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Control of Nausea and Vomiting with Ondansetron in Patients Treated with Intensive Non-cisplatin Chemotherapy for Acute Myeloid Leukaemia

J. Bart Braken, John M. M. Raemaekers, Peter P. Koopmans and Ben E. de Pauw

18 consecutive patients with acute myeloid leukaemia (AML) treated with 34 cycles of intensive chemotherapy received ondansetron as antiemetic treatment. 14 patients were chemotherapy-naive, while 4 patients were treated for relapsed leukaemia. All patients received at least one cycle of chemotherapy, 11 patients (61%) received two cycles and 5 patients (28%) received three cycles. The remission induction regimen consisted of cytarabin 200 mg/m^2 daily from day 1 to day 7, in combination with an anthracycline or amsacrin on 3 days. During the second and third cycle the dose of cytarabin was increased. Ondansetron was administered as follows: 8 mg intravenously before the start of chemotherapy, followed by 8 mg orally three times daily for 10 days. 50% of patients had no episodes of vomiting during the first cycle of chemotherapy and 78% had less than five episodes of vomiting over 10 days. 72% of patients had no or only mild nausea. These high response rates were maintained during the subsequent cycles. No side-effects due to ondansetron were registered. These data indicate that ondansetron is efficacious in preventing nausea and vomiting in patients with AML treated with intensive chemotherapy.
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INTRODUCTION

SEVERE NAUSEA and vomiting are common side-effects of treatment with antineoplastic agents. Recent studies suggest that serotonine, released from enterochromaffine cells in the intestinal tract, stimulating 5-hydroxytryptamine-type 3 ($5HT_3$) receptors located in the area postrema in the medulla oblongata and on vagal afferent fibres of the upper gastrointestinal tract, play a major role in the development of nausea and vomiting [1–3]. High-dose metoclopramide is the most frequently used antiemetic drug in patients treated with chemotherapy, but it has, apart from anti-$5HT_3$ receptor properties, antidopaminergic activity, causing unpleasant and unpredictable extrapyramidal

side-effects [4]. Especially in patients with severe thrombocytopenia as a result of leukaemia, these side-effects are potentially life-threatening. In the last decade a number of highly selective $5HT_3$ receptor antagonists devoid of such side-effects have been developed and have now been introduced into clinical practice. Most clinical studies concern the antiemetic activity of $5HT_3$ receptor antagonists in patients receiving high-dose cisplatin on a single day, while only a small number of trials studied the efficacy in non-cisplatin chemotherapy [2, 3, 5–10]. We evaluated the efficacy of ondansetron in patients with acute myeloid leukaemia receiving non-cisplatin chemotherapy for a prolonged period of 7 days.

PATIENTS AND METHODS

18 consecutive patients (10 women and 8 men), mean age 46 years, range 23–74 years, with acute myeloid leukaemia participated in this trial. 14 patients were chemotherapy-naive and 4 patients were treated for relapsed leukaemia. Patients with severe concurrent illness, central nervous system involvement or gastrointestinal obstruction were excluded. Patients did not receive antiemetic therapy other than ondansetron, or benzodiazepines. None of the patients had received antiemetic therapy during the 24 h prior to chemotherapy. All patients gave their informed consent and received at least one cycle of treatment. During the first cycle of chemotherapy 14 patients received cytarabin 200 mg/m^2 daily days 1–7. 3 patients received cytarabin 1000 mg/m^2 daily days 1–6 and 1 patient received 5-aza-2-deoxycytidine 540 mg daily days 1–6 instead of cytarabin 200 mg/m^2 daily days 1–7. Daunorubicin 45 mg/m^2 daily, idarubicin 12.5 mg/m^2 daily or amsacrin 120 mg/m^2 daily was given for 3 days. 11 patients (61%) received a second cycle of chemotherapy. 3 patients received cytarabin 200 mg/m^2 daily days 1–7 and daunorubicin 45 mg/m^2 daily days 1–3. 8 patients received cytarabin 1000 mg/m^2 daily days 1–6, 6 of them in combination with amsacrin 120 mg/m^2 daily days 5–7 and 2 of them with idarubicin 12.5 mg/m^2 daily days 1, 3 and 5. 5 patients (28%) received a third cycle of chemotherapy. 4 patients received cytarabin 4000 mg/m^2 daily days 1–4 in combination with daunorubicin 45 mg/m^2 daily days 5–7. 1 patient received cytarabin 1000 mg/m^2 daily days 1–6 and amsacrine 120 mg/m^2 daily days 5–7. Ondansetron was given intravenously as a loading dose of 8 mg 30 min before start of chemotherapy, followed by two tablets of 8 mg during day 1. On the subsequent days 2–10 they received three tablets of 8 mg each day. All patients received selective gut decontamination consisting of cotrimoxazol, colistine and amphotericin B.

Patients were hospitalised and scored the severity of nausea and frequency of vomiting on a diary card for all 10 study days. The severity of nausea was graded as none, mild, moderate or severe. An episode of vomiting was defined as one vomit within 1 min. The absolute number of vomits during the whole period of 10 days was counted for each of the individual patients. Control of vomiting was graded in the following way: complete response (CR), no episodes of vomiting at all; partial response (PR), one to five episodes of vomiting in 10 days; failure (F), more than five episodes of vomiting in 10 days. Patients classified as having a failure to ondansetron received additional antiemetic treatment consisting of continuous intravenous infusion of diphenhydramine + chlorpromazine.

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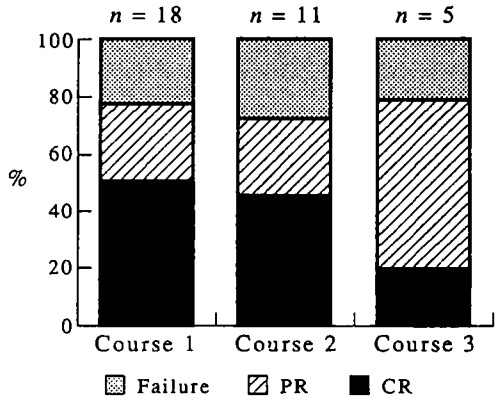

Fig. 1. Control of vomiting in the consecutive cycles of chemotherapy. CR, Complete response; PR, partial response; F, failure.

RESULTS

All 18 patients received at least one cycle of chemotherapy, 11 (61%) of them had two cycles and 5 patients (28%) underwent three cycles of chemotherapy. The emetic potential of chemotherapy increased during subsequent cycles due to increasing dose of cytarabin. Since 7 patients (38%) received autologous bone marrow transplantation or essentially different chemotherapy during subsequent cycles they were considered not evaluable in the second and third cycle.

The results on control of vomiting during the 10 study days of each cycle are represented in Fig. 1. 50% of patients had no episodes of vomiting at all and 28% had one to five episodes of vomiting during the first cycle of chemotherapy. This accounts for an overall response rate (CR + PR) of 78%. The response of individual patients during subsequent cycles is given in Table 1. These results demonstrate that the high response rates observed during the first cycle were maintained during subsequent cycles, with an overall response rate of 72 and 80% in the second and third cycle, despite the increasing dose of cytarabin in cycles 2 and 3. During the first cycle four (22%) failures occurred. It is remarkable that 3 of these patients achieved PR during the subsequent cycles.

Table 1. Control of vomiting in individual patients receiving two or three cycles of chemotherapy

Patient	1st cycle	2nd cycle	3rd cycle
1	CR	CR	–
2	CR	CR	–
3	CR	CR	CR
4	PR	F(8)	–
5	PR	PR	PR
6	CR	CR	–
7	CR	CR	F
8	F(7)	F(13)	–
9	F(8)	PR	–
10	F(7)	F(4)	PR
11	F(3)	PR	PR

CR, Complete response; PR, partial response; F, failure, number of vomits in parentheses.

The results of control of nausea are presented in Fig. 2. 72% of patients had no episodes of nausea or only mild nausea and 28% of patients suffered moderate nausea. These high responses in the prevention of nausea were maintained during the subsequent cycles. The response rates of chemotherapy-naive patients appeared not to be different from those treated for relapsed leukaemia. No side-effects attributable to ondansetron were registered.

DISCUSSION

The mechanism of chemotherapy-induced emesis is not fully elucidated, but serotonin seems to be an important mediator of nausea and vomiting in these patients. Presently three highly selective $5HT_3$-receptor antagonists are introduced into clinical practice, i.e. ondansetron, granisetron and tropisetron.

In this phase II trial we studied the potential of ondansetron in the control of nausea and vomiting in 18 patients with acute myeloid leukaemia treated with an intensive non-cisplatin chemotherapy regimen for 7 subsequent days. According to Gralla [4] the cytostatic drugs administered to our patients have a moderately emetogenic potential. Ondansetron given in a dose of 8 mg three times orally preceeded by an intravenous loading dose of 8 mg, proved to be very efficacious in the control of nausea and vomiting without causing side-effects. The absolute number of vomits during the whole period of 10 days was counted for each of the individual patients. Although this way of analysing the results is more strict than in other studies, these results produced the best information on the efficacy of ondansetron for each of the individual patients during the entire study period and subsequent cycles. Not all patients were evaluable during subsequent cycles, since 7 patients (38%) received autologous bone marrow transplantation or essentially different chemotherapy during subsequent cycles. Patients 10 and 11 erroneously received additional antiemetic treatment in the second and first cycle, respectively, before having five episodes of vomiting. Nevertheless these patients are included in the analysis and reported as failures on ondansetron. Ondansetron appears to be very efficacious in the control of vomiting and this response is maintained during the second and third cycle. During the first cycle, 78% of the patients had less than five episodes of vomiting during the study period of 10 days with an overall absence of vomiting in 50% of the patients. In the second cycle the overall response rate (CR + PR) was 72% with 45% complete responders. The results of the third course are difficult to interpret because of the small population of 5 patients. Although the CR rate decreased to 20%, the overall response rate remained nearly unchanged at 80%. Similar high response rates were observed in control of nausea with 72% of the patients experiencing no or only mild nausea during all three cycles. It is remarkable that the same high response rates in control of nausea and vomiting were maintained during subsequent cycles despite an increasing dose of cytarabin.

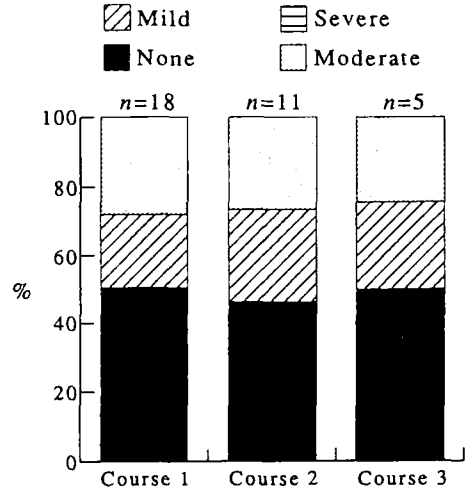

Fig. 2. Assessment of nausea in the consecutive cycles of chemotherapy.

3 patients (9–11) had an improved response on ondansetron during subsequent cycles. Patient 9 had eight episodes of vomiting during the first course and only five episodes during the second course. Since this is only a decrease of three vomits over a 10-day period, while the patient experienced moderate nausea during both cycles, this is considered to be a rather insignificant improvement. This is also the case in patient 10, who improved from seven episodes of vomiting during the first course to four in the second and third course. Also in patient 11 the improvement of three episodes of vomiting during 10 study days in the first cycle to only one in the second and third cycle is very small and considered insignificant.

The response rates of the four chemotherapy-naive patients appeared to be not different from the pretreated patients. This group is, however, too small to conclude that ondansetron is equally effective in chemotherapy-naive patients and patients treated for relapsed leukaemia.

Adverse events spontaneously mentioned by the patients or observed by the investigator are reported, but the patients were not actively interviewed on this subject during the study. 6 patients (33%) experienced an exanthema which disappeared in all patients after withdrawal of cotrimoxazol, which was part of selective gut decontamination. None of the hitherto reported adverse events, such as headache, constipation or diarrhoea, were spontaneously mentioned by the patients. It has to be emphasised that the patients were not actively interviewed on this item. Consequently, the rate of minor side-effects like WHO grade I headache, diarrhoea or constipation may be underestimated in comparison with previous studies. However, there appears to be no consensus on the incidence of these adverse events so far, since Marty *et al.* [5] described headache in 15 out of 89 patients, whereas Cubeddu *et al.* [3] observed headache and diarrhoea more frequently in the placebo group of their controlled study.

Obviously the quality of life during the period of intensive chemotherapy is significantly improved, since the patients experienced virtually no complaints of nausea and vomiting. The 4 patients who were treated for relapsed leukemia all preferred ondansetron over the antiemetic treatment consisting of diphenhydramine + chlorpromazine, which they received during previous chemotherapy. They stated that they had better control of nausea and vomiting during ondansetron and experienced no adverse events like drowsiness, which is frequently encountered during diphenhydramine + chlorpromazine. In addition, the convenience of oral administration of ondansetron as opposed to the laborious nature of preparation and infusion of intravenous solutions for alternative antiemetic regimens, has considerable advantages for both patients and nursing personnel.

The data from this open phase II study clearly demonstrate the efficacy of ondansetron in preventing nausea and vomiting even in patients treated with prolonged, intensive, moderately emetogenic chemotherapy. Further studies are warranted in

order to optimise the dose schedule of ondansetron in this particular group of patients.

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Phase II Study of Daily Oral Miltefosine (Hexadecylphosphocholine) in Advanced Colorectal Cancer

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34 patients with metastatic colorectal cancer were treated with the ether lipid miltefosine (hexadecylphosphocholine). Most patients received 3×50 mg daily, while in 11 patients the dose could be escalated to 4 × 50 mg daily. Nausea and vomiting were the most frequent side-effects occurring in all but 3 patients, nephrotoxicity was observed in 11 patients. Leucocytosis was observed in 24 and thrombocytosis in 17 patients. 28 patients are evaluable for response. 1 patient obtained a partial response of liver metastases for a duration of 8 months. 3 patients had stable disease while 24 progressed during treatment. We conclude that miltefosine in this dose and schedule has limited activity in colorectal cancer.
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INTRODUCTION

THE DISMAL outlook for patients with metastatic colorectal cancer and the lack of essential progress in chemotherapy in this common disorder is the continuous impulse to test new drugs on their activity in this disease. Miltefosine (hexadecylphosphocholine) is a synthetic phospholipid derivative with distant similarity to lecithin. The precise mode of action of miltefosine is not known but it is assumed to be related to interference with membrane functions [1, 2].

In vitro, miltefosine showed activity against the human colon carcinoma cell line Co 115 in the soft agar colony assay, and *in vivo* against DMBA- and MNU-induced breast cancer in the rat and against a transplanted KB tumour and Lewis lung carcinoma in the nude mouse.

Pharmacokinetic studies in the rat revealed that orally administered miltefosine was absorbed slowly with plasma peak concentrations reached after 48 h. In rats and dogs anorexia and weight-loss were observed as the main toxicity. There were no signs of bone marrow toxicity.

In the phase I study nausea and vomiting was the dose-limiting side-effect [3]. The maximum tolerated dose was 200 mg/day with the best tolerability observed with a fractionated daily dosing. At the dose of 150 mg daily only 1 out of 6 patients had grade 3 gastro-intestinal toxicity. There were no signs of any other toxicity. For phase II studies a starting dose of 100 mg/day with dose escalation to 150 mg/day was recommended.

We performed a phase II study with oral miltefosine in patients with metastatic colorectal cancer.

PATIENTS AND METHODS

Patients were required to have histologically proven progressive metastatic colorectal cancer, a WHO performance status of 2 or better, white blood cells (WBC) $\geq 3.0 \times 10^9$/l, platelet

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