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Comparison of Three Protracted Antiemetic Regimens for the Control of Delayed Emesis in Cisplatin-treated Patients

Isabel Moreno, Rafael Rosell, Albert Abad, Agusti Barnadas, Joan Carles, Nuria Ribelles, Victoria Solano and Albert Font

Antiemetic activity of three protracted regimens for the control of cisplatin-evoked delayed emesis was explored. 63 patients were randomly assigned to receive one of three protracted antiemetic schedules over 4 days. Group C patients received dexamethasone 8 mg twice daily on days 2 and 3, then 4 mg twice daily on days 4 and 5; in group B, alizapride 2.5 mg/kg four times daily on days 2–5 plus dexamethasone as in group C was administered; and in group A, metoclopramide 0.5 mg/kg four times daily on days 2–5 plus dexamethasone was given at the same dose-schedule as in groups C and B. Complete protection from delayed vomiting was achieved in 44% of group C, 30% of B and 70% of group A ($P = 0.02$). Mild side-effects were noted in all three groups. A higher complete protection for delayed emesis was obtained in metoclopramide–dexamethasone-treated patients. Neither of the regimens used in the protection of delayed emesis controlled late nausea.
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INTRODUCTION

AN ACCEPTABLE CONTROL of acute cisplatin-induced emesis has been achieved with intermittent high-dose metoclopramide plus the addition of dexamethasone and diphenhydramine or lorazepam [1–3]. Less often are efforts marshalled to successfully develop protracted antiemetic trials to enhance the prevention of delayed emesis. The incidence of delayed emesis has been as low as 16–25% [1, 4], but later when patients received cisplatin doses of 120 mg/m^2 incidence was as high as 74% [5]. In our experience, in spite of complete protection (CP) of acute cisplatin-evoked emesis in half of the high-dose (3 mg/kg × 2) metoclopramide-treated patients, delayed emesis syndrome was witnessed in 65%. In this randomised trial when alizapride was given instead of metoclopramide with both dexamethasone and lorazepam, although less acute CP was recorded, the frequency of delayed emesis (68%) remained similar to the metoclopramide arm [6].

These findings prompted us to undertake the current trial in which three protracted antiemetic regimens are compared: metoclopramide–dexamethasone, alizapride–dexamethasone or single dexamethasone. The object of this trial, therefore, is to evaluate the control of delayed vomiting and nausea.

PATIENTS AND METHODS

From October 1987 to November 1988, 63 chemotherapy-naive patients were included in this trial. All patients with histologically-proven cancer were to receive cisplatin-based chemotherapy and those with a Karnofsky index equal to or greater than 60% were eligible. Each patient received cisplatin at doses between 60 and 120 mg/m^2 administered over 30 min intravenously on an in-patient basis on day one. They also received other chemotherapeutic agents in several of the following combinations: ifosfamide 3 g/m^2, mitomycin 8 mg/m^2, vindesine 3 mg/m^2, etoposide 170 mg/m^2, cyclophosphamide 600 mg/m^2 or 5-flurouracil (5-FU) 1000 mg/m^2. All patients were hospital in-patients during the 24 h before cisplatin administration. Each patient signed an informed consent.

This study was a randomised, single-blind, parallel group trial. All 63 patients were randomly allocated to receive an acute antiemesis regimen consisting of either MDL : intravenous metoclopramide (3 mg/kg × 2 doses) diluted in 250 ml of 0.9% sodium chloride given 30 min pre- and 90 min post-cisplatin. A

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single 20 mg intravenous dexamethasone dose was given 35 min prior to cisplatin, and one 1.5 mg/m^2 oral lorazepam dose 30 min before cisplatin, or ADL : intravenous alizapride (15 mg/kg × 2 doses) diluted in 250 ml of 0.9% sodium chloride and given 30 min pre- and 90 min post-cisplatin, plus intravenous dexamethasone and oral lorazepam as described above.

24 h after cisplatin, the 63 patients were randomised to further receive 1 of 3 protracted regimens for delayed emesis: metoclopramide–dexamethasone (group A), alizapride–dexamethasone (group B), or dexamethasone alone (group C).

Approximately a third of the patients from each arm (MDL or ADL) were included in group C. Following a table of numbers at random and taking only one number, the number of the first patient was established for group C, selecting one out of every three of the following cases. The rest of the patients were included in groups A or B, maintaining the same treatment of benzamide in the delayed emesis as in the protection of acute emesis.

Group A included 20 patients who received MDL as acute antiemesis regimen and, in addition, were assigned to receive metoclopramide, 0.5 mg/kg, orally, four times daily for 4 days (24–120 h postcisplatin) plus dexamethasone, 8 mg, intramuscularly twice daily (24–72 h postcisplatin), then 4 mg intramuscularly twice daily for the next 2 days (72–120 h postcisplatin). Group B included 20 patients who received ADL as acute antiemesis regimen as well as alizapride, 2.5 mg/kg, orally, four times daily for 4 days (24–120 h post cisplatin) plus dexamethasone at the same dose and schedule as mentioned in group A. In group C, 12 of the 23 patients included received acute antiemesis MDL and 11 received ADL. Dexamethasone was administered for 4 days (24–120 h postcisplatin) at the same dose and schedule as in group A and B.

The primary efficacy parameter was the number of emesis episodes recorded by each patient. Any liquid-producing vomiting was recorded as an emetic episode. One to five "dry heaves" (vomiting, non-productive of liquid) within any 5-min period were also counted as a single emetic episode. In-hospital observation of patients was done during the initial 24 h postcisplatin. Side-effects were also directly observed and recorded. These included assessment of sedation, number of bowel movements and the occurrence of akatisia or acute dystonic reactions.

The response of each patient to the treatment was defined as follows: complete response, no emesis over the 24 h; major response, one to two episodes of emesis; minor response, three to five episodes; treatment failure, more than five episodes of emesis in 24 h. 24 h after receiving cisplatin, all patients gave their assessment of acute antiemetic control. By means of 100-mm visual analogue scales (VAS), patients indicated the degree of emesis control and nausea they felt. Previous trials have shown this instrument to be feasible, reliable and with acceptable convergent validity [2, 5–8].

All patients were requested to record the severity of delayed nausea and vomiting by filling out daily 100-mm VAS. At the same time, they were to keep a daily record of the number of delayed emetic episodes and also note down the occurrence of side-effects. Data were obtained for each of four consecutive 24 h periods from 24 to 120 h following the initial 24 h postcisplatin observation period. Patients were also contacted daily in person or by telephone during the same 4-day period by an investigator who kept an independent record of the number of delayed emetic episodes and the incidences of adverse effects.

χ^2 test or, where appropriate, Fisher's exact test, was used to compare the frequencies of events observed. All tests were two-tailed and $P < 0.05$ was considered significant. The ANOVA with repeated measures test was used to evaluate the results, mathematical calculations were made using module 2V of the BMDP programme and the normal distribution of variables was arrived at using the transformation $x = x + 3/8$ [9].

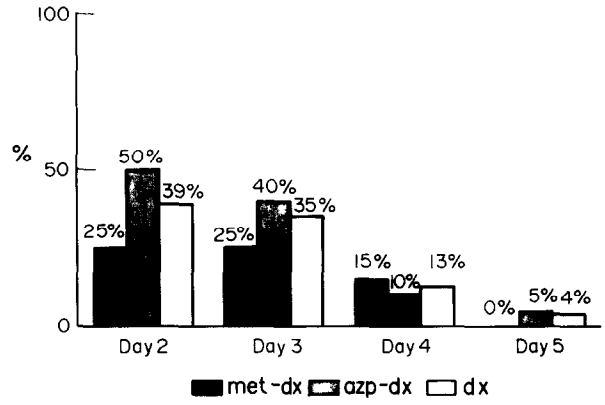

Fig. 1. Frequencies of delayed emesis from day 2 to 5 postcisplatin administration.

RESULTS

Patients' characteristics, which are depicted in Table 1, appear well balanced, with males predominant. The most common primary cancer site was the lung and approximately 95% of patients in each arm received cisplatin at doses equal to or greater than 100 mg/m^2. Incidence and severity (mean values in mm) of tardy emesis in the three protracted antiemesis regimens are presented in Figs 1 and 2.

There are clear statistically significant differences between the two arms during the acute period (MDL, ADL) (P = 0.00001). The relation between those antiemetic combinations used on day 1 and those used for delayed emesis protection showed no statistically significant differences (P = 0.4). The emesis protection vs. time relation was statistically significant (P = 0.00003) with greater difference being evident on days 1, 2 and 3.

The results highlight two important factors which must be kept in mind when planning antiemetic regimens; the antiemetic treatment employed in the acute period and the time factor which indicates that there are fewer emetic episodes at 72 h post cisplatin administration.

Although percentages recorded for each of the 4 study days

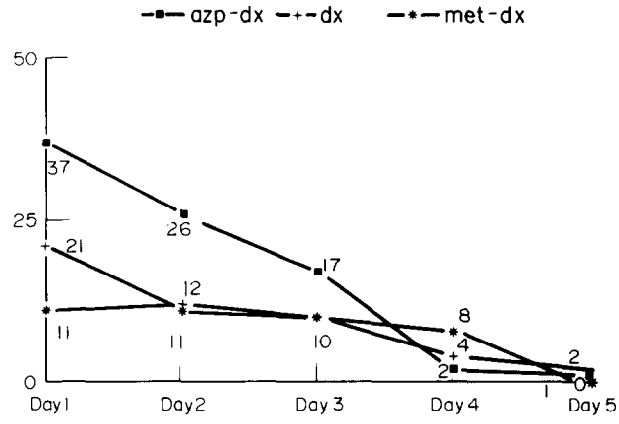

Fig. 2. Severity of delayed emesis for the three groups, scored on a visual analogue scale. Values on the vertical axis represent severity.

Table 1. Patients' characteristics

	Metoclopramide + dexamethasone	Alizapride + dexamethasone	Dexamethasone
No. of patients	20	20	23
Age in years			
Mean (range)	60 (38–75)	62 (40–73)	62 (40–75)
Men : Women	19 : 1	18 : 2	21 : 2
Karnofsky index			
80–90%	11	14	17
60–70%	9	6	6
Type of cancer			
Lung	18	16	12
Others	2	4	11
Cisplatin dose (mg/m^2)			
< 99	1	2	1
> 99	19	18	22

Table 2. Results

	Metoclopramide + dexamethasone (%)	Alizapride + dexamethasone (%)	Dexamethasone (%)
Acute emesis			
Patients with CP	65*	25	35
Patients with CP + MR	95*	45	73
Delayed emesis			
In non-acute emesis patients	8*	80	37
In acute emesis patients	71	67	67
Overall patients	30*	70	56

* $P < 0.05$.
CP = complete protection.
MR = major response.

in all three arms did not reach a statistically significant level, a greater control of delayed vomiting was observed in arm A. The percentage of delayed emesis in the entire study period was 30% in arm A as opposed to 70% in group B ($P = 0.02$) and 56% in group C. The beneficial effect of both these acute antiemetic regimens on the incidence of late emesis was analysed, stratifying patients who had no acute emesis and those who experienced any emetic episodes. As can be seen in Table 2, 65% in group A had no acute emesis as compared with 25% in group B (ADL) $P = 0.02$. Major response was obtained in 95% of group A and 45% of group B ($P = 0.0006$), but the difference was not significant when A and B were compared with group C in which CP was observed in 35% and major response in 73%. A caveat has to be taken into consideration in analysing group C patients. This group was different from A and B because it was made up of 12 MDL and 11 ADL treated patients. In assessing the efficacy of regimen C we looked at the biases introduced by grouping patients already treated with the two acute antiemesis regimens, but this factor did not modify the results, as delayed vomiting occurred in 56% of these patients (58% in MDL treated patients and 55% in ADL). The incidence of delayed nausea in the group of patients who received further protracted antiemesis with metoclopramide–dexamethasone (group A) was 70%. In spite of employing protracted antiemesis regimen B or C, incidence of late nausea was 90 and 74%, respectively, with no significant differences observed.

Drowsiness was the most frequent side-effect found in all 3 protracted antiemesis arms and was recorded in 70, 65 and 61% for A, B and C groups, respectively. On the whole, somnolence was mild. No extrapyramidal reactions were observed.

DISCUSSION

A lower CP rate for acute emesis was observed in ADL, 25% as compared with 65% in MDL-treated patients (group A). This fact may well contribute to unbalancing the difference in the delayed emesis prevention rate found (70% in group A and 30% in group B). Notwithstanding, protracted metoclopramide–dexamethasone also emerges as superior when compared with group C (dexamethasone alone), the latter is a mixed group with half of the patients receiving ADL as acute antiemesis treatment, and half MDL. Furthermore, a difference in favour of group A (metoclopramide–dexamethasone) is scored when patients are stratified by having no acute emesis (see Table 2), 92% delayed vomiting CP in group A vs. 20% in group B and 63% in group C.

The figure of 70% CP from delayed cisplatin-emetic syndrome obtained with regimen A (metoclopramide–dexamethasone) concurs with the pioneering results documented by Kris *et al.* [7] with the same protracted antiemetic schedule achieving 52% CP as opposed to 35% with dexamethasone alone or 11% with placebo. The occurrence of side-effects was also similar, somnolence being the most common. Negative results have been reported with metoclopramide–dexamethasone or dexamethasone alone [10]. Neither oral metoclopramide (60 mg/day) nor ondansentron (24 mg/day) provided a good control of delayed emesis [11]. This agrees with the finding of Roila *et al.* [12] who were unable to report enhanced CP from delayed emesis when protracted oral metoclopramide was compared with placebo, although better CP from nausea was seen with metoclopramide or dexamethasone. In our study, neither of the three antiemetic regimens demonstrated effectiveness in the protection of delayed nausea.

In conclusion, we do believe that protracted metoclopramide–dexamethasone in a schedule which covers the main delayed post-cisplatin emesis period is at present an effective tool, giving protection in 70% of patients, without meaningful side-effects.

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Drug-sensitivity Testing in Patients with Human Oesophageal Squamous Cell Carcinoma

Masanori Terashima, Kenichiro Ikeda, Chihaya Maesawa, Hidenobu Kawamura, Kaoru Ishida, Masao Sato and Kazuyoshi Saito

To evaluate the response to chemotherapeutic agents against human oesophageal cancer, 19 samples were tested by the human tumour clonogenic assay (HTCA), 21 samples by subrenal capsule assay (SRCA) and 33 samples by SRCA with immunosuppressant (IS-SRCA). The evaluability rate of was 21% for HTCA, 95% for SRCA and 91% for IS-SRCA. No active agent was detected by HTCA, however, 29% of the drugs tested by SRCA and 22% by IS-SRCA were considered to be active. Histological analysis revealed substantial inflammatory infiltrates and poor tumour cell preservation with SRCA; however, infiltrates were minimal and there was a high degree of tumour cell preservation with IS-SRCA. The response rates of IS-SRCA were comparable with those of prior clinical tests for each drug. These results suggested that IS-SRCA is the most useful drug sensitivity test for human oesophageal cancer.
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INTRODUCTION

UNTIL RECENTLY, little information about the use of systemic chemotherapy for oesophageal cancer has been available. This type of carcinoma was thought to be completely refractory to chemotherapy; however, recently, considerable attention has been paid to the study of systemic chemotherapy with oesophageal cancer, and relatively good response rates have been obtained compared with other gastro-intestinal tumours [1]. However, the prognosis is still worse than for other types of gastrointestinal tumours because of the poor general condition in many patients and the rapidity of tumour progression. To improve the response rate to chemotherapy and prognosis of these patients, the selection of chemotherapeutic agent is very important not only with respect to the administration of active agents but also the avoidance of adverse effects of resistant agents. However, attempts to evaluate drug response prior to treatment in oesophageal cancer have not yet been reported.

The present study was designed to evaluate and compare the usefulness of human tumour clonogenic assay (HTCA), subrenal capsule assay (SRCA) and SRCA with immunosuppressant (IS-SRCA) as chemosensitivity tests in human oesophageal squamous cell carcinoma.

MATERIALS AND METHODS

Tumours

Fresh surgical specimens were obtained at the time of operation from patients with squamous cell carcinoma of the oesophagus treated at our department; 19 for HTCA, 21 for SRCA and 33 for IS-SRCA.

Mice

Immunocompetent male BDF_1 mice were obtained from NIHON CLEA (Kawasaki, Japan). Mice were kept in specific pathogen-free conditions and used for experiments when 6–8 weeks old.

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