Randomised double blind crossover study comparing ondansetron, granisetron and tropisetron. A cost–benefit analysis

Abstract The goals of this work were to compare the relative efficacy of ondansetron, granisetron and tropisetron in a randomised double blind crossover trial, evaluating objective, subjective and pharmacoeconomic parameters. To this end, 136 patients were enrolled, 120 of whom were eligible and evaluable. Each patient received three identical chemotherapy cycles with an antiemetic protocol which consisted in dexamethasone 20 mg i.v. and a tapering dose schedule for 4 days, and a single i.v. dose of an antiserotoninergic drug in each cycle. Arm A patients received tropisetron 5 mg; arm B patients, granisetron 3 mg; and arm C patients, ondansetron 24 mg. Numbers of patients and days with emetic episodes, grade of nausea, patient preference, headaches, need for metoclopramide, nursing or medical consultation, or admission to emergency room or ward were evaluated. There was no difference in the percentage incidence of acute or delayed nausea and vomiting. Twenty-five per cent of patients preferred tropisetron, 30% preferred granisetron, and 45% preferred ondansetron \( (P<0.01) \). Toxicity was mild in less than 10% of patients. Direct and indirect costs of treatment varied from 19.74 to 28.53 euros for tropisetron, 31.07–46.51 euros for granisetron and 22.76–62.61 euros for ondansetron. There was no difference in objective activity. In the schedules studied, patients preferred ondansetron. Indirect costs amount to less than 10% of the total antiemetic cost. Direct costs varied widely and should be considered whenever an antiemetic drug is selected.

Key words Antiemetics · Cost–benefit analysis · Emesis · Randomised controlled clinical trial

Introduction

Nausea and vomiting are two of the most frequent adverse effects in the treatment of patients with cancer [18, 56, 107]. There appears to be a direct relationship between the presence of nausea and vomiting and the quality of life index commonly studied [87]. Chemotherapy-induced emesis is mediated by afferent input from the chemoreceptor trigger zone, vagal afferent fibres from the gastrointestinal tract, and the cerebral cortex [98]. Until the 1980s metoclopramide was the basis of antiemetic treatments, with or without added steroids [11]. Nevertheless, the protection this provides against platinum derivatives is not complete, and effective doses are associated with extrapyramidal side-effects, which increase in frequency when treatment is administered over several consecutive days [33]. The use of high-dose metoclopramide to prevent emesis associated with cisplatin allowed the discovery of the role of serotonin type 3 \( (5-HT_3) \) receptors (formerly called M
receptors) in vomiting [28], and specific antiserotonergic drugs were developed [65].

Drugs with a partial agonistic effect on the type 3 serotonin receptor (5-HT₃ antagonists) [1, 2, 38, 39, 88, 100] have shown an antiemetic potential superior to that of antidopaminergic drugs, especially in highly emetogenic chemotherapy programmes, such as regimens including cisplatin [21, 44]. Furthermore, 5-HT₃ antagonists have the advantage of showing no tendency to cause sedation or the extrapyramidal effects seen with antidopaminergic agents. Constipation and headaches are the main side-effects that have been assigned to 5-HT₃ antagonists. Acute emesis induced by moderately emetogenic chemotherapy, such as doxorubicin, cyclophosphamide, epirubicin and carboplatin, is also prevented by 5-HT₃ antagonists added to dexamethasone [9, 10, 12, 19, 25, 47, 53]. Thus, 5-HT₃ antagonists in combination with dexamethasone are the most cost-effective choices in the prevention of acute emesis induced by a high single dose and low and repeated doses of cisplatin and, probably, in the prevention of acute emesis induced by moderately emetogenic chemotherapies [81].

In the last few years, drug analogues have been synthesised whose relative potency, bioavailability, toxic spectrum and cost are debated. Ondansetron (GR38032F) [21, 44, 63, 90, 96], granisetron (BRL43694) [17, 34, 37, 61, 78, 92] and tropisetron (ICS 205–930) [94] have been available in Spain since 1994. Randomised trials comparing ondansetron versus granisetron [31, 50, 70, 86] or tropisetron [16, 49] published at that time showed small differences depending on the trials. The present study was designed to compare the antiemetic effect of ondansetron, granisetron and tropisetron in patients receiving highly and moderately emetogenic chemotherapy. The secondary aim was to analyse the cost associated with each treatment according to established criteria of real cost.

Randomisation process

The trial was a randomised three-arm, double blind, crossover study. No stratification was implemented. It was considered that 120 patients would be needed for detection of an increase of 20% in total antiemetic protection (unilateral test with an increase from two-thirds to three-quarters in total control, which was considered clinically relevant) with an error type alpha of 0.05 and a power of 0.9 [6]. No correction was made for paired data or for continuity. An interim analysis was initially projected after 60 patients were included to detect possible significant differences in response at the 0.01 level, allowing an early termination of the study.

Patients received each antiemetic drug in each chemotherapy cycle in a random order after written consent. The administration sequence of chemotherapy was determined at random following a closed-envelopes procedure. The treatment assignment remained sealed in a randomised envelope until the decision to participate in the trial was made. The treatment assignments were not revealed to patients or to the physician in charge, but only to the pharmacist and the nursing personnel charged with administering the drug. The treatments were codified as A, B and C by the Department of Pharmacy and delivered to the nursing staff at the Day Hospital in closed bags, with the medical oncologists blinded to their identities. Thus, six groups of 20 patients received each drug sequence: ABC, ACB, BAC, BCA, CAB, and CBA. After 120 had been entered, another round of randomisation was implemented for missed data. The key code for each letter was sealed and stored in the Department of Pharmacy until the last patient had received the three cycles of chemotherapy and the statistical analysis had been performed (blind). After preliminary analysis of the data, the correspondence codes were disclosed on 21 January 1997, as follows: A, tropisetron; B, granisetron; C, ondansetron.

Antiemetic doses and schedule

Patients received each antiemetic drug in each chemotherapy cycle by a short i.v. infusion (50 ml normal saline in 10 min, 30 min before chemotherapy) with the following doses: ondansetron, 24 mg; granisetron 3 mg; tropisetron 5 mg. All patients received dexamethasone 20 mg i.v. at the same time, and a tapering oral schedule of 2 mg twice a day for 2 days and 1 mg twice a day for 2 further days. Metoclopramide was not prescribed initially, but it was allowed on demand for patients with therapeutic failures or delayed emesis; need for metoclopramide was considered a measure of therapeutic failure.

Response evaluation

The evaluation of nausea/emesis was made by the physician in charge, who was unaware of treatment codes. Response was evaluated according to the Common Toxicity Criteria for nausea and vomiting. For nausea: grade 0 was no toxicity; grade 1, able to eat a reasonable intake; grade 2, intake significantly decreased, but can eat; grade 3, no significant intake. For vomiting: grade 0, none; grade 1, one episode in 24 h; grade 2, two to five episodes in 24 h; grade 3, six to ten episodes in 24 h; grade 4, more than 10 episodes in 24 h, requiring parenteral support. An emetic episode was defined as a single vomit or retching or any number of continuous vomits or retching more than 5 min apart [29].

Number of emetic episodes, grade of nausea, headache, nursing or medical consultation, need for metoclopramide therapy or emergency or hospital admission were registered for 1 week after each cycle in a personal interview (diary cards were considered noncompliant in a fraction of old and low social strata patients).