Original Article

Olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting (CINV): a retrospective study

Leonard Chiu, Nicholas Chiu, Ronald Chow, Liying Zhang, Mark Pasetka, Jordan Stinson, Breanne Lechner, Natalie Pulenzas, Sunil Verma, Edward Chow, Carlo DeAngelis

Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada

Contributions: (I) Conception and design: L Chiu, E Chow, C DeAngelis; (II) Administrative support: L Chiu, N Chiu; (III) Provision of study materials or patients: C DeAngelis, E Chow; (IV) Collection and assembly of data: L Chiu, L Zhang; (V) Data analysis and interpretation: L Chiu, L Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Edward Chow, MBBS, MSc, PhD, FRCPC. Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue Toronto, Ontario M4N 3M5, Canada. Email: edward.chow@sunnybrook.ca.

Background: While the efficacy of olanzapine in the prophylaxis of chemotherapy-induced nausea and vomiting (CINV) has been documented, the literature on the use of olanzapine as a rescue medication for breakthrough CINV has been scarce. The following study retrospectively evaluated the safety and efficacy of olanzapine for the treatment of breakthrough CINV. The efficacy and safety of olanzapine in the prophylactic setting was also examined in a smaller cohort.

Methods: Electronic medical records of adult patients aged >17 years receiving a prescription for olanzapine from the Odette Cancer Centre Pharmacy at Sunnybrook Hospital between January 2013 and June 2015 were reviewed retrospectively. Inclusion criteria required receiving one or more doses of olanzapine for the rescue or prophylaxis of CINV and documentation of the outcome.

Results: A total of 154 patients and 193 treatment cycles were included in the breakthrough setting, while a total of 16 patients and 20 treatment cycles were included in the prophylaxis setting. In the breakthrough setting, 88% of cases experienced improved nausea, while 21% of cases reported improved vomiting. In the prophylactic setting, 100% of cases experienced improved nausea, while 65% achieved improved vomiting. A total of 43% of cases in the breakthrough setting and 65% of cases in the prophylactic setting experienced sedation.

Conclusions: Olanzapine is effective in improving CINV in both the prophylactic and breakthrough settings. The safety, efficacy, and appropriate dosage of olanzapine for the rescue of breakthrough CINV should be prospectively evaluated in a randomized controlled trial (RCT).

Keywords: Olanzapine; chemotherapy-induced nausea and vomiting (CINV); breakthrough emesis; prophylaxis; efficacy

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a well-documented adverse effect for patients undergoing chemotherapy treatment (1-5). Left untreated, CINV may result in serious complications, thus potentially compromising outcome if dose reduction or discontinuation of therapy is required (6). At present, current antiemetic guidelines recommend that a three-drug combination of a 5-HT_3 antagonist, dexamethasone, and neurokinin 1 (NK-1) inhibitors be used in the prophylaxis of acute CINV in the highly emetogenic chemotherapy (HEC) settings, while a two-drug combination of palonosetron and dexamethasone is recommended in the moderately emetogenic chemotherapy settings (MEC) (7,8). For

delayed CINV, a combination of dexamethasone and aprepitant is recommended in the HEC settings, while dexamethasone or aprepitant can be used in MEC settings (7,8). However, despite prophylactic treatment, CINV may nevertheless arise. Failure to control CINV with the aid of prophylactic antiemetics is defined as breakthrough CINV (8), and at present, many medications are recommended by clinical guidelines but no specific agent for this type of CINV is preferred (8).

Olanzapine is an antipsychotic medication with clinically observed antiemetic effects (9). The Food and Drug Administration (FDA) approved drug blocks multiple neurotransmitters: dopamine at D1, D2, D3 and D4 brain receptors, serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, and 5-HT_6 receptors, catecholamines at alpha-1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors (10).

Since 2000, when a case report first documented the efficacy of olanzapine in relieving the chronic nausea of a leukemia patient (11), several phase I and II studies (12-18), other randomized controlled trials (RCTs) (19-23), and recent systematic reviews and meta-analyses (24,25), have been published which document the effective use of olanzapine as a prophylactic antiemetic in controlling CINV. However, only two studies have documented the use of olanzapine for the rescue of breakthrough CINV (26,27).

With the relatively few number of studies in the literature documenting olanzapine in the breakthrough setting, the primary objective of this study was to determine the efficacy and safety of olanzapine when given as a rescue medication to patients who experience breakthrough CINV. The secondary objective was to determine the efficacy and safety of olanzapine as a prophylaxis treatment of CINV.

Methods

Study design and patient selection

Following approval from the Toronto Academic Health Sciences Network (TAHSN) Research Ethics Board, electronic medical records of adult patients aged >17 years receiving a prescription for olanzapine from the Odette Cancer Centre Pharmacy at Sunnybrook Hospital between January 2013 and June 2015 were reviewed retrospectively. Inclusion criteria required receiving one or more doses of olanzapine for the rescue or prophylaxis of CINV and documentation of the outcome. In the prophylactic setting, olanzapine was administered for the first three days after chemotherapy, starting on the day of chemotherapy, twice a day. In the breakthrough setting, each patient must have received some form of standard prophylactic antiemetic before the administration of a first-line rescue antiemetic. First-line rescue antiemetic is defined as the subsequent antiemetic medication given after clinical failure of prophylactic antiemetics. Olanzapine was administered as the first-line rescue antiemetic for the majority of patients. Other patients may have used prochlorperazine as first-line rescue medication, but switched to olanzapine because of clinical failure or the medication induced side effects severe enough to warrant discontinuation by the patient. Olanzapine administration for breakthrough CINV must have been given after clinical failure of prophylactic antiemetics and/or failure of non-olanzapine containing first-line rescue. In the rescue setting, each medication was always administered separately and sequentially. Patients were excluded if olanzapine was used before chemotherapy.

In both the rescue and prophylactic settings, the primary outcome measure was the percentage of patients who took olanzapine and found it to improve nausea or vomiting. In both the nausea and vomiting endpoints, failure was defined as the patient indicating CINV to be same or worse upon olanzapine use. Secondary outcome measures included the percentage of patients who took olanzapine and developed side effects.

Patients were stratified by chemotherapy emetogenicity level and type, number of prophylactic antiemetics received, dosage of olanzapine used, treatment intent, as well as by risk factors such as age, gender, and alcohol consumption. Chemotherapy emetogenicity levels were separated into high, medium and low potentials, prophylactic anti-emetics divided into groups of single, double, or triple agents, dosage of olanzapine was examined in either 2.5 or 5 mg, and treatment intent into adjuvant, neoadjuvant, palliative, or curative. Risk factors were separated into age younger than 55 versus age 55 years or older and alcohol use less than 5 drinks/week versus use of 5 drinks/week or more.

Assessment procedures

At the Odette Cancer Centre, patients are followed up with a phone call by a pharmacist or pharmacy research assistant 72 hours after every cycle of chemotherapy. Any outcomes of CINV for the initial cycle after this 72-hour period would be made in the next treatment cycle in the hospital or within the 72 hour period follow-up in the next cycle. An assessment of CINV was documented in the patient's electronic medical records. In both the prophylactic and

Table 1 Patient demographics and baseline risk factors

Characteristic	Total (n=170, 100%)	
	No.	%
Age (years)		
Median	51	
Range	20–85	
Gender		
Female	142	83.5
Male	28	16.5
Primary cancer site		
Breast	97	57.0
Gastrointestinal	16	9.4
H/N	16	9.4
Gynecology	15	8.8
Hematology	15	8.8
Lung	9	5.3
Genitourinary	1	0.6
Other	1	0.6
Baseline risk factors		
Age (years)		
≤55	108	63.5
>55	62	36.5
Alcohol use >5 drinks/week		
No	162	95.3
Yes	8	4.7
Any caffeine use		
No	105	61.8
Yes	65	38.2
Any tobacco use		
No	158	92.9
Yes	12	7.1

breakthrough setting, patients were asked whether they experienced "improved", "worse", or "same" CINV after taking olanzapine.

Statistical methods

Descriptive analysis was conducted using median and ranges for continuous variables and proportions for categorical variables. To compare olanzapine outcomes on clinical factors, Wilcoxon rank-sum (for two categories of olanzapine outcomes) or Kruskal-Wallis (for >2 categories of olanzapine outcomes) nonparametric test was used for continuous variables and Chi-squared test or Fisher exact test was used as appropriate for categorical variables. Two-sided P value <0.05 was considered statistically significant. All analyses were performed by Statistical Analysis Software (SAS version 9.4 for Windows).

Results

Patient characteristics

A total of 170 patients and 213 treatment cycles were included: 142 women and 28 men with a mean age of 50.9 years (range, 19–77) (*Table 1*). The most common primary cancer site was breast cancer (n=97, 57%) (*Table 1*). Other demographic information, including baseline risk factors such as alcohol and caffeine consumption, can be found in *Table 1*.

Efficacy and safety parameters in the breakthrough setting

A total of 154 patients and 193 treatment cycles were included in the breakthrough setting (*Table 2*). *Table 3* documents the proportion of patients with different olanzapine outcomes for nausea and vomiting in the breakthrough setting.

Subgroup analysis revealed that the effectiveness of olanzapine for breakthrough CINV was not dependent on the cycle it starts on (P=0.3), nor was it dependent on the emetogenic potential (P=0.1), the treatment intent (P=0.2), or the type (P=0.3) of the chemotherapy regimen. In addition, there is no significant relationship between having a single, double, or triple prophylactic antiemetic regimen and subsequent olanzapine outcomes (P=0.4). In addition, there was no significant difference on side effects or outcomes between the use of a 2.5 or 5 mg dose of olanzapine. No significant relationship between baseline demographics and different olanzapine outcomes were found either.

Efficacy and safety parameters in the prophylactic setting

A total of 16 patients and 20 treatment cycles were included in the prophylaxis setting (*Table 4*). In all 16 patients and 20 cases, olanzapine use was indicated by patients to have improved nausea in the prophylactic setting, while

Table 2 Treatment cycles and antiemetics in the breakthrough setting

Characteristic	([a]n=193, 100%)	
	No.	%
Number of treatment cycles with olanzapine use		
Median	1	
Range	1–12	
Emetogenic potential		
High	140	72.5
High/low	10	5.2
Low	8	4.1
Medium	35	18.1
Olanzapine dose		
2.5 mg	182	94.3
5 mg	11	5.7
Treatment intent		
Adjuvant	63	32.6
Neoadjuvant	38	19.7
Palliative	20	10.4
Curative	48	24.9
Prophylactic anti-emetics		
Single (dexamethasome or 5-HT_3 antagonist)	15	7.8
Double (5-HT_3 antagonist and aprepitant)	51	26.4
Triple (5-HT_3 antagonist, dexamethasome, aprepitant)	129	66.8
Type of rescue medications		
Olanzapine	87	45.1
Prochlorperazine, olanzapine	61	31.6
Olanzapine, prochlorperazine	17	8.8
Olanzapine, domperidone	11	5.7
Prochlorperazine, domperidone, olanzapine	12	6.2
Prochlorperazine, olanzapine, metoclopramide	6	3.1

[a], treatment cycles.

Table 3 Proportion of patients with different outcomes upon use of olanzapine for breakthrough CINV or the prevention of CINV

Olanzapine outcomes	Rescue setting (n=193, 100%)		Prophylaxis setting (n=20, 100%)	
	No.	%[a]	No.	%[b]
Improved nausea	170	88.1	20	100.0
Improved vomiting	42	21.8	7	35.0
Failure nausea[c]	23	11.9	0	0
Failure vomiting[d]	6	3.1	0	0

[a], total number of chemotherapy cycles [193] is used as the denominator for calculating the proportions in this setting; [b], total number of chemotherapy cycles [20] is used as the denominator for calculating the proportions in this setting; [c], failure nausea is defined as worse or same nausea level despite the use of olanzapine; [d], failure vomiting is defined as worse or amount of vomiting despite the use of olanzapine. CINV, chemotherapy-induced nausea and vomiting.

7 cases (35%) achieved improved vomiting (*Table 3*). A total of 65% of the cases indicated the feeling of sedation after olanzapine use, while 35% of the cases indicated experiencing constipation (*Table 5*).

As in the breakthrough setting, subgroup analysis revealed that the effectiveness of olanzapine for the prevention of CINV was not dependent on the cycle it starts on (P=0.98), the emetogenic potential (P=0.6), the treatment intent (P=0.9), or the type (P=0.4) of the chemotherapy regimen. Moreover, there was no significant relationship between having a single, double, or triple prophylactic antiemetic regimen and subsequent olanzapine outcomes (P=0.5). Although there was no significant difference between the use of a 2.5 or 5 mg dose of olanzapine with respect to the antiemetic outcome or the incidence of constipation, there was a significant difference between the two doses with regards to the incidence of sedation. The use of a 5 mg olanzapine dose was associated with significantly higher proportions of sedation compared to a 2.5 mg dose (P=0.03).

Discussion

The efficacy of olanzapine in the prophylaxis of CINV has been documented (12-23). However, literature on the use of olanzapine as a rescue medication for breakthrough CINV has been scarce, with only two studies investigating the use of olanzapine for this purpose (26,27). As such, we focus on the two articles by Chanthawong *et al.* (26) and Navari *et al.* (27) as a framework for our discussion.

The current study retrospectively details the efficacy and safety of olanzapine for the treatment of breakthrough CINV. It is the largest study of this nature to date, with a total of 154 patients and 193 treatment cycles in the

Table 4 Treatment cycles and antiemetics in the prophylactic setting

Characteristic	(n[a]=20, 100%)	
	No.	%
Number of treatment cycles with olanzapine use		
Median	1	
Range	1–10	
Emetogenic potential		
High	16	80.0
Low	2	10.0
Medium	2	10.0
Olanzapine dose		
2.5 mg	14	70.0
5 mg	6	30.0
Treatment intent		
Adjuvant	3	15.0
Neoadjuvant	2	10.0
Palliative	7	35.0
Curative	6	30.0
Prophylactic anti-emetics		
Double (5-HT_3 antagonist and aprepitant)	8	40.0
Triple (5-HT_3 antagonist, dexamethasome, aprepitant)	10	50.0
Olanzapine	20	100.0

[a], treatment cycles.

breakthrough setting. With approximately 88% of cases indicating that olanzapine improved breakthrough nausea, the proportion in this study is, as expected, higher than the 68% of patients in the Navari study that indicated no nausea (27), and the complete response in nausea rate of 50% reported by Chanthawong *et al.* (26). The proportion of improved vomiting (22%) in our study is considerably lower than the no emesis (70%) and complete response in emesis (60.9%) rates reported by Navari *et al.* and Chanthawong *et al.*, respectively. In the Chanthawong study, complete response in nausea was as no emetic episodes, no rescue therapy and no nausea, while the complete response in emesis was defined as no emetic episodes and no rescue therapy. It should be noted that the doses used by Navari *et al.* and Chanthawong *et al.* were 10 mg daily and 5 mg twice a day, respectively. Given that the methodology used in this study is different from the ones used by Chanthawong *et al.* and Navari *et al.*, the results are not comparable. Specifically, the study by Chanthawong *et al.* is a phase II prospective open label clinical trial that measured the rates of complete response for breakthrough emesis, retching and nausea using the Index of Nausea, Vomiting and Retching: INVR tool. The study by Navari *et al.* is a randomized phase III trial that measured rates of complete response using a visual analog scale from 0 to 10, with 0 indicating no nausea and 10 indicating a maximal level of nausea. On the other hand, the retrospective nature of this study and the limited information available from the electronic medical records limited this study's ability to report on the more commonly used endpoints in antiemetic

Table 5 Proportion of patients who took olanzapine and developed certain side-effects

Side effect	Rescue setting (n=193, 100%)		Prophylaxis setting (n=20, 100%)	
	No.	%[a]	No.	%[b]
Sedation	82	42.5	13	65.0
Sedation with continuation of olanzapine	57	29.5	12	60.0
Sedation with discontinuation of olanzapine	25	13.0	1	5.0
Constipation	61	31.6	7	35.0
Mild, constipation, no medication prescribed	19	9.8	1	5.0
Severe constipation with prescribed medications	42	21.8	6	30.0

[a], total number of chemotherapy cycles [193] is used as the denominator for calculating the proportions in this setting; [b], total number of chemotherapy cycles [20] is used as the denominator for calculating the proportions in this setting.

clinical trials such as no emesis and no nausea. Moreover, the proportions of improvement for nausea and vomiting may be under-estimated. As documentation is predicated on phone-call follow-up, improvement of CINV may not always be communicated by patients.

This study is the first to report the proportion of patients that experienced side effects in the breakthrough setting, with 42% of cases experiencing sedation and 32% experiencing constipation. With 65% of patients experiencing sedation in the prophylactic setting, this study reports the incidence of sedation to be lower than the 73% indicated by a study by Tan *et al.* (19). It should be noted that in our study, olanzapine was administered in smaller 2.5 or 5 mg doses than the 10 mg dose used by Tan *et al.* Our findings that a 2.5 mg dose of olanzapine in the prophylactic setting is associated with similar CINV outcomes, but a smaller incidence of sedation than a 5 mg dose further support the recommendation of dosage reduction.

While it is well known that the emetogenicity of chemotherapy administered, gender, age, as well as a history of low prior alcohol intake, can affect patients' risk factors for CINV (28), it is relatively unknown whether the before mentioned baseline risk factors can affect the efficacy of olanzapine use. Our study found no significant differences between patients with baseline risk factors and those without, in both the prophylaxis and breakthrough settings. Our study also found that the effectiveness of olanzapine in both the prophylaxis and breakthrough settings is not dependent on the cycle it started on.

This study is limited by its retrospective design. Specifically, information on the intensity of breakthrough nausea or the number of breakthrough vomiting episodes before and after the use of olanzapine was not recorded, and thus, more standard definitions of failure in the treatment of breakthrough CINV could not be used. In addition, patients received different combinations of prophylactic anti-emetics that may have confounded the efficacy of olanzapine for breakthrough CINV. However, measures have been taken to minimize its limitations. For example, our analysis showed that there was no significant difference between receiving a single agent prophylactic anti-emetic (dexamethasone or a 5-HT_3 antagonist), a double agent antiemetic (a 5-HT_3 antagonist coupled with a NK-1 inhibitor), or a triple agent anti-emetic (a 5-HT_3 antagonist, dexamethasone, and a NK-1 inhibitor) with respect to the efficacy of olanzapine as rescue medication for breakthrough CINV.

In conclusion, this study found olanzapine to be effective in improving CINV in both the prophylactic and breakthrough settings. The incidence of sedation in both settings was found to be lower than the only other reported incidence of sedation of 73%, though it should be noted that our study used lower doses. Given the similar benefit afforded by a 2.5 and 5 mg dose, we recommend the use of lower doses of olanzapine in both the prophylactic and breakthrough settings. The safety, efficacy, and appropriate dosage of olanzapine for the rescue of breakthrough CINV should be prospectively evaluated in a RCT.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Toronto Academic Health Sciences Network (TAHSN) Research Ethics Board.

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