Anti-Cancer Drugs 1996, 7, pp. 734–737

Treatment of cisplatin-related nausea and vomiting with a combination of ondansetron and metoclopramide: a pilot study

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Forty chemotherapy-naive patients receiving high-dose cisplatin were included in a pilot study of a combination of ondansetron plus metoclopramide as antiemetic therapy. Patients received ondansetron 16 mg plus metoclopramide 0.5 mg/kg in 250 cm^3 of normal saline i.v. 15 min before cisplatin administration on day 1; then ondansetron 8 mg was given orally b.i.d. and metoclopramide 0.5 mg/kg was given intramuscularly t.i.d. for 4 days. This combination was given to all patients receiving the first cycle of chemotherapy. At the second cycle of chemotherapy all patients received the same antiemetic treatment as above plus methylprednisolone 125 mg i.v. on day 1 and then intramuscularly once a day for 4 days. There were 20 females and 20 males with a mean performance status of 1 (range 0–2) and a mean age of 58 years (range 36–68). Ten patients had ovarian carcinoma, eight patients had uterine adenocarcinoma and 22 had non-small cell lung carcinoma. The mean cisplatin dose was 96 mg/m^2. All patients denied significant alcohol consumption. At cycle 1, complete protection against acute emesis was achieved in 22 patients (55%), major protection in 12 cases (30%), minor protection in four patients (10%) and failure in two cases (5%). On the other hand, the efficacy of this combination on delayed vomiting was not striking. For delayed vomiting, complete protection was observed in nine patients (23%), major protection in 13 cases (33%), minor protection in 10 patients (25%) and failure in eight cases (20%). At cycle 2, patients also received methylprednisolone showing complete protection from vomiting in 19 cases (47%) and major protection in 12 cases (30%). Results achieved with ondansetron plus metoclopramide are in the range reported for ondansetron alone in the medical literature. Although this study was not prospectively carried out in a randomized fashion, the results are not suggestive of a possible positive effect of metoclopramide addition to ondansetron. On the other hand, these results stress the role that corticosteroids may play in the control of delayed emesis. Toxicity was predictable and the frequency of side-effects was in the range reported in other studies with ondansetron.

Key words: Chemotherapy, methylprednisolone, metoclopramide, ondansetron, vomiting.

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Introduction

The discovery of the new antagonists of the serotonin (5-HT_3) receptors has certainly opened a new era in the management of chemotherapy-related side effects and, generally, in supportive care of cancer patients. The three anti-HT_3 drugs currently available, i.e. granisetron, ondansetron and tropisetron, are roughly equiactive against cisplatin-induced emesis and show maximal activity when combined with dexamethasone or other corticosteroids.[1,2] The anti-HT_3 drugs have been shown to be more effective against acute emesis than metoclopramide, alizapride and chlorpromazine.[3–5] Although the effects of anti-HT_3 drugs against acute emesis are remarkable, the protective effects on cisplatin-related delayed nausea and vomiting are still not entirely satisfactory, as evidenced by the contradictory results reported in the medical literature.[1,6,7]

The pathophysiology of chemotherapy-induced vomiting is rather complex and still not entirely understood.[8] However, it is evident that the anti-HT_3 agents and the antidopaminergic drugs act at two different levels in preventing emesis, even if the latter compounds may also antagonize setotonin when employed at high doses.[9] As suggested by others,[10] these two classes of antiemetic drugs need not necessarily be mutually exclusive. Thus antiserotoninergic and antidopaminergic agents may be tentatively combined in a regimen with the aim of ameliorating nausea and/or vomiting since they may well act at two different targets in preventing chemotherapy-related emesis. Bregni *et al.*[11] carried out a pilot study with tropisetron plus haloperidol, a rather specific antidopaminergic drug, in a series of patients treated with high-dose melphalan or cyclophosphamide. This study showed a reduction in the median number of emetic episodes as compared to a previous comparable series treated with tropisetron alone.

To date no clinical study has been carried out

simultaneously employing an antiserotoninergic drugs and a dopamine receptor blocking agent, such as metoclopramide. Based on this rationale, we carried out a single arm, open-label, pilot study employing the combination of an ondansetron plus metoclopramide as protective therapy against both acute and delayed emesis in a series of outpatients treated with high-dose cisplatin.

Materials and methods

Before entry into the trial patients had to fullfil the following eligibility criteria: informed consent; no previous chemotherapy; age ≥ 18 but ≤ 75 years; performance status according to the ECOG scale ≤ 2; serum creatinine ≤ 1.2 mg%; BUN ≤ 50 mg%; creatinine clearance > 60 ml/min; serum bilirubin < 1.2 mg%; serum transaminases < 2 times normal value; absence of obstructive gastrointestinal disease, brain metastases, active gastrointestinal disease and uncontrolled renal, hepatic, neurologic or metabolic diseases. Alcohol consumption, drug abuse or use of psychotropic agents was not allowed. The uncontrolled consumption of corticosteroids or other drugs or occurrence of anticipatory vomiting caused patients to be withdrawn from the trial. All enrolled patients had to receive a single day chemotherapy regimen consisting of cisplatin ≥ 80 mg/m^2 in combination with vinca alkaloids, anthracyclines, taxanes or oxazaphosphorines.

Patients were carefully monitored for acute emesis (vomiting during the first 24 h after chemotherapy) and then followed up for 4 days to evaluate the effects of antiemetic therapy on delayed nausea and vomiting. The intensity of nausea and the number of emetic episodes (including dry retches) were calculated by direct daily interview and by the use of a diary card. The clinical effectiveness of antiemetic treatment against vomiting was classified as (i) complete protection (no emetic episodes), (ii) major protection (one or two emetic episodes), (iii) minor protection (three to five emetic episodes) and (iv) failure (more than five emetic episodes). Nausea was recorded according to the degree of interference with normal daily life: (i) no nausea, (ii) mild nausea (present but with no interference with normal daily life), (iii) moderate nausea (interference with normal daily life) and (iv) severe nausea (bedridden because of nausea). Complete protection plus major protection were defined also as major response.

The antiemetic treatment plan included: ondansetron 16 mg plus metoclopramide 0.5 mg/kg in 250 cm^3 of normal saline i.v. 15 min before cisplatin administration on day 1; then ondansetron 8 mg was given orally b.i.d. and metoclopramide 0.5 mg/kg intramuscularly t.i.d. for 4 days. This combination was given to all patients receiving the first cycle of chemotherapy. Before the second cycle of chemotherapy all patients received the same antiemetic treatment as above plus methylprednisolone 125 mg i.v. on day 1 and then intramuscularly once a day for 4 days. Data are reported as relative rates expressed as percentage approximated to the nearest unit. Comparisons between response rates were analyzed by Fisher's exact test.

Results

Patient population

Forty consecutive patients were included in the study. The main clinical characteristics of enrolled patients are depicted in Table 1. There were 20 females and 20 males with a median performance status of 1 (range 0–2) and a median age of 58 years (range 36–68). Ten patients had ovarian carcinoma treated with cisplatin 100 mg/m^2 on day 1 plus epirubicin 100 mg/m^2 on day 1 or cyclophosphamide 750 mg/m^2 on day 1; eight patients had uterine adenocarcinoma treated with cisplatin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on day 1 + 8; and 22 had non-small cell lung carcinoma treated with cisplatin 100 mg/m^2 on day 1 plus vinorelbine

Table 1. Clinical and demographic characteristics of patients

Patient characteristics	No. of patients (%)
No. enrolled patients	40 (100%)
Age (years)	
median	58
range	36–68
Sex	
male	20 (50%)
female	20 (50%)
Performance status (ECOG)	
median	1
range	0–2
Primary tumor	
lung	22 (55%)
ovary	10 (25%)
uterus	8 (20%)
Alcohol consumption	
yes	0
no	40 (100%)
Mean cisplatin dose (mg/m^2)	96

25 mg/m^2 on day 1 + 8, or mitomicyn C 8 mg/m^2 on day 1 and vindesine 3 mg/m^2 on day 1 + 8 + 15. The mean cisplatin dose was 96 mg/m^2. All patients denied significant alcohol consumption. All patients received cisplatin diluted in 500 cm^3 of normal saline as a 1 h infusion with a standard pre-hydration protocol and a post-hydration phase with forced diuresis with 250 cm^3 of 18% mannitol.

Clinical efficacy

The protective effects of ondansetron plus metoclopramide on acute emesis recorded at cycle 1 was significant. Complete protection against acute emesis was achieved in 22 patients (55%), major protection in 12 cases (30%), minor protection in four patients (10%) and failure in two cases (5%). On the other hand, the efficacy of this combination on delayed vomiting was not striking. The activity of the combination of ondansetron and metoclopramide on cisplatin-related delayed vomiting is depicted in Figure 1. Overall, complete protection from vomiting was observed in nine patients (23%), major protection in 13 cases (33%), minor protection in 10 patients (25%) and failure in eight cases (20%). On the other hand, complete protection from nausea was seen in eight patients (20%), with mild nausea in 16 cases (40%), moderate nausea in 14 (35%) and severe nausea in two patients (5%).

All patients were treated with a second cycle of chemotherapy after 21–28 days during which they received an antiemetic regimen consisting of methylprednisolone in addition to ondansetron and metoclopramide. The effect of corticosteroid on delayed emesis was quite evident. Complete protection from vomiting was achieved in 19 patients (47%) and major protection in 12 cases (30%). Minor protection was recorded in 13% of cases and treatment failure in 10%. If data recorded during cycle 1 with ondansetron plus metoclopramide without methylprednisolone were compared in terms of complete protection to data achieved in cycle 2 with the addition of methylprednisolone, the observed difference was statistically significant ($p = 0.034$).

Safety

The antiemetic schedule was well tolerated by the vast majority of patients. The most frequently reported side effects were headache, constipation and somnolence. No case of extrapyramidal side effect was observed. Headache was recorded in five cases (12%) during cycle 1 and in four patients (10%) during cycle 2. Constipation was observed in nine patients (22%) during cycle 1 and in seven cases (17%) during cycle 2. However, it was difficult to establish the exact role of antiemetic therapy in causing constipation since many antineoplastic drugs may themselves cause neurotoxic side effects. Epigastric burning was observed in three patients (7%) during cycle 2, probably related to methylprednisolone.

Discussion

Without any antiemetic treatment the vast majority of patients treated with chemotherapeutic regimens including high-dose cisplatin experience very severe emesis which may seriously impair patients' quality of life and compliance to otherwise successful antineoplastic treatments.[12] Cisplatin-related emesis may occur 'acutely', i.e. during the first 24 h after chemotherapy administration, or may present as a 'delayed' side-effect even 5 days after completion of chemotherapy.[13] These two distinct phases may

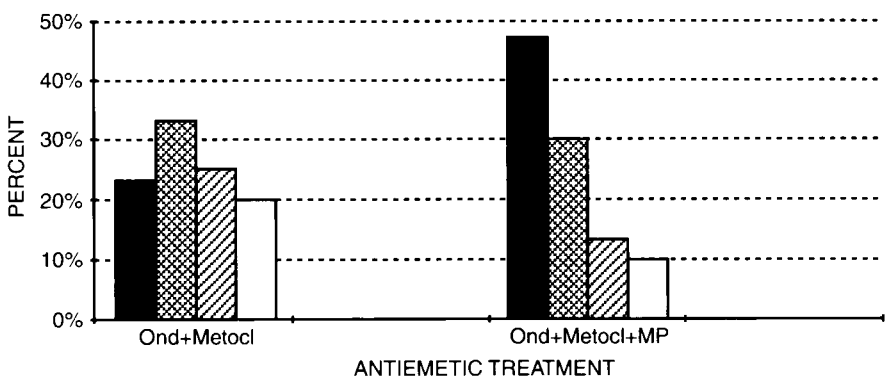

Figure 1. Effects on delayed emesis: ■, complete protection; , major protection; , minor protection; □, failure.

reflect a rather complex pathophysiology of cisplatin-induced emesis, the multifactorial etiology of which may render a single antiemetic strategy unable to prevent both acute and delayed emesis.[8]

Several studies have clearly demonstrated that the anti-HT_3 drugs alone and in combination with corticosteroids are very effective in protecting cancer patients from acute emesis which follows cisplatin-based chemotherapy.[1–7] On the other hand, clinical results achieved with anti-HT_3 drugs with or without corticosteroids in the management of delayed nausea and vomiting are still not entirely satisfactory, and are not strikingly better that those reported with antidopaminergic drugs plus corticosteroids.[3,4,5,7] Since anti-HT_3 agents and antidopaminergic drugs may act at two different levels against emesis, their combined use has been recently suggested.[10,11] In this study we tested the combination of ondansetron plus metoclopramide as antiemetic therapy against cisplatin-related nausea and vomiting. At cycle 1, protection against acute emesis has been quite satisfactory with a major response in 85% of cases, but the major response rate against delayed toxicity has been not encouraging (56%). The addition of methylprednisolone at cycle 2 resulted in a clear amelioration of complete protection (23% without versus 47% with methylprednisolone) against delayed emesis even if results are still not satisfactory. Toxicity was predictable and the frequency of side effects was in the range reported in other studies with ondansetron.

The figures obtained with ondansetron plus metoclopramide are well within the range reported for ondansetron alone in the medical literature[3] and, although this study was not prospectively carried out in a randomized fashion, they are not suggestive of a possible positive effect of metoclopramide addition to ondansetron. On the other hand, the above-reported data stress the role that corticosteroids may play in the control of delayed vomiting.

In conclusion, although the above-reported data have been obtained in a single-arm, open study, the clinical results obtained with the simultaneous administration of ondansetron and metoclopramide do not seem better than those reported with ondansetron alone[3,4] and lower than those achieved with the addition of corticosteroids.[1,2] The addition of corticosteroid drugs to ondansetron results in an improvement in delayed emesis control.

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(Received 21 May 1996; accepted in revised form 23 July 1996; accepted 30 July 1996)