RESEARCH ARTICLE

Efficacy of Aprepitant in Patients with Advanced or Recurrent Lung Cancer Receiving Moderately Emetogenic Chemotherapy

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Abstract

Aims and Background: To evaluate the efficacy of a combination of aprepitant and conventional antiemetic therapy in patients with advanced or recurrent lung cancer receiving moderately emetogenic chemotherapy (MEC). Methods: Patients with advanced or recurrent lung cancer who were treated with MEC regimens at the Department of Respiratory Medicine, Fukuoka University Hospital, were included and classified into the following groups: control group (treatment: 5-HT3 receptor antagonists + dexamethasone) and aprepitant group (treatment: 5-HT3 receptor antagonists + dexamethasone + aprepitant). The presence or absence of chemotherapy-induced nausea and vomiting (CINV) was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0; patients with grade 1 or above were considered positive for CINV. Food intake per day, completion of planned chemotherapy, and progression-free survival (PFS) achieved by chemotherapy were investigated. Results: The complete suppression rate of nausea in the aprepitant group was significantly higher than that in the control group (p = 0.0043). Throughout the study, the food intake in the aprepitant group was greater than that in the control group, with the rate being significantly higher, in particular, on day 5 (p = 0.003). The completion rate of planned chemotherapy was also higher in the aprepitant group (p = 0.042). PFS did not differ significantly, but tended to be improved in the aprepitant group. Conclusions: The aprepitant group showed significantly higher complete suppression of nausea, food intake on day 5, and completion of planned chemotherapy than the control group.

Keywords: CINV - aprepitant - complete suppression rate of nausea - food intake

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most severe adverse effects of anticancer treatments, and its prolonged manifestation can cause dehydration, electrolyte imbalance, and poor nutrition. Further, CINV reduces patients' quality of life (QOL) and can prevent the continuation of chemotherapy. Therefore, prevention of CINV and symptom management are important (Richardson et al., 1988).

Several mechanisms underlie the induction of CINV by chemotherapy. First, chemotherapeutic agents stimulate enterochromaffin cells that signal the vomiting center in the bulbar lateral reticular formation using the neurotransmitter 5-hydtroxytryptamine (5-HT) via 5-HT3 receptors in the gastrointestinal tract either directly through the vagus nerve or through the chemoreceptor trigger zone (CTZ). Second, the agent can directly stimulate the CTZ, transmitting to the vomiting center via the dopamine or 5-HT3 receptors (Navari, 2009a; Navari, 2009b). Furthermore, in a newly elucidated pathway, chemotherapeutic agents can increase secretion of substance P in the area postrema and the nuclei of the solitary tract in the medulla oblongata, which binds to neurokinin 1 (NK 1) receptor in the central nervous system. Thus, this represents a new target in antiemetic therapy (Huskey et al., 2003; Navari, 2009a; Navari, 2009b).

The risk of CINV depends on the type of chemotherapeutic agents, which are classified into 4 emetic risk groups (Kris et al., 2006). Cisplatin, the main drug for treating lung cancer, is classified as a highly emetic chemotherapy (HEC). Several clinical trials have demonstrated the efficacy of NK1-receptor antagonists in HEC (Hesketh et al., 2003; Poli-Bigelli et al., 2003; de Wit et al., 2004), and the American Society of Clinical Oncology (ASCO), Multinational Association of Supportive Care in Cancer (MASCC) and National Comprehensive Cancer Network(NCCN) guidelines recommend combined administration of 5-HT3 receptor

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antagonists, steroids, and NK1-receptor antagonists (Kris et al., 2006; Ettinger et al., 2007). In Japan, 5-HT3 receptor antagonists + steroids were previously the standard of care, because NK1-receptor antagonists had not been approved. However, the NK1-receptor antagonist aprepitant gained market approval in 2009. Since then, the Japanese antiemetic guidelines, which were updated in 2010, recommend its usage in treatment regimens including HEC (Takeuchi & Saeki, 2010).

On the other hand, there is less evidence to support the efficacy of aprepitant in treatment regimens with moderately emetogenic chemotherapy (MEC) in patients with lung and other cancers. Palonosetron, which has a long half-life (~40 h) and a high affinity and selectivity for 5-HT3 receptors, has antiemetic effects in both the acute phase and the delayed phase (after 24 h) by blocking 5-HT3 receptors (Wong et al., 1995; Rojas et al., 2008; Saito et al., 2009). Based on these results, palonosetron is recommended for use in regimens including MEC in the guidelines by American Society of Clinical Oncology (ASCO) and Multinational Association of Supportive Care in Cancer (MASCC) (Roila et al., 2010; Basch et al., 2011). Rapoport et al. investigated the effects of antiemetic therapies in 848 patients (52% with breast cancer, 20% with colorectal cancer, 13% with lung cancer, and 4.6% with ovarian cancer) who were treated with MEC and started antiemetic therapy from the first course of chemotherapy. In this a double-blind comparative study, they compared the antiemetic effects between the triple treatment (aprepitant + ondansetron + dexamethasone) and the double treatment (ondansetron + dexamethasone) groups. They found a significant improvement in antiemetic effects by adding aprepitant (Rapoport et al., 2010), suggesting its preventive effect in patients with lung cancer treated with MEC regimens.

Herein, we report the results of a retrospective study on the efficacy of aprepitant in patients with advanced and recurrent lung cancer receiving MEC.

Materials and Methods

Patient groups

Patients with advanced or recurrent lung cancer who were treated with MEC regimens at the Department of Respiratory Medicine, Fukuoka University Hospital were included and classified into the control group (receiving 5-HT3 receptor antagonists + dexamethasone) and the aprepitant group (receiving 5-HT3 receptor antagonists + dexamethasone + aprepitant). The treatment period of the first course of chemotherapy for each patient was included.

Treatment administration

5-HT3 receptor antagonists were administered by 30-min infusion prior to chemotherapy. Aprepitant was administered orally at 125 mg on day 1 prior to chemotherapy and 80 mg each on day 2 and 3. Dexamethasone was administered by 30-min infusion prior to chemotherapy in combination with the 5-HT3 receptor antagonists.

Investigation methods

The total study period was from the initiation of chemotherapy until day 5. The presence or absence of CINV was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Grade 1 or higher was considered as being positive for CINV.

The amount of food intake per day was obtained as a percent. The completion rate of planned chemotherapy and the progression-free survival (PFS) achieved by the chemotherapy were also analyzed.

The statistical analysis of outcomes in both groups were performed using the χ^2 test for the complete suppression rate of nausea, 2-sided 2-sample t-tests for the amount of food intake and the completion rate of planned chemotherapy, and log-rank test for PFS. The statistical significance level was set at $p < 0.05$.

Results

The characteristics of the patients in each group are shown in Table 1. There were 27 and 25 patients in the control and aprepitant group, respectively. The mean ages were 70.7 and 65.7 years, respectively. Most of the chemotherapy regimenss were CBDCA combination therapy, and some included amrubicin. The occurrence of CINV is shown in Figure 1. Throughout the study period, the complete suppression rate of vomiting was 96% in the control group and 100% in the aprepitant group. Complete response (CR) rate was defined as the complete suppression of vomiting and no salvage therapy. CR was

Table 1. Patients Characteristics and Chemotherapy Regimens Administered to the Study Population

	Control group (n=27)	Aprepitant group (n=25)
Male	20	19
Female	7	7
Age, years (range)	70.7 (34-38)	65.7 (44-83)
Regimen		
CBDCA+PAC (+BEV)	8	3
CBDCA+GEM	6	1
CBDCA+VP-16	4	7
CBDCA+PEM (+BEV)	3	9
CBDCA+TS-1	2	3
CBDCA+DOC	0	1
Other	4	1

CBDCA, Carboplatin; PAC, paclitaxel; GEM, gemcitabine; VP-16, Etoposide; PEM, pemetrexed; TS-1, tegafur gimeracil and oteracil potassium; DOC, docetaxel, BEV, bevacizumab

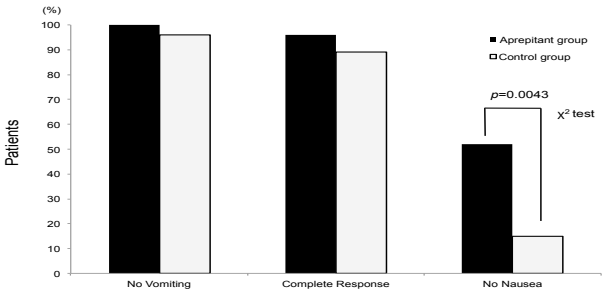

Figure 1. No Vomiting (complete suppression rate of vomiting)**, Complete Response** (defined as no emetic episodes and no use of rescue medication) **and No Nausea** (complete suppression rate of nausea) **Rates in Each of the Two Groups**

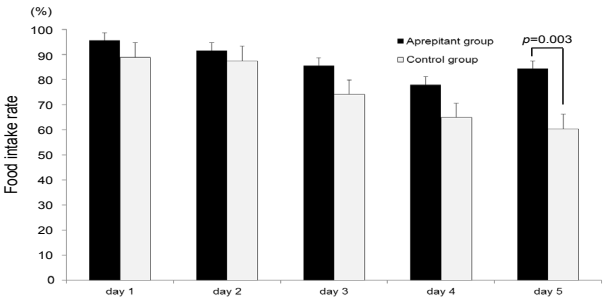

Figure 2. Food Intake Rate from Days 1 to 5 in Each of the Two Groups

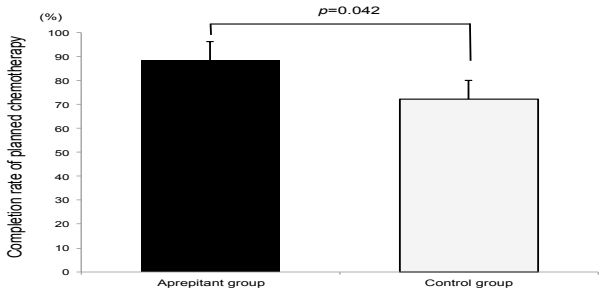

Figure 3. Completion rate of Planned Chemotherapy in Each of the Two Groups

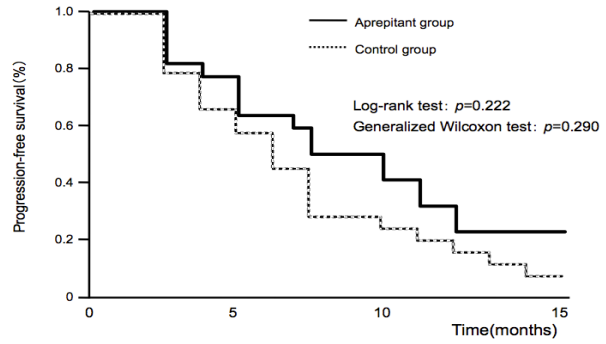

Figure 4. Kaplan-Meier PFS Curves by Treatment Arm

89% in the control group and 96% in the aprepitant group. The complete suppression rate of nausea was 14.8% and 52% in the control and aprepitant group, respectively. The aprepitant group had a significantly higher rate than the control group ($p = 0.0043$). The amount of food intake was greater throughout the study period in the aprepitant group, with significantly higher on day 5 in the aprepitant group (60.4% vs. 84.4%, $p = 0.003$) (Figure 2). The completion rate of planned chemotherapy was also higher in the aprepitant group (73.3% vs. 88.2%, $p = 0.042$) (Figure 3). PFS did not significantly differ, but it tended to be improved in the aprepitant group (Figure 4).

Discussion

CINV is a severe adverse effect in patients and can reduce QOL. As such, prevention and treatment of CINV are important. The present study investigated CINV during MEC treatment. MEC-induced vomiting in the acute phase is well controlled by 5-HT3 receptor antagonists (Perez et al., 1998; Jordan et al., 2007). However, delayed vomiting and nausea throughout the treatment period are still not well controlled during MEC, causing negative attitudes towards treatment and hindering the continuation of chemotherapy. Although steroids are recommended for treating delayed nausea and vomiting, their side effects remain a concern for many clinical oncologists (Vardy et al., 2006). On the other hand, anticipatory nausea and vomiting can occur by 'conditioning' mechanisms in patients who have experienced nausea and vomiting from chemotherapy (Morrow & Morrell, 1982). Anticipatory vomiting occurs in 11% of patients, and anticipatory nausea occurs in 29% of patients who receive chemotherapy (Andrykowski, 1988). In general, antiemetic agents cannot treat anticipatory nausea and vomiting, and the best countermeasure is to avoid nausea and vomiting from the beginning of chemotherapy (Andrykowski, 1988; Morrow et al., 1991). This retrospective study evaluated the efficacy of aprepitant in combination with conventional antiemetic therapy in patients receiving MEC. We found no significant difference in the complete suppression rate of vomiting or the CR rate between the control group and the aprepitant group. However, the complete suppression rate of nausea was significantly higher in the aprepitant group. These results suggest that nausea is not completely suppressed with conventional 5-HT3 receptor antagonists + dexamethasone in patients receiving MEC, and that adding aprepitant effectively suppresses nausea. However, it should be noted that the suppression rate remained at 52%; 85% of which incorporated palonosetron as the 5-HT3 receptor antagonist, suggesting that triplet aprepitant + palonosetron + dexamethasone is effective in completely suppressing nausea associated with MEC.

Physical fitness is important for administering chemotherapy as scheduled. The amount of food intake during the treatment period is especially important for the continuation of therapy. In this study, we compared the amount of food intake during the first 5 days from the beginning of the chemotherapy between the groups. The amount of food intake was greater in the aprepitant group throughout the 5-day period with a significant difference on day 5. Patients often demonstrate a decline in the amount of food intake on days 4 to 5, as was the case in this study. Although the amount of food intake declined during this period, the difference between the control group and the aprepitant group grew larger. Indeed, there was even a tendency towards recovery in the amount of food intake in the aprepitant group on day 5. Furthermore, the aprepitant group showed a significantly higher completion rate of planned chemotherapy compared with the control group. We hypothesize that the treatment could be continued, because the increased food intake sustained a higher level of physical fitness. In addition, we assessed the antitumor effect of chemotherapy by progression free survival (PFS). Although there was no significant difference in PFS between the groups, this could have been due to the small number of patients. There was a tendency toward a longer PFS in the aprepitant group, suggesting a contribution to the increased treatment completion rate. This result also was considered to have contributed significantly as a result of the treatment plan can be carried out by maintaining of food intake.

Aprepitant used in combination with standard antiemetic therapy (5-HT3 receptor antagonist and corticosteroid) was well tolerated and effective in preventing CINV associated with Moderate moderate

emetogenic antitumor agents of in Japanese lung cancer patients.

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