Effectiveness of Olanzapine for the Treatment of Breakthrough Chemotherapy Induced Nausea and Vomiting

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Objective: *To evaluate safety and efficacy of olanzapine for breakthrough emesis in addition to standard antiemetic regimen in cancer patients receiving highly emetogenic chemotherapy.*
Material and Method: *A phase II prospective open label clinical trial was conducted in tertiary care based hospital. Forty-six cancer patients diagnosed with solid tumors were enrolled to receive at least one cycle of highly emetogenic chemotherapy (HEC) every two to four weeks. Each patient was provided standard antiemetic consisting of the generic form of ondansetron plus corticosteroids and metoclopramide according to clinical practice guideline. Olanzapine was administered as 5 mg orally every 12 hours for two doses in patients experiencing breakthrough emesis for at least one episode despite standard prevention. The efficacy and tolerability were evaluated every six hours for 24 hours (utilizing Index of Nausea, Vomiting and Retching: INVR tool).*
Results: *Of 46 evaluable patients receiving HEC and additional olanzapine between September 2009 and July 2010, the complete response of breakthrough emesis, retching, and nausea control among patients were 60.9%, 71.7%, and 50.0%, respectively. Adverse events reported were mild and tolerable including dizziness, fatigue, and dyspepsia.*
Conclusion: *Olanzapine is considered to be safe and effective treatment of breakthrough vomiting in cancer patients undergoing highly emetogenic chemotherapy in the present study.*

Keywords: *Olanzapine, Chemotherapy induced nausea and vomiting, Breakthrough vomiting, Ondansetron, Metoclopramide, Dexamethasone*

J Med Assoc Thai 2014; 97 (3): 349-55
Full text. e-Journal: *http://www.jmatonline.com*

Nausea and vomiting is the most notorious adverse drug reaction (ADR) and hardly inevitable when treating cancer patients with antineoplastic drugs. Inadequate or ineffective antiemetics may result in poor emesis control. The major consequence of uncontrolled chemotherapy induced nausea and vomiting (CINV) could affect quality of life among cancer patients[1,2]. Several international oncology associations have developed standard practice guidelines for prevention and treatment of CINV in cancer patients undergoing treatment with highly emetogenic chemotherapy (HEC). Dexamethasone in combination with 5-HT_3 receptor antagonist and aprepitant (triple therapy) have been successfully implemented as standard therapy for emesis controlled[3-5]. Nonetheless, a number of patients are still suffering from uncontrolled CINV despite having received the standard triple therapy[6]. In addition, the use of novel second generation 5-HT_3 receptor antagonist, palonosetron, and neurokinin-1 (NK_1) antagonist, aprepitant, as a component of standard treatment might not be accessible in many patients due to their socioeconomic status.

Among several alternative agents investigated, olanzapine (atypical antipsychotics) has shown its efficacy in controlling of CINV from various evidences. The mechanism of action of olanzapine is to inhibit several neurotransmitters including dopamine, and serotonin that involve in the etiology of emesis. In addition, olanzapine possess a high affinity on several types of receptors including muscarinic, cholinergic, adrenergic and histamine, which possibly increase its effectiveness in controlling of nausea and vomiting[6-12]. In 2011, Navari et al conducted a randomized, phase III study with 241 naïve patients who had been treated with HEC to compare the effectiveness of additional of aprepitant in 120 patients versus olanzapine in 121 patients for prevention of CINV.

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Both groups received palonosetron in combination with dexamethasone to prevent acute and delayed CINV. The result demonstrated that patients who received olanzapine reporting a comparable complete response (CR) to those of patients receiving aprepitant. There were no serious adverse effects reported[13]. Based on the Navari study, olanzapine is considered to be an effective agent in the prevention of acute and delayed vomiting and could be considered as an alternative regimen when standard antiemetic is not warranted.

As we gain more evidences to support the use of olanzapine in controlling acute and delayed CINV, the evidence of olanzapine in the treatment of breakthrough CINV is still minimal. This is pilot study to evaluate the efficacy and safety of olanzapine for the treatment of breakthrough CINV in cancer patients treated with HEC in Thai hospital based setting.

Material and Method

Patient selection

Eligibility criteria included patients aged older than 18 years who were diagnosed with cancer treated with HEC. Other criterion included no nausea or vomiting for at least 24 hours prior to the treatment with chemotherapy, ECOG performance status ≤2, serum creatinine of <1.5 mg/dl, bilirubin of ≤2 mg/dl, SGOT or SGPT ≤ three times of the upper limit normal, absolute neutrophil count of ≥1,500 mm^3, platelets of ≥100,000 cells/mm^3, hemoglobin level of >10 g/dL, and hematocrit of >30%. Patients who had failed on standard antiemetic in prevention of CINV as defined by at least one episode of vomiting were recruited into the study.

Ineligible criteria included patients with severe cognitive compromise, history of central nervous system disease (such as epilepsy, brain metastasis), prior abdominal radiotherapy at the time of study, history of chronic alcoholism, history of cardiac arrhythmia, history of chronic heart failure or acute myocardial infarction within six months, history of diabetes with HbA1c level greater than 10%, or fasting blood sugar (FBS) greater than 180 mg/dL, unable or refused to cooperate in the evaluation form of nausea and vomiting, or were pregnant or breastfeeding at time.

All patients were obtained written informed consent. The present clinical study was approved by the Khon Kaen University Ethics Committee for Human Research based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines.

Study design and treatment regimen

This was a phase II prospective open labeled clinical trial conducted between November 2009 and July 2010. All eligible patients were treated with the institutional standard prevention for CINV prior to HEC therapy. The institutional standard regimen consisted of generic form ondansetron 24 mg IV BID and dexamethasone 10 mg IV BID on day 1. Oral metoclopramide 10 mg TID plus dexamethasone 10 mg BID were given on day 2 to 4. Oral olanzapine 5 mg tablet was given to patients who failed on standard prevention of CINV (breakthrough) within 30 minutes after the first vomiting episode. Another dose of olanzapine was given at 12 hours following the first dose concurrently with standard prevention regimen. If patient failed to respond from olanzapine therapy, lorazepam 0.5 to 2 mg oral every four to six hour as needed would be added as a rescue medication.

Study visits and assessment procedures

The investigators recorded patient information, including demographic data (gender, age, weight, height, body surface area) and medical data [diagnosis, ECOG performance status, risk factors for CINV (age, histories of nausea or vomiting, alcohol drinking, motion sickness, nausea and vomiting during pregnancy, CINV in the previous cycle, and anxiety or stress conditions)]. Information on chemotherapy administration, antiemetic regimen and other drug use was also documented. CINV in patients was evaluated by utilizing the Index of Nausea, Vomiting and Retching (INVR tool) every 12 hours. The INVR constitutes a 5-point Likert-type scale to address the frequency and distress associated with all three symptoms: nausea, vomiting, and retching episodes in the previous 12 hours for real-time symptom management[14].

Patient with breakthrough emesis were followed up after receiving olanzapine treatment every six hours for 24 hours. The frequencies of vomiting, nausea, and retching were recorded. The olanzapine treatment responses were classified as complete response (no vomiting), partial response (1 vomiting episode), minor response (2-4 vomiting episodes) and failure (>4 vomiting episodes) respectively.

Adverse drug reactions were evaluated by using the Naranjo's algorithm to estimate the occurrence probability. The severity of ADR assessed as defined by Common Terminology Criteria for Adverse Events version 4.03 (CTCAE V.4.03)[15]. Patient who had refractory vomiting (failure response)

despite being treated with olanzapine were given lorazepam 0.5 to 2 mg oral every six hours as a rescue medication in addition to previous standard antiemesis.

Statistical analysis

Complete response was chosen as the primary outcome measurement for breakthrough emesis control. The secondary outcome measurements were incidence of retching, nausea, and ADRs. Patient characteristics, incidence of nausea and vomiting and ADR were reported. The percentage of patients who had a complete response (CR) and other ADRs with olanzapine treatment was calculated using SPSS (Version 19.0. Armonk, NY: IBM Corp.). The results are presented as percentage, frequency, median (range).

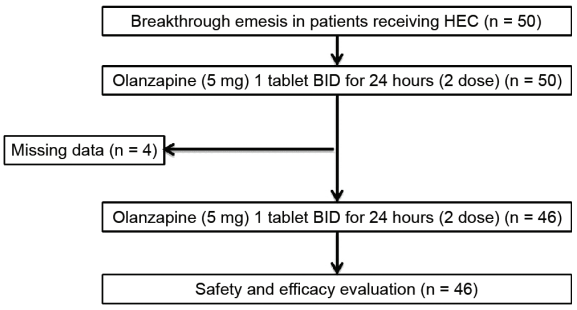
Results

Patient characteristics

Fifty cancer patients who received HEC were enrolled for the treatment with oral olanzapine. Four patients were not evaluable due to incomplete data collection. Forty-six patients, 32 male (69.5%) and 14 females (30.5%), were included in the analysis of olanzapine effectiveness (Fig. 1). The median patient ages were 33.5 (18-73) years old in male and 18 (18-25) years old in female, respectively. Most of the patients who experienced CINV were younger than 50 years old (n = 41, 89.1%). In addition, 27 patients (58.7%) experiencing CINV had no history of drinking alcohol and 12 patients (26.1%) had no history of motion sickness. Nonetheless, four patients (9.52%) had a history of morning sickness and 27 patients (58.70%) reported a history of CINV. The patients characteristic are presented in Table 1.

Primary outcome

Complete response of breakthrough emesis control was observed in 60.9% (n = 28) of patients. In addition, partial response, minor response and failure response were observed in 17.4%, 19.5%, and 2.2% of patients respectively, as illustrated in Table 2.



HEC = highly emetogenic chemotherapy; BID = twice a day

Fig. 1 Study algorithm.

Secondary outcomes

Complete retching control was reported in 71.7% (n = 33) of cases. In addition, partial response, minor response, and failure response were observed in 8.7%, 15.2%, and 4.4% of patients, respectively as depicted in Table 2. Complete response in nausea

Table 1. Characteristics of the patients

Characteristic (n = 46)	Number of patients (%)
Risk factors for CINV	
Age	
Less than 50 years of age	41 (89.1)
50 years of age or older	5 (10.9)
History of alcohol intake	
Never	27 (58.7)
Low alcohol intake (less than 1 drink/day)	6 (13.0)
Drinking alcohol on a regular basis (at least 1 drink/day)	13 (28.3)
History of motion sickness	
No	34 (73.9)
Yes	12 (26.1)
Experience of vomiting during pregnancy	
No	0 (0.0)
Yes	4 (100.0)
Previous vomiting experience with chemotherapy	
No	19 (41.3)
Mild	7 (15.2)
Moderate	16 (34.8)
Severe	4 (8.7)
History of anxiety	
No	24 (52.2)
Yes	22 (47.8)
Number of risk factor*	
0	6 (13.0)
1	15 (32.6)
2	14 (30.4)
3	5 (10.9)
4	1 (2.2)
5	5 (10.9)
6	0 (0.0)
Total	46 (100.0)

* Number of risk factors are defined as number of risks associated with CINV including age, history of alcohol intake, history of motion sickness, history of vomiting during pregnancy, history of vomiting related to chemotherapy, and history of anxiety

CINV = chemotherapy induced nausea and vomiting

Table 2. Effectiveness of olanzapine for breakthrough emesis, retching and nausea following 24 hours treatment period

Outcome	Response criteria				
	Complete response	Partial response	Poor response	Failure response	Total
Emesis	28 (60.9)	8 (17.4)	9 (19.5)	1 (2.2)	46
Retching	33 (71.7)	4 (8.7)	7 (15.2)	2 (4.4)	46
Nausea	23 (50.0)	6 (13.0)	6 (13.0)	11 (24.0)	46

were reported in 50.0% (n = 23) of patients. In addition, partial response, minor response, and failure response were observed in 13.0%, 13.0%, and 24.0% of patients, respectively as shown in Table 2.

Safety profile of this treatment with olanzapine was also evaluated in terms of ADR. One patient (2.2%) reported dyspepsia whereas four patients (8.7%) experienced fatigue. In addition, dizziness was also found in three patients (6.5%). The causality of all adverse events due to olanzapine was assessed utilizing the Naranjo's algorithm score resulting in possible level. All adverse events were reported in concordance with CTCAE 4.03, which was found to be low to moderate in severity (grade 1-2).

Discussion

Breakthrough CINV has been reported in approximately 30% of patients receiving chemotherapy and is still challenging in terms of effective management[7,14,15]. Several evidences suggest that additional antiemetics could be used in conjunction with standard prevention regimen therapy to alleviate the symptoms. The antiemetic with different mechanism of action typically recommended includes benzodiazepines such as lorazepam and neuroleptics such as olanzapine. Olanzapine is a second-generation antipsychotic that exerts antiemetic properties through inhibition of D_2, 5-HT_3, 5-HT_6, and H_1 receptors[7,8]. Pharmacokinetic properties of olanzapine such as long half-life (33 hours) has implied its used for prolonged emesis control[16]. Olanzapine is widely distributed in brain, kidney, liver, spleen, lung, and adipose tissue with a high volume of distribution of 1,150 liters, indicating its ability to remain in systemic for an extended period of time after initial olanzapine dosing[16].

The effectiveness of olanzapine treatment for breakthrough emesis in term of complete response in the present clinical study is reported as 60.9%. Complete response in retching and nausea was observed in 71.7% and 50.0% of patients receiving olanzapine respectively. The effectiveness outcomes of olanzapine in controlling breakthrough emesis from the present study are in agreement with the results reported from previous study performed by Navari et al[17]. The results of this particular clinical study revealed that patients who received olanzapine plus dexamethasone for breakthrough CINV achieved significantly higher CR rate than that of patients who received conventional prochlorperazine and metoclopramide (66% vs. 20% vs. 36%, respectively). Nonetheless, the results of Navari et al demonstrated a slightly higher CR rate than that observed in the present study (CR 66% vs. CR 60.9%, respectively)[17], perhaps due to differences in olanzapine dosing regimen. In the present study, patients were provided olanzapine (5 mg oral BID for two doses) in addition to standard regimen for a shorter period of only 24 hours while the above mentioned study provided olanzapine 5 mg oral BID for 72 hours following breakthrough emesis episodes. The present clinical study evaluated CR at 24 hours following olanzapine initiation as we hypothesized the immediate response based on the clinical pharmacokinetic data. Olanzapine peak plasma level occurs generally five to eight hours after an oral dose and supposes to correlate with initial therapeutic effect. Nevertheless, the study by Navari et al[17] evaluated olanzapine therapeutic effect at steady state plasma concentration that typically correlated with highest therapeutic effect. In addition, the patients enrolled in the present study were treated with HEC indicating higher emetogenic potential as compared to MEC in the other study[17]. This might have led to inferior outcome results of the present study.

A more recent investigation performed by Navari et al reported effectiveness of olanzapine compared to metoclopramide as a rescue medication for patients who were receiving HEC and developed breakthrough CINV. This clinical controlled study randomized patients to receive either olanzapine 10 mg oral OD or metoclopramide 10 mg oral TID for three consecutive days. Nausea and vomiting were observed for 72 hours after dosage initiation. One hundred eight patients who had breakthrough CINV were evaluable. During the 72 hours observation

period, CR in emesis control was achieved in 70% of patients receiving olanzapine versus 31% ($p<0.01$) in metoclopramide group respectively. Complete nausea control was also observed in 68% vs. 23% ($p<0.01$), respectively[18]. Thus, the present study has demonstrated a lower CR in emesis control as compared to the recent study by Navari et al (70% vs. 60.8%, respectively). The difference in standard antiemetic regimen between the two studies might have played a major role in clinical outcomes evaluated. The present study provided generic form of ondansetron 24 mg IV BID and dexamethasone 10 mg IV BID on day 1 for prevention of acute emesis and oral metoclopramide 10 mg TID plus dexamethasone 10 mg BID on day 2 to 4 for prevention of delayed emesis. This institutional standard doublet regimens used were obviously inferior to that of triple standard regimens consisting of dexamethasone 12 mg IV, palonosetron 0.25 mg IV, and fosaprepitant 150 mg IV on day 1 and dexamethasone 8 mg orally daily on days 2 to 4 from the recent study performed by Navari et al[18].

In terms of safety, ADRs from olanzapine in the present study was minimal and spontaneously resolved without intervention (e.g., extrapyramidal side effect). These ADRs were less in intensity than those ADRs reported from the first generation antipsychotics due to olanzapine's rapid dissociation at the dopamine receptor binding site resulting in more transient and reversible effects. The occurrence of olanzapine ADRs in the present study involved dyspepsia, fatigue, and dizziness with no serious ADR (grade 3 or grade 4) reported, similar to those observed recently by Navari et al[18]. Cancer patients are predisposed to several complications either resulting from their treatment modalities or advancing disease. This could also interfere with the interpretation of ADRs. The present study strictly utilized Naranjo's algorithm to estimate the occurrence probability. The CTCAE version 4.03 was also used to ascertain the severity of ADR. Therefore, the interpretation of ADRs could have been assured. Along with the ADRs, most cancer patients are in distress and susceptible to neuropsychological abnormalities such as insomnia, anxiety, or depression. Several drugs are indicated for neuropsychological disorder treatment. They include selective serotonin reuptake inhibitors (SSRIs), selective serotonin & norepinephrine inhibitors (SNRIs), tricyclic antidepressants, and atypical antipsychotic agents (such as olanzapine). Evidence suggests that olanzapine could provide some benefit on alleviating these issues[19,20]. Tan et al performed assessment of health-related quality of life in patients treated with olanzapine for a period of five days compared with standard CINV prevention. Not only providing emesis control, olanzapine could also improve the quality of life in terms of global health status, emotional functioning, social functioning along with disease related symptoms for instance fatigue, nausea and vomiting, insomnia, and loss of appetite ($p<0.01$)[21]. The present clinical study also observed therapeutic benefit in controlling anxiety and discomfort symptoms among cancer patients undergoing HEC treatment. The investigators had followed patients for anxiety symptoms every six hours after initiated olanzapine for 24 hour period and found that 73.9% of patients reported no anxiety or concern about nausea. This might have been implied health-related quality of life improvement following olanzapine.

Conclusion

The present study demonstrated the effectiveness and safety of olanzapine in the treatment of nausea and vomiting in patients treated with HEC. Olanzapine could be considered for treatment of patients with high-risk for breakthrough emesis despite standard prevention. Based on study results, olanzapine 5 mg every 12 hours (total of two doses) for at least 24 hours could be recommended for breakthrough emesis in conjunction with the standard prevention. Improving control in emesis, retching, nausea could be expected within 24 hours. Patients with underlying anxiety may also benefit from this suggested regimen. Currently, a triple antiemetic regimen is considered as first line treatment of emesis control in most developed countries. In some regions where NK-1 receptor antagonists are not readily accessible through National Formulary, based on several evidences the author suggested that olanzapine could potentially be considered as an alternative first line antiemetic in future clinical study.

What is already known on this topic?

Olanzapine containing regimen is considered to be an effective agent in the prevention of acute and delayed CINV based on current antiemetic guideline[5]. A three-day regimen of olanzapine, based on Navari et al, was established to support the use of olanzapine in breakthrough CINV treatment[18]. The olanzapine treatment was more effective in controlling breakthrough emesis compared to standard treatment.

What this study adds?

The present study demonstrated the efficacy and safety of olanzapine short-term regimen in the treatment of breakthrough CINV in oncology patients treated with HEC in Thai hospital based setting. Further study is needed to compare between olanzapine short-term regimen and standard regimen.

Acknowledgement

Fund for the present clinical study was provided by Faculty of Pharmaceutical Sciences, Khon Kaen University. Sincere thanks to Dr. Jeffrey Johns, Dr. Nutjaree Pratheepawanit Johns for their administrative assistance and Mrs. Aporanee Chaiyakum, Dr. Denpong Patthanasetthanon for their kind advice.

Potential conflicts of interest

None.

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ประสิทธิผลการให้ยาโอลันซาปีน ในการรักษาการคลื่นไส้อาเจียนชนิด breakthrough สำหรับผู้ป่วยมะเร็งที่ได้รับการรักษาด้วยยาเคมีบำบัด โรงพยาบาลศรีนครินทร์

สุธาร จันทะวงศ์, สุภัสร์ สุบงกช, เอื้อมแข สุขประเสริฐ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิผลและความปลอดภัยของยา olanzapine ในการรักษาอาการคลื่นไส้อาเจียนชนิด breakthrough ร่วมกับยาต้านการคลื่นไส้อาเจียนสูตรมาตรฐานในผู้ป่วยที่ได้รับการรักษาด้วยยาเคมีบำบัดที่มีฤทธิ์กระตุ้นการคลื่นไส้อาเจียนระดับสูง*

วัสดุและวิธีการ: *Phase II prospective open label clinical trial ในผู้ป่วยจำนวน 46 ราย ที่ได้รับการวินิจฉัยว่าเป็น solid tumor ที่ได้รับการรักษาด้วยยาเคมีบำบัดที่มีฤทธิ์กระตุ้นการคลื่นไส้อาเจียนระดับสูงอย่างน้อยหนึ่งรอบการรักษาทุก 2-4 สัปดาห์ ผู้ป่วยทุกรายจะได้รับการป้องกันภาวะคลื่นไส้อาเจียนด้วยยาต้านการคลื่นไส้อาเจียนสูตรมาตรฐาน อันได้แก่ยา ondansetron ร่วมกับ dexamethasone และ metoclopramide ตามแนวทางเวชปฏิบัติในการดูแลผู้ป่วยมะเร็ง ผู้ป่วยที่มีอาการคลื่นไส้อาเจียนชนิด breakthrough จะได้รับการรักษาด้วยยา olanzapine 5 มิลลิกรัม รับประทานครั้งละ 1 เม็ดทุก 12 ชั่วโมง เป็นเวลาหนึ่งวัน ร่วมกับการให้ยาต้านการคลื่นไส้อาเจียนสูตรมาตรฐานและติดตามประสิทธิผลและความปลอดภัยทุก 6 ชั่วโมง เป็นเวลา 24 ชั่วโมง โดยใช้แบบประเมินอาการคลื่นไส้อาเจียนมาตรฐาน (ประยุกต์จาก Index of Nausea, Vomiting and Retching: INVR)*

ผลการศึกษา: *จากการประเมินผลการศึกษาในผู้ป่วยจำนวน 46 ราย (ระหว่างเดือนกันยายน พ.ศ.2552 ถึง กรกฎาคม พ.ศ.2553) พบว่าผู้ป่วยทั้งหมดที่ได้รับการรักษาอาการคลื่นไส้อาเจียนชนิด breakthrough ด้วยยา olanzapine ได้ complete response ของ emesis, retching และ nausea control เท่ากับร้อยละ 60.9, 71.7 และ 50.0 ตามลำดับ สำหรับอาการไม่พึงประสงค์จากการใช้ยา olanzapine นั้นเกิดขึ้นมีระดับความรุนแรงต่ำและผู้ป่วยสามารถทนได้ ซึ่งได้แก่ dizziness, fatigue และ dyspepsia*

สรุป: *ยา olanzapine มีประสิทธิผลและความปลอดภัยในการรักษาอาการคลื่นไส้อาเจียนชนิด breakthrough ในผู้ป่วยที่ได้รับการรักษาด้วยยาเคมีบำบัดที่มีฤทธิ์กระตุ้นการคลื่นไส้อาเจียนระดับสูง*
