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Original Article

Combination of palonosetron, aprepitant, and dexamethasone as primary antiemetic prophylaxis for cisplatin-based chemotherapy

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ABSTRACT

Background: The purpose of this study was to evaluate the efficacy of combined treatment with the long-acting 5-hydroxytryptamine receptor-3 antagonist, palonosetron, the neurokinin-1 receptor antagonist, oral aprepitant, and dexamethasone as primary antiemetic prophylaxis for cancer patients receiving highly emetogenic cisplatin-based chemotherapy.

Methods: Chemotherapy-naïve patients received the triple combination of palonosetron (0.25 mg), aprepitant (125 mg on day 1 and 80 mg on days 2 and 3), and dexamethasone (20 mg) from the beginning of highly emetogenic chemotherapy with cisplatin-based ($\geq$50 mg/m^2) regimens. The primary endpoint was a complete response (no emetic episodes and no rescue antiemetics) during the days 1–6.

Results: Sixty-nine hospitalized patients receiving chemotherapy from September 2012 to October 2014 were analyzed. Complete response of vomiting and nausea-free was achieved in 97.1% and 85.5% of patients in the first cycle, respectively, and 96.7% and 83.6% of patients in the second cycle, respectively. Common adverse events in all 69 patients included constipation (43%), hiccup (26%), and headache (4%).

Conclusion: The combination of palonosetron, aprepitant, and dexamethasone as primary antiemetic prophylaxis for cancer patients with highly emetogenic cisplatin-based chemotherapy is effective.

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At a glance commentary

Scientific background of the subject

Chemotherapy-induced nausea and vomiting because of cisplatin-based chemotherapy strongly affects the quality of life of cancer patients. Primary antiemetic prophylaxis with the first-generation 5-hydroxytryptamine receptor-3 antagonist plus dexamethasone still resulted in about 20% patients experiencing acute and/or delayed emesis during the first cycle of cisplatin-based chemotherapy.

What this study adds to the field

The triple combination of palonosetron, aprepitant, and dexamethasone as primary antiemetic prophylaxis is safe and highly effective in preventing chemotherapy-induced nausea and vomiting in the days following administration of highly emetogenic cisplatin-based chemotherapy. Nearly, all the patients experienced no episodes of vomiting and good control of nausea was maintained following chemotherapy.

Clinicians should be aware that chemotherapy-induced nausea and vomiting (CINV) remains one of the most feared side effects of chemotherapy. CINV as a consequence of cisplatin-based chemotherapy strongly affects the quality of life for cancer patients [1,2]. According to recent international guidelines [3,4], cisplatin-based (at dose of $\geq$50 mg/m^2) regimens are considered to be highly emetogenic forms of chemotherapy (HEC), with a >90% risk of inducing CINV [5].

The first-generation 5-hydroxytryptamine receptor-3 antagonist (5-HT$_3$RAs), ondansetron, granisetron, dolasetron, and tropisetron, have provided significant improvement in the management of acute CINV [6] but have been shown to be ineffective in controlling delayed CINV, even when administered in multiple doses 24 h or more following chemotherapy [7]. Palonosetron is a novel, potent, selective second-generation 5-HT$_3$RA with a longer half-life (40 h) [8], and a higher receptor binding affinity (>30-fold) with respect to other 5-HT$_3$RAs [9]. The superiority of single-dose palonosetron (0.25 mg IV) over single-dose ondansetron (32 mg IV) or dolasetron (100 mg IV) for the prevention of emesis and delayed nausea has been demonstrated in phase III comparative trials [10–13]. Aprepitant, the first approved substance P/neurokinin-1 (NK$_1$) receptor antagonist (NK$_1$RA), has been shown to significantly improve the prevention of acute and delayed CINV following HEC [14]. A 3-day oral aprepitant regimen in combination with standard antiemetics (ondansetron plus dexamethasone) was shown to offer enhanced protection against emesis associated with anthracycline- and cyclophosphamide-based breast cancer regimens or cisplatin-based HEC when compared with standard antiemetics alone [15,16]. All antiemetic guidelines are unanimous in recommending a combination of aprepitant, dexamethasone, and a 5-HT$_3$RA within the first 24 h for acute CINV with HEC [3,4,17].

In a previous study [18], we investigated the efficacy of adding aprepitant as a secondary antiemetic prophylaxis for cases in which a first-generation 5-HT$_3$RA plus dexamethasone failed to achieve full antiemetic protection during the first cycle of a cisplatin-based regimen. Approximately 20% of patients receiving primary antiemetic prophylaxis with granisetron plus dexamethasone experienced acute and/or delayed emesis during the first cycle of cisplatin-based chemotherapy. The addition of aprepitant as a secondary antiemetic prophylaxis in subsequent cycles provided about 70% complete emesis protection in patients who failed primary prophylaxis. On the basis of these results, the aim of this prospective study was to evaluate the efficacy of a combination of the long-acting palonosetron, 3-day aprepitant and dexamethasone as primary antiemetic prophylaxis in patients receiving HEC (cisplatin $\geq$50 mg/m^2), and to determine whether the antiemetic efficacy of the triple combination could be sustained.

Materials and methods

Patients

Patients were enrolled in the study consecutively, and data were collected prospectively. All chemo-naïve patients in this study were scheduled to receive chemotherapy with a dose of at least 50 mg/m^2 cisplatin followed immediately by a continuous infusion of 5-fluorouracil (5-FU) with or without other chemotherapeutic agents. Cisplatin was given on day 1 and the other drugs on day 1 and subsequent days. Participants were required to be at least 18 years of age, with no prior history of cisplatin-containing chemotherapy, and the Eastern Cooperative Oncology Group (ECOG) performance status grades of 0–3. Individuals with a concurrent severe illness, nausea, or vomiting in the period 24 h before chemotherapy, other known causes of nausea, or vomiting (e.g., central nervous system metastases, gastrointestinal obstruction, and hypercalcemia), or concurrent therapy with corticosteroids or benzodiazepines (unless given for night sedation) were excluded from the study. Demographic data and patient characteristics were examined and reported as frequencies and percentages [Table 1]. All patients were hospitalized during the administration of chemotherapy. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No.: 103-3856B).

Antiemetic therapy

This was a single-institution study. The same chemotherapeutic drug was used at identical doses during each treatment cycle. Each chemotherapy cycle consisted of cisplatin (50–100 mg/m^2), and 20% mannitol (100–150 mL) administered in 500 mL of normal saline for 3 h. Palonosetron (Aloxi, Pierre Fabre, Medicament Production Aquitaine Pharm International, Idron, France) 0.25 mg in 100 mL of normal saline was given as a 30-min intravenous infusion before cisplatin administration. Oral aprepitant (Emed, Merck Sharp, and Dohme Corp., a subsidiary of Merck and Co., Inc., PA, USA) was administered once daily on day 1 at a dose of 125 mg, and at