OPEN ACCESS

NEPA efficacy and tolerability during (neo)adjuvant breast cancer chemotherapy with cyclophosphamide and doxorubicin

Winnie Yeo ,[1] Thomas KH Lau,[2] Carol CH Kwok,[3] Kwai T Lai,[4] Vicky TC Chan,[2] Leung Li,[2] Vivian Chan,[4] Ashley Wong,[2] Winnie MT Soo,[2] Eva WM Yeung,[2] Kam H Wong,[2] Nelson LS Tang,[4] Joyce JS Suen,[2] Frankie KF Mo[4]

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjspcare-2019-002037).

[1]Department of Clinical Oncology, State Key Laboratory of Translational Oncology, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, Hong Kong
[2]Department of Clinical Oncology, Prince of Wales Hospital, New Territories, Hong Kong
[3]Department of Clinical Oncology, Princess Margaret Hospital, Hong Kong, Hong Kong
[4]Department of Chemical Pathology, Li Ka Shing Institute of Health Sciences, Chinese University of Hong Kong, New Territories, Hong Kong

Correspondence to
Dr Winnie Yeo, Hong Kong, Hong Kong; winnieyeo@cuhk.edu.hk

Received 17 September 2019
Revised 21 December 2019
Accepted 6 January 2020

To cite: Yeo W, Lau TKH, Kwok CCH, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bmjspcare-2019-002037

ABSTRACT

Objectives This is a prospective study evaluating NEPA in patients with breast cancer (the NEPA group), who received (neo)adjuvant AC chemotherapy (consisting of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2). The primary objectives were to assess the efficacy and safety of NEPA in controlling chemotherapy-induced nausea and vomiting (CINV). The secondary objectives were to compare CINV between the NEPA group and historical controls (the APR group) who received aprepitant in an earlier prospective randomised study.

Patients and methods 60 patients participated in the NEPA group; 62 were in the APR group. Eligibility criteria of both groups were similar, that is, Chinese patients with breast cancer who were treated with (neo)adjuvant AC. NEPA group received NEPA and dexamethasone; APR group received aprepitant, ondansetron and dexamethasone. Individuals filled in self-reported diary, visual analogue scale for nausea and Functional Living Index-Emesis questionnaire.

Results Within the NEPA group, 70.0%, 85.7% and 60.0%, respectively reported complete response in the acute, delayed and overall phases in cycle 1 AC. When compared with the historical APR group during cycle 1 AC, NEPA group achieved significantly higher rates of complete response, complete protection, total control, 'no significant nausea' and 'no nausea' in the delayed phase; similar findings were noted in the overall phase with significantly better quality of life. Superior efficacy of NEPA was maintained over multiple cycles. Both antiemetic regimens were well tolerated.

Conclusion In this study on Chinese patients with breast cancer who were uniformly receiving AC, NEPA was effective in controlling CINV.

Trial registration number NCT03386617.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) are distressing symptoms for patients undergoing anticancer therapies. Ineffective control of CINV could affect individual's quality of life (QOL) and lead to poor suboptimal therapeutic compliance, thereby affect the chance of cure from cancer.[1–3] For patients with breast cancer, one of the most common (neo)adjuvant chemotherapeutic regimen administered is a combination of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), referred to many as AC chemotherapy. AC has been regarded as highly emetogenic and as such, international guidelines on CINV have recommended the use of optimal antiemetic regimen, which consists of the combination of a neurokinin-1 (NK1) receptor antagonist, a 5-hydroxytryptamine type-3 (5-HT3) receptor antagonist and a corticosteroid.[4–6] Aprepitant, netupitant and rolapitant are NK1 receptor antagonists that have been reported to be efficacious.[7–9]

Netupitant is a novel, potent and selective NK1 receptor antagonist. The initial randomised phase II study evaluated the combination of palonosetron 0.5 mg (and dexamethasone) with different doses of netupitant among patients who were planned for cisplatin-containing chemotherapy, and revealed that netupitant 300 mg in combination with palonosetron was superior in terms of complete response rate (no emesis, no rescue medication) during the acute as well as delayed phases of CINV.[7]

NEPA (Akynzeo) is a fixed-dose combination drug with a hard gelatin capsule which contains three 100 mg netupitant tablets and one soft gelatin capsule of 0.5 mg palonosetron. Two pivotal phase III studies have been conducted to assess the efficacy and safety of NEPA among patients with cancer on chemotherapy. In the study reported by Aapro *et al*, NEPA was compared with palonosetron (both in combination with dexamethasone) in 1449 chemotherapy-naïve patients who were planned for AC chemotherapy; NEPA was shown to be superior in controlling CINV during acute, delayed and overall phases.[10] In another report by Gralla *et al*,[11] the efficacy over multiple cycles alongside the safety profiles of NEPA were being confirmed in 413 patients who were planned for highly emetogenic chemotherapy. Furthermore, quality of life was also shown to be better in patients who were treated with NEPA-containing antiemetic regimen.[10 11]

In this prospective study, the primary objectives were to evaluate efficacy and safety of NEPA among Chinese patients with breast cancer who were undergoing AC chemotherapy. The secondary objectives were to compare the efficacy and tolerability of NEPA-based antiemetic regimen in the current study with a historical control group who were given aprepitant-based antiemetic regimen in a previously reported prospective randomised study.[12]

PATIENTS AND METHODS

For the purpose of description in this report, patients enrolled into this two-centre prospective study of NEPA would be categorised into the NEPA group.

Patient eligibility included: female aged over 18 years, of Chinese ethnicity, with early stage breast cancer and who were chemotherapy-naïve and planned for adjuvant or neoadjuvant (termed as '(neo)adjuvant') AC cytotoxic regimen. Other eligibility criteria included Eastern Cooperative Oncology Group performance status 0–1, being able to read, understand and complete study diary and questionnaires in Chinese.

Main exclusion criteria included prior radiotherapy or planned radiation therapy to the abdomen or pelvis within the week prior to study treatment; history of grade 2–3 nausea per National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0 (NCI CTCAE V.4.0) or having vomited in the 24 hours prior to the start of study treatment; history of any severe or uncontrolled illnesses and infection; history of intake of study medication within 7 days, systemic corticosteroids within 72 hours, any medication with known or potential antiemetic activity within 24 hours prior to the start of study treatment; history of aprepitant intake, psychiatric or central nervous system disorders interfering with ability to comply with study protocol. Consent was obtained from individual eligible patient into the study.

Study treatment

On day 1 of each chemotherapy cycle, each patient took one capsule of NEPA (netupitant 300 mg/palonosetron 0.50 mg) with dexamethasone 12 mg 1 hour prior to the start of chemotherapy. On days 2–3, patients took dexamethasone 4 mg twice per day. Patients were instructed to take rescue therapy if needed for nausea or vomiting (online supplementary table S1).

Starting from the day of chemotherapy (day 1), each patient recorded her symptom of vomiting and nausea in a diary for 120 hours after the AC infusion. The diary recorded date and time of vomiting episodes (if any) and the use of rescue medication; on days 2–6, the patient also rated her symptom of nausea for the preceding 24 hours using visual analogue scale (VAS; 0 mm implied no nausea; 100 mm implied nausea that was 'as bad as it could be'). On day 6, individual patient would also complete the questionnaire on Functional Living Index-Emesis (FLIE). The research assistant/nurse would call individual patient during days 2–6, to remind her to take study medications, to encourage her to complete the study diary and the FLIE questionnaire.

Assessment of antiemetic efficacy

The variables used to measure antiemetic 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). These assessments were done primarily over the 'overall' phase, and would also be conducted separately during 'acute' and 'delayed' phases. In addition, 'the time to first vomiting episode' (based on self-reported date and time of vomiting episodes recorded in the diary) was assessed. Assessments started from the initiation of AC (0 hour) to 120 hours after chemotherapy infusion over three phases: 'acute' phase referred to 0–24 hours after initiation of AC, 'delayed' phase referred to 24–120 hours, while 'overall' phase referred to 0–120 hours.

QOL was evaluated by self-reported validated instrument for measurement of impact of CINV on daily living-FLIE questionnaire Chinese version.[13] FLIE consists of the nausea domain (nine items) and the vomiting domain (nine items). Each item can be scored on a 1-point to 7-point scale. For the majority of items, the higher the score the worse the impact on the patient's QOL; for remaining items, higher scores reflect better QOL. For the purpose of analysis, the latter are transformed back to having the same direction as the former items. FLIE was administered before

the initiation of chemotherapy infusion on day 1, and immediately after completion of the diary on day 6.

To assess treatment compliance, the time, date and number of tablets taken on each day was being recorded. Adverse events (AEs) were graded according to NCI CTCAE V.4.0.

Statistical analysis

The targeted patient number for the NEPA group was 60. Based on the average nausea scores as measured by VAS, it was regarded that the SD of around 20 and a 10 mm difference were relevant in clinical practice. Assumed that the historical response rate was 40%, in order to detect 25% difference with one-sided 5% level and 80% power, the target number of patient was 60.

The modified intention-to-treat (met) approach was used for all efficacy analyses. Only patients who had received chemotherapy and had completed the 0–120 hours study procedures in cycle 1 AC and with no major protocol violations (ie, those affecting the primary efficacy endpoint) would be included in the analysis.

To address the primary objectives of this report, efficacy analysis of the NEPA-based antiemetic regimen was based on the number and percentage (including 95% CI) of patients who achieved 'complete response', 'no vomiting', 'no significant nausea', 'no nausea', 'no use of rescue therapy', 'complete protection' and 'total control' during the acute (0–24 hours), delayed phase (24–120 hours) and overall phase (0–120 hours) postchemotherapy infusion in cycle 1 of AC. Findings would be summarised descriptively.

Safety analysis were based on studied population and presented for all cycles. The incidences of serious adverse events (SAEs) and AEs of grade ≥2 occurring in >3% of patients would be summarised.

For the secondary objectives of this report, historical controls that consisted of a group of 62 patients who were randomised into an aprepitant-based antiemetic arm in a previously reported prospective placebo-controlled study was included for comparative analyses; for the purpose of description, this was categorised as the APR group. Patients' eligibility, chemotherapeutic regimen and study assessments in the APR group were similar to the NEPA group,[12] that is, early stage Chinese patients with breast cancer who were undergoing four cycles of adjuvant AC. The APR group received aprepitant 125 mg, ondansetron 8 mg, dexamethasone 12 mg, before AC and ondansetron 8 mg 8 hours later on day 1, followed by aprepitant 80 mg daily on days 2–3. It is noted that direct comparison is not possible between two groups. Thus, for efficacy, indirect comparison between the NEPA and APR groups, the number and percentage (including 95% CI) of patients +were assessed for the following parameters during the acute (0–24 hours), delayed phase (24–120 hours) and overall phase (0–120 hours) after the initiation of cycle 1 of AC would be compared: 'complete response', 'no vomiting', 'no significant nausea', 'no nausea', 'no use of rescue therapy', 'complete protection' and 'total control'. The time to first vomiting (time to failure) was compared between the two groups using the log-rank test. QOL would also be compared in the first AC cycle. In addition, the proportion of patients with 'complete response', 'complete protection' and'total control' in the acute, delayed and overall phases during multiple cycles would be compared between the two groups. For safety assessment, incidences of SAEs and AEs of grade ≥2 occurring in >3% of patients would be summarised by treatment group. Comparisons between the two groups were made using Wilcoxon Rank Sum test for continuous data and chi-square tests for dichotomous data with a 2-sided sgnificance level of 5%.

Table 1 Baseline characteristics of studied populations (n=122)

	NEPA, N (%)	Historical controls (APR), N (%)
Median age (years; range)	56 (30–69)	46.5 (32–66)
Median body weight (kg; range)	55.6 (38.9–87.9)	57.8 (40.8–97.2)
Median body height (cm; range)	157 (146–170)	159 (147–171)
Median body surface area (m^2; range)	1.56 (1.31–1.94)	–
Primary tumour pathology		
Ductal	55 (91.7)	59 (95.2)
Lobular	3 (5.0)	1 (1.6)
Other	2 (3.3)	2 (3.2)
Stage of cancer		
I	3 (5.0)	18 (29.0)
II	40 (66.7)	28 (45.2)
III	17 (28.3)	16 (25.8)
History of motion sickness	21 (35.0)	14 (22.6)
History of vomiting during pregnancy		
Yes	24 (40.0)	22 (35.5)
Never pregnant	4 (6.7)	12 (19.4)
Regular alcoholic drink	2 (3.3)	1 (1.6)
AC regimen		
3-week cycle	45 (75.0)	62 (100)
2-week cycle	15 (25.0)	0
AC treatment setting		
Neoadjuvant	18 (30.0)	0
Adjuvant	42 (70.0)	62 (100)

RESULTS

Sixty patients were enrolled into the NEPA group and were assessable for study outcomes. The compliance rates of these 60 patients throughout the four cycles of AC were 100%. Patient characteristics are listed in table 1. The median age was 56 years, 35% had history of motion sickness, 40% had history of vomiting during pregnancy, 91.7% had invasive ductal carcinoma and 66% had stage II breast cancer.

Table 2 Emesis end points during cycle 1 of AC in the acute (0–24 hours), delay (24–120 hours) and overall phases (0–120 hours)

	Acute (0–24 hours), n (%)		Delay (24–120 hours), n (%)		Overall (0–120 hours), n (%)	
	NEPA	Historical controls (APR)	NEPA	Historical controls (APR)	NEPA	Historical controls (APR)
No vomiting	43 (71.7)	44 (72.1)	37 (86.0)	34 (75.6)	37 (61.7)	34 (54.8)
No use of rescue therapy	51 (85.0)	60 (98.4)	46 (90.2)	51 (83.6)	46 (76.7)	51 (82.3)
No significant nausea	52 (86.7)	54 (88.5)	47 (90.4)	40 (74.1)	47 (78.3)	41 (66.1)
No nausea	42 (70.0)	38 (62.3)	32 (76.2)	18 (47.3)	32 (53.3)	19 (30.6)
Complete response	42 (70.0)	44 (72.1)	36 (85.7)	29 (64.4)	36 (60.0)	29 (46.8)
Complete protection	40 (66.7)	41 (67.2)	34 (85.0)	23 (56.1)	34 (56.7)	24 (38.7)
Total control	38 (63.3)	33 (54.1)	29 (76.3)	15 (45.5)	29 (48.3)	16 (25.8)

Efficacy and safety of NEPA-containing antiemetic regimen

In the acute, delayed and overall phases in cycle 1 of AC, 70.0%, 85.7% and 60.0% of patients reported complete response, respectively; 66.7%, 85.0% and 56.7% of reported complete protection, respectively and 63.3%, 76.3% and 48.3% reported total control, respectively. Details of the proportion of patients having 'no vomiting', 'no significant nausea' and 'no nausea' in the three phases are listed in table 2. With regard to AEs (table 3), the NEPA-based antiemetic regimen was generally well tolerated. AEs of grade ≥2 that occurred in >3% of the studied patients included neutropaenia (35%), cough (5%), dyspepsia (5%), infections (3.3%), oral mucositis (3.3%), pain (3.3%), rectal haemorrhage (3.3%) and upper respiratory infection (8.3%). Eleven patients had experienced SAEs; these included neutropaenia fever (seven patients; 11.7%), fever (two patients; 3.3%), upper respiratory infection (one patient; 1.7%) and wound infection (one patient; 1.7%).

Comparison of efficacy and safety between the NEPA and the historical controls (APR) groups

The emesis end points between the two groups during cycle 1 of AC are listed in table 2. During the acute phase, apart from a significantly higher proportion of patients in the APR group who did not require rescue medication (NEPA vs APR: 85.0% vs 98.4%, p=0.007), there was no difference found in other measured parameters. In the delayed phase, significantly higher proportions of patients in the NEPA group achieved complete response (NEPA vs APR: 85.7% vs 64.4%, p=0.023), complete protection (85.0% vs 56.1%, p=0.004), total control (76.3% vs 45.5%, p=0.008), 'no significant nausea' (90.4.7% vs 74.1%, p=0.029) and 'no nausea' (76.2% vs 47.3%, p=0.008). This has led to significantly higher proportions of patients in the NEPA group achieving complete protection (56.7% vs 38.7%, p=0.047), total control (48.3% vs 25.8%, p=0.010) and 'no nausea' (53.3% vs 30.6%, p=0.011) in the overall phase.

The median time to first vomiting after the initiation of chemotherapy was not reached (range: 57.5 hours—not reached) in the NEPA group and 64.4 hours (range 39.0 hours—not reached) in the APR group (HR 0.660, 95% CI 0.388 to 1.121, p=0.1238) (figure 1).

Analysis on the impact on daily living during cycle 1 AC revealed that while there was no difference in FLIE scores between the two arms prior to initiation of AC chemotherapy on day 1, there was significantly better QOL (lower FLIE scores) in terms of nausea domain (mean score (SD) for NEPA vs APR groups: 17.55 (28.03) vs 27.44 (25.70), respectively, p=0.0015) and total score (mean score (SD) NEPA vs APR groups: 12.14 (23.26) vs 15.5 (16.03), respectively, p=0.0020) among patients in the NEPA group on day 6 of AC. Moreover, when compared with 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 APR group for the nausea domain (mean score (SD) for NEPA vs APR groups: 17.52 (27.97) vs 26.74 (25.51), respectively, p=0.0017) (table 4).

Table 5 shows the efficacy data between the two arms over multiple cycles. Significantly higher proportions of patients in the NEPA group achieved the following: in the acute phase, total control in cycle 4 (NEPA vs APR: 86.7% vs 71.2%, p=0.0382); in the delayed phase, complete response (cycle 1, 85.7% vs 64.4%,

Table 3 Adverse events of grade ≥2 that occurred in >3% in either studied populations

	NEPA (n=60)					Historical controls (APR) (n=62)				
	Grade					Grade				
Adverse events	0	1	2	3	4	0	1	2	3	4
Alanine transaminase	60	0	0	0	0	60	0	2	0	0
Constipation	32	28	0	0	0	52	8	2	0	0
Cough	56	1	3	0	0	53	9	0	0	0
Dyspepsia	55	2	3	0	0	60	1	1	0	0
Febrile neutropaenia	60	0	0	0	0	57	0	0	5	0
Infections	58	0	2	0	0	62	0	0	0	0
Mucositis—oral cavity	21	37	2	0	0	43	15	3	1	0
Neutropaenia	37	2	12	2	7	27	0	14	8	13
Pain	57	1	0	2	0	62	0	0	0	0
Rectal haemorrhage	58	0	2	0	0	62	0	0	0	0
Upper respiratory infection	52	3	3	2	0	62	0	0	0	0

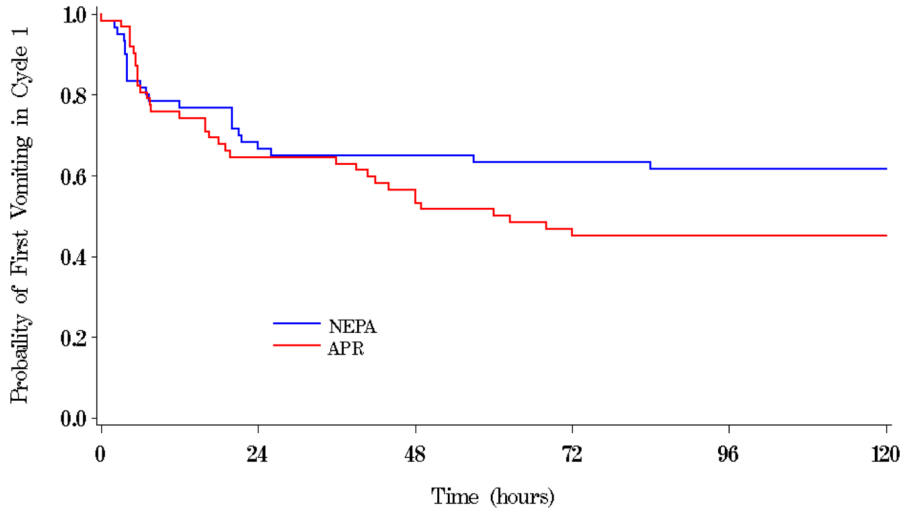

Figure 1 Time to first vomiting episode during cycle 1 of AC. X-axis—time (hours) ranged from 0 to 120 hours; Y-axis—probability of first vomiting in cycle 1.

p=0.0226; cycle 2, 92.2% vs 65.5%, p=0.0010; cycle 3, 98.1% vs 68.5%, p<0.0001; cycle 4, 98.1% vs 66.0%, p<0.0001), complete protection (cycle 1, 85.0% vs 56.1%, p=0.0044; cycle 2, 90.2% vs 68.0%, p=0.0060; cycle 3, 94.2% vs 69.4%, p=0.0009; cycle 4, 92.4% vs 73.9%, p=0.0101), and total control (cycle 1, 76.3% vs 45.5%, p=0.0075; cycle 2, 79.6% vs 54.5%, p=0.0099; cycle 3, 91.7% vs 62.5%, p=0.0009; cycle 4, 86.5% vs 66.7%, p=0.0215), in all the four cycles; in the overall phase, complete response in cycle 3 (86.7% vs 68.3%, p=0.0162) and cycle 4 (86.7% vs 71.2%, p=0.0382), complete protection in cycle 1 (56.7% vs 38.7%, p=0.0471) and cycle 3 (81.7% vs 61.7%, p=0.0151) and total control in all the four cycles (cycle 1, 48.3% vs 25.8%, p=0.0099; cycle 2, 65.0% vs 45.0%, p=0.0277; cycle 3, 73.3% vs 43.3%, p=0.0009; cycle 4, 75.0% vs 52.5%, p=0.0108).

Toxicity data from the two groups are listed in table 3. Patients in the NEPA group had significantly lower rates of grade ≥2 neutropaenia (NEPA vs APR: 35.0% vs 56.5%%, p=0.0088) and neutropenic fever (0% vs 8.1%, p=0.0312), but a higher incidence of upper respiratory infection (8.3% vs 0%, p=0.0263). No significant difference in other AEs was detected (table 3). There were no differences in the incidences of SAEs between the two groups (18.3% vs 11.3%, p=0.2728).

Table 4 Quality of life based on FLIE assessment in the overall phase (0–120 hours)

	Mean score (SD)	
Average FLIE score	NEPA	Historical controls (APR)
Day 1 FLIE—total score	0.02 (0.11)	0.39 (2.03)
Day 1 FLIE—vomiting domain	0 (0)	0.09 (0.54)
Day 1 FLIE—nausea domain	0.03 (0.23)	0.69 (4.01)
Day 6 FLIE—total score	12.14 (23.26)	15.5 (16.03)
Day 6 FLIE—vomiting domain	6.74 (22.40)	3.49 (13.14)
Day 6 FLIE—nausea domain	17.55 (28.03)	27.44 (25.70)
(Day 6–day 1) FLIE—total score	12.15 (23.25)	11.23 (15.66)
(Day 6–day 1) FLIE—vomiting domain	6.74 (22.98)	3.40 (13.18)
(Day 6–day 1) FLIE—nausea domain	17.52 (27.97)	26.74 (25.51)

FLIE, Functional Living Index-Emesis.

DISCUSSION

AC chemotherapy is one of the most commonly administered adjuvant regimen for patients with breast cancer. International guidelines have regarded this treatment or similar regimen to be highly emetogenic, and a combination of an NK1 receptor antagonist, a

Table 5 Complete response and total control over multiple cycles in the acute (0–24 hours) and delayed (24–120 hours) and overall phases (0–120 hours)

	Acute (0–24 hours), %		Delay (24–120 hours), %		Overall (0–120 hours), %	
	NEPA (%)	Historical controls, APR (%)	NEPA (%)	Historical controls, APR (%)	NEPA (%)	Historical controls, APR (%)
Complete response						
Cycle 1	70.0	72.1	85.7	64.4	60.0	46.8
Cycle 2	85.0	91.7	92.2	65.5	78.3	66.7
Cycle 3	88.3	90.0	98.1	68.5	86.7	68.3
Cycle 4	88.3	89.8	98.1	66.0	86.7	71.2
Complete protection						
Cycle 1	66.7	67.2	85.0	56.1	56.7	38.7
Cycle 2	85.0	83.3	90.2	68.0	76.7	63.3
Cycle 3	86.7	81.7	94.2	69.4	81.7	61.7
Cycle 4	88.3	78.0	92.4	73.9	81.7	67.8
Total control						
Cycle 1	63.3	54.1	76.3	45.5	48.3	25.8
Cycle 2	81.7	73.3	79.6	54.5	65.0	45.0
Cycle 3	80.0	66.7	91.7	62.5	73.3	43.3
Cycle 4	86.7	71.2	86.5	66.7	75.0	52.5

5-HT3 receptor antagonist and corticosteroids has been recommended.[4–6]

Efficacy data on the first-generation NK1 receptor antagonist, aprepitant, has been inconsistent. The initial report on patients undergoing high-dose cisplatin-containing chemotherapeutic regimen demonstrated that the addition of aprepitant to ondansetron and dexamethasone significantly improved complete responses rates for controlling CINV during the acute, delayed as well as overall phases.[8] A few studies have targeted at patients receiving AC or AC-like chemotherapy. In a placebo-controlled study that randomised patients to an aprepitant arm versus a non-aprepitant arm, aprepitant was shown to be more efficacious in the first as well as multiple cycles of AC-like chemotherapy, with significant higher rates of complete response, delay time to first emesis and better quality of life demonstrated.[14 15] However, it has to be noted that despite these positive findings, the actual proportion of patients not achieving complete response during multiple cycle assessment was as high as 65%, while nearly 40% still suffered from significant nausea.[14 15] When applying the same antiemetic regimens in a homogenous group of Chinese patients with breast cancer undergoing AC chemotherapy, our previous study revealed that although QOL in terms of vomiting domain of the FLIE assessment was significantly better in the aprepitant arm, there was no difference between the aprepitant and non-aprepitant arms with respect to all other study end points.[12] Specifically, despite aprepitant, only 47% of the studied population experienced complete response, 39% had complete protection, 26% total control, while 45% experienced vomiting and 69% had nausea, reflecting that in spite of aprepitant, control of CINV remained suboptimal.

Data on randomised studies testing NEPA have been reported relatively more recently.[7 10 11] In a pivotal study among patients who were receiving AC or AC-like chemotherapy,[10] the combination of NEPA with dexamethasone was shown to be superior to palonosetron with dexamethasone, both administered on day 1. Complete response rates were significantly better in the NEPA-containing arm in the acute (88% vs 85%), delayed (77% vs 70%) and overall (74% vs 67%) phases, although other study end points were not improved.[10]

Data on direct comparison of aprepitant and NEPA was subsequently available in the study by Zhang *et al*, which involved patients who were receiving cisplatin-containing regimen.[16] Over 800 Asian patients were randomised to one of the two antiemetic regimens: the NEPA-containing arm consisted of NEPA and dexamethasone 12 mg on day 1, followed by dexamethasone 8 mg daily on days 2–4; the control arm received aprepitant 125 mg, granisetron 3 mg and dexamethasone 20 mg on day 1, followed by aprepitant 80 mg daily on days 2–3 and dexamethasone 8 mg daily on days 2–4. Study results revealed similar rates of complete response, 'no vomiting', 'no nausea' and 'no significant nausea' between the two arms, while significantly fewer patients required rescue therapy in the NEPA arm.

The current report consisted of two patient populations who were recruited into two separate prospective studies. It is limited by each study having consisted of a relatively small patient number and having adopted the earlier study as historical controls. Nonetheless, the current report is strengthened by the fact that both the NEPA study and the historical study enrolled a homogenous patient population, namely, patients of Chinese ethnicity with breast cancer who had early stage disease and were all uniformly treated with AC chemotherapy. It shows that NEPA-based antiemetic regimen could achieve good control of CINV. Furthermore, even though the same classes of antiemetic agents were used, NEPA-based regimen resulted in high rates of complete response, complete protection, total control and 'no significant nausea' during cycle 1 of AC. As a consequence, the impact of CINV on daily living was significantly less in the NEPA group. The performance of NEPA in achieving control over CINV echoed the findings of Zhang *et al* discussed earlier.[16] On the other hand, in contrast to the landmark study by Aapro *et al*,[10] the control rates of delayed phase CINV were more elevated than the acute phase among NEPA-treated patients within the present report. Similar observation has been reported in other studies.[12 17] We hypothesise that this could be a result of the synergistic effects of two effective antiemetic agents, with NEPA processing a relatively longer half-life and dexamethasone being administered over a protracted period of 3 days from the initiation of chemotherapy.

It is noteworthy that while the improvement in outcomes in the NEPA group could be attributed to the higher potency of NEPA, another contributing factor could be the incorporation of different antiemetics on days 2–3 after AC, with aprepitant in the APR group and dexamethasone in the NEPA group. Initial studies on patients receiving AC have combined NEPA with dexamethasone on day 1 of the chemotherapy cycle.[10 12 14 15] and such practice has been recommended in the European Society for Medical Oncology and the American Society of Clinical Oncology guidelines.[4 6] On the other hand, the National Comprehensive Cancer Network guideline have regarded AC as highly emetogenic, and as a result, have recommended the use of dexamethasone over a more protracted period.[5] Based on the present study with NEPA, the authors are inclined to support the continuing administration of dexamethasone in an attempt to achieve better control of CINV during the delay and overall phases.

In summary, the present report confirms the antiemetic efficacy and tolerability of NEPA in the control of CINV during treatment with highly emetogenic AC chemotherapy. Despite the positive statistical findings associated with clinically meaningful improvement in patients' experience of CINV, it is evident that nearly 40% of the studied patients undergoing AC still experienced vomiting while 22%–47% still suffered from significant nausea and

overall nausea. Additional agents, such as olanzapine, may enhance the antiemetic efficacy of the current regimen,[4 5] and further research is required to optimise the symptoms and alleviate potential sequelae associated with CINV in our patient population.

Contributors WY conceived of the original idea for the study, obtained ethical approval, contributed to patient enrolment and the preparation of the dataset, interpreted results and edited the paper. FKFM carried out the statistical analysis, the preparation of the dataset, interpreted results and contributed to drafts of the paper. TKHL, CCHK, KTL, VTCC, LL, VC, AW, WMTS, EWMY, KHW, NLST and JJSS contributed to patient enrolment and the preparation of the dataset and commented on drafts of the paper.

Funding This study was supported by an education grant from Mundipharma and Madam Diana Hon Fun Kong Donation for Cancer Research.

Disclaimer Mundipharma supported the study design of NEPA but had no role in the study design of the APR group or the design of comparative analysis, data collection and analysis, decision to publish or preparation of the manuscript. Madam Diana Hon Fun Kong Donation for Cancer Research had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing interests WY has been involved in CINV Network in Asia and has been a speaker on CINV, organised by Mundipharma.

Patient consent for publication Not required.

Ethics approval The study was approved by the Joint CUHK-NTEC Institution Review Board of the Chinese University of Hong Kong and of the Hong Kong Hospital Authority, and the Kowloon West Cluster Research Ethics Committee of the Hong Kong Hospital Authority.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iD

Winnie Yeo http://orcid.org/0000-0002-0863-8469

REFERENCES

1 Coates A, Abraham S, Kaye SB, *et al*. On the receiving end--patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol* 1983;19:203–8.
2 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.
3 Lau TKH, Yip CHW, Yeo W. State of the art antiemetic therapy for cancer patients. *Curr Oncol Rep* 2016;18:2.
4 Hesketh PJ, Bohlke K, Lyman GH, *et al*. Antiemetics: American Society of clinical oncology focused guideline update. *J Clin Oncol* 2016;34:381–6.
5 National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. antiemesis version 1, 2019. Available: http://www.nccn.org
6 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.
7 Hesketh PJ, Rossi G, Rizzi G, *et al*. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. *Ann Oncol* 2014;25:1340–6.
8 Hesketh PJ, Grunberg SM, Gralla RJ, *et al*. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003;21:4112–9.
9 Schwartzberg LS, Modiano MR, Rapoport BL, *et al*. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. *Lancet Oncol* 2015;16:1071–8.
10 Aapro M, Rugo H, Rossi G, *et al*. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol* 2014;25:1328–33.
11 Gralla RJ, Bosnjak SM, Hontsa A, *et al*. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. *Ann Oncol* 2014;25:1333–9.
12 Yeo W, Mo FKF, Suen JJS, *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.
13 Martin AR, Pearson JD, Cai B, *et al*. 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.
14 Warr DG, Hesketh PJ, Gralla RJ, *et al*. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol* 2005;23:2822–30.
15 Herrstedt J, Muss HB, Warr DG, *et al*. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer* 2005;104:104:1548–55. Erratum in: Cancer 2006;106:1641.
16 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.
17 Badalamenti G, Incorvaia L, Messina C, *et al*. One shot NEPA plus dexamethasone to prevent multiple-day chemotherapy in sarcoma patients. *Support Care Cancer* 2019;27:3593–7. Erratum in: Supportive Care Cancer 2019;27(9):3599.