Control of emesis by intravenous granisetron in breast cancer patients treated with 5-FU, epirubicin and cyclophosphamide

Abstract  Granisetron, a potent and selective 5-hydroxytryptamine receptor (5-HT₃) antagonist was reported to be an effective anti-emetic agent both in animal studies and in patients given highly emetogenic chemotherapy. A sample of 43 patients with breast cancer was accrued from September to November 1992 in a phase II study to assess the efficacy of granisetron in patients receiving FEC (5-FU, epirubicin, cyclophosphamide). Each patient received 3 mg intravenous granisetron as a single dose just prior to chemotherapy. Oral metoclopramide was prescribed to each patient as a rescue anti-emetic. The emetic episodes and degree of nausea were evaluated on a daily basis. Good control of emesis (0–2 episodes of vomiting) and nausea (mild or no nausea) was in the range 77%–98% and 77%–93% respectively. There was a complete response (no emetic episodes throughout the 6-day period) in 16 patients (37.2%). Onset of emesis tends to occur on day 1 and tend to subside after day 3; 85% of patients had onset of emesis in the first 2 days after chemotherapy. Control of emesis and nausea tends to improve after day 3, which could be the result of the reduced emetogenicity of the combination FEC with time. Altogether, 77% had good control of acute emesis; control of delayed emesis was better with 84% achieving a major response on day 2 after chemotherapy, which improved to more than 90% after day 4. Granisetron was generally tolerated with headache being the most common side-effect followed by constipation and flushing. This study suggests that granisetron is an effective and well-tolerated anti-emetic agent, which deserves randomised trials to elucidate its efficacy further.

Key words  Granisetron  Anti-emesis  Emesis control in chemotherapy

Introduction  Cytostatic-induced nausea and vomiting are important and common clinical problems which contribute significantly to rejection of chemotherapy as a treatment modality amongst patients with cancer. Being able to control this side-effect will ensure compliance and improve the quality of life of patients on chemotherapy. The most commonly used anti-emetic is metoclopramide. At low doses, metoclopramide blocks dopamine D₂ receptors and facilitates release of acetylcholine from nerve endings in the myenteric plexus of the upper gut, resulting in anti-emesis. When used alone or in combination with dexamethasone or diphenhydramine, metoclopramide has been reported to give complete protection in 40%–50% of patients. However, its anti-
dopamine-receptor effects also lead to undesirable extra-pyramidal side-effects [5].

Cytostatic-induced nausea and vomiting is believed to be mediated by 5-hydroxytryptamine (5-HT) rather than dopamine. Metoclopramide at higher doses antagonises 5-HT receptor but with a consequent increase in incidence and severity of extra-pyramidal side-effects.

Granisetron is a selective 5-HT3 receptor antagonist. Early pilot studies have shown encouraging results. Studies with male ferrets showed a high success rate of single-dose granisetron in preventing vomiting following high-dose cisplatin [1]. Studies in human volunteers demonstrated good tolerance with a favourable toxicity profile.

Since 1987, granisetron has been tested in patients receiving cytotoxic therapy and has been shown to achieve control of cytostatic-drug-induced emesis both as a prophylactic and an intervention agent with major efficacy ranging from 74% to 92% [9].

### Patients and methods

A group of 43 patients with breast cancer, given the combination FEC (5-FU, epirubicin, cyclophosphamide) in the Department of Medical Oncology, Singapore General Hospital, was accrued between September and November 1992 for this study. The clinical characteristics of the patients are summarized in Table 1. Absence of major organ dysfunction was a prerequisite for selection for study. Exclusion criteria were as follows: age less than 18 years; Zubrod status above 2; gastrointestinal obstruction; central nervous system metastasis; anti-emetic therapy in the 24 h prior to chemotherapy; vomiting in the 24 h prior to chemotherapy; pregnancy. Patients who had received prior chemotherapy were not excluded from this study.

#### Trial design and treatment

Patients who received FEC were given this combination as a bolus on an outpatient basis.

An intravenous granisetron 3-mg bolus was given just prior to chemotherapy as a single dose, and tablet metoclopramide was prescribed to all patients as a rescue anti-emetic.

#### Assessment

A diary card, recording the number of episodes of emesis and the degree of nausea experienced each day from days 1 to 6, was started for each patient recruited. All patients were instructed to note the number of vomiting or retching episodes and the degree of nausea after the chemotherapy had been given, and phone calls were made each day by the principal investigator to the patients from days 1 to 6. The number of vomiting and reaching episodes and the degree of nausea were recorded each day for 6 days on the diary card. At the same time, evidence of any side-effects of granisetron was sought during the period of enquiry.

An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. The degree of nausea was assessed according to the following scale: none, no nausea; mild, did not interfere with normal daily life; moderate, interfered with normal daily life; severe, bedridden because of nausea.

Treatment efficacy was assessed according to the episodes of emesis and the severity of nausea (Table 2). The effect on a patient, with respect to emesis and nausea, was considered "good" if there was complete or major response.

### Results

#### Anti-emetic effects

There was complete response in emesis in 16 patients (37.2%) throughout the 6-day assessment period; 12 patients (30%) had no nausea throughout the assessment period; 27 patients (63%) had a complete response in emesis on day 1 with improvement noted after day 3 until 40 patients (93%) had no emetic episodes on day 6. The same trend was also seen in the degree of nausea experienced during the 6-day assessment period, 20 patients (47%) having no nausea on day 1 with an increase in complete response until 34 patients were free from nausea (79%) on day 6. Onset of emesis was seen in 16 patients on day 1, 7 patients on day 2, 1 patient on day 3 and 2 patients on day 4 (Table 4). Four patients (7%) experienced severe nausea during the assessment period, 3 of whom experienced it on day 1 (Tables 3, 4).

Treatment failed in 4 patients on day 1, 3 patients on day 2, 2 patients on day 3, 2 patients on day 4, 1 patient on day 5 and in no patient on day 6.

#### Side-effects

Granisetron was well tolerated. Side-effects reported were generally mild.

The frequency of the side-effects is summarized in Table 5. The most common side-effect was headache.