Original Article

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients Receiving Highly or Moderately Emetogenic Chemotherapy: A Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

Context. Chemotherapy-induced nausea and vomiting (CINV) can severely impair patients' quality of life (QOL). Psychotropics, especially olanzapine, have a strong antiemetic effect.

Objectives. To determine whether olanzapine could reduce the frequency of CINV and improve patients' QOL during chemotherapy.

Methods. This was a randomized, double-blind, placebo-controlled trial. Forty-four patients scheduled to receive highly or moderately emetogenic chemotherapy were enrolled. All patients received a 5-hydroxytryptamine$_3$ receptor antagonist, steroid, and neurokinin-1 receptor antagonist. Patients were randomly assigned to take 5 mg/day of oral olanzapine (OL group, $n = 22$) or placebo (control group, $n = 22$) daily from the day before chemotherapy (Day 0) to Day 5. The primary endpoint was the rate of patients who achieved total control (no vomiting, no use of rescue medications, and maximum nausea of <5/100 mm on a visual analogue scale). The secondary endpoint was Functional Living Index-Emesis questionnaire score on Days 0 and 6.

Results. The rate of patients achieving total control was significantly higher in the OL group (86% and 64% in acute and delayed phases, respectively) than in the control group (55% and 23%, $P = 0.045$, $P = 0.014$, respectively). Furthermore, the OL group experienced a better QOL than the control group, as reported on the Functional Living Index-Emesis questionnaire ($P = 0.0004$).

Conclusion. The addition of 5 mg/day of oral olanzapine to standard therapy can reduce the frequency of CINV and improve QOL of patients receiving highly or moderately emetogenic chemotherapy. J Pain Symptom Manage 2014;47:542–550.

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Key Words
Olanzapine, chemotherapy-induced nausea and vomiting, delayed emesis, FLI-E, appetite improvement

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is known to be one of the major adverse effects of cancer therapy. A patient's quality of life (QOL) can be severely impaired by CINV, which causes dehydration, aspiration pneumonia, and malnutrition. CINV can be controlled by the prophylactic use of antiemetic drugs. Because several types of receptors in the supraspinal central nervous system are related to CINV, combination therapy with a 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist and corticosteroid is able to significantly improve the treatment of CINV.[1] Recent studies have demonstrated that the neurokinin-1 (NK-1) receptor antagonist, aprepitant, is also effective for the prevention of CINV by another mechanism.[2] Therefore, the current standard therapy for CINV in highly emetogenic chemotherapy (HEC) is the combination of a 5-HT$_3$ receptor antagonist, NK-1 receptor antagonist, and corticosteroid, according to the American Society of Clinical Oncology guidelines.[3] Use of this three-drug combination therapy has clearly decreased the incidence of CINV in the acute phase. For example, among patients receiving high-dose cisplatin, the rate of patients who achieved complete response (no vomiting and no use of rescue medications) was 89.2% in the acute phase.[4] However, it is still difficult to prevent CINV induced by HEC or moderately emetogenic chemotherapy (MEC) in the delayed phase (24−120 hours after the initiation of chemotherapy). The mechanism underlying the discrepancy in antiemetic effects between the acute and delayed phases is not clearly understood,[5,6] and improvement of CINV in the delayed phase remains an important problem to be solved.

Olanzapine is widely used as an antipsychotic drug for patients with schizophrenia and intractable depression. In the supraspinal region, olanzapine inhibits the release and/or binding of multiple neurotransmitters with their specific receptors: dopamine at D_1, D_2, D_3, and D_4 brain receptors, serotonin at 5-HT$_{2a}$, 5-HT$_{2c}$, 5-HT$_3$, and 5-HT$_6$ receptors, catecholamines at alpha adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H_1 receptors.[7,8] The antiemetic effects of antipsychotics are well known in palliative medicine.[9] Olanzapine, in particular, is expected to be a highly effective antiemetic drug because it is involved in a variety of neuromodulative mechanisms affecting 5-HT$_2$, 5-HT$_3$, and D_2 receptors. There are some previous reports on the effects and safety of olanzapine for treating CINV. Pirl and Roth[10] and Passik et al.[11] reported the antiemetic effects of olanzapine which was used singly. Passik et al. and Navari et al. reported the safety and positive effects of olanzapine as an antiemetic drug for CINV, especially in the delayed phase.[12−14] The addition of olanzapine to dexamethasone and the 5-HT$_3$ antagonist palonosetron has been shown to be safe and highly effective for controlling acute- and delayed-phase CINV in patients receiving HEC and MEC.[15] However, it is still unknown whether adding olanzapine to the current standard antiemetic therapy for CINV could reduce the incidence and severity of CINV.

We hypothesized that adding olanzapine to the other antiemetic drugs could further decrease the incidence of CINV and improve patients' QOL. The purpose of this study was to determine the effects of the addition of olanzapine to standard antiemetic therapy for CINV after HEC and MEC by using a randomized double-blind method. We estimated the incidence of CINV by objectively measuring its frequency and estimated the severity of CINV using a patient-subjective scale.

Methods

Patients

This double-blind, randomized, controlled clinical trial was conducted at two hospitals from June 15, 2010, to August 30, 2012. The study protocol was reviewed and approved by an independent ethics committee (No. 21-141, April 23, 2010) or institutional review