Evaluation of contemporary olanzapine- and netupitant/palonosetron-containing antiemetic regimens for chemotherapy-induced nausea and vomiting

Christopher CH Yip, L Li, Thomas KH Lau, Vicky TC Chan, Carol CH Kwok, Joyce JS Suen, Frankie KF Mo, Winnie Yeo *

A B S T R A C T

Introduction: This post-hoc analysis retrospectively assessed data from two recent studies of antiemetic regimens for chemotherapy-induced nausea and vomiting (CINV). The primary objective was to compare olanzapine-based versus netupitant/palonosetron (NEPA)-based regimens in terms of controlling CINV during cycle 1 of doxorubicin/cyclophosphamide (AC) chemotherapy; secondary objectives were to assess quality of life (QOL) and emesis outcomes over four cycles of AC.

Methods: This study included 120 Chinese patients with early-stage breast cancer who were receiving AC; 60 patients received the olanzapine-based antiemetic regimen, whereas 60 patients received the NEPA-based antiemetic regimen. The olanzapine-based regimen comprised aprepitant, ondansetron, dexamethasone, and olanzapine; the NEPA-based regimen comprised NEPA and dexamethasone. Patient outcomes were compared in terms of emesis control and QOL.

Results: During cycle 1 of AC, the olanzapine group exhibited a higher rate of 'no use of rescue therapy' in the acute phase (olanzapine vs NEPA: 96.7% vs 85.0%, P=0.0225). No parameters differed between groups in the delayed phase. The olanzapine group had significantly higher rates of 'no use of rescue therapy' (91.7% vs 76.7%, P=0.0244) and 'no significant nausea' (91.7% vs 78.3%, P=0.0408) in the overall phase. There were no differences in QOL between groups. Multiple cycle assessment revealed that the NEPA group had higher rates of total control in the acute phase (cycles 2 and 4) and the overall phase (cycles 3 and 4).

Conclusion: These results do not conclusively support the superiority of either regimen for patients with breast cancer who are receiving AC.

Hong Kong Med J 2023;29:49–56
https://doi.org/10.12809/hkmj209182

[1] **CCH Yip**
[1] **L Li,** MB, BS, FHKAM (Medicine)
[1] **TKH Lau,** MB, BS, FHKAM (Medicine)
[1] **VTC Chan,** MB, BS, FHKAM (Medicine)
[2] **CCH Kwok,** MB, BS, FHKAM (Radiology)
[2] **JJS Suen,** MB, BS, FHKAM (Radiology)
[1] **FKF Mo,** PhD
[1] **W Yeo *,** MB, BS, FHKAM (Medicine)

[1] *Department of Clinical Oncology, Prince of Wales Hospital, Hong Kong*
[2] *Department of Clinical Oncology, Princess Margaret Hospital, Hong Kong*

* Corresponding author: winnieyeo@cuhk.edu.hk

New knowledge added by this study

- The olanzapine-based regimen (aprepitant, ondansetron, dexamethasone, and olanzapine) and the NEPA-based regimen (netupitant, palonosetron, and dexamethasone) demonstrated similar efficacies in terms of controlling chemotherapy-induced nausea and vomiting among patients with early-stage breast cancer.
- Quality of life did not significantly differ between patients receiving the olanzapine-based regimen and patients receiving the NEPA-based regimen.

Implications for clinical practice or policy

- The available data suggest that olanzapine-containing antiemetic regimens can be used without aprepitant, particularly when seeking to reduce medical expenses.
- Antiemetic efficacy may potentially be enhanced if NEPA is administered in combination with dexamethasone and olanzapine as a four-drug antiemetic regimen.

Introduction

Patients with breast cancer receiving (neo)adjuvant treatment exhibit improved prognoses.[1] However, chemotherapy regimens for breast cancer are associated with various degrees of chemotherapy-induced nausea and vomiting (CINV). The doxorubicin/cyclophosphamide (AC) regimen is one of the most frequently prescribed regimens for patients with breast cancer who are receiving (neo) adjuvant chemotherapy; AC is among the highly

評估現代兩項針對化療引起的噁心和嘔吐進行的研究——含有奧氮平與奈妥吡坦 / 帕洛諾司瓊的止吐方案

葉鎮熙、李良、劉君恒、陳冬青、郭子熹、孫再詩、巫國輝、楊明明

簡介：我們使用了最近兩項針對化療引起的噁心和嘔吐（CINV）進行的止吐研究的數據，報告了一項回顧性分析。主要目標是比較阿黴素 / 環磷酰胺（AC）化療第1週期中含有奧氮平與奈妥吡坦 / 帕洛諾司瓊（NEPA）兩項止吐方案在控制CINV中的作用；次要目標是評估四個AC週期的生活質量和嘔吐結果。

方法：本研究包括了120例接受了AC的中國籍早期乳腺癌患者，每個止吐方案各佔60例。基於奧氮平的四藥物治療止吐方案由阿瑞匹坦、昂丹司瓊、地塞松及奧氮平組成，而基於NEPA的三藥物治療方案則由NEPA（奈妥吡坦及帕洛諾司瓊組合）和地塞松組成。本研究比較患者的嘔吐控制及生活質量。

結果：在AC的第1週期，奧氮平組於急性階段的「不使用急救療法」的發生率較NEPA組為高（96.7%比85%，P=0.0225）。所有研究參數在延遲階段均未發現差異。在總體階段，奧氮平組的「不使用急救療法」（91.7%比76.7%，P=0.0244）和「無明顯噁心」（91.7%比78.3%，P=0.0408）的發生率明顯更高。 兩組的生活質量未檢測到差異。多周期評估顯示，基於NEPA的方案在急性階段（週期2和4）及整個階段（週期3和4）的總體控制率較高。

結論：在接受AC的乳腺癌患者的臨床設置中，這項研究的結果最終不能支持上述的其中一種止吐方案比另外一種止吐方案優越。

emetogenic chemotherapies with ≥90% risk of nausea and vomiting.

In situations where a neurokinin-1 receptor antagonist (NK1RA) is accessible, most current guidelines for AC(-like) chemotherapy recommend the use of a prophylactic triplet antiemetic regimen that consists of an NK1RA, a 5-hydroxytryptamine type-3 receptor antagonist (5HT3RA), and a corticosteroid, with or without olanzapine.[2-4] In addition to earlier NK1RAs (eg, aprepitant, fosaprepitant, and rolapitant), netupitant/palonosetron (NEPA) [Akynzeo], which is a combination of an NK1RA (netupitant 100 mg) and a second-generation 5HT3RA (palonosetron 0.5 mg), has been available in the past decade. Although palonosetron constitutes a more potent 5HT3RA,[5] it also has synergistic interactions with netupitant that include interference with 5HT3 receptor cross-talk and enhancement of the netupitant-mediated effect on NK1 receptor internalisation.[6,7]

In a recent systematic review and meta-analysis, Yokoe et al[8] compared different antiemetic regimens to assess their control of CINV in patients receiving highly emetogenic chemotherapy regimens. The authors arbitrarily defined the 'conventional' regimen as a three-drug regimen that contained dexamethasone, a first- or second-generation 5HT3RA, and an earlier NK1RA compound (aprepitant, fosaprepitant, or rolapitant); they defined 'new' regimens as regimens that contained NEPA or olanzapine. The results indicated that, compared with conventional regimens, new regimens containing NEPA were more effective in terms of producing a complete response (ie, absence of vomiting and no use of rescue therapy). Additionally, Yokoe et al[8] showed that olanzapine-containing regimens were most effective in terms of producing a complete response, particularly when olanzapine was added to a triplet regimen of an NK1RA, a 5HT3RA, and dexamethasone. These findings were supported by the results of a prospective randomised study published in 2020, which directly compared an olanzapine-containing four-drug regimen with a standard triplet antiemetic regimen (consisting of aprepitant, ondansetron, and dexamethasone) for the prevention of CINV in patients receiving AC chemotherapy.[9]

Here, we conducted a post-hoc analysis through retrospective assessment of individual patient data from two previously reported prospective antiemetic studies that involved Chinese patients with breast cancer.[9,10] We hypothesised that a four-drug antiemetic regimen (consisting of an NK1RA, a 5HT3RA, dexamethasone, and olanzapine) would remain superior to a three-drug regimen (consisting of an NK1RA, a 5HT3RA, and dexamethasone) that included NEPA as a combination NK1RA and 5HT3RA agent. The primary objective was to compare the efficacies of olanzapine- and NEPA-containing antiemetic regimens in terms of controlling CINV during the first cycle of AC. The secondary objectives were: (1) to assess quality of life (QOL) outcomes in patients receiving these treatments during the first cycle of AC, and (2) to assess emesis control outcomes in patients receiving these treatments over multiple cycles of AC.

Methods

Patients

This study constituted a post-hoc analysis of data from two recently reported prospective studies. The first prospective study investigated emesis outcomes in patients with breast cancer who received a standard triplet antiemetic regimen (ie, aprepitant, ondansetron, and dexamethasone) with or without olanzapine[9]; after the first study, a second prospective study was conducted to assess the antiemetic efficacy of NEPA and dexamethasone.[10] These studies were conducted with institutional ethics approval and were registered at ClinicalTrials.gov (NCT03386617 and NCT03079219, respectively). For the post-hoc analysis, data were extracted from the first study regarding patients who received an olanzapine plus aprepitant-containing four-drug antiemetic regimen;

data were extracted from the second study regarding patients who received NEPA and dexamethasone. These patients were categorised into the 'olanzapine' and 'NEPA' groups, respectively.

Inclusion criteria were similar for the two studies. Specifically, patients were eligible if they were women of Chinese ethnicity, were aged >18 years, had early-stage breast cancer, and planned to receive a regimen of (neo)adjuvant AC. All study participants were required to read, understand, and complete study questionnaires and diaries in Chinese. Exclusion criteria included abnormal bone marrow, renal, or hepatic functions; receipt or planned receipt of radiation therapy to the abdomen or pelvis within 7 days prior to initial administration of study treatment; presence of grade 2 to 3 nausea, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0,[11] or vomiting within 24 hours prior to initial administration of the study treatment; presence of an active infection or any uncontrolled disease; a history of illicit drugs, including marijuana or alcohol abuse; mental incapacitation; and/or presence of a clinically significant emotional or psychiatric disorder. Written consent was provided by eligible patients prior to enrolment in the studies.

Study treatment

Patients in the olanzapine group received olanzapine 10 mg, aprepitant 125 mg, dexamethasone 12 mg, and ondansetron 8 mg before chemotherapy on day 1; they also received ondansetron 8 mg 8 hours after chemotherapy. Subsequently, they received aprepitant 80 mg daily on days 2-3 and olanzapine 10 mg daily on days 2-5.

Patients in the NEPA group received one capsule of NEPA (netupitant 300 mg/palonosetron 0.50 mg) with dexamethasone 12 mg before chemotherapy on day 1. Subsequently, they received dexamethasone 4 mg twice per day on days 2-3.

Study assessments

At the initiation of chemotherapy on day 1, individual patients were provided a diary to record the date and time of their symptoms of vomiting and nausea for 120 hours after the AC infusion; the use of any rescue medication was also recorded. On days 2-6, patients rated their symptoms of nausea for the previous 24 hours using a visual analogue scale (in which 0 mm implied no nausea, whereas 100 mm implied nausea that was 'as bad as it could be'). Additionally, on day 1 (before infusion of AC) and day 6 (after completion of the diary), patients completed the Functional Living Index-Emesis (FLIE) questionnaire. A research nurse/assistant called individual patients on days 2-6 to remind them to take the study medications, complete the patient diary, and complete the FLIE questionnaire.

Assessment of efficacy and safety

Antiemetic efficacy was measured across three overlapping time periods. The 'acute' phase comprised 0 to 24 hours from the infusion of AC; the 'delayed' phase comprised 24 to 120 hours from the infusion of AC; the 'overall' phase comprised 0 to 120 hours from the infusion of AC.

Variables used to assess antiemetic efficacy were 'complete response', 'no vomiting', 'no significant nausea', 'no nausea', 'no use of rescue therapy', 'complete protection', and 'total control'; definitions of these variables are provided in Table 1. The proportions of patients who exhibited these variables were recorded separately. Additionally, the 'time to first vomiting' in cycle 1 was determined using information recorded in patients' diaries.

Quality of life was evaluated using the Chinese version of self-reported FLIE questionnaires from individual patients.[12] The FLIE questionnaire consists of a nausea domain (9 items) and a vomiting domain (9 items). All scores were transformed to ensure that higher scores indicated worse impact on QOL.

Statistical analyses

A modified intention-to-treat approach was used for all efficacy analyses; specifically, analyses included patients who had received chemotherapy, had completed the study procedures from 0 to 120 hours in cycle 1 of AC, and had no major protocol violations.

To achieve the primary objective of this study, the efficacies of the two antiemetic regimens were based on the proportions (including 95% confidence intervals) of patients who achieved complete response during the acute, delayed, and overall phases after AC infusion in cycle 1. Other parameters compared in cycle 1 of AC were 'time to first vomiting', 'no vomiting', 'no significant nausea', no nausea', 'no use of rescue therapy', 'complete protection', and 'total control'.

To achieve the secondary objectives, QOL was compared between the two antiemetic regimens

TABLE 1. Definitions of variables used to assess antiemetic efficacy

Variable	Definition
No vomiting	No vomiting or retching, including among patients who received rescue therapy
No significant nausea	Nausea VAS value <25 mm
No nausea	Nausea VAS value <5 mm
Complete response	No vomiting and no use of rescue therapy
Complete protection	No vomiting, no rescue therapy, and nausea VAS value <25 mm
Total control	No vomiting, no rescue therapy, and nausea value <5 mm

Abbreviation: VAS = visual analogue scale

based on assessments of the nausea domain, vomiting domain, and total score (sum of nausea and vomiting domains) of the FLIE questionnaire during cycle 1 of AC. Emesis control over multiple cycles was compared between the two antiemetic regimens by assessing the proportions (including 95% confidence intervals) of patients who achieved 'complete response', 'complete protection', and 'total control' in the acute, delayed, and overall phases.

Comparisons between the two antiemetic regimens were made using the Wilcoxon rank-sum test for continuous data and Pearson's Chi squared test for dichotomous data. Two-sided P values <0.05 were considered statistically significant. The SAS Software version 9.4 (SAS Institute, Cary [NC], United States) was used for analyses.

TABLE 2. Baseline characteristics of Chinese patients with early-stage breast cancer included in this analysis*

		Olanzapine group (n=60)	NEPA group (n=60)
Age, y		54.5 (36-71)	56 (30-69)
Body weight, kg		57.3 (41.6-82.7)	55.6 (38.9-87.9)
Body height, cm		157 (143-168.8)	157 (146-170)
Body surface area, m^2		1.56 (1.34-1.88)	1.56 (1.31-1.94)
Primary diagnosis	Ductal	56 (93.3%)	55 (91.7%)
	Lobular	2 (3.3%)	3 (5.0%)
	Other	2 (3.3%)	2 (3.3%)
Stage of cancer	I	2 (3.3%)	3 (5.0%)
	II	38 (63.3%)	40 (66.7%)
	IIIa	4 (6.7%)	12 (20.0%)
	IIIb	6 (10.0%)	3 (5.0%)
	IIIc	10 (16.7%)	2 (3.3%)
Motion sickness	Yes	10 (16.7%)	21 (35.0%)
Vomiting during pregnancy	Yes	33 (55.0%)	24 (40.0%)
	Never pregnant	8 (13.3%)	4 (6.7%)
Habit of taking alcoholic drinks†	Yes	0	2 (3.3%)
Ever smoker	Yes	3 (5.0%)	3 (5.0%)
ECOG PS	0	59 (98.3%)	59 (98.3%)
	1	1 (1.7%)	1 (1.7%)
Treatment setting	Neoadjuvant	12 (20.0%)	18 (30.0%)
	Adjuvant	48 (80.0%)	42 (70.0%)
Compliance with study medications	Cycle 1	60 (100%)	60 (100%)
	Cycle 2	57 (95.0%)	60 (100%)
	Cycle 3	56 (93.3%)	60 (100%)
	Cycle 4	57 (95.0%)	60 (100%)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; NEPA = netupitant/palonosetron

* Data are shown as No. (%) or median (range)

† Including patients who drank very occasionally

Results

Patient characteristics

Data from 120 patients were included in this study; 60 patients each were enrolled in the NEPA and olanzapine groups. Fifty-six patients (93.3%) in the olanzapine group completed all four cycles of AC, whereas 60 patients (100%) in the NEPA group completed all four cycles of AC.

Patient characteristics, including characteristics that could potentially affect CINV, are shown in Table 2. The olanzapine and NEPA groups had very similar patient characteristics, with median ages of 54.5 and 56 years, respectively. Nearly two-thirds of patients in each group had Stage II breast cancer (63.3% and 66.7%, respectively). The percentage of patients with a history of motion sickness was higher in the NEPA group (35%) than in the olanzapine group (16.7%). Furthermore, 30% of patients in the NEPA group and 20% of patients in the olanzapine group received AC as neoadjuvant treatment.

Efficacy assessment

Antiemetic efficacies during cycle 1 of AC in the olanzapine and NEPA groups are shown in Table 3. Complete response rates in acute, delayed, and overall phases in cycle 1 did not differ between groups. In the acute phase, the olanzapine group exhibited a higher rate of 'no use of rescue therapy' (olanzapine vs NEPA: 96.7% vs 85.0%, P=0.0225). No parameters differed between groups in the delayed phase. In the overall phase, the olanzapine group exhibited significantly higher rates of 'no use of rescue therapy' (91.7% vs 76.7%, P=0.0244) and 'no significant nausea' (91.7% vs 78.3%, P=0.0408).

The median time to first vomiting was not reached in either group (P=0.3902). Quality of life results during cycle 1 of AC in the olanzapine and NEPA groups, determined using the FLIE questionnaire, are shown in the Figure. There were no significant differences in the nausea domain, vomiting domain, or total score of the FLIE questionnaire between the two groups.

Antiemetic efficacies over multiple cycles of AC in the olanzapine and NEPA groups are shown in Table 4. In the acute phase, the NEPA group exhibited significantly higher rates of total control in cycle 2 (olanzapine vs NEPA: 59.6% vs 81.7%, P=0.0087) and cycle 4 (63.2% vs 86.7%, P=0.0032). No parameters differed between groups in the delayed phase. In the overall phase, the NEPA group exhibited significantly higher rates of total control in cycle 3 (55.4% vs 73.3%, P=0.0430) and cycle 4 (54.4% vs 75.0%, P=0.0195).

TABLE 3. Comparison of antiemetic efficacy during cycle 1 of doxorubicin/cyclophosphamide between olanzapine and netupitant/palonosetron groups*

	Acute (0-24 hours)			Delayed (24-120 hours)†			Overall (0-120 hours)		
	Olanzapine group	NEPA group	P value	Olanzapine group	NEPA group	P value	Olanzapine group	NEPA group	P value
No vomiting	44 (73.3%)	43 (71.7%)	0.8380	41 (93.2%)	37 (86.0%)	0.1574	41 (68.3%)	37 (61.7%)	0.4439
No use of rescue therapy	58 (96.7%)	51 (85.0%)	0.0225	55 (94.8%)	46 (90.2%)	0.1908	55 (91.7%)	46 (76.7%)	0.0244
No significant nausea	57 (95.0%)	52 (86.7%)	0.0754	55 (96.5%)	47 (90.4%)	0.1392	55 (91.7%)	47 (78.3%)	0.0408
No nausea	46 (76.7%)	42 (70.0%)	0.4090	35 (76.1%)	32 (76.2%)	0.9909	35 (58.3%)	32 (53.3%)	0.5813
Complete response	42 (70.0%)	42 (70.0%)	1.0000	39 (92.9%)	36 (85.7%)	0.1636	39 (65.0%)	36 (60.0%)	0.5716
Complete protection	42 (70.0%)	40 (66.7%)	0.6947	37 (88.1%)	34 (85.0%)	0.6810	37 (61.7%)	34 (56.7%)	0.5774
Total control	39 (65.0%)	38 (63.3%)	0.8490	31 (79.5%)	29 (76.3%)	0.7373	31 (51.7%)	29 (48.3%)	0.7150

Abbreviation: NEPA = netupitant/palonosetron

* Data are shown as No. (%), unless otherwise specified

† Calculated based on the same number of patients assessed for acute phase

Discussion

Chemotherapy-induced nausea and vomiting is a frustrating adverse effect for patients receiving anticancer treatment.[13] The administration of optimal antiemetic prophylaxis can help to maintain QOL, while potentially improving patient compliance in terms of completing planned therapies. In current antiemetic prophylaxis guidelines, the European Society of Medical Oncology/Multinational Association of Supportive Care in Cancer, the American Society of Clinical Oncology, and the United States National Comprehensive Cancer Network offer several options regarding antiemetic regimens for patients receiving AC(-like) chemotherapy. These options mainly involve the combination of a 5HT3RA and corticosteroids, with or without an NK1RA and olanzapine.[2-4] In particular, the incorporation of olanzapine, an antipsychotic drug with antagonistic effects on various receptors (eg, dopamine and serotonin receptors),[14] is increasingly regarded as a component of antiemetic prophylaxis for patients receiving anticancer treatment.

In an attempt to identify the best antiemetic regimen, Yokoe et al[8] conducted a meta-analysis of randomised trials that tested various antiemetic regimens. The results indicated that olanzapine-based regimens demonstrated the best efficacy. Specifically, olanzapine in combination with an NK1RA, a 5HT3RA, and dexamethasone exhibited the greatest efficacy; other olanzapine-containing regimens (consisting of a 5HT3RA and dexamethasone) were also superior to regimens that lacked olanzapine. Moreover, even in the presence of earlier NK1RAs (eg, aprepitant, fosaprepitant, or rolapitant), regimens lacking olanzapine remained inferior.

Similar to the findings with olanzapine, Yokoe et al[8] reported that triplet antiemetics involving NEPA were superior to conventional NK1RAs (eg, aprepitant, fosaprepitant, or rolapitant). Furthermore, Zhang et al[15] directly compared NEPA-based antiemetic regimens with aprepitant-based triplet regimens in a randomised study that involved 800 patients who underwent administration of a cisplatin-containing regimen. Their results revealed that patients receiving NEPA and dexamethasone exhibited similar control of CINV, compared with patients receiving aprepitant, granisetron, and dexamethasone; however, NEPA-treated patients had a significantly lower requirement for rescue therapy. Additionally, in a recent study focused on patients with breast cancer who were undergoing AC chemotherapy, patients who received NEPA and dexamethasone demonstrated significantly higher rates of complete response, complete protection, and total control with enhanced QOL, compared to historical controls who received aprepitant, ondansetron, and dexamethasone; these benefits persisted over multiple cycles of chemotherapy.[10]

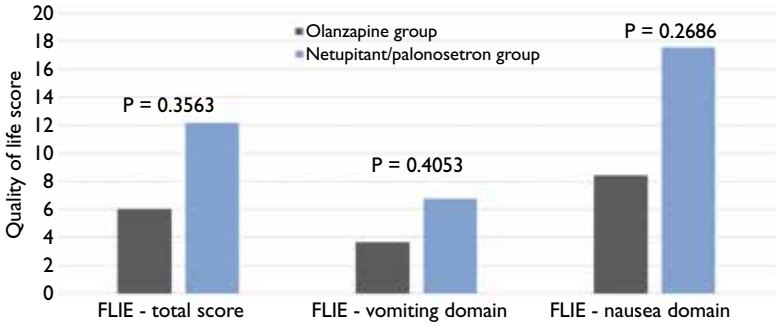

FIG. Comparison of quality of life (assessed using Functional Living Index-Emesis questionnaire) throughout cycle 1 of doxorubicin/cyclophosphamide between olanzapine and netupitant/palonosetron groups

Abbreviation: FLIE = Functional Living Index-Emesis

TABLE 4. Comparison of complete response, complete protection, and total control over multiple cycles between olanzapine and netupitant/palonosetron groups*

	Acute (0-24 hours)			Delayed (24-120 hours)†			Overall (0-120 hours)		
	Olanzapine group	NEPA group	P value	Olanzapine group	NEPA group	P value	Olanzapine group	NEPA group	P value
Complete response									
Cycle 1	42 (70.0%)	42 (70.0%)	1.0000	39 (92.9%)	36 (85.7%)	0.1636	39 (65.0%)	36 (60.0%)	0.5716
Cycle 2	45 (78.9%)	51 (85.0%)	0.3938	40 (88.9%)	47 (92.2%)	0.2355	40 (70.2%)	47 (78.3%)	0.3124
Cycle 3	46 (82.1%)	53 (88.3%)	0.3462	42 (91.3%)	52 (98.1%)	0.1209	42 (75.0%)	52 (86.7%)	0.1092
Cycle 4	47 (82.5%)	53 (88.3%)	0.3672	42 (89.4%)	52 (98.1%)	0.0682	42 (73.7%)	52 (86.7%)	0.0774
Complete protection									
Cycle 1	42 (70.0%)	40 (66.7%)	0.6947	37 (88.1%)	34 (85.0%)	0.6810	37 (61.7%)	34 (56.7%)	0.5774
Cycle 2	42 (73.7%)	51 (85.0%)	0.1297	37 (88.1%)	46 (90.2%)	0.7448	37 (64.9%)	46 (76.7%)	0.1616
Cycle 3	43 (76.8%)	52 (86.7%)	0.1672	38 (88.4%)	49 (94.2%)	0.1750	38 (67.9%)	49 (81.7%)	0.0861
Cycle 4	44 (77.2%)	53 (88.3%)	0.1096	39 (88.6%)	49 (92.5%)	0.2225	39 (68.4%)	49 (81.7%)	0.0972
Total control									
Cycle 1	39 (65.0%)	38 (63.3)	0.8490	31 (79.5%)	29 (76.3%)	0.7373	31 (51.7%)	29 (48.3%)	0.7150
Cycle 2	34 (59.6%)	49 (81.7%)	0.0087	29 (85.3%)	39 (79.6%)	0.5067	29 (50.9%)	39 (65.0%)	0.1217
Cycle 3	37 (66.1%)	48 (80.0%)	0.0903	31 (83.8%)	44 (91.7%)	0.1446	31 (55.4%)	44 (73.3%)	0.0430
Cycle 4	36 (63.2%)	52 (86.7%)	0.0032	31 (86.1%)	45 (86.5%)	0.9542	31 (54.4%)	45 (75.0%)	0.0195

* Data are shown as No. (%), unless otherwise specified

† Calculated based on the same number of patients assessed for acute phase

To our knowledge, no study has directly compared olanzapine- and NEPA-containing regimens. Using an indirect comparison approach, the present study showed that the olanzapine-based regimen had higher rates of 'no use of rescue therapy' and 'no significant nausea' in cycle 1 of AC, compared to the NEPA-based regimen. In contrast, assessments in subsequent cycles revealed that the NEPA-based regimen led to higher rates of total control in the acute phase (cycles 2 and 4) and the overall phase (cycles 3 and 4). The lack of difference in QOL between the two groups of patients may be related to the difference in adverse-effect profiles of the antiemetics used. For instance, the continued use of dexamethasone on days 2-3 in the NEPA group may have affected QOL among those patients because of its effects on mood, insomnia, gastrointestinal symptoms, and metabolic profiles.[16] Indeed, a recent meta-analysis showed that, among patients receiving AC or moderately emetogenic chemotherapy, 3 days of dexamethasone did not provide additional benefit compared to 1 day of the agent.[17] However, olanzapine has been associated with sedation and somnolence.[18] Thus, after the completion of a phase 2 trial in Japan that suggested olanzapine was more effective at 5 mg than at 10 mg,[19] the same group of investigators conducted a phase 3 study in which they tested the addition of daily olanzapine 5 mg to an aprepitant-based three-drug regimen; the results showed that, even at a lower dose of olanzapine, the olanzapine-containing regimen remained more efficacious than the olanzapine-free regimen for patients receiving cisplatin.[20] Other adverse effects have been reported. Our analysis of olanzapine in combination with aprepitant, ondansetron and dexamethasone revealed a significantly higher incidence of grade ≥2 neutropenia in the olanzapine arm than in the standard arm, although this altered incidence was not associated with a significant difference in neutropenic fever.[9] A few cases of olanzapine-induced neutropenia have been reported[21]; additionally, a recent randomised antiemetic study showed that patients who received an olanzapine-containing regimen had a higher frequency of severe neutropenia (without an increased incidence of neutropenic fever).[22] Although the underlying mechanism remains unknown, the results of the aforementioned Japanese study[20] suggest that olanzapine 5 mg could reduce the incidence of neutropenia. In contrast, in our previous trial regarding a NEPA-based regimen, we found that patients in the NEPA arm had significantly lower incidences of grade ≥2 neutropenia and neutropenic fever, compared to historical controls who received an aprepitant-based regimen.[9,10]

This study had some potential limitations. First, dexamethasone was only used for 1 day in the olanzapine-based regimen, whereas it was administered for 3 days in the NEPA-based regimen; this difference may have influenced the findings.

Second, the use of data from two separate studies may have affected the generalisability of the findings because of slight variations in patient characteristics; the lack of blinding in both studies also increased the potential for patient-related reporting biases. Nonetheless, the original studies were consecutively conducted during the period from 2017 to 2019; both the data from Chinese patients enrolled in a homogenous group with early-stage breast cancer who were receiving (neo)adjuvant AC chemotherapy and the present analysis were analysed based on individual patient data. These factors support the validity of our comparison approach.

Conclusion

In conclusion, the present findings do not conclusively support the superiority of either the olanzapine-based regimen or the NEPA-based regimen in terms of antiemetic efficacy or QOL among patients with breast cancer who are receiving AC. Our previous study demonstrated that aprepitant has a limited effect when used with a 5HT3RA and dexamethasone[23]; we also found that NEPA was superior to aprepitant.[10] Overall, the available data suggest that olanzapine-containing antiemetic regimens can be used without aprepitant, particularly when seeking to reduce medical expenses. Moreover, the available data support the previous conclusion that, in parts of the world where socio-economic limitations restrict the availability of NK1RAs, the use of olanzapine combined with a 5HT3RA and dexamethasone may be an effective low-cost alternative antiemetic regimen.[8,24] Antiemetic efficacy may be enhanced if NEPA is administered in combination with dexamethasone and olanzapine as a four-drug antiemetic regimen; however, the efficacy of an olanzapine plus NEPA regimen in terms of controlling CINV should be confirmed in a trial setting.

Author contributions

Concept or design: W Yeo.
Acquisition of data: FKF Mo, W Yeo.
Analysis or interpretation of data: W Yeo, CCH Yip, FKF Mo.
Drafting of the manuscript: W Yeo, CCH Yip.
Critical revision of the manuscript for important intellectual content: L Li, TKH Lau, VTC Chan, CCH Kwok, JJS Suen, FKF Mo.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

W Yeo has been involved in the Chemotherapy-Induced Nausea and Vomiting (CINV) Network in Asia and has provided lectures on CINV at events organised by Mundipharma International Limited, which supported the design of the NEPA study[10] analysed in this post-hoc analysis but had no role in the present comparative analysis, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgement

We thank Ms Dong KT Lai, Ms Elizabeth Pang, Ms Vivian Chan, and Ms Maggie Cheung of the Department of Clinical Oncology, The Chinese University of Hong Kong for their support in contributing to patient enrolment and study monitoring.

Declaration

Data from this study were presented at the European Society of Medical Oncology Asia Virtual Congress 2020 on 27 November 2020.

Funding/support

This study was supported by an education grant from Madam Diana Hon Fun Kong Donation for Cancer Research (Grant No.: CUHK Project Code 7104870). The Donation had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethics approval

The studies examined in this post-hoc analysis were approved by The Joint Chinese University of Hong Kong–New Territories East Cluster Institution Review Board of The Chinese University of Hong Kong and the Hong Kong Hospital Authority, and the Kowloon West Cluster Research Ethics Committee of the Hong Kong Hospital Authority (Ref No.: CREC 2016.013, CREC 2017.1609 and KW/FR-18-019[119-19]). All patient data in this study were anonymous and were based on the abovementioned reported studies. There was no additional work on retrieving patient records in this study.

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379:432-44.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology, Antiemesis Version 1; 2019.
3. Herrstedt J, Roila F, Warr D, et al. 2016 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following high emetic risk chemotherapy. Support Care Cancer 2017;25:277-88.
4. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline update. J Clin Oncol 2017;35:3240-61.
5. Popovic M, Warr DG, Deangelis C, et al. Efficacy and safety of palonosetron for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis of randomized controlled trials. Support Care Cancer 2014;22:1685-97.
6. Thomas AG, Stathis M, Rojas C, Slusher BS. Netupitant and palonosetron trigger NK1 receptor internalization in NG108-15 cells. Exp Brain Res 2014;232:2637-44.
7. Stathis M, Pietra C, Rojas C, Slusher BS. Inhibition of substance P-mediated responses in NG108-15 cells by

netupitant and palonosetron exhibit synergistic effects. Eur J Pharmacol 2012;689:25-30.
8. Yokoe T, Hayashida T, Nagayama A, et al. Effectiveness of antiemetic regimens for highly emetogenic chemotherapy-induced nausea and vomiting: a systematic review and network meta-analysis. Oncologist 2019;24:e347-57.
9. Yeo W, Lau TK, Li L, et al. A randomized study of olanzapine-containing versus standard antiemetic regimens for the prevention of chemotherapy-induced nausea and vomiting in Chinese breast cancer patients. Breast 2020;50:30-8.
10. Yeo W, Lau TK, Kwok CC, et al. NEPA efficacy and tolerability during (neo)adjuvant breast cancer chemotherapy with cyclophosphamide and doxorubicin. BMJ Support Palliat Care 2022;12:e264-70.
11. National Cancer Institute. Cancer Therapy Evaluation Program. 2021. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40. Accessed 3 Feb 2023.
12. Martin AR, Pearson JD, Cai B, Elmer M, Horgan K, Lindley C. Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the Functional Living Index-Emesis (FLIE) with 5-day recall. Support Care Cancer 2003;11:522-7.
13. Griffin AM, Butow PN, Coates AS, et al. On the receiving end. V: patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 1996;7:189-95.
14. Bymaster FP, Nelson DL, DeLapp NW, et al. Antagonism by olanzapine of dopamine D1, serotonin2, muscarinic, histamine H1 and alpha 1-adrenergic receptors in vitro. Schizophr Res 1999;37:107-22.
15. Zhang L, Lu S, Feng J, et al. A randomized phase III study evaluating the efficacy of single-dose NEPA, a fixed antiemetic combination of netupitant and palonosetron, versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC). Ann Oncol 2018;29:452-8.
16. Roila F, Ruggeri B, Ballatori E, et al. Aprepitant versus metoclopramide, both combined with dexamethasone, for the prevention of cisplatin-induced delayed emesis: a randomized, double-blind study. Ann Oncol 2015;26:1248-53.
17. Okada Y, Oba K, Furukawa N, et al. One-day versus three-day dexamethasone in combination with palonosetron for the prevention of chemotherapy-induced nausea and vomiting: a systematic review and individual patient data-based meta-analysis. Oncologist 2019;24:1593-600.
18. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med 2016;375:134-42.
19. Abe M, Hirashima Y, Kasamatsu Y, et al. Efficacy and safety of olanzapine combined with aprepitant, palonosetron, and dexamethasone for preventing nausea and vomiting induced by cisplatin-based chemotherapy in gynecological cancer: KCOG-G1301 phase II trial. Support Care Cancer 2016;24:675-82.
20. Hashimoto H, Abe M, Tokuyama O, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:242-9.
21. Malhotra K, Vu P, Wang DH, Lai H, Faziola LR. Olanzapine-induced neutropenia. Ment Illn 2015;7:5871.
22. Gjafa E, Ng K, Grunewald T, et al. Neutropenic sepsis rates in patients receiving bleomycin, etoposide and cisplatin chemotherapy using olanzapine and reduced doses of dexamethasone compared to a standard antiemetic regimen. BJU Int 2021;127:205-11.
23. Yeo W, Mo FK, Suen JJ, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. Breast Cancer Res Treat 2009;113:529-35.
24. Babu G, Saldanha SC, Kuntegowdanahalli Chinnagiriyappa L, et al. The efficacy, safety, and cost benefit of olanzapine versus aprepitant in highly emetogenic chemotherapy: a pilot study from South India. Chemother Res Pract 2016;2016:3439707.