A dose-finding study of granisetron, a novel antiemetic, in patients receiving high-dose cisplatin

Abstract In this double-blind study, the efficacy and safety of a single intravenous dose of a novel antiemetic, granisetron, was assessed at two dose levels (40 µg/kg and 160 µg/kg). A group of 355 patients were given prophylactic granisetron prior to receiving high-dose cisplatin chemotherapy. In the first 24 h, 57% and 59% of patients, respectively, experienced no vomiting and no more than mild nausea. Two further doses of granisetron (40 µg/kg) were permitted in the first 24 h to treat any emergent symptoms of nausea and vomiting; 66 patients (39%) in the 40-µg/kg treatment group and 56 patients (34%) in the 160-µg/kg group received at least one additional dose. Additional treatment with granisetron resulted in resolution or improvement of symptoms in at least 73% of these patients. Over the 7-day study period, 52% of patients in the lower-dose group and 48% in the higher required no further conventional antiemetic therapy. The two different dose levels were equal both in terms in efficacy and safety. Granisetron was well tolerated throughout the dose range of the study [40–240 µg kg⁻¹ (24 h)⁻¹]. The commonest adverse event was headache, seen in 14%–16% of patients. In all but one case this resolved spontaneously or responded to simple treatment.

Key words Antiemetic · Cisplatin Granisetron
Introduction

One of the problems in the management of patients undergoing cytostatic chemotherapy is poor patient compliance, which may result from the severe nausea and vomiting that can be induced by these toxic agents. Current antiemetic treatment often involves the administration of drug combinations sometimes at high doses. Although these can prove effective, such therapy may involve prolonged and repeated infusions over several hours. Moreover, these drugs can produce undesirable side-effects, which may be serious [12].

Recent research has suggested that the nausea and vomiting produced by cisplatin therapy are mediated by activation of the 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptor [2]. Thus effective antiemetic therapy might be provided by 5-HT<sub>3</sub> receptor antagonists. Indeed, the standard treatment is currently high-dose metoclopramide, a dopamine antagonist that is thought to possess 5-HT<sub>3</sub> receptor antagonist properties at high doses [17]. However, although metoclopramide provides some protection against emesis, in cisplatin-induced emesis, high-dose metoclopramide provides protection in approximately 60% of patients [11]. Further protection is gained if metoclopramide is given with corticosteroids, where up to 70% of patients gain relief from emesis [1]. However, metoclopramide is known to produce undesirable side-effects such as akathisia and extra-pyramidal effects [14] and it is often administered with other agents such as diphenhydramine to minimise such adverse events. Current antiemetic regimens are therefore cumbersome and complicated to administer.

Clearer understanding of the mechanisms involved in the emetic response led to the development of a novel selective 5-HT<sub>3</sub> receptor antagonist, granisetron (SmithKline Beecham Pharmaceuticals). Animal studies [5] have shown it to be highly effective in the treatment of cisplatin-induced vomiting. Granisetron not only prevented emesis when used prophylactically, but was also effective in stopping vomiting once it was established. Extensive studies in patients have shown it to be effective and well tolerated [7].

The study described here was initiated in July 1988 to investigate the efficacy and safety of two different doses of granisetron, in a large number of patients, as a prophylactic antiemetic therapy. The use of granisetron for breakthrough nausea and vomiting was also assessed.

An interim analysis of the study has been reported previously [20]. This paper includes data up to the close of the study in May 1991.

Patients and methods

Patients

This was a multicentre, multinational study with 30 centres in six countries taking part. Patients were selected if they were due to receive cytostatic chemotherapy for the first time for treatment of their malignant disease. Each patient was to receive treatment with a regimen of chemotherapy that included high-dose cisplatin (more than 49 mg/m<sup>2</sup>), given on the first day.

Patients were excluded if they had previously [7] have had marked hepatic dysfunction, renal dysfunction, primary or secondary brain tumour, cardiovascular disease, active gastric ulcer or gastric compression. All patients gave their informed consent to participation in the study and were free to withdraw at any time. Ethical Committee approval of the protocol was required prior to the start of the study.

Study design

The study was a double-blind comparison of two doses of granisetron: either 40 μg/kg or 160 μg/kg, and patients were randomly assigned to the two treatment groups. Patients were admitted to hospital for the first 24 h of the study to permit direct observations to be made. Evaluation of the antiemetic efficacy and safety of granisetron was continued for a further 6 days with diary cards on which to record results.

A solution of granisetron was prepared in 0.9% sodium chloride to a total volume of 50 ml. It was administered as a 30-min intravenous infusion, and completed 5 min before cisplatin therapy. All patients were treated with cisplatin, either alone or in combination with other cytostatic agents. If a combination of agents was used, patients received cisplatin first. Cisplatin, at a dose of 50 mg/m<sup>2</sup> or more, was administered as an intravenous infusion over a period not exceeding 6 h.

If patients experienced moderate or severe nausea or vomiting, up to two further doses of open-label granisetron (40 μg/kg) were permitted during the first 24 h. These were administered as 5-min infusions, at least 10 min apart. The decision on whether to administer granisetron at this stage was taken by the physician in charge.

Any further treatment required was provided by standard antiemetics. After discharge from hospital this was supplied by giving patients oral metoclopramide (10-20 mg at 4- to 6-h intervals) to take at home.

Assessment of efficacy

The patient's subjective assessments of nausea and vomiting in the 6 h before treatment were recorded immediately before administration of granisetron. The assessments were repeated 6, 12, 18 and 24 h after the start of the granisetron infusion and then once daily for the remaining 6 days.

Any nausea recorded was rated as mild, moderate or severe. Vomiting was categorised by the number of episodes: either none, one, two to four or more than four, where a vomiting episode was either a vomit productive of stomach contents or a dry retch. Nausea and vomiting together were used to classify patient response to treatment according to the following schedule:

- Complete responder: a patient who experienced no vomiting and had no nausea or only mild nausea in the 24 h after the initial administration of granisetron