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Original article

A randomized study of olanzapine-containing versus standard antiemetic regimens for the prevention of chemotherapy-induced nausea and vomiting in Chinese breast cancer patients

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ABSTRACT

Objectives: Chemotherapy-induced nausea and vomiting (CINV) are distressing symptoms. This randomized study evaluated the antiemetic efficacies of standard antiemetic regimen with/without olanzapine.

Patients and methods: Eligible patients were chemotherapy-naive Chinese breast cancer patients who were planned for (neo)adjuvant doxorubicin/cyclophosphamide. Antiemetic regimen for all studied population included aprepitant, ondansetron and dexamethasone; patients were randomized to Olanzapine (with olanzapine) or Standard arms (without olanzapine). Patients filled in self-reported diaries and completed visual analogue scales for nausea, as well as Functional Living Index-Emesis questionnaires. Blood profiles including fasting glucose and lipids were monitored.

Results: 120 patients were randomized. In Cycle 1 doxorubicin/cyclophosphamide, the Olanzapine arm had significantly higher rates of "Complete Response" than the Standard arm: 65.0% vs 38.3% in the overall period ($p = 0.0035$), 70.0% vs 51.7% in the acute period ($p = 0.0397$) and 92.9% vs 74.2% in the delayed period ($p = 0.0254$). Olanzapine arm also had significantly higher rates of "No significant nausea" and "No nausea" during all 3 time-frames and better QOL. Similar findings were also revealed throughout multiple cycles. Pre-study abnormalities in glucose and lipids occurred in 39.7% and 34.2% of the studied population respectively; there were no differences in these parameters between the two arms at end-of-study assessment.

Conclusion: The addition of olanzapine to standard aprepitant-based antiemetic regimen provides clinically meaningful improvement in controlling CINV. This was associated with a positive impact on QOL and tolerable toxicity profiles among Chinese breast cancer patients receiving doxorubicin/cyclophosphamide chemotherapy. Further studies on metabolic profiles of breast cancer patients are warranted.

1. Introduction

Adjuvant chemotherapy has been shown to improve outcomes of patients with early breast cancer, but chemotherapy-induced nausea and vomiting (CINV) have been regarded by many

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patients as the two most disturbing side effects, affecting their well-being and quality of life [1–3]. One of the most common chemotherapy regimens, the AC regimen, includes cyclophosphamide (600 mg/m2) in combination with doxorubicin (60 mg/m2). Although individual drug on its own would be considered as a form of moderately emetogenic chemotherapy (MEC) agent, AC has been considered to be a highly emetogenic chemotherapeutic regimen (HEC) by various international guidelines including the American Society of Clinical Oncology (ASCO) [4], the National Comprehensive Cancer Network (NCCN) [5] and the Multinational Association of Supportive Care in Cancer (MASCC) [6]. To optimize antiemetic care for patients receiving HECs, the recommended antiemetic prophylaxis consists of the combination of a neurokinin-1 receptor antagonist (NK1RA), a 5-hydroxytryptamine type-3 receptor antagonist (5HT3RA) and a corticosteroid [4–6]. However, despite such recommendations, it has been shown that the proportion of patients who could achieve Complete Response (i.e. no vomiting with no rescue therapy) was only about 50%, while over 70% may still experience nausea after chemotherapy [7–9].

Olanzapine is an atypical antipsychotic drug which antagonizes several neurotransmitter receptors including dopamine and 5-HT receptors. Its use for the prevention of CINV has initially been suggested by early phase II studies [10–12]. Subsequent randomized trials that followed attempted to compare olanzapine-containing antiemetic regimens with standard arms of antiemetic prophylaxis. Although some studies have shown better antiemetic control in the olanzapine-containing regimens [13–15], contrary findings have been reported in others [16,17]. Such disparities were likely due to differences in antiemetic regimens used in the standard arms, which ranged from the use of single agent ondansetron [14] to a combination of aprepitant, dexamethasone and palonesetron [16,17]. Moreover, findings were also hampered by other factors including small patient number, heterogeneous patient characteristics and different cytotoxic regimens being administered among the studied patients [13–17].

The antiemetic efficacy of olanzapine has been better tested in the landmark study reported by Navari et al. [9], in which 380 patients with various malignancies were given a triplet antiemetic regimen of NK1RA, 5HT3RA and dexamethasone, with or without olanzapine. Patients treated with the olanzapine-containing antiemetic regimen were found to have better control of CINV. However, apart from a small Japanese study which involved 44 patients [18], the benefit of adding olanzapine to the triplet antiemetic regimen have not been confirmed.

The present study consisted of a homogenous group of Chinese breast cancer patients who were uniformly planned to receive (neo)adjuvant AC chemotherapy. The primary objective was: (1) to compare the olanzapine-containing anti-emetic regimen (Olanzapine arm) and optimal standard anti-emetic regimen that included an NK1RA, a 5HT3RA and dexamethasone (Standard arm) with respect to their antiemetic efficacies in the first cycle of AC. The secondary objectives were: (1) to compare quality of life in the first cycle of AC chemotherapy between patients in the Olanzapine and the Standard arms; (2) to compare the tolerability and efficacy of study treatments during the 4 cycles of AC chemotherapy. Additionally, since the protracted use of olanzapine has been associated with weight gain and onset of diabetes mellitus, the study also included monitoring of metabolic profiles.

2. Patients and methods

This is a single center, randomized study. The study was approved by the Joint CUHK-NTEC Institution Review Board of the Chinese University of Hong Kong. The study was registered at ClinicalTrials.gov (Identifier: NCT03079219).

Patients were eligible if they were female of Chinese ethnicity, over 18 years of age, with Stage I-III breast cancer, and were planned for (neo)adjuvant AC chemotherapy regimen. Other eligibility criteria included ECOG Performance Status 0–1, being able to read, understand and complete study questionnaires and diaries in Chinese. Eligible patients were consented to take part in the study.

Patients were excluded from the study if they had abnormal complete blood counts, renal or liver functions; if they had received or would receive radiation therapy to the abdomen or pelvis in the week prior to study treatment; had grade 2–3 nausea as per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v 4.0) or vomited in the 24 h prior to the start of study treatment; had a history of treatment with MEC or HEC; had an active infection or any uncontrolled disease; had a history of illicit drugs, including marijuana or alcohol abuse; were mentally incapacitated, had significant emotional or psychiatric disorder; or had history of hypersensitivity to aprepitant, ondansetron or dexamethasone.

2.1. Study treatment

Randomization was conducted in a 1:1 fashion on Olanzapine arm and Standard arm. Randomized block design was applied to ensure balanced assignment to each treatment arm. No blinding was applied. Since oral aprepitant had been part of the standard departmental protocol for AC chemotherapy while longer-acting 5HT3 antagonist such as palonosetron was not available in the study centre, the Standard arm consisted of aprepitant 125 mg, ondansetron 8 mg and dexamethasone 12 mg before chemotherapy, and ondansetron 8 mg 8 h later on day 1; followed by aprepitant 80 daily and dexamethasone 4 mg twice daily on days 2–3. The Olanzapine arm consisted of olanzapine 10 mg with other antiemetics as in the Standard arm on day 1; aprepitant 80 daily on days 2–3 and olanzapine 10 mg daily on days 2–5. Patients were instructed to take rescue therapy if needed for nausea or vomiting (Supplementary File, Table S1).

2.2. Study assessments

Individual patient filled in self-administered Functional Living Index-Emesis (FLIE) questionnaire prior to study treatment on day 1. A diary was given to each patient so that she could record the anti-emetic efficacy following the chemotherapy infusion for 120 h. The diary recorded daily the date and time of any vomiting episodes and the use of rescue medication. Within the diary, there were also nausea ratings (by visual analogue scale, VAS; 0 mm implied no nausea; 100 mm implied nausea that was “as bad as it could be”); on days 2–6, each patient rated the symptoms of nausea for the preceding 24 h using the VAS. After patients had completed the diary in the morning of day 6, they immediately completed the FLIE questionnaire again. The nurse coordinator or research assistant called individual patient during days 2–6, in order to remind them to take the study medications as directed, to encourage them to complete the patient diary, and to remind them to complete the FLIE questionnaire.

2.3. Assessment of efficacy and safety

Three time-frames were assessed; assessments started from the initiation of AC chemotherapy infusion (0 h) up to beginning of day 6 (~120 h). “Acute” period referred to 0–24 h after the initiation of AC, “delayed” period referred to 24–120 h, while “overall” period referred to 0–120 h.

The variables used to measure anti-emetic efficacy were: the proportion of patients with “Complete Response” (defined as no

vomiting and no use of rescue therapy), the proportion of patients reporting "No vomiting" (no vomiting or retching including patients who received rescue therapy), "No significant nausea" (nausea VAS <25 mm), "No nausea" (nausea VAS <5 mm), "No use of rescue therapy", "Complete Protection" (no vomiting with no rescue therapy and nausea VAS <25 mm), and "Total Control" (no vomiting with no rescue therapy and nausea VAS <5 mm) [8,9,19]. These assessments were done primarily over the "overall" period, and were also conducted separately during "acute" and "delayed" periods. In addition, "the time to first vomiting episode" (based on self-reported date and time of vomiting episodes recorded in the diary) was assessed.

Quality of life was evaluated by the Chinese version of the self-reported FLIE questionnaire by individual patients. This is a validated instrument for the measurement of impact of CINV on daily living [20] (Supplementary File, Table S2).

Adverse events were graded according to NCI CTCAE v 4.0. Treatment compliance was monitored, with the number of tablets taken each day assessed. In addition to routine investigations (complete blood counts, renal and liver functions, bone profiles and electrocardiogram prior to each cycle of chemotherapy and baseline hepatitis B surface antigen), the following tests were done: prior to study treatment, fasting glucose and lipids; during mid-cycle of chemotherapy, complete blood counts; and at end of study, fasting glucose and lipids.

2.4. Statistical analysis

In order to have 80% power to detect a 10 mm difference in the nausea ratings as measured by VAS with a two-sided 5% level test, the targeted patient number was total of 120 patients (approximately 60 patients per treatment group). The modified intention-to-treat (mITT) approach was used for all efficacy analyses. Only patients who had received chemotherapy, taken all the doses of the study drugs and had at least one post-treatment assessment were included in the analysis.

To address the primary efficacy analysis, the Olanzapine arm was compared to the Standard arm in terms of rates of "Complete Response" in the overall, acute and delayed periods. Efficacy outcomes of secondary interests included "No vomiting", "No significant nausea", "No nausea", "No use of rescue therapy", "Complete Protection" and "Total Control") during these 3 time periods. Comparisons between the two arms were made using Wilcoxon Rank Sum test for continuous data and chi-square test for dichotomous data with a 2-sided significance level of 5%.

The time to first vomiting (time to failure) in the first cycle of AC was compared between the two arms using cox regression analysis.

For the analysis of the FLIE questionnaire, the nausea domain, vomiting domain and total score (the sum of the two domains) in the overall period were compared between the two arms using Wilcoxon Rank Sum test for continuous data.

For efficacy analyses over multiple cycles, "Complete Response", "Complete Protection", and "Total Control" over multiple cycles in the acute (0–24 h), delayed (24–120 h) and overall periods (0–120 h) were assessed using chi-square test for dichotomous data.

To address the tolerability and safety, analyses on the incidences of adverse events (AEs) were evaluated by treatment arm. The incidences of specific AEs, other AEs occurring in $\geq$5% of patients in either arm of the study, and any occurrence of serious adverse events (SAEs) were summarized by treatment group. The comparison between the treatment arms was performed by using chi-square test.

3. Results

One hundred and twenty patients were randomized and received at least one cycle of AC (60 in the Olanzapine arm and 60 in the Standard arm); they were included in the efficacy analysis for cycle 1. One hundred and fifteen patients completed all 4 cycles of AC cycles (56 in the Olanzapine arm and 59 in the Standard arm); the reason for not completing four AC cycles included adverse event (1 patient), patient withdrawal (3) and cancer progression (1). The compliances to study treatments at Cycle 1, Cycle 2, Cycle 3 and Cycle 4 were 100%, 96.7%, 95.8% and 96.7%, respectively.

Patient characteristics, included those that could potentially affect CINV [21], are listed in Table 1. For the overall patient population, the median age was 55 years, 76.7% had history of motion sickness, 50% had history of vomiting during pregnancy; only 1 patient had regular alcoholic consumption while 2 patients were smokers at study entry. Ninety-five percent had invasive ductal carcinoma, 62.5% had stage II disease, 22.5% received AC as part of neoadjuvant therapy while 5.8% received a dose-dense 2-weekly AC regime with support of granulocyte colony stimulating factor.

3.1. Efficacy assessment

The efficacy outcomes during cycle 1 of AC chemotherapy are listed in Table 2. There were significantly higher rates of "Complete Response" in the Olanzapine arm compared to the Standard arm; the corresponding figures for the overall period, acute period and delayed period were respectively 65.0% vs 38.3% ($p = 0.0035$), 70.0% vs 51.7% ($p = 0.0397$) and 92.9% vs 74.2% ($p = 0.0254$). In addition, except for "No use of rescue therapy" in the acute period, and "No use of rescue therapy", "No nausea", "Complete Protection" and "Total Control" in the delayed period, there were significantly higher proportions of patients reporting "No vomiting", "No significant nausea", "No nausea", "No use of rescue therapy", "Complete Protection" and "Total Control" in the Olanzapine arm during the 3 study periods.

The median time to first vomiting after the initiation of chemotherapy was not reached (range: not reached-not reached) in the Olanzapine arm and 26.5 h (range 10.2- not reached) in the Standard arm (HR 0.414, 95% confidence interval 0.237–0.723, $p = 0.0019$) (Fig. 1).

Analysis of the impact on daily living during cycle 1 AC revealed that while there were no differences in FLIE scores between the two arms prior to initiation of AC chemotherapy on Day 1, there was significantly better quality of life (lower FLIE scores) in terms of nausea domain (mean score [SD] for Olanzapine arm vs Standard arm: 8.39 [17.02] vs. 27.71 [28.33] respectively, $p < 0.0001$) and total score (mean score [SD] for Olanzapine arm vs Standard arm: 6.01 [13.31] vs. 19.2 [20.78] respectively, $p < 0.0001$) among patients in the Olanzapine arm on Day 6 of AC therapy. Moreover, when compared to FLIE scores prior to AC treatment, the increase in FLIE scores on Day 6 (reflecting worsening in quality of life) was significantly higher in the Standard arm for the nausea domain (mean score [SD] for Olanzapine arm vs Standard arm: 7.60 [17.56] vs. 26.99 [28.86] respectively, $p < 0.0001$) and the total score (mean score [SD] for Olanzapine arm vs Standard arm: 5.33 [13.73] vs. 18.35 [20.77] respectively, $p < 0.0001$) (Table 3).

Table 4 shows the efficacy data between the two arms over multiple cycles. In general, the proportions of patients achieving "Complete Response","Complete Protection" and "Total Control" in all the time periods were higher in the Olanzapine arm. Specifically, apart from findings already reported in cycle 1, the proportions of patients achieving "Complete Response" was significantly higher in Olanzapine arm in the overall period (75.0% vs 57.6%, $p = 0.0492$) in cycle 3.

Table 1
Baseline characteristics of studied population (N = 120).

	Olanzapine, N (%)	Standard, N (%)
Median age (years; range)	54.5 (36–71)	55.5 (32–71)
Median body weight (kg; range)	57.3 (41.6–82.7)	58.9 (44.5–100.4)
Median body height (cm; range)	157 (143–168.8)	156 (147–169.4)
Median body surface area (m2; range)	1.56 (1.34–1.88)	1.58 (1.38–2.05)
Primary tumour pathology:		
Ductal	56 (93.3)	58 (96.7)
Lobular	2 (3.3)	0
Other	2 (3.3)	2 (3.3)
Stage of Cancer:		
I	2 (3.3)	3 (5.0)
II	38 (63.3)	37 (61.7)
III	20 (33.4)	20 (33.4)
History of motion sickness:	10 (16.7)	18 (30.0)
History of vomiting during pregnancy:		
Yes	33 (55.0)	27 (45.0)
Never Pregnant	8 (13.3)	11 (18.3)
Regular alcoholic drink	0	1 (1.7)
History of Smoking:		
Current	0	2 (3.3)
Former	3 (5.0)	5 (8.3)
Never	57 (95.0)	53 (88.3)
ECOG 0	59 (98.3)	57 (95.0)
AC regimen:		
3-week cycle	57 (95.0)	56 (93.3)
2-week cycle	3 (5.0)	4 (6.7)
AC treatment setting:		
Neoadjuvant	12 (20.0)	15 (25.0)
Adjuvant	48 (80.0)	45 (75.0)
Use of GCSF during AC cycles	30 (50.0)	23 (38.3)
Dose reduction required for AC from cycle 2 onward	0	3 (5.0)

Table 2
Emesis Endpoints during Cycle 1 of AC in the Acute (0–24 h), Delayed (24–120 h) and Overall time frames (0–120 h).

	Acute (0–24 h)			Delay (24–120 h)			Overall time frame (0–120 h)		
	Olanzapine (%)	Standard (%)	P	Olanzapine (%)	Standard (%)	P	Olanzapine (%)	Standard (%)	P
No vomiting	73.3	51.7	0.0142	93.2	77.4	0.0420	68.3	40.0	0.0018
No use of rescue therapy	96.7	88.3	0.0654	94.8	86.8	0.0923	91.7	76.7	0.0244
No significant nausea	95.0	75.0	0.0017	96.5	65.0	0.0316	91.7	63.3	0.0002
No nausea	76.7	53.3	0.0074	76.1	62.5	0.1955	58.3	33.3	0.0060
Complete response	70.0	51.7	0.0397	92.9	74.2	0.0254	65.0	38.3	0.0035
Complete protection	70.0	50.0	0.0253	88.1	73.3	0.1084	61.7	36.7	0.0062
Total control	65.0	41.7	0.0104	79.5	64.0	0.0911	51.7	26.7	0.0050

*Wilcoxon Rank Sum test for continuous data and chi-square test for dichotomous data.

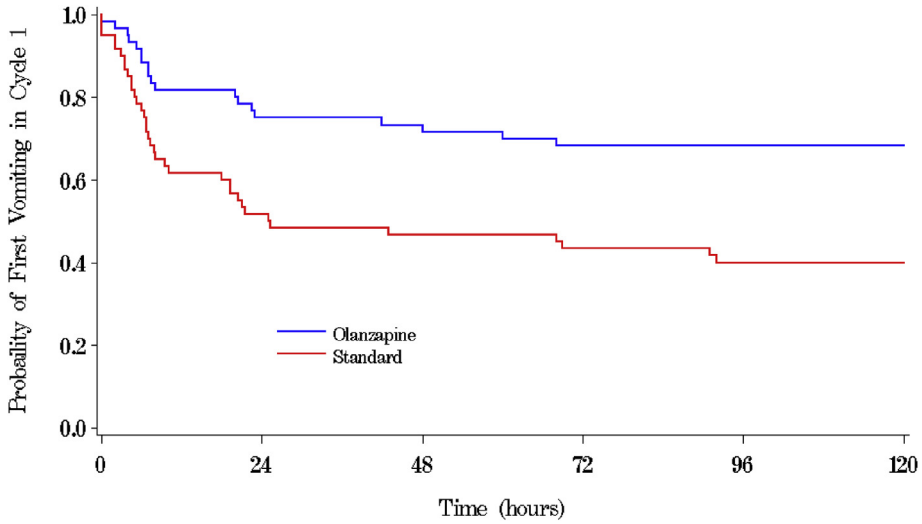

Fig. 1. Time to first vomiting episode during Cycle 1 of AC. X-axis – Time (hours) ranged from 0 to 120 h; Y-axis – Probability of First Vomiting in Cycle 1.

3.2. Toxicity assessment

When compared with the Standard arm, patients in the Olanzapine arm had a significantly lower incidence of >/ = grade 2 nausea (15.0% vs. 1.7%, p = 0.0076) while a non-significant lower rate of vomiting was also observed (1.7% vs 10%, p = 0.0505). On the other hand, there was a significantly higher rate of >/ = grade 2 neutropenia in the Olanzapine arm (61.7% vs. 38.3%, p = 0.0106), but this did not translate into a higher incidence of neutropenic fever (20.0% vs 11.7%, p = 0.2112). There was no significant difference in other adverse events (Table 5a). There were no differences in the incidences of serious adverse events, chemotherapy dose delay and dose reduction between Olanzapine and Standard arms.

Table 5b lists the metabolic profiles of the patients during the study. Pre-treatment assessments showed that nearly 40% of the studied population had abnormal fasting glucose (31.9% had impaired glucose tolerance and 7.8% had diabetes mellitus), while 34.2% had abnormal total cholesterol (31% had abnormal HDL-cholesterol, 3.4% had abnormal LDL-cholesterol) and 21% had abnormal triglyceride levels. At end of study, 51.4% of studied population had abnormal fasting glucose, (37.6% of the studied population had impaired glucose tolerance and 13.8% had diabetes mellitus), while 58.2% had abnormal total cholesterol (43.8% had abnormal HDL-cholesterol, 14.6% had abnormal LDL-cholesterol) and 48.2% had abnormal triglyceride levels. Between the Olanzapine and Standard arms, the median body weight prior to study treatment were 57.3 kg and 58.9 kg respectively; at end of study, the median body weight were 57.8 kg and 57.9 kg respectively.

4. Discussion

Nausea and vomiting are two of the most distressing symptoms associated with anti-cancer therapies. Inability to control CINV is known to impair quality of life and also jeopardizes a patient's ability to complete the full course of anti-cancer treatment. For patients on AC chemotherapy or other MEC and HEC, prior guidelines had recommended antiemetic regimens to include NK1RA and 5HT3RA together with corticosteroids.

Studies on the role of olanzapine in the control of CINV and related meta-analyses [22–24] have led to the inclusion of this agent as antiemetic in more recent international guidelines. Since the early phase II studies [10–12,25], a number of randomized studies on olanzapine have been reported [13–17,26,27]. In the study reported by Wang et al., lung cancer patients who underwent gemcitabine and cisplatin therapy were being randomized to ondansetron with or without olanzapine; olanzapine-containing regimen was reported to be superior in controlling both acute and delayed CINV [14]. When olanzapine was added to a backbone of 5HT3RA dexamethasone (administered for one or more days), a number of studies reported better control of CINV [13,15,26,27] while one did not show additional benefit with the agent [28]. Two other studies have compared the combination of olanzapine, ondansetron and dexamethasone with aprepitant, ondansetron and dexamethasone; both reported similar antiemetic efficacies between the two arms [16,17], and as such it has led Babu et al. to conclude that olanzapine could be a cost-effective alternative for the prevention of CINV in patients who need to receive HEC [17].

The present study is one of the few studies that assess the role of olanzapine in addition to the commonly recommended optimal triplet antiemetic regimen that consists of an NK1RA, a 5HT3RA and dexamethasone. In the large randomized phase III study reported by Navari et al. that included patients receiving different HEC regimens [9], the proportion of patients without nausea was significantly greater among the olanzapine-treated patients than those without olanzapine in acute (74% vs 45%), delayed (42% vs 25%) and overall periods (37% vs 22%). The Complete Response rates were also significantly increased with olanzapine in the acute (86% vs 65%), delayed (67% vs 52%) and overall (64% vs 41%) periods. More recently, a similar study design was adopted in another study that involved patients with haematological malignancies; the Complete Response rates were also significantly increased with olanzapine in the delayed (61% vs 30%) and overall (55% vs 26%) periods [29]. A third study testing a similar regimen consisted of only 44 patients with various malignances who were receiving HEC or MEC; nonetheless, the results was also in favour of the addition of olanzapine to the standard 3-agent antiemetic regimen [18]. The on-going J-FORCE study continues to assess the efficacy of olanzapine in addition to the current available antiemetic regimens [30].

The present study is unique in terms of having accrued a homogenous group of early stage breast cancer patients of Chinese ethnicity who were planned for a uniform (neo)adjuvant AC chemotherapeutic regimen. Data in terms of "Complete Response" and symptoms of nausea in the Standard arm were in line with the findings from our previous study, and confirmed that the triplet antiemetic regimen was inadequate in optimizing the control of CINV among patients receiving AC [8]. The study is in support of the findings of Navari et al. [9]. That is, the addition of olanzapine to aprepitant, ondansetron and dexamethasone provided higher rates of "Complete Response" in all three study periods. In addition, patients in the Olanzapine arm were more likely to have "No vomiting", "No significant nausea", "No nausea", "No use of rescue therapy", "Complete Protection" and "Total Control" during the 3 study periods as well as better quality of life. The benefit of olanzapine has been achieved in the absence of dexamethasone after day 1 of AC chemotherapy. On the other hand, whether the inclusion of dexamethasone on days 2–3 may further enhance the antiemetic efficacy of the Olanzapine-containing regimen could not be addressed by the current study. The addition of olanzapine was

Table 3
Quality of life based on FLIE assessment in the Overall time frame (0–120 h).

Average FLIE Score	Mean score [SD]		p
	Olanzapine arm	Standard arm	
Day 1 FLIE – total score	0.68 (3.08)	0.85 (3.19)	0.6513
Day 1 FLIE – vomiting domain	0.56 (2.63)	0.98 (3.30)	0.7175
Day 1 FLIE – nausea domain	0.80 (3.56)	0.72 (3.46)	0.5553
Day 6 FLIE – total score	6.01 (13.31)	19.2 (20.78)	<0.0001
Day 6 FLIE – vomiting domain	3.63 (11.45)	10.69 (19.99)	0.0682
Day 6 FLIE – nausea domain	8.39 (17.02)	27.71 (28.33)	<0.0001
(Day 6 – Day 1) FLIE – total score	5.33 (13.73)	18.35 (20.77)	<0.0001
(Day 6 – Day 1) FLIE – vomiting domain	3.07 (11.69)	9.72 (19.18)	0.1436
(Day 6 – Day 1) FLIE – nausea domain	7.60 (17.56)	26.99 (28.86)	<0.0001

*Wilcoxon Rank Sum test for continuous data.

Table 4
Complete response and total control over multiple cycles in the Acute (0–24 h) and Delayed (24–120 h) and Overall time frames (0–120 h).

	Acute (0–24 h)			Delayed (24–120 h)			Overall time frame (0–120 h)		
	Olanzapine (%)	Standard (%)	P	Olanzapine (%)	Standard (%)	P	Olanzapine (%)	Standard (%)	P
Complete Response									
Cycle 1	70.0	51.7	0.0397	92.9	74.2	0.0254	65.0	38.3	0.0035
Cycle 2	79.0	66.1	0.1217	88.9	87.2	0.8093	70.2	57.6	0.1598
Cycle 3	82.1	66.1	0.0502	91.3	87.2	0.2282	75.0	57.6	0.0492
Cycle 4	82.5	71.2	0.1510	89.4	81.0	0.2621	73.7	57.6	0.0689
Complete Protection									
Cycle 1	70.0	50.0	0.0253	88.1	73.3	0.1084	61.7	36.7	0.0062
Cycle 2	73.7	64.1	0.2803	88.1	86.8	0.8656	64.9	55.9	0.3229
Cycle 3	76.8	64.1	0.1459	88.4	84.2	0.5853	67.9	54.2	0.1347
Cycle 4	77.2	66.1	0.1856	88.6	79.5	0.2524	68.4	52.5	0.0805
Total Control									
Cycle 1	65.0	41.7	0.0104	79.5	64.0	0.1711	51.7	26.7	0.0050
Cycle 2	59.6	57.6	0.8250	85.3	79.4	0.5246	50.9	45.8	0.5816
Cycle 3	66.1	57.6	0.3517	83.8	79.4	0.6342	55.4	45.8	0.3037
Cycle 4	63.2	59.3	0.6717	86.1	80.0	0.4921	54.4	47.5	0.4555

*Wilcoxon Rank Sum test for continuous data.

Table 5a
Adverse events of >/ = grade 2 that occurred in >5% in either arm of studied population and adverse events of special interest.

AE	Worst Grade	Olanzapine	Standard	Total	p
Anorexia	0–1	60 (100.0)	57 (95.0)	117 (97.5)	0.1218
	>/ = 2	0	3 (5.0)	3 (2.5)	
Diarrhoea	0–1	58 (96.7)	56 (93.3)	114 (95.0)	0.2363
	>/ = 2	2 (3.3)	4 (6.7)	6 (5.0)	
Dyspepsia	0–1	59 (98.3)	57 (95.0)	116 (96.7)	0.2499
	>/ = 2	1 (1.7)	3 (5.0)	4 (3.3)	
Fatigue	0–1	56 (93.3)	52 (86.7)	108 (90.0)	0.1183
	>/ = 2	4 (6.7)	8 (13.3)	12 (10.0)	
Hypercholesterolemia	0–1	59 (98.3)	60 (100)	119 (99.2)	0.5000
	>/ = 2	1 (1.7)	0	1 (0.8)	
Hyperglycemia	0–1	59 (98.3)	60 (100)	119 (99.2)	0.5000
	>/ = 2	1 (1.7)	0	1 (0.8)	
Hypertriglyceridemia	0–1	58 (96.7)	60 (100)	118 (98.3)	0.2479
	>/ = 2	2 (3.3)	0	2 (1.7)	
Insomnia	0–1	59 (98.3)	58 (96.7)	117 (97.5)	0.3782
	>/ = 2	1 (1.7)	2 (3.3)	3 (2.5)	
Mucositis	0–1	57 (95.0)	58 (96.7)	115 (95.8)	0.3178
	>/ = 2	3 (5.0)	2 (3.3)	5 (4.2)	
Nausea	0–1	59 (98.3)	51 (85.0)	110 (91.7)	0.0076
	>/ = 2	1 (1.7)	9 (15.0)	10 (8.3)	
Neutropenia	0–1	23 (38.3)	37 (61.7)	60 (50.0)	0.0106
	>/ = 2	37 (61.7)	23 (38.3)	60 (50.0)	
Neutropenia Fever	0–1	48 (80.0)	53 (88.3)	101 (84.2)	0.2112
	>/ = 2	12 (20.0)	7 (11.7)	19 (15.8)	
Non-Neutropenia Fever	0–1	60 (100.0)	60 (100.0)	120 (100.0)	–
	>/ = 2	0	0	0	
Neutropenia Sepsis	0–1	59 (98.3)	60 (100.0)	119 (99.2)	0.5000
	>/ = 2	1 (1.7)	0	1 (0.8)	
Non-Neutropenia Sepsis	0–1	60 (100.0)	60 (100.0)	120 (100.0)	–
	>/ = 2	0	0	0	
Rash	0–1	59 (98.3)	60 (100.0)	119 (99.2)	0.5000
	>/ = 2	1 (1.7)	0	1 (0.8)	
Vomiting	0–1	59 (93.3)	54 (90.0)	113 (94.2)	0.0505
	>/ = 2	1 (1.7)	6 (10.0)	7 (5.8)	

not associated with increase toxicities. Specifically, while it has been noted that olanzapine is associated with increased somnolence and fatigue [9,17], only 6 patients (five grade 1 and one grade 2) in the Olanzapine arm and 5 patients in the Standard arm (all grade 1) in the present study experienced dizziness and no sedation has been reported. This could have been due to the fact that patients in the Olanzapine arm were advised to take olanzapine during evening time on days 2–5 after AC. Moreover, metabolic profiles were tracked in the studied patients. Baseline investigations revealed that abnormal fasting glucose occurs in 40% of the overall patient population while 34% had abnormal cholesterol levels; these patients were advised on lifestyle modifications. Further, at the discretion of the attending clinicians, some of the patients were referred to medical clinics for long term management; as a result, a minority might have commenced on medication to control their metabolic abnormalities during chemotherapy. At the end of the study, there was an apparent increase in the proportion of patients having abnormal glucose and lipids profiles, but there was no difference between the two arms. Our previous study on early stage breast cancer patients who were followed up 3 years or more after adjuvant chemotherapy have shown similar findings of dyslipidaemias [31]. The current findings

Table 5b
Pre-study and end-of-study metabolic profiles in the studied population.

		Olanzapine	Standard	p
Fasting glucose (Pre-study, N = 116;End-of-study, N = 109)	Median (range) mmol/l			
	Pre-study	5.5 (4.5–12.6)	5.40 (4.6–7.7)	0.8998
	End-of-study	5.5 (4.6–11.0)	5.6 (4.5–9.9)	0.6836
	% with abnormal levels			
	Pre-study	23 (39.0)	23 (40.3)	0.8803
	End-of-study	24 (47.1)	32 (55.2)	0.3977
	% with impaired fasting glucose			
	Pre-study	17 (28.8)	20 (35.1)	0.4686
	End-of-study	17 (33.3)	24 (41.4)	0.3869
	% diabetes mellitus			
	Pre-study	6 (10.2)	3 (5.3)	0.1729
	End-of-study	7 (13.7)	8 (13.8	0.9918
Total cholesterol (Pre-study, N = 120; End-of-study, N = 110)	Median (range) mmol/l			
	Pre-study	4.85 (3.6–7.2)	4.80 (3.4–7.1)	0.7284
	End-of-study	5.3 (3.5–7.7)	5.6 (3.2–7.5)	0.3099
	% with abnormal levels			
	Pre-study	18 (30.0)	23 (28.3)	0.3358
	End-of-study	28 (53.8)	36 (62.1)	0.3827
LDL cholesterol (Pre-study, N = 116 End-of-study, N = 103)	Median (range) mmol/l			
	Pre-study	2.7 (1.3–4.7)	2.6 (1.5–5.2)	0.6372
	End-of-study	3.1 (1.2–5.4)	3.1 (1.0–5.4)	0.9658
	% with abnormal levels			
	Pre-study	3 (5.2)	1 (1.7)	0.2499
	End-of-study	8 (16.0)	7 (13.2)	0.6880
HDL cholesterol (Pre-study, N = 116;End-of-study, N = 105)	Median (range) mmol/l			
	Pre-study	1.65 (0.9–2.8)	1.50 (0.7–2.3)	0.0910
	End-of-study	1.3 (0.6–2.5)	1.4 (0.7–2.5)	0.0741
	% with abnormal levels			
	Pre-study	21 (36.2)	15 (25.9)	0.2285
	End-of-study	26 (51.0)	20 (37.0)	0.1501
Triglycerides (Pre-study, N = 120; End-of-study, N = 110)	Median (range) mmol/l			
	Pre-study	1.2 (0.5–4.3)	1.1 (0.4–4.4)	0.5491
	End-of-study	1.6 (0.8–7.4)	1.7 (0.6–10.9)	0.9570
	% with abnormal levels			
	Pre-study	13 (21.7)	13 (21.7)	1.0000
	End-of-study	24 (46.2)	29 (50.0)	0.6869
Body weight (Pre-study, N = 120; End-of-study, N = 120)	Median (range) mmol/l			
	Pre-study	57.3 (41.6–82.7)	58.9 (44.5–100.4)	0.2184
	End-of-study	57.8 (42.3–81.2)	57.8 (46.5–105.0)	0.4326

*Wilcoxon Rank Sum test for continuous data and chi-square test for dichotomous data.
Definitions for biochemistry: Normal fasting glucose <5.6 mmol/l; impaired fasting glucose 5.6–6.9 mmol/l; diabetes mellitus, fasting glucose >/ = 7.0 mmol/l; normal total cholesterol <5.2 mmol/l; normal LDL cholesterol <4.1 mmol/l; normal HDL cholesterol >1.3 mmol/l; normal triglycerides <1.7 mmol/l.

are limited by the fact that detailed follow-up on the management of the detected metabolic abnormalities were lacking; nonetheless, the data indicate that many patients had already had abnormal glucose and lipid metabolism at the time of their breast cancer diagnosis. Another limitation in this study would be the lack of information with respect to patients' anxiety and physical activity, as well as quantification of their motion sickness and vomiting during pregnancy, as these could be potential confounding factors. Further, due to the absence of a placebo-controlled design for this study, a placebo effect of olanzapine could not be ruled out.

In conclusion, the present study is the first study to reveal that the addition of olanzapine to standard antiemetic regimen containing aprepitant, ondansetron and dexamethasone in Chinese breast cancer patients who were receiving (neo)adjuvant AC chemotherapy improves the control of CINV in a statistically significant and clinically meaningful manner and is associated with better quality of life. The benefit with incorporating olanzapine according to the present study regimen could reduce the need of dexamethasone requirement on days 2–3 after chemotherapy. Special attention is noted on the metabolic abnormalities identified at breast cancer diagnosis among the study population, and further assessment of the effects of lifestyle modifications and appropriate medical therapy is warranted for this aspect.

Contribution

Conception and design: Winnie Yeo, Thomas Lau.
Assembly of data: All authors.
Data analysis and interpretation: Frankie Mo, Winnie Yeo.
Manuscript writing: All authors.
Final approval of manuscript: All authors.

Ethical standards

All procedures performed in this study were in accordance with the ethical standards of the institutional committee (the Joint CUHK-NTEC Institution Review Board of the Chinese University of Hong Kong) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Data availability statement

The data that support the findings of this study are available from the Comprehensive Cancer Trials Unit of the Department of Clinical Oncology, Chinese University of Hong Kong, but restrictions apply to the availability of these data. These data were used under permission for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request.

Declaration of competing interest

WY reports consultancy/advisory roles and receipt of personal fees for Novartis, Pfizer, AstraZeneca, Eli Lilly, Roche, Mundipharma and Amgen.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.01.005.

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