Antiemetic effects of granisetron and dexamethasone combination therapy during cisplatin-containing chemotherapy for head and neck cancer: dexamethasone dosage verification trial

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Abstract

Background. Chemotherapy-induced nausea and vomiting (CINV) remains a significant problem for patients and is associated with a substantial deterioration in quality of life; appropriate use of antiemetic drugs is crucial in maintaining the quality of life in patients undergoing chemotherapy.

Methods. This randomized, crossover trial evaluated the antiemetic efficacy and safety of 8 mg per day (low-dose) and 16 mg per day (standard-dose) dexamethasone, in combination with the 5-HT₃ receptor antagonist granisetron, in 36 patients receiving cisplatin (CDDP)-containing chemotherapy for head and neck cancer. Following chemotherapy, the antinausea/vomiting inhibition rate for each dexamethasone dose was measured.

Results. During the 24-h period following administration of chemotherapy (acute phase), the antinausea/vomiting inhibition rates (no nausea and no episodes of vomiting) for 8 mg and 16 mg dexamethasone were comparably high (58.3% and 63.8%, respectively; \( P = 0.8092 \)). Similar results were seen on days 2−5 following chemotherapy. Efficacy during the acute phase, based on the number of instances of vomiting and degree of nausea, was also comparably high for the two dexamethasone doses (overall efficacy rates were 94.4% and 88.8%, respectively, for 8 mg and 16 mg dexamethasone; \( P = 0.7637 \)). Both doses maintained an 80% or higher response rate until day 3, and neither dose produced severe side effects.

Conclusion. The results suggest that granisetron and dexamethasone combination therapy is useful in controlling acute and delayed nausea and vomiting induced by CDDP-containing chemotherapy for head and neck cancer. Furthermore, 8 mg and 16 mg dexamethasone have equivalent antiemetic efficacy.

Key words Chemotherapy · Nausea · Vomiting · Granisetron · Dexamethasone

Introduction

The optimal strategy to avoid chemotherapy-induced nausea and vomiting (CINV) continues to present challenges for the oncologist and pharmacotherapist, and appropriate use of antiemetic drugs is crucial in maintaining the quality of life in patients undergoing chemotherapy. Cisplatin (CDDP)-containing chemotherapy is becoming a widespread treatment choice for head and neck cancer. However, as nausea and vomiting frequently occur following CDDP administration, controlling these symptoms is a crucial component of the overall treatment plan.

The recent advent of 5-HT₃ receptor antagonists has made it possible to control the acute nausea and vomiting (CINV) that often follow immediately after CDDP-containing chemotherapy. While these agents are effective in the acute phase, they are not sufficiently effective in controlling delayed nausea and vomiting occurring beyond the 24-h period following chemotherapy administration. To address this issue, the antiemetic efficacy of 5-HT₃ receptor antagonists in combination with drugs that exhibit a delayed antiemetic effect has been investigated, with results suggesting that steroids, such as dexamethasone, offer a promising adjunct to 5-HT₃ receptor antagonists.

Various national and international treatment guidelines state that when using dexamethasone in combination with 5-HT₃ receptor antagonists to control chemotherapy-induced nausea, the recommended dose of dexamethasone is 20 mg for preventing acute nausea and vomiting and 16 mg for preventing delayed nausea and vomiting. However, the appropriateness of these doses for the Japanese population is questionable, for several reasons. Firstly, in Japan, the dosage of CDDP used in the treatment of head
and neck cancer is lower, at 70 mg/m², compared with 100 mg/m² used in other countries. Secondly, some differences may be seen in the metabolism of steroids between ethnic groups. As steroids are not indicated for antiemetic control in Japan, insufficient data are currently available related to their optimal dosing.

This study was conducted to measure the optimal dose of dexamethasone, in combination with the 5-HT₃ receptor antagonist granisetron, for antiemetic therapy during CDDP-containing chemotherapy for head and neck cancer in a Japanese patient population. Using a randomized crossover trial design, the efficacy and safety of 8 mg and 16 mg dexamethasone were assessed. Evaluated endpoints were the complete nausea and vomiting inhibition rate, the complete nausea inhibition rate, the complete vomiting inhibition rate, overall drug efficacy, degree of appetite loss, and side effects. The overall drug efficacy was assessed using criteria established by Suminaga et al., while the degree of appetite loss was measured by using version 2.0 of the National Cancer Institute common toxicity criteria (NCI-CTC).

Subjects, materials, and methods

Subjects

The trial involved 36 adults (≤75 years of age) who were admitted to Yokohama City University Hospital and Yokohama City University Medical Center from May 2003 to December 2003 with stage III or IV advanced head and neck cancer. Each recruited patient was to receive two courses of CDDP-containing chemotherapy (CDDP, 60 mg/m² per day) every 4 weeks without pretreatment. All subjects consented to participate following a full explanation of the trial’s objectives and content. The protocol was reviewed and approved by the ethics committee of the Yokohama City University School of Medicine and Yokohama Medical Center, Yokohama City University.

Exclusion criteria were: (1) concurrent illnesses such as severe heart disease, renal disease, and liver disease; (2) nausea and/or vomiting prior to treatment; (3) illnesses from which nausea and/or vomiting were a result, e.g., bowel obstruction, and peptic ulcer; (4) performance status (PS) of 4; (5) past history of hypersensitivity to drugs; (6) currently taking other antiemetic drugs and/or antipsychotic medication; (7) pregnant or possibly pregnant; and (8) deemed unsuitable by a doctor. In addition, patients who underwent radiation therapy or who experienced brain metastasis during the course of the trial were handled separately at the time of data analysis.

Design and treatment allocation

At the registration center, candidates were assessed for their suitability to participate in the trial and registered if deemed fit. The 36 participants (this number being settled upon by referring to a randomized crossover study for evaluating the antiemetic effect of the concomitant use of granisetron and dexamethasone against CDDP-induced delayed emesis in Japanese lung cancer patients) were randomized by a hospital-based controller to two groups: the “dexamethasone 8 mg per day antecedent group” and the “dexamethasone 16 mg per day antecedent group” (Fig. 1). All patients received intravenous granisetron 3 mg 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration in accordance with treatment regulations set by the Ministry of Health, Labour and Welfare of Japan. CDDP was intravenously administered for 3 h. The 8-mg antecedent group received 8 mg dexamethasone for course 1, switching to 16 mg for course 2. The 16-mg antecedent group received 16 mg dexamethasone for course 1, switching to 8 mg for course 2. The potential for carry-over effects between courses was minimized, if not eliminated, by a 3-week treatment-free interval between the two courses.

Dosage and administration

Dexamethasone 8-mg antecedent group

- Course 1: granisetron 3 mg + dexamethasone 8 mg were administered intravenously 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration.
- Course 2: granisetron 3 mg + dexamethasone 16 mg were administered intravenously 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration.

Dexamethasone 16-mg antecedent group

- Course 1: granisetron 3 mg + dexamethasone 16 mg were administered intravenously 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration.
- Course 2: granisetron 3 mg + dexamethasone 8 mg were administered intravenously 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration.

Fig. 1. Study design. The 36 participants were randomized to two groups: the “dexamethasone 8 mg per day antecedent group” and the “dexamethasone 16 mg per day antecedent group”. All patients received intravenous granisetron 3 mg daily. The 8-mg antecedent group received 8 mg dexamethasone for course 1, switching to 16 mg for course 2. The 16-mg antecedent group received 16 mg dexamethasone for course 1, switching to 8 mg for course 2. DEX, Dexamethasone; R, randomization.