GR38032F. *Cancer Treat Res* 1987; **14**: 333–6.
21. Andrews PLR, Bailey HE, Hawthorn J, *et al.* GR38032F, a novel 5-HT_3 receptor antagonist, can abolish emesis induced by cyclophosphamide or radiation in the ferret. *Br J Pharmacol* 1987; **91** (suppl): 417.
22. Markham A, Sorkin EM. Ondansetron: an update of its therapeutic use in chemotherapy induced and post-operative nausea and vomiting. *Drugs* 1993; **45**: 9316–52.
23. Schalhorn B. Systematic pain treatment in children with tumours. *Fortschritt Med* 1992; **110**: 60–3.
24. Schmoll HJ. Introduction: the clinical challenge. *Eur J Cancer* 1991; **27** (suppl 1): 1–2.
25. Levitt M, Warr D, Yelle L, *et al.* Ondansetron compared with dexamethasone and metoclopramide as antiemetics in the chemotherapy of breast cancer with cyclophosphamide, methotrexate and fluorouracil. *N Engl J Med* 1993; **328**: 1081–4.
26. Ballard HS, Bottino G, Bottino J. Ondansetron and chest pain. *Lancet* 1992; **340**: 1107.
27. Sagrada A, Turconi M, Bonali P, *et al.* Antiemetic activity of the new 5-HT_3 antagonist DAU 6215 in animal models of cancer chemotherapy and radiation. *Cancer Chemother Pharmacol* 1991; **28**: 470–4.
28. Roila F, Del Favero A. Ondansetron clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **29**: 95–109.
29. Schiantarelli P, Marini MG, Vidi A, *et al.* Pharmacokinetic properties in experimental animals and volun-

teers of DAU 6215, a 5-HT_3 receptor antagonist indicated for emesis induced by anticancer therapy. In: Bianchi AL, Grélot AD, Miller GI, eds. *Mechanisms and control of emesis*. Paris: John Libbey 1992; **223**: 227–33.
30. Brown GW. Ondansetron and chemotherapy-induced emesis. In: Marty M, ed. *Proc Int Congr on Chemotherapy Neoadjuvants 3*. Berlin: Springer 1991: abstr.
31. Hartung J. *Statistik*. München: Oldenbourg 1982: 205.
32. Dicato MA. Oral treatment with ondansetron in an outpatient setting. *Eur J Cancer* 1991; **27** (suppl 1): 18–9.
33. Jones AL, Cunningham D. The clinical care of patients receiving chemotherapy. In: Andrews PLR, Sanger GJ, eds. *Emesis in anti-cancer therapy. Mechanisms and treatment*. London: Chapman & Hall 1993; **11**: 229–46.
34. Jantunen IT, Muhonen TT, Katja VV, *et al.* 5-HT_3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy—a randomized study. *Eur J Cancer* 1993; **29A**: 1669–72.
35. Gebbia V, Cannata G, Testa A, *et al.* Ondansetron versus granisetron in the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 1994; **7**: 1945–52.
36. Fauser A, Bleiberg H, Chevallier B, *et al.* A double-blind randomized comparative trial of iv dolasetron (D) vs iv metoclopramide (M) in prevention of emesis in moderately-emetogenic chemotherapy (CT). *Proc Am Soc Clin Oncol* 1995; **14**: A1748 (abstr).
37. Bertheault-Cvitkovic F, Tubiana-Hulin M, Chevalier B, Clavel M, Rossy JF, Warrell RP. Gallium nitrate (GN) vs pamidronate (APD) for acute control of cancer-related hypercalcemia (CRH): interim results of a randomized, double-blind, multi-national study. *Proc Am Soc Clin Oncol* 1995; **14**: A369 (abstr).
38. Conroy T, Cappelaere P, Fabbro M, *et al.* Acute antiemetic efficacy and safety of dolasetron mesylate, a 5-HT_3 antagonist, in cancer patients treated with cisplatin. *Annu J Clin Oncol* 1994; **17**: 97–102.
39. Tonato M, Roila F, Del Favero A. Methodology of antiemetic trials: a review. *Ann Oncol* 1991; **2**: 107–14.
40. Bécouarn Y, Bui NB, David M, Lakdja F, Brunet R, Chauvergne J. Improved control of cisplatin-induced emesis with a combination of high doses of methylprednisolone and metoclopramide: a single-blind randomized trial. *Eur J Cancer Clin Oncol* 1986; **22**: 1421–4.
41. Alba E, Batus R, Castro I, Ojeda B, Andrés L de. Metoclopramida más difenhidramina frente a clorpromacina en los vómitos inducidos por cisplatino. Estudio aleatorizado, cruzado y a doble ciego. *Med Clin* 1987; **89**: 410–2.
42. Mellink WA, Blijham GH, van Deyk WA. Amitriptyline plus fluphenazine to prevent chemotherapy-induced emesis in cancer patients: a double-blind randomized crossover study. *Eur J Cancer Clin Oncol* 1994; **20**: 1147–50.
43. Martin-Jimenez M, Diaz-Rubio E. Clinical evaluation of the simultaneous blockade of the dopamine D-2, histamine H-1, and muscarinic cholinergic receptors in cancer chemotherapy-induced emesis: results of a controlled trial. *Cancer Chemother Pharmacol* 1986; **18**: 168–71.
44. Grunberg SM, Hesketh PJ. Control of chemotherapy-induced emesis. *N Engl J Med* 1993; **329**: 1790–6.
45. Yarker YE, McTavish D. Granisetron—an update of its therapeutic use in nausea and vomiting induced by antineoplastic therapy. *Drugs* 1994; **48**: 761–93.
46. Lee CR, Plosker GL, McTavish D. Tropisetron—a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential as an antiemetic. *Drugs* 1993; **46**: 925–43.
47. Watanabe H, Hasegawa A, Shinozaki T, *et al.* Possible cardiac side effects of granisetron, an antiemetic agent, in patients with bone and soft-tissue sarcomas receiving cytotoxic chemotherapy. *Cancer Chemother Pharmacol* 1995; **35**: 278–82.
48. Morganroth J, McGinn C. Anti-arrhythmic effect of a 5-hydroxytryptamine M-receptor antagonist, ICS 205-930. *Am J Cardiol* 1988; **61**: 470–1.
49. Audhuy B, Cappelaere P, Martin M, *et al.* A double-blind, randomised comparison of the anti-emetic efficacy of two intravenous doses of dolasetron mesilate and granisetron in patients receiving high dose cisplatin chemotherapy. *Eur J Cancer* 1996; **32A**: 807–13.

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