学 位 論 文 の 要 旨

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学 位 論 文 名　A Phase II Study of Palonosetron, Aprepitant, Dexamethasone and Olanzapine for the Prevention of Cisplatin-based Chemotherapy-induced Nausea and Vomiting in Patients With Thoracic Malignancy

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論 文 内 容 の 要 旨

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a distressing symptom that reduces patient quality of life. Cisplatin combination therapy, which is classified as a highly emetogenic chemotherapy (HEC), is a standard treatment for advanced lung cancer. The three-drug combination of a 5-hydroxytryptamine type 3 receptor antagonist, a neurokinin 1 receptor antagonist and dexamethasone is recommended for patients receiving HEC. However, standard antiemetic therapy is not completely effective in all patients.

Olanzapine inhibits neurotransmitter pathways known to be involved in nausea and vomiting, including serotonergic, dopaminergic, alpha-1 adrenergic, histaminic, and muscarinic receptors. Several studies have reported the efficacy of olanzapine for CINV.

We conducted an open-label, single-center, single-arm Phase II study to evaluate the efficacy of olanzapine in combination with standard antiemetic therapy in preventing CINV in patients with thoracic malignancy receiving their first cycle of cisplatin-based chemotherapy.

MATERIALS AND METHODS

Eligible patients were 20 years of age or older with histologically or cytologically confirmed thoracic malignant disease who were scheduled to receive first-course cisplatin (≥ 60 mg/m^2) combination therapy.

Enrolled patients received standard antiemetic therapy and olanzapine. Palonosetron was intravenously administered at a dose of 0.75 mg 30–60 min prior to chemotherapy administration on day 1. Aprepitant was orally administered at a dose of 125 mg 60–90 min prior to chemotherapy administration on day 1 and at a dose of 80 mg on days 2 and 3. Dexamethasone was intravenously administered at a dose of 9.9 mg 30–60 min prior to chemotherapy administration on day 1 and was then orally administered at a dose of 8 mg on days 2–4. Olanzapine was orally administered at a dose of 5 mg once per day at night on days 1–5.

The primary endpoint was complete response (CR: no vomiting and no use of rescue therapy) during the overall phase (0–120 h post-chemotherapy). Secondary endpoints were CR rates in the acute (0–24 h post-chemotherapy) and delayed (24–120 h post-chemotherapy) phases and rates of complete control (CC; no vomiting, no rescue, no significant nausea), total control (TC: no vomiting, no rescue, no nausea), and adverse events in the acute, delayed, and overall phases. We set the threshold overall CR rate at 65% and the expected CR rate at 85% for the present study. To reach 5% (one-sided) significance and 80% statistical power, we calculated that a minimum sample size of 28 patients was required. Assuming a 10% exclusion rate, the planned sample size was 30 patients.

The institutional review board of Shizuoka Cancer Center approved the design of this study. All enrolled patients provided written informed consent.

RESULTS AND DISCUSSION

Thirty patients with thoracic malignancy were enrolled from May 2015 through October 2015. The median age was 64 years (range: 36–75 years). The most common chemotherapy regimen was 75 mg/m^2 cisplatin and 500 mg/m^2 pemetrexed, which was administered to 14 patients.

The overall phase CR rate (primary endpoint) was 83% (90% confidence interval: 70–92%; 95% confidence interval: 66–93%). CR rates for the acute and delayed phases were 100% and 83%, respectively. In the acute, delayed, and overall phases, CC rates were 93%, 73%, and 70%, respectively, and TC rates were 77%, 70%, and 63%, respectively.

There were no Grade 3 or Grade 4 adverse events. Although four patients (13%) experienced Grade 1 somnolence, no patients discontinued olanzapine.

The 83% CR rate observed during the overall phase met the primary endpoint, and the lower limit of the 90% confidence interval for the overall phase CR rate was 70%, suggesting that the addition of 5 mg oral olanzapine to standard antiemetics may reduce CINV in patients

with thoracic malignancy receiving cisplatin-based chemotherapy. The secondary endpoints and safety profiles were also favorable in this study.

Navari et al. reported the results of a phase III trial that evaluated the additional efficacy of 10 mg oral olanzapine for the prevention of CINV in patients receiving their first course of HEC. The proportion of patients who reported no nausea and the CR rates were significantly higher in the olanzapine arm compared with the placebo arm. However, sedation was observed more frequently in patients receiving olanzapine compared with those receiving placebo. The optimal dose of olanzapine for CINV may be 5 mg, considering efficacy and safety.

The present study has several limitations. First, it was a small single-arm study (n = 30) conducted at a single institution. Second, this study was conducted only in subjects with thoracic malignancy. Therefore, a phase III study to verify the efficacy and safety of 5 mg oral olanzapine with standard triplet antiemetic therapy is under contemplation.

CONCLUSIONS

The addition of 5mg oral olanzapine to standard antiemetic therapy demonstrates promising efficacy in preventing cisplatin-based CINV and an acceptable safety profile in patients with thoracic malignancy.