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Evaluation of palonosetron and dexamethasone with or without aprepitant to prevent carboplatin-induced nausea and vomiting in patients with advanced non-small-cell lung cancer

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ABSTRACT

Objectives: Although antiemetic management has improved, better control of chemotherapy-induced nausea and vomiting (CINV), particularly during the delayed phase, is needed. The benefit of combination therapy using dexamethasone and the second-generation 5-hydroxytryptamine-3 receptor antagonist palonosetron compared with that of other such receptor antagonists in carboplatin-based chemotherapy is unclear. The effectiveness of adding aprepitant for CINV treatment in moderate emetogenic chemotherapy is also unknown. We compared the efficacy and safety of triple antiemetic therapy using aprepitant, palonosetron, and dexamethasone with that of double antiemetic therapy using palonosetron and dexamethasone in patients with advanced non-small-cell lung cancer receiving carboplatin-containing chemotherapy.

Methods: Chemotherapy-naïve patients with non-small-cell lung cancer were enrolled in this prospective controlled study. Eighty patients were randomly assigned to groups receiving either double antiemetic therapy with palonosetron and dexamethasone, or triple antiemetic therapy with aprepitant, palonosetron, and dexamethasone. Complete response rate (no vomiting episode and no rescue therapy) was evaluated as the primary endpoint during the 5-day post-chemotherapy period.

Results: The aprepitant add-on and double therapy groups showed overall complete response rates of 80.5% (95% confidence interval [CI]: 68.4–92.6%) and 76.9% (95% CI: 63.7–90.1%; odds ratio [OR]: 0.81; 95% CI; 0.27–2.36; $p = 0.788$), respectively. Complete responses in the acute and delayed phases and overall incidences of treatment-related adverse events were similar between groups.

Abbreviations: AUC, area under the curve; CINV, chemotherapy-induced nausea and vomiting; ECOG, Eastern Cooperative Oncology Group; HEC, highly emetogenic chemotherapy; 5-HT_3, 5-hydroxytryptamine-3; MEC, moderately emetogenic chemotherapy; NK-1, neurokinin-1; NSCLC, non-small-cell lung cancer; QOL, quality of life.

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Conclusion: According to the selection design, triple antiemetic therapy with aprepitant, palonosetron, and dexamethasone was not considered as an option for further studies.

1. Introduction

Lung cancer is a leading cause of cancer-related deaths worldwide [1]. Combination chemotherapy with a platinum compound (cisplatin or carboplatin) can improve survival and quality of life (QOL) in management of advanced non-small-cell lung cancer (NSCLC) [1,2]. Adverse events occur in many patients undergoing chemotherapy, and chemotherapy-induced nausea and vomiting (CINV) continue to be among the most troubling side effects [3,4]. CINV can worsen the general condition and overall QOL of patients [3,5]. Prevention of CINV is among the most important issues in continuing chemotherapy and achieving treatment success.

Chemotherapy agents are generally classified by their emetogenic effects, namely, "highly emetogenic chemotherapy" (HEC), "moderately emetogenic chemotherapy" (MEC), and "low or minimal emetogenic chemotherapy", according to the frequency and strength of vomit-inducing effects [4,6,7]. Carboplatin is categorized as a MEC agent, and dexamethasone with a 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist are recommended for concurrent use as antiemetics [3,4,7]. Although carboplatin is regarded as less emetic than cisplatin and is widely used in combination therapy, we previously showed that carboplatin-based chemotherapy showed relatively strong emetic properties, particularly during the delayed phase of the trial [8].

Palonosetron is a second-generation 5-HT_3 receptor antagonist with greater 5-HT_3 receptor binding affinity and a longer half-life compared with other 5-HT_3 receptor antagonists [9]. Saito et al. demonstrated that palonosetron and dexamethasone controlled CINV more effectively than a first-generation 5-HT_3 receptor antagonist with dexamethasone in patients receiving HEC regimens. During the delayed phase, significantly more patients treated with palonosetron than granisetron had complete responses [10]. As for MEC regimens, Murakami et al. showed that patients treated with palonosetron had a significantly lower incidence of nausea and lower vomiting incidence in the delayed and overall phase in their study, compared with those receiving granisetron [11]. Unfortunately, few studies have prospectively assessed whether palonosetron with dexamethasone is superior to other 5-HT_3 receptor antagonists combined with dexamethasone in non-doxorubicin cyclophosphamide MEC regimens. Additionally, the effect of aprepitant add-on therapy in combination with palonosetron remains unknown.

Here, we present a randomized controlled study comparing triple antiemetic therapy with aprepitant, palonosetron, and dexamethasone versus double therapy (palonosetron and dexamethasone) in patients with advanced NSCLC receiving carboplatin-based first-line chemotherapy. We evaluated complete response rates (no vomiting and no rescue therapy) to verify whether adding aprepitant to palonosetron and dexamethasone improved antiemetic control in patients receiving carboplatin-based chemotherapy.

2. Patients and methods

2.1. Study design

The present study was a multicenter, prospective, open-label, parallel-group, randomized controlled trial conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Review Board of each participating institution. Each patient gave written informed consent for study inclusion. The trial was registered with the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN ID 10056).

2.2. Patient eligibility

Chemotherapy-naïve patients with pathologically-confirmed inoperable stage-IIIB or -IV NSCLC (aged ≥20 years), with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and receiving carboplatin-based chemotherapy, were eligible for inclusion. Additional eligibility criteria included adequate hematopoietic, renal, and hepatic function. Exclusion criteria included the following: nausea and vomiting within 24 h; use of antiemetic agents and corticosteroids within 24 h before administration of chemotherapy; use of pimozide; uncontrolled diabetes mellitus; and conditions likely to induce emesis regardless of chemotherapy, including symptomatic brain metastasis, gastrointestinal obstruction, and an active gastrointestinal ulcer.

2.3. Treatment schedule

Patients with squamous cell carcinoma were treated with paclitaxel (200 mg/m^2 or nanoparticle, albumin-bound at 100 mg/m^2) and carboplatin (at an area under the curve [AUC] of 6 on day 1 of a 21-day cycle) or S-1 (orally 40 mg/m^2 twice per day on days 1–14) and carboplatin (on day 1 of a 28-day cycle). Patients with non-squamous NSCLC were treated with pemetrexed (500 mg/m^2) and carboplatin (at an AUC of 6 on day 1 of a 21-day cycle) or paclitaxel and carboplatin. In some eligible cases, bevacizumab was added. Carboplatin dosage was calculated according to the Calvert formula. Glomerular filtration rate was estimated from the Cockcroft–Gault formula. Patients were randomly assigned to receive palonosetron and dexamethasone (control group) or aprepitant with palonosetron and dexamethasone (aprepitant group). Randomization was performed centrally by computer software and stratified by sex, age, and non-platinum chemotherapy agent. The control group received palonosetron (0.75 mg) on day 1 and dexamethasone (8 mg) on days 1–3. For the aprepitant group, aprepitant (125 mg on day 1 and 80 mg on days 2–3) was administered in addition to control treatments. Patients receiving paclitaxel or pemetrexed, were administered prophylactic dexamethasone, H_1 and H_2 blockers, folic acid, and vitamin B_{12} according to package instructions. For paclitaxel, 12 mg dexamethasone was added at day 1 to prevent anaphylactic reactions. Dexamethasone dose was reduced in the aprepitant group according to those used in previous studies [8,12]. Additional antiemetic agents and other supportive treatments were administered at the discretion of the treating physicians.

2.4. Evaluation of response and toxicity

During the 120 h after carboplatin administration, patients completed a daily questionnaire regarding vomiting and nausea frequency. Physicians recorded rescue antiemetic therapy use during the study period. The primary endpoint was defined as a complete response rate in the overall phase (during the 120 h after chemotherapy administration). Secondary endpoints included the following: complete response rate in the acute (first 24 h after chemotherapy administration) and delayed phases (24–120 h after chemotherapy); nausea in the overall, acute, and delayed phases;