

MINI-REVIEW

Olanzapine for Preventing Nausea and Vomiting Induced by Moderately and Highly Emetogenic ChemotherapyShi-Yong Wang^{1*}, Zhen-Jun Yang², Lu Zhang¹**Abstract**

Nausea and vomiting are common adverse events in chemotherapy. In spite of the serious effects on the quality of life and further treatment, they remain overlooked by physicians, and no standard treatment has been developed. Neurokinin-1 (NK-1) receptor antagonists and palonosetron are the major agents in the standard regimen for treating moderately and highly emetogenic chemotherapy-induced nausea and vomiting (CINV). However, NK-1 receptor antagonists first became commercially available at the end of 2013 and palonosetron has not been extensively applied in China. Olanzapine was recommended as a therapy for moderate and severe CINV in antiemesis-clinical practice guidelines in oncology in 2014 for the first time. It is an atypical antipsychotic agent, which can block multiple receptors on neurotransmitters. During more than 10 years, olanzapine has demonstrated significant effects in preventing CINV and treating breakthrough and refractor CINV, which was observed in case reports, precise retrospective studies, and phase I, II and III clinical trials, with no grade 3 to 4 adverse events. In particular, it is superior to aprepitant and dexamethasone in delayed nausea and vomiting. Therefore, this compound is worthy of further investigation.

Keywords: Olanzapine - chemotherapy-induced nausea and vomiting - malignant neoplasm - clinical trials

Asian Pac J Cancer Prev, 15 (22), 9587-9592

Introduction

In the 1970s, developed countries represented by the United States put forward a definite anti-cancer strategy, including patient registry, education, screening, study and comprehensive treatment. As a result, the total incidence of cancer in these western countries decreased (Moore et al., 2014; Siegel et al., 2014). However, in developing countries such as China, the incidence of malignant tumors is on the rise. According to the annual report published in January 2014, the Chinese new cancer incident cases and deaths were 3,093,039 and 1,956,622 in 2010, and are estimated to increase to 6 and 4 million in 2020, respectively (Chen et al., 2014). In addition, it is forecasted that global new cancer cases will peak to 20 million by 2030 with total deaths reaching 12.9 million (Daher, 2012). Thus, cancer will remain a leading disease, threatening humans in the future. In the 21st century, as small-molecule targeted therapy (Li et al., 2014), monoclonal antibodies (Sliwkowski and Mellman, 2013), immunotherapy (Copier et al., 2011; Ito and Chang 2013) and anti-angiogenesis methods (Walti et al., 2013) are gradually applied, with considerable cancer-related clinical trials conducted, cancer treatment becomes more and more standardized. However, due to lack of effective early diagnostic methods, most malignant neoplasms are diagnosed in advanced stage and therefore unsectable;

chemotherapy remains a major therapeutic approach to improve cancer prognosis and cure (Hassan and Yusoff, 2010; Uchino et al., 2012; Janelins et al., 2013; NCCN., 2014). However, the primary regimen often has to be adjusted or even discontinued due to adverse events, with the chemotherapy-induced nausea and vomiting (CINV) being the most common one, which not only greatly increases the economic burden (Keat and Ghani, 2013) but also produces dehydration, electrolyte disturbance, sub-nutrition, anorexia, weight loss, hypodynamia, sleep deficit, esophageal laceration, and massive hemorrhage, which seriously reduce patients' quality of life (QoL) and are even life-threatening. These limitations hamper the progress of chemotherapy (Hassan and Yusoff, 2010; Uchino et al., 2012; Janelins et al., 2013).

The National Comprehensive Cancer Network (NCCN) and Multinational association of supportive care in cancer (MASCC) have formulated and revised the CINV antiemetic guidelines several times (Roila et al., 2010). In China, the antiemetic guidelines were also published in 2014. However, because of cognition deficiency by physicians and the affordability of antiemetic drugs, the antiemetic treatment is extremely variable. In these guidelines, combination of Neurokinin-1 (NK-1) receptor antagonist or 5-hydroxytryptamine₃ (5-HT₃) antagonist and dexamethasone is recommended as standard regimen for moderate and severe CINV

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(Hassan and Yusoff, 2010). However, the NK-1 receptor antagonist is new on the Chinese market and the second 5-HT₃ antagonist, palonosetron, is too expensive and not assigned for medical insurance. In China, the two agents are not extensively applied. Fortunately, NCCN recommended another regimen containing olanzapine, an ancient psychiatric drug, in NCCN 2014. The regimen is superior to the standard one containing aprepitant in efficacy, especially for delayed nausea (Navari et al., 2011; Brafford and Glode, 2014; Flank et al., 2014; Hocking and Kichenadasse, 2014; Wang et al., 2014), and should be spread in developing countries. However oncological physicians know little about olanzapine's effect on CINV prevention. There is no literature available introducing it systematically. There are two articles published in 2014 (Brafford and Glode, 2014; Flank et al., 2014), which only gave a brief introduction. This paper reviewed the progression of olanzapine for the prevention of CINV as well as its mechanism in detail.

Early Case Reports, Clinical Trials and Retrospective Study

It is not by coincidence that olanzapine is used as an antiemetic agent. Indeed, antipsychotic agents have been used to treat nausea for a long time. Interestingly, benzodiazepine class compounds such as lorazepam and alprazolam can prevent nausea in chemotherapy (Navari, 2014). In addition, phenothiazine, haloperidol and metoclopramide can treat nausea. However, they act by blocking dopamine 2 receptor (D₂ receptor), thereby inducing extrapyramidal symptoms such as akathisia, dystonia and tardive dyskinesia. Fortunately, these symptoms are decreased with recent atypical antipsychotic agents such as clozapine and olanzapine, which display reduced binding ability with D₂ receptor. Olanzapine is mainly used for schizophrenia, manic psychosis and bipolar affective disorders (McIntyre et al., 2013). This drug was used to treat CINV for the first time in 2000 by the psychiatrist Pirl (2000) at the Massachusetts General Hospital (USA). He treated a female patient with acute lymphocytic leukemia who had a history of depression and anxiety but had not been hospitalized for treatment. Prior to and following chemotherapy, the patient presented with severe psychic symptoms, accompanied with nausea and vomiting. Various antiemetic regimens, including ondansetron or granisetron plus dexamethasone, and antipsychotic agents, including lorazepam, perphenazine and fluoxetine, were poorly efficacious, with severe extrapyramidal symptoms. When 5mg olanzapine was administered before bedtime, psychic and gastrointestinal symptoms were significantly improved. Therefore, more research is needed to determine if olanzapine can be used as an effective antiemetic medication.

In 2002, Passik et al (2002) conducted a small clinical trial in 15 patients with advanced cancer requiring opioid analgesics, accompanied with moderate nausea, but no vomiting. The subjects received 2 days of washout and placebo "run-in" followed by 2 day periods of treatment with olanzapine (2.5, 5, and 10mg, respectively). Three days prior to experiment, parameters were recorded as the

baseline data. All 3 olanzapine doses were associated with significant reduction in nausea compared to baseline. In addition, substantial benefits to quality of life, especially in the 5mg group, were obtained. No extrapyramidal symptoms were observed.

In 2003, Passik et al (2003) and colleagues carried out a retrospective study and identified 28 patients with olanzapine for the prevention of delayed emesis from the 95 cancer patients evaluated. Eleven patients (39.3%) had at least one instance of nausea recorded while undergoing olanzapine treatment and seven (25%) showed an episode of vomiting. During a total 95 cycles of chemotherapy, 21 incidents of nausea (22.1%) and 10 instances of vomiting (10.5%) were recorded, and adverse events were rarely observed. These data suggest that olanzapine could be used to treat CINV. The authors then recommended relevant clinical trials.

Phase I Clinical Trials

In 2004, Passik and collaborators (2004) reported results of a phase I clinical trial, based on a previous small clinical trial and retrospective study. This study used a 4-cohort dose escalation (2.5, 5.0, 7.5 and 10mg) with 3 to 6 patients per cohort. All patients received standard therapy for the prevention of nausea and vomiting. Olanzapine was administered at 5mg daily for 2 days prior to chemotherapy and continued with 10mg for 8 days (d 0-7). Fifteen patients completed the study. No grade 4 toxicities were observed, while 3 patients experienced grade 3 depression. The maximum tolerated dose (MTD) appeared to be 5mg (for days -2 and -1) prior to chemotherapy and 10mg during chemotherapy (for d0-7). Four of 6 patients receiving highly emetogenic chemotherapy and the nine patients receiving moderately emetogenic chemotherapy all reached complete response (CR) (no vomiting episodes). In 2013, Yuan (2013) performed another phase I clinical trial in China, with a slightly different design. This study enrolled 18 patients who received olanzapine the night before chemotherapy combining granisetron (3mg) and dexamethasone (10mg), administered on days 1 to 3. The limiting dose was identified by grade 3 adverse events (CTC-AE 4.0) and the MTD was determined by the presence of grade 3 adverse events in 2 of the 6 patients in the same group. Patients were divided into 6 cohorts of 3 according to olanzapine doses (2.5, 5, 7.5, 10, 15 and 20mg). The cohort could be expanded to 6 evaluable patients if a dose-limiting toxicity (DLT) was not observed with the first dose cohort among the initial 3 patients. If two DLT were observed in the same dose cohort, dose-escalation was halted and a lower dose was assessed until the MTD was determined. In the absence of DLT, the dose was escalated until 20mg. With the 15mg dose, one of the initial 3 patients reported grade 3 dry mouth and 1 individual reported grade 3 somnolence among the subsequent 3 patients. Therefore, this dose was not escalated. Grade 2 and above adverse events included somnolence, dizziness, akathisia, dry mouth, constipation, fatigue and bone marrow suppression. The incidence of somnolence was 56% (compared to 0, 67 and 100% obtained for 2.5, 5, and 7.5mg doses, respectively).

The incidence of 50% obtained for akathisia with 2.5mg dose did not increase with drug dose. Interestingly, body weights increased by day 15 with 2.5, 5 and 7.5mg doses, and at days 7 when patients were treated with 10 and 15mg of drug. Fasting blood glucose was stable. Overall, olanzapine is well tolerated by Chinese cancer patients, with a MTD of 15mg and recommended dose of 10mg.

Phase II Clinical Trials

Navari et al reported two phase II clinical trials, respectively in 2005 and 2007, both with olanzapine, 5-HT₃ antagonist and dexamethasone, but differing in the design and administration route (Navari et al., 2005; Navari et al., 2007): specifically, the 5-HT₃ antagonists used were granisetron and palonosetron in 2005 and 2007, respectively; olanzapine (5mg per day) was administered 2 days prior to chemotherapy in 2005, 2 days later than in the 2007 regimen; in 2007, dexamethasone was only used the day of chemotherapy, at a dose of 8mg in the moderately emetogenic chemotherapy (Table 1).

CR of vomiting was more than 72 % in acute, delayed and overall (d1-5) periods, and 5-13% higher in 2005 in comparison with the 2007 study. Among patients receiving highly emetogenic chemotherapy, the control rate of nausea was 100% in all periods in 2005; this rate was 100% in the acute period, but only 50% in delayed and overall periods in 2007. Among patients receiving moderately emetogenic chemotherapy, control rates of nausea were 13 to 15% higher in 2007 compared with 2005. These results supported the idea that single oral palonosetron is unable to control delayed nausea and vomiting, especially in patients receiving highly emetogenic chemotherapy. More frequent administrations of palonosetron or combination with olanzapine (days 2 to 5) should be considered. In both trials, no grade 3 to 4 adverse events were reported, and no significant difference in the effect on nausea and vomiting during multiple chemotherapy cycles were observed between both regimens.

Phase III Clinical Trials

Chinese scientists published a phase III clinical trial in 2009 when palonosetron was just made available, with NK-1 antagonist not yet found on the Chinese market (Tan et al., 2009). In this trial, the 2-agent (5-HT₃

Table 1. Comparison between the Antiemetic Regimens of the Two Phase II Clinical Trials

Antiemesis regimen	Prior to and Following the Chemotherapy		
	d-2,-1	d1	d2-4
2005			
Olanzapine	5mg	10mg	10mg
Granisetron		10µg/kg	
Dexamethasone		20mg	d2-3,8mg bid;d4,4mg bid
2007			
Olanzapine		10mg	10mg
Palonosetron		0.25mg	
Dexamethasone		20mg(HEC);8mg(MEC)	

*HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; d-2,-1, two days prior to chemotherapy; d1, the day of chemotherapy; d2-4, 3 days following chemotherapy (days 2, 3 and 4)

antagonist plus dexamethasone) and 3-agent (olanzapine, 5-HT₃ antagonist plus dexamethasone) regimens were compared. A total of 229 patients receiving highly or moderately emetogenic chemotherapy were randomly assigned to the test group (olanzapine 10mg *p.o.* plus azasetron 10mg *i.v.* and dexamethasone 10mg *i.v.* at day 1; daily olanzapine 10mg at days 2-5) or the control group (azasetron 10mg *i.v.* and dexamethasone 10mg *i.v.* at day 1; daily dexamethasone 10mg *i.v.* at days 2-5). All patients filled the observation table daily from day 1 to 5 and QoL questionnaire (EORTC QLQ-C30) at days 0-6. The primary endpoint was CR of vomiting. The secondary endpoints were QoL during chemotherapy administration, drug safety and toxicity.

Compared with the control group, the CR of acute nausea and vomiting in the test group was not statistically different (>87%), but the CR for delayed nausea and vomiting improved by 39.21 and 22.05%, respectively, in patients with highly emetogenic chemotherapy, and 25.01 and 13.43% in patients with moderately emetogenic chemotherapy, respectively (Table 3). However, compared with the 2005 phase II clinical trial, which also used the first-generation 5-HT₃ receptor antagonist, CR of acute nausea and vomiting was reduced by around 10% and CR values for delayed nausea and vomiting were even lower, with only 69.64% (100% in 2005, Table 2). In this case, dexamethasone was increased to 20mg at day 1, and dexamethasone and olanzapine could be added at days 2 to 5. Dexamethasone may generate some adverse effects such as insomnia (45%), indigestion/epigastric discomfort (27%), agitation (25%), increased appetite (19%), weight gain (17%), acne (15%), discontinued treatment of depression (7%) and dental ulcer (3%) (Vardy et al., 2006). The above neuropsychical symptoms including insomnia and agitation might be partially relieved with combined olanzapine, which deserves further investigation. In addition, in the phase III clinical trial (Tan et al., 2009), in spite of patients having received chemotherapy, olanzapine did not induce obvious grade 3 to 4 toxic effects, with the major adverse event of somnolence. Of note, QoL parameters such as global health status, emotional function, social function, fatigue,

Table 2. Comparison of Complete Response of Nausea and Vomiting of the Two Phase II Clinical Trials (%)

Periods (h)	2005		2007	
	HEC(N=10)	MEC(N=20)	HEC(N=8)	MEC(N=32)
Vomiting control				
Acute (0-24)	100	100	100	97
Delayed (24-120)	80	85	75	75
Overall (0-120)	80	85	75	72
Nausea control				
Acute (0-24)	100	85	100	100
Delayed (24-120)	100	65	50	78
Overall (0-120)	100	65	50	78

Table 3. Comparison of Complete Response of Delayed Nausea and Vomiting in the Phase III clinical Trial (%)

Groups	Delayed Nausea		Delayed Vomiting	
	HEC	MEC	HEC	MEC
TG	69.64	83.07	78.57	89.23
CG	30.43	58.06	56.52	75.8

*TG, test group; CG, control group

insomnia and appetite, were significantly improved in the test group ($p < 0.01$).

In 2011, Navari et al (2011) carried out a phase III clinical trial to compare the effectiveness of olanzapine and aprepitant in preventing CINV in patients receiving highly emetogenic chemotherapy. A total of 241 chemotherapy-naïve patients were randomly assigned to the olanzapine and aprepitant groups, respectively. In the olanzapine group, the regimen was 10mg of oral olanzapine, 0.25mg of IV palonosetron, and 20mg of IV dexamethasone on pre-chemotherapy at day 1, and 10mg/day of oral olanzapine alone at days 2-4 following chemotherapy. In the aprepitant group, the regimen was 125mg of oral aprepitant, 0.25mg of IV palonosetron, and 12mg of IV dexamethasone at day 1, 80mg of oral aprepitant at days 2 and 3, and 4mg of dexamethasone bid. at days 2-4. The primary endpoint was CR of vomiting and nausea. Results are shown in Table 4.

Compared with the aprepitant group, CR of vomiting was increased by 10, 4 and 4% in the acute, delayed and overall periods, while CR of nausea was increased insignificantly in the acute period, but by 31% in both delayed and overall periods. In the first phase III clinical trial assessing olanzapine in 2009, CR of vomiting were 91.07, 78.57 and 78.57% in the acute, delayed and overall periods; CR of nausea were 94.64, 69.64 and 69.64% in the acute, delayed and overall periods, similar to the outcomes obtained for the olanzapine group in the present study (Tan et al., 2009). Interesting data were obtained in two international, multi-center and large-scale studies evaluating aprepitant in 2003 (Hesketh et al., 2003; Poli-Bigelli et al., 2003): in the aprepitant group (aprepitant, ondansetron and dexamethasone) and standard-control group (ondansetron and dexamethasone), CR of vomiting in the acute, delayed and overall periods were 89.2, 75.4 and 72.7% vs 82.8, 67.7 and 62.7%, respectively, and CR of nausea were 72.3, 51.0 and 47.5% vs. unknown, 53 and 49%, respectively. These results were similar to those obtained for the aprepitant group (Table 4), demonstrating the definitive and stable efficacy of olanzapine and aprepitant in CINV. The results obtained in these trials were highly reproducible and credible, further confirming the benefit of olanzapine in delayed nausea. However, CR of olanzapine for delayed nausea was only 69%. In the present study, olanzapine was administered alone at days 2 to 5 after chemotherapy initiation; most likely, CR of nausea might be improved if dexamethasone was added like in the 2005 clinical study (Table 1 and 2). And again, CR of delayed nausea for olanzapine and aprepitant were only 51-53% in the above 2 large-scale marketing

studies on aprepitant (Hesketh et al., 2003; Poli-Bigelli et al., 2003).

The international standard 3-agent antiemetic regimen for prevention of moderately and highly CINV contains NK-1 receptor antagonist, 5-HT₃ antagonist and dexamethasone, which show a satisfactory effect on acute-but poor on delayed vomiting. Therefore, since olanzapine has shown satisfactory antiemetic effect, especially on delayed nausea, a combined therapy with olanzapine and the above 3 drugs were assessed. In 2013, Mizukami et al (2013) reported a randomized, double-blind and placebo-controlled phase III clinical trial on a novel regimen containing 4 agents. A total of 44 patients were assigned into the 3-drug standard and test groups, respectively. In the test group, 5mg olanzapine was added at days 1 to 5 to the 3-drug standard regimen (NK-1 receptor antagonist, 5-HT₃ antagonist and dexamethasone). Interestingly, CR of vomiting in the acute, delayed and overall periods reached 100% in the test group, and 86, 73 and 68% in the 3-drug standard group, respectively. These data indicated that CR in the delayed and overall periods were increased by 27-32% in the test group compared with the standard group ($P < 0.05$); in addition, the FLI-E score was also significantly improved ($P = 0.0004$). The incidences of delayed nausea were 0 and 20% in the test and standard groups, respectively ($P = 0.0036$). These results suggested the efficacy of the 4-agent regimen and usefulness of olanzapine in combination with dexamethasone in delayed nausea and vomiting.

Olanzapine in Breakthrough CINV

The treatment of breakthrough nausea and vomiting is difficulty in CINV and no effective regimen is recommend in the NCCN 2014 antiemetic guidelines, except for adding one or multiple unused antiemetic agents. In 2013, a very valuable double-blinded and randomized phase III clinical study was conducted with chemotherapy-naïve patients (Navari et al., 2013). The antiemetic regimen was the standard 3-drug regimen containing fosaprepitant, 5-HT₃ antagonist and dexamethasone. Among 280 patients receiving highly emetogenic chemotherapy containing cisplatin, those who developed breakthrough emesis or nausea were randomized to receive olanzapine, 10mg daily oral doses for 3 days, or metoclopramide, 10mg orally, tid. for 3 days. During the 72-h observation period, 39 out of 56 (70%) patients receiving olanzapine showed no emesis, while only 16/52 (31%) patients with no emesis were obtained in the group receiving metoclopramide ($p < 0.01$). In addition, 68% patients administered olanzapine showed no nausea (0, scale 0-10, M.D. Anderson Symptom Inventory) during the 72-h observation period, while metoclopramide treatment resulted in 23% (12 of 52) such patients. These data suggested olanzapine to be excellent in controlling and treating breakthrough emesis and nausea. Further analysis indicated that by adding CR of breakthrough nausea and vomiting obtained with olanzapine to the initial CR of CINV, the resulting CR of delayed nausea and vomiting might reach 85.23%, i.e. an increase of 16% compared to the 69% obtained for olanzapine alone in the

Table 4. Comparison of the Results between Olanzapine and Aprepitant Groups (%)

Groups	Following The Chemotherapy		
	d1	d2-5	d1-5
Vomiting control			
OLA (N=121)	97	77	77
APR (N=120)	87	73	73
Nausea control			
OLA (N=121)	87	69	69
APR (N=120)	87	38	38

*OLA, olanzapine; APR, aprepitant

aforementioned phase III clinical study (Tan et al., 2009). These findings further demonstrated that olanzapine in combination with dexamethasone might be beneficial for delayed CINV.

Olanzapine in Refractory CINV

In 2014, Vig et al (2014) reported therapeutic results of olanzapine in 33 patients with refractory CINV. These subjects were screened from 85 patients (January 2008 to January 2012) receiving antiemetic regimen as recommended in NCCN 2013. They developed breakthrough CINV and had been given dopamine 2 receptor antagonist and benzodiazepine. CR was 65-70% in patients with at least one single dose of 10mg olanzapine except for those with nausea and vomiting by other causes, and was not correlated to previous chemotherapy, antiemetic regimen and age. The study further expanded the indications of olanzapine from prevention of emesis and treatment of breakthrough CINV to treatment of refractory chemotherapy-related CINV. No common olanzapine-related adverse events were noted.

Prospects

Olanzapine is an atypical antipsychotic agent, which can block multiple receptors on neurotransmitters. During the 10 years since the occasional CINV treatment, olanzapine has been described with significant effects on CINV prevention and treatment of breakthrough and refractory CINV by phase I,II and III clinical trials as well as retrospective studies, with no grade 3 to 4 adverse event. In addition, NK1 receptor antagonist and palonosetron have not been extensively applied in China. Combining our study (wang et al., 2014) and the NCCN 2014 antiemetic guidelines, olanzapine should be recommended for the treatment of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, as follows: for single-day chemotherapy, olanzapine 10mg, 5-HT3 antagonist and dexamethasone 20mg should be administered at day 1, followed by olanzapine 10mg in combination with dexamethasone 10mg for 2 to 3 additional days; for a 3-day chemotherapy, olanzapine 10mg, 5-HT3 antagonist and dexamethasone 20mg should be given at days 1-3, followed by olanzapine 10mg in combination with dexamethasone 10mg for 4 to 6 additional days. Nevertheless, no clinical trial has been carried out to support the combination regimen with olanzapine for the treatment of CINV in multi-day chemotherapy; consequently, special attention should be paid to this regimen.

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