

# Quality of Life Associated with Nausea and Vomiting from Anthracycline-Based Chemotherapy: A Pooled Data Analysis from Three Prospective Trials

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Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** Breast cancer • Cytotoxic • Nausea and vomiting • Functional Living Index–Emesis

## ABSTRACT

**Background.** There is limited work on the impact of chemotherapy-induced nausea and vomiting (CINV) on quality of life (QoL) in adriamycin-cyclophosphamide (AC)-treated patients with breast cancer. The objectives of the study were the following: (a) to confirm if symptoms of CINV led to lower QoL during AC; (b) to evaluate the pattern of changes in patients' QoL during multiple cycles of AC; and (c) to assess if the QoL in an earlier cycle affected the QoL in subsequent cycles of AC.

**Materials and Methods.** This is a secondary pooled data analysis that included 303 Chinese patients with breast cancer who received 1,177 cycles of adjuvant AC in three prospective antiemetic studies. QoL data were based on Functional Living Index–emesis (FLIE) scored over three to four AC cycles. CINV symptoms assessed included “no significant nausea” (NSN), “significant nausea” (SN), “no vomiting” (NoV), “vomiting” (V), and complete response (CR).

**Results.** Across all AC cycles, the mean scores for the FLIE nausea domain for patients who experienced NSN versus

SN were 10.92 versus 53.92, respectively ( $p < .0001$ ), with lower scores indicating better QoL; the mean scores for the FLIE vomiting domain for patients who experienced NoV versus V were 1.44 versus 19.11, respectively ( $p < .0001$ ), with similar results across subsequent cycles. Analysis of the effect of the QoL in cycle 1 on the QoL of subsequent cycles revealed the following: for the nausea domain, among patients who had cycle 1 FLIE scores  $\geq$  versus  $<$  the mean, the corresponding scores in cycle 2 were 6.87 versus 36.71 ( $p < .0001$ ); whereas those for cycle 3 were 7.07 versus 36.87 ( $p < .0001$ ); and those for cycle 4 were 5.92 versus 21.48 ( $p < .0001$ ). Similar findings were observed for the vomiting domain. Netupitant + palonosetron or aprepitant/olanzapine-based antiemetics had significantly better QoL outcomes.

**Conclusion.** CINV had a significant impact on the QoL of patients with breast cancer treated with AC over multiple cycles. *The Oncologist* 2021;26:e2288–e2296

**Implications for Practice:** In this post-hoc analysis of three prospective studies on chemotherapy-induced nausea and vomiting (CINV), quality of life (QoL) using contemporary antiemetic regimens in Chinese breast cancer patients receiving doxorubicin-cyclophosphamide (AC) was evaluated. During the first and subsequent AC cycles, QoL was significantly better for patients who did not experience vomiting or significant nausea. QoL in an earlier cycle affected the QoL in subsequent AC cycles. Furthermore, recent regimens involving olanzapine/aprepitant or netupitant-palonosetron were associated with a positive impact in QoL. Antiemetic guideline-consistent practice and higher clinician awareness of the impact of CINV on QoL can further mitigate the negative effects of CINV on QoL.

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## INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) are common side effects experienced by patients receiving anti-neoplastic treatment. Symptoms of CINV can cause physical, nutritional and metabolic disturbances to patients with cancer, thus influencing their quality of life (QoL) and anxiety level [1–3]. This is challenging from a health care perspective because a deterioration in QoL could lead to patient withdrawal from future chemotherapy cycles, which may worsen patients' overall prognosis.

There is much evidence showing that CINV has a negative impact on QoL of patients during the course of a chemotherapy cycle [2, 4–7]. Although patients with both nausea and vomiting suffer the worst deterioration in QoL, studies have also indicated that nausea has a greater negative impact on daily life than vomiting [3, 5, 8–11]. More recent work has focused on QoL when newer antiemetics have been used and showed positive impact of specific antiemetics on QoL [12] although such work is limited.

Studies have also attempted to address the timing and duration of CINV in relation to impact on daily living. A U.S. trial comprising 671 patients with cancer found that the continued presence of nausea had a more debilitating impact on patients' QoL compared with a severe bout of nausea [9]. In a prospective, multicenter, observational study in The Netherlands that studied 277 patients over three cycles of highly emetogenic (HEC) or moderately emetogenic (MEC) chemotherapy, the researchers found that the delayed symptoms of CINV had a greater impact on the QoL than acute symptoms [6]. Based on the symptoms and QoL assessments during the first three cycles of HEC or MEC, another study reported that the experience of CINV in both acute and delayed phases typically reported worse QoL than those who either only had symptoms in the delayed phase or had no symptoms during the two phases; in addition, patients who developed CINV in an earlier cycle experienced significant interferences in their QoL in subsequent chemotherapy cycles [2]. In a prospective, multicenter, observational study across Europe and the U.S. with 322 patients who were undergoing their first cycle of either HEC or MEC treatment [8] the impairment in their QoL has been suggested to be attributable to the greater length of time over which delayed CINV was experienced. Apart from the duration of nausea and vomiting, prior studies have also shown that the intensity of the nausea and vomiting affect the QoL of patients by different magnitudes [4, 13–15].

Although CINV is known to impact the QoL of patients during their course of treatment [4, 5, 13–15], there is limited literature currently available that explores the relative impact of CINV on the QoL of patients between the first and subsequent cycles of chemotherapy, in specific chemotherapy regimens or QoL impact when newer antiemetics are used.

Hence, the objectives of this study were the following: (a) to confirm that QoL during adriamycin-cyclophosphamide (AC) chemotherapy is associated with the presence of symptoms of CINV in different antiemetic regimens; (b) to evaluate the changes in the QoL of patients with breast cancer throughout multiple cycles of AC; and (c) to assess if patients' QoL in an earlier AC cycle affected their QoL in subsequent cycles.

## PATIENTS, MATERIALS, AND METHODS

This study is a secondary pooled data analysis from 304 patients with breast cancer who were receiving AC chemotherapy. Patients were enrolled into three prospective studies comparing the antiemetic efficacies of five different antiemetic regimens [16–18], including the following: group 1, ondansetron/day 1 dexamethasone; group 2, ondansetron /day 1 dexamethasone/aprepitant; group 3, ondansetron/day 1–3 dexamethasone/aprepitant; group 4, aprepitant/ondansetron/day 1 dexamethasone/olanzapine; and group 5, netupitant/palonosetron/day 1–3 dexamethasone, respectively (Table 1). The studies were approved by the Joint Chinese University of Hong Kong- New Territories East Cluster (CUHK-NTEC) Institution Review Board of the CUHK and of the Hong Kong Hospital Authority and the Kowloon West Cluster Research Ethics Committee of the Hong Kong Hospital Authority. The two more recent studies were registered at ClinicalTrials.gov (Identifier: NCT03386617 and NCT03079219 respectively).

Patient inclusion criteria across the three studies were similar. All three studies included patients if they were ethnically Chinese, female, were more than 18 years of age, and were diagnosed with breast cancer, were chemotherapy-naïve and scheduled to receive their first course of chemotherapy consisting of intravenous doxorubicin ( $60 \text{ mg/m}^2$ ) and cyclophosphamide ( $600 \text{ mg/m}^2$ ), and were able to read, understand, and complete study questionnaires and diaries.

Patient exclusion criteria across the three studies were also similar. All three studies excluded patients if they had received or would receive radiation therapy to the abdomen or pelvis in the week prior to the studies' treatment, vomited in the 24 hours prior to the study treatment, had an active infection or any uncontrolled disease, were mentally incapacitated or had a significant emotional/ psychiatric disorder, or had a history of hypersensitivity to study drugs. Patients that understood and agreed to the study procedures were consented to participate in the studies.

Patients' QoL during their course of chemotherapy was measured using the self-reported validated instrument for measuring the impact of CINV on daily living the Functional Living Index–Emesis (FLIE) questionnaire (Chinese version) [19]. FLIE comprises a nausea domain (nine items) and a vomiting domain (nine items) with each item scored on a 1–7-point scale. The scores were converted as per scale's guidelines, with lower scores reflecting better QoL. Patients were requested to complete the FLIE questionnaire on day 1 (before the initiation of chemotherapy infusion) and on day 6 of their chemotherapy cycle. The difference between the two days (day 6 – day 1) was recorded as the impact of CINV on patients' QoL.

The efficacy of antiemetic regimens was measured by the proportion of patients reporting a “complete response” (CR) (defined as no vomiting and no use of rescue therapy), “no vomiting” (NoV) (defined as no vomiting), “vomiting” (V) (defined as any episodes of vomiting), “no significant nausea” (NSN) (defined as a visual analogue scale [VAS]  $< 25 \text{ mm}$  on a 100 mm visual analog scale), and “significant nausea” (SN) (defined as a VAS  $\geq 25 \text{ mm}$  on a 100 mm visual analog scale). Patients were asked to record their symptoms of vomiting and nausea in a diary for the ensuing 120 hours after the chemotherapy infusion on day 1; to rate their symptoms of

**Table 1.** Treatment arms of the three prospective studies on Chinese patients with breast cancer undergoing adriamycin-cyclophosphamide chemotherapy

Studies	Treatment arms	Day 1	Day 2	Day 3	Day 4	Day 5
Study A <sup>a</sup>	Group 1	Ondansetron 8 mg twice	Ondansetron 8 mg twice	Ondansetron 8 mg twice		
	Group 2	Dexamethasone 20 mg Aprepitant 125 mg Ondansetron 8 mg twice Dexamethasone 12 mg	Aprepitant 80 mg	Aprepitant 80 mg		
Study B	Group 3	Aprepitant 125 mg	Aprepitant 80 mg	Aprepitant 80 mg		
		Ondansetron 8 mg twice Dexamethasone 12 mg	Dexamethasone 8 mg	Dexamethasone 8 mg		
	Group 4	Aprepitant 125 mg	Aprepitant 80 mg	Aprepitant 80 mg		
		Ondansetron 8 mg twice Dexamethasone 12 mg Olanzapine 10 mg	Olanzapine 10 mg	Olanzapine 10 mg	Olanzapine 10 mg	Olanzapine 10 mg
Study C	Group 5	Netupitant 300 mg <sup>b</sup> Palonosetron 0.5 mg <sup>b</sup>				
		Dexamethasone 12 mg	Dexamethasone 8 mg	Dexamethasone 8 mg		

<sup>a</sup>Placebo controlled study.<sup>b</sup>These were combined in a capsule, NEPA.

nausea using VAS and to record the date and time of any vomiting episodes or use of rescue medication for the preceding 24 hours on days 2–6.

### Statistical Analysis

FLIE scores of patients who suffered CINV were compared with those who did not. Variables that were included in this analysis were CINV symptoms (NSN, SN, V, and NoV) and CR (objective 1).

Data based on FLIE assessment on day 1 (prior to AC) and on day 6 (120 hours after AC) of each cycle was assessed descriptively (objective 2). For comparison, groups 1, 2, and 3 were categorized as the reference group; the means for group 4 and group 5 were compared with the reference group using multiple comparison (i.e., ANOVA analysis). Null hypothesis was defined as no difference in the means between groups 1, 2, and 3 versus group 4 versus group 5. F-statistics were calculated; once this was significant ( $p < .05$ ), multiple comparisons with least square method (LSD) would be performed to find out which pair of means were different.

Also, QoL data from a prior cycle were compared with those obtained from subsequent cycles (objective 3). The following were determined: the QoL data in cycles 2, 3, and 4, contingent on the QoL data in cycle 1; the QoL data in cycles 3 and 4 contingent on that in cycle 2; and the QoL data in cycle 4 contingent on that in cycle 3. Comparisons between two groups were made using *t* test for continuous data and  $\chi^2$  test for dichotomous data with a two-sided significance level of 5%. Statistical analysis performed were based on SAS version 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Baseline Patients' Characteristics

The baseline demographic and clinical characteristics of the participants are listed in Table 2. The study sample consisted of 304 patients with breast cancer, who provided a total of 1,177 assessments of nausea and vomiting over four cycles of AC. For patients in groups 1 and 2, QoL data were available for cycles 1, 2, and 3; QoL data were available for group 3, 4, and 5 patients for all four cycles. All participants in the study were female, with a median age of 52 years (range, 26–71). The most frequent primary diagnosis was invasive ductal cancer (94%), whereas the most common stage of cancer was stage II (58.2%). Most participants had a history of motion sickness (75.3%) but not a history of consuming alcoholic drinks (1.3%).

### QoL in Association with Symptoms of CINV (NSN, SN, V, and NoV) and CR

#### Vomiting

There were 616 cycles with “NoV” and 361 cycles with “V.” The mean number of vomit was 1.0 (range 0–5). Across cycle 1 and all cycles, there were significant differences in the mean FLIE scores for both the nausea and vomiting domains between patients who experienced NoV and V in the overall phase of a treatment cycle. For the nausea domain across all cycles, a mean score of 6.89 was scored by patients who experienced NoV versus 36.71 in patients who experienced V ( $p < .001$ ). For the vomiting domain, a mean score of 1.44 was scored by patients who experienced NoV versus 19.11 for those who experienced V

( $p < .001$ ). The same trends were observed for the acute and delayed phases across cycle 1 and all cycles (Table 3).

### Nausea

Similarly, significant differences were found in the mean FLIE scores for the nausea and vomiting domains between patients who experienced NSN versus SN in the overall phase of a treatment cycle. For the nausea domain across all cycles, a mean score of 50.12 was scored by patients who experienced SN versus 8.27 for those with NSN ( $p < .001$ ). For the vomiting domain, the respective mean scores were 25.5 versus 2.73 ( $p < .001$ ). The same trends were observed for the acute and delayed phases across cycle 1 and all cycles (Table 3).

### Complete Response

In cycle 1, patients who achieved CR had significantly lower FLIE scores than those who did not. For the nausea domain, the respective mean (standard deviation) scores were 7.45 (15.97) versus 36.63 (29.30) ( $p < .001$ ). For the vomiting domain, the respective scores were 1.22 (5.74) versus 17.46 (27.72) ( $p < .001$ ). Similar results were observed during the assessment of multiple cycles (Fig. 1A, 1B).

## Changes in QoL During Multiple Cycles of AC

### Vomiting

The FLIE scores for the vomiting domain on day 1 and day 6 of patients' chemotherapy treatment, across four cycles, are displayed in Figure 2A. In general, the FLIE scores for the nausea domain for patients rose between day 1 and day 6, indicating a deterioration in QoL due to chemotherapy-related CINV during this period. However, patients' day 1 FLIE scores in the subsequent cycle tended to return to levels similar to that of day 1 scores of the previous cycle. A similar observation can be made for subsequent day 6 FLIE scores. Patients in group 1 reported the highest FLIE scores on day 6 across the first three cycles, at 24.03, 26.7, and 28.74 respectively. Patients in groups 4 and 5 had lower FLIE scores on day 6 for cycles 3 and 4.

Throughout each of the four cycles of AC, the mean scores of group 4 were significantly lower than that of groups 1, 2, and 3, indicating better QoL for patients in group 4 (Table 4). Similarly, when the mean scores of groups 1, 2, and 3 were being compared with group 5, there were significantly lower scores (i.e., better QoL) among patients in group 5 for all four cycles of AC.

### Nausea

The FLIE scores for nausea on day 1 (prechemotherapy) and day 6 (after chemotherapy) of patients' chemotherapy treatment, across four cycles, are displayed in Figure 2B. In general, the FLIE scores for nausea for patients rose between day 1 and day 6, indicating a deterioration in QoL due to chemotherapy-related nausea. However, patients' subsequent day 1 FLIE scores tended to return to levels similar to those of day 1 scores of the previous cycle. A similar observation can be made for subsequent day 6 FLIE scores. Patients in group 1 scored highest for the FLIE scores on day 6 across all cycles, with a peak score of 40.29 on day 6 in cycle 3. This was followed by group 2, with a peak score

**Table 2.** Baseline characteristics

Characteristics	n (%)
No. of patients enrolled	
Group 1	62
Group 2	62
Group 3	60
Group 4	60
Group 5	60
No. patients in each AC cycle	
Cycle 1	304
Cycle 2	292
Cycle 3	290
Cycle 4	291
Primary diagnosis	
Ductal	286 (94.0)
Lobular	6 (2.0)
Other	12 (4.0)
Stage of cancer	
I	35 (11.5)
II	177 (58.2)
III	92 (30.3)
History of motion sickness	229 (75.3)
History of vomiting during pregnancy	123 (40.5)
History of alcoholic drinks	4 (1.3)
AC regimen	
Every 3 weeks	282 (92.8)
Every 2 weeks	22 (7.2)
Treatment setting	
Neoadjuvant	45 (14.8)
Adjuvant	259 (85.2)

Abbreviation: AC, adriamycin-cyclophosphamide.

of 28.86 on day 6 of cycle 2. Patients in groups 4 and 5 had lower FLIE scores on day 6 in cycles 3 and 4.

Across the four cycles of AC, the mean scores of group 4 were significantly lower (i.e., better QoL) than those of groups 1, 2, and 3 (Table 4). Similarly, the mean scores of group 5 were also significantly lower than those of groups 1, 2, and 3 for all four cycles of AC.

## Effect of QoL in an Earlier AC Cycle on QoL in Subsequent Cycles

### Vomiting

In cycle 1, the mean FLIE score for the vomiting domain was 10.03. Among patients who had FLIE scores equal to or above the mean (18.1%) and those with FLIE scores below the mean (81.9%), there were significant differences in the mean FLIE scores in subsequent cycles. The respective scores were 32.08 versus 3.71 in cycle 2 ( $p < .001$ ), 31.87 versus 3.26 in cycle 3 ( $p < .001$ ), and 15.13 versus 3.03 in cycle 4 ( $p < .001$ ). Using the mean FLIE scores in cycles 2 and 3 as cutoffs, similar trends were also observed for the subsequent cycles (Table 5).



**Table 3.** Post-chemotherapy day 6 FLIE scores in association with symptoms of chemotherapy induced nausea and vomiting during the acute, delayed, and overall phase: cycle 1 and multiple cycles

Phase	Mean FLIE scores					
	NSN	SN	<i>p</i>	NV	V	<i>p</i>
Overall phase						
Cycle 1						
Nausea domain	10.92	53.92	<.0001	8.64	37.34	<.0001
Vomiting domain	3.82	25.35	<.0001	1.24	18.53	<.0001
Multiple cycles						
Nausea domain	8.27	50.12	<.0001	6.89	36.71	<.0001
Vomiting domain	2.73	25.50	<.0001	1.44	19.11	<.0001
Acute phase						
Cycle 1						
Nausea domain	17.35	55.90	<.0001	15.91	37.97	<.0001
Vomiting domain	6.23	31.28	<.0001	5.28	19.65	<.0001
Multiple cycles						
Nausea domain	12.27	53.06	<.0001	12.22	36.50	<.0001
Vomiting domain	4.18	31.54	<.0001	4.37	19.73	<.0001
Delayed phase						
Cycle 1						
Nausea domain	11.46	54.05	<.0001	10.25	39.84	<.0001
Vomiting domain	4.05	25.51	<.0001	1.37	21.17	<.0001
Multiple cycles						
Nausea domain	8.77	50.50	<.0001	8.07	38.00	<.0001
Vomiting domain	3.04	25.57	<.0001	2.05	20.06	<.0001

Abbreviations: FLIE, Functional Living Index-emesis; NSN, no significant nausea; NV, no vomiting; SN, significant nausea; V, vomiting.

### Nausea

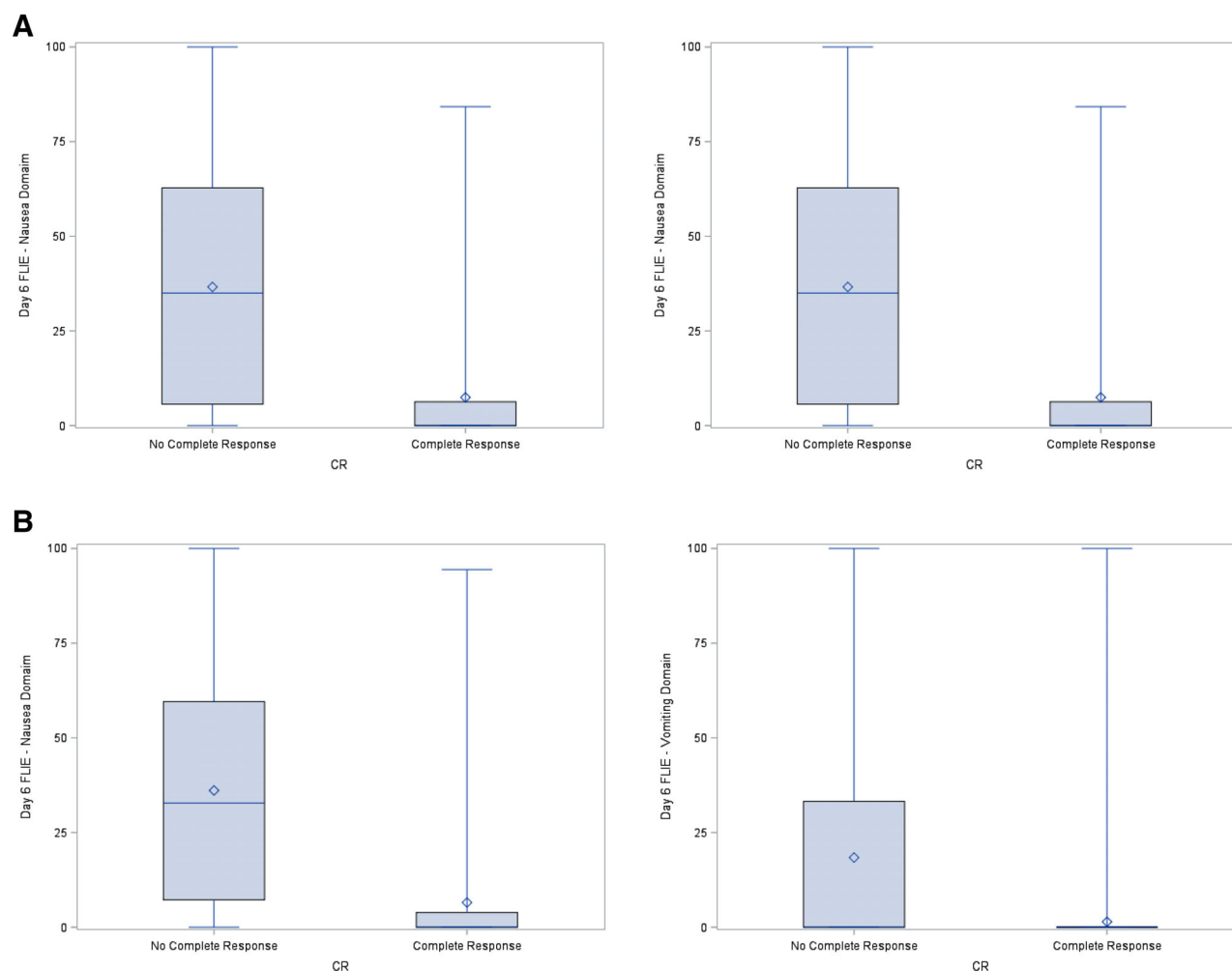
In cycle 1, the mean FLIE score for the nausea domain was 23.45. Between patients who had FLIE scores equal to or above the mean (37.5%), and those with FLIE scores below the mean (62.7%), there were significant differences in the mean FLIE scores in subsequent cycles. The respective scores were 36.71 versus 7.86 in cycle 2 ( $p < .001$ ), 36.87 versus 7.07 in cycle 3 ( $p < .001$ ), and 21.48 versus 5.92 in cycle 4 ( $p < .001$ ). The same trends were observed when comparing the differences in mean scores of subsequent cycles using the mean scores in cycles 2 and 3 as cutoffs (Table 5).

### DISCUSSION

Patients' QoL was found to have significant impact from symptoms of CINV. Patients who suffered from vomiting and significant nausea and those who failed to achieve CR reported worse QoL when compared with others. QoL fluctuated during a course of chemotherapy cycle, and the QoL in a preceding cycle could affect the QoL in successive cycles of chemotherapy. Newer antiemetics were shown to have less impact of CINV on QoL, particularly those using netupitant or aprepitant based antiemetic protocols. This information reaffirms similar findings from older studies [2, 4–7] and confirms that there is a considerable QoL impact from CINV even when newer and more potent antiemetics are used. However, this impact is lower when newer

guidelines, which recommend NK1 receptor antagonist-based antiemetic regimens, are being adopted into daily clinical practice. This is being reflected by the current data analysis that has been based on five groups of patients, with four of them receiving NK1 receptor antagonist-based antiemetic regimens (including one group having received additional olanzapine).

The present study is one of the few studies that evaluated the impact of CINV on the QoL of patients with breast cancer across multiple cycles of AC chemotherapy. We found that QoL was significantly associated with symptoms of CINV during all the three phases (acute, delayed, and overall) within a chemotherapy cycle. Additionally, the symptom of nausea was found to have a greater impact on the QoL than that of vomiting. This finding is in line with results from previous studies [5, 8, 11, 20] and highlights the importance of controlling nausea (alongside vomiting) after chemotherapy. However, at the same time, it has been acknowledged that although vomiting has mostly been well controlled, nausea remains a significant problem in practice, and optimal management of CINV is yet to be achieved [21]. It is noteworthy that other factors, in addition to CINV per se, may impair QoL after chemotherapy. In a multicenter Canadian trial consisting of 832 chemotherapy-naïve patients who received their first cycle of either MEC or HEC, the investigators suggested that the degree of disruption to the QoL was not entirely attributable to the development of CINV, but that other aspects, such as the chemotherapy



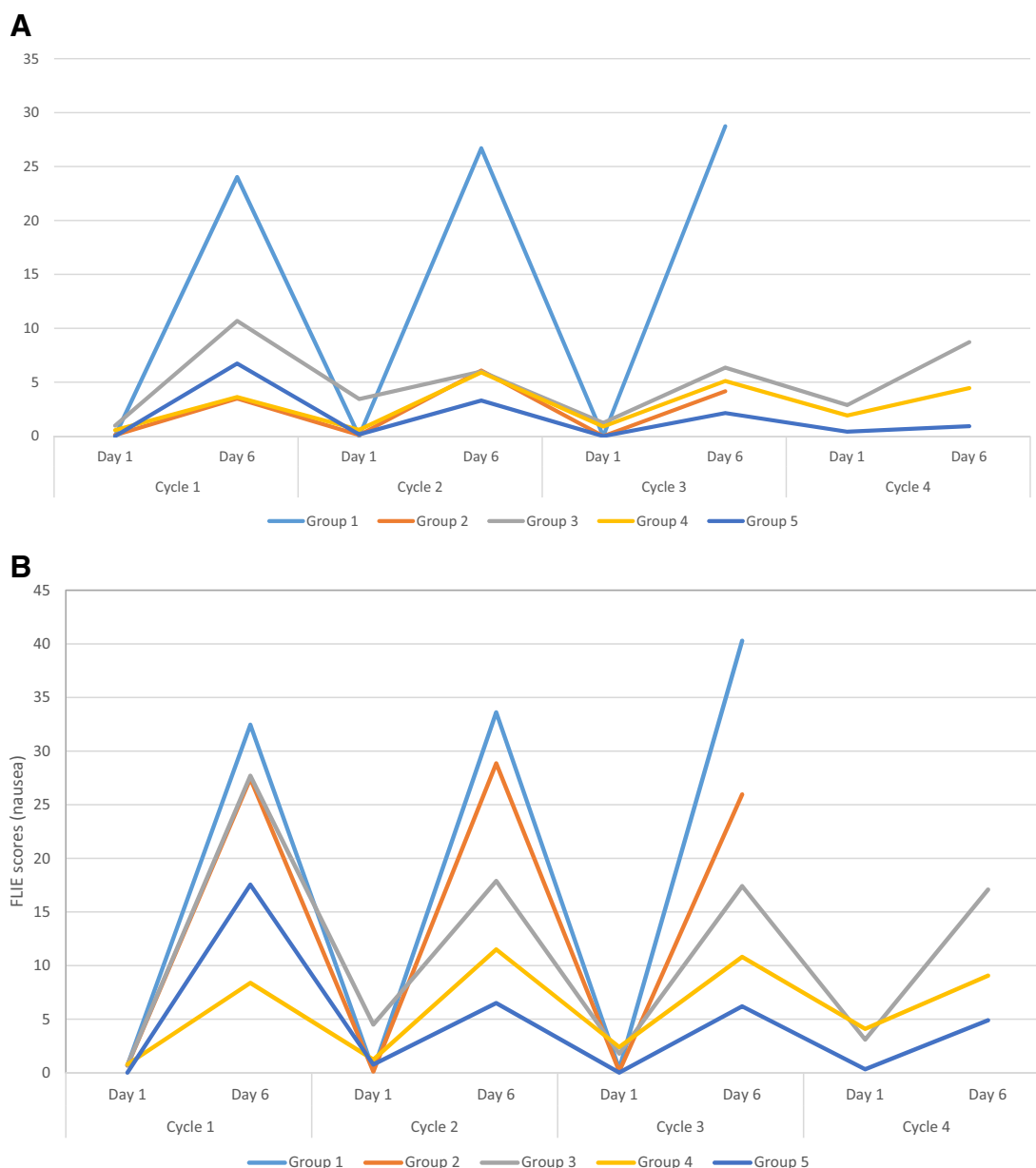
**Figure 1.** Correlation of day 6 FLIE with CR in overall phase: cycle 1 (A), nausea domain (left), vomiting domain (right); multiple cycles (B), nausea domain (left), vomiting domain (right). Abbreviations: CR, complete response; FLIE, Functional Living Index–emesis.

itself and the type and duration of the antiemetics used after chemotherapy, also played important roles on QoL [22]. On the other hand, a secondary analysis performed on data from 200 patients with cancer found that the presence of a cluster of gastrointestinal symptoms (nausea, vomiting, and/or appetite loss) was associated with a greater negative impact on QoL, more so than nausea, vomiting, and appetite loss individually or nausea and/or vomiting, suggesting an undesirable synergistic effect of these symptoms on patients' QoL [10]. Furthermore, other studies have reported that subjects who were preoccupied with sense of despair, weakness, anxiety, and distress also experienced a worse QoL [23] and that a higher expectancy of prechemotherapy nausea was associated with a poorer QoL [9].

There have only been a few studies currently available that describe the dynamics of QoL over multiple cycles of chemotherapy. Although Farrell et al. demonstrated the positive relationship between symptoms of CINV and outcomes of QoL in the first and second cycle of anthracycline-containing chemotherapy [3], the dynamics of the QoL between the two cycles were not reported. When Cohen et al. assessed patients over three cycles of chemotherapy, there was a suggestion that the day-to-day functioning

within each cycle of chemotherapy improved over time [2]. In the more recent era of NK1 receptor antagonist availability, Hilarius et al. assessed the QoL during multiple cycles of chemotherapy and reported that not only did the occurrence of CINV affect the QoL during the first cycle, but the proportion of patients reporting CINV having an impact on their daily lives did not change significantly during the second and third treatment cycle [6].

The present study is one of the few studies that evaluated the impact of CINV on the QoL of patients with breast cancer across multiple cycles of AC chemotherapy. In support of the findings of Cohen et al., the current study reveals that the QoL status was not static but fluctuated over time during the course of a chemotherapy cycle. There was also a suggestion that patients receiving ondansetron/dexamethasone scored worst on QoL, whereas patients receiving contemporary antiemetic prophylaxis, such as netupitant + palonosetron– or aprepitant/olanzapine-containing regimens, scored better in QoL assessment. Furthermore, the role of dexamethasone in the different groups in this study could influence CINV rates and, indirectly, QoL. Among the patients who received ondansetron/dexamethasone prophylaxis, their QoL was found to deteriorate further during subsequent cycles of



**Figure 2.** Quality of life based on FLIE across four cycles of AC chemotherapy: vomiting domain (A); nausea domain (B). Abbreviation: FLIE, Functional Living Index–emesis.

chemotherapy. Apart from suboptimal antiemetic prophylaxis upfront, the lack of improvement could be due to the inadequate use of rescue medications, which could be linked to the general reluctance in taking medications among Chinese patients [16]. Such observations highlight the importance of optimal upfront antiemetic prophylaxis, and are supported by the observation that, among patients who received contemporary antiemetic prophylaxis, a progressive improvement in QoL with lessening impact on daily functioning was seen in succeeding cycles of AC.

To our knowledge, the current study is one of the first that attempts to assess the relationship between QoL in an earlier cycle and the corresponding QoL over subsequent cycles. Our findings revealed that patients who had lower QoL in cycle 1 had significantly worse QoL in cycles

2, 3, and 4. Furthermore, the QoL outcomes in cycle 2 similarly affected the QoL in cycles 3 and 4, and the same conclusion could also be made for findings between cycles 3 and 4.

The present study is unique in terms of having a homogenous group of female patients with breast cancer of Chinese ethnicity who were not only chemotherapy-naïve, but also all received the same chemotherapy regimen consisting of adriamycin and cyclophosphamide. This study is also the first to evaluate the impact of CINV on QoL across four cycles of AC chemotherapy. However, there are limitations in the current analysis. First, the three studies included in the present analysis were conducted on different patient cohorts over different periods in time; thus, apart from differences in antiemetic prophylaxis used, there could also have been variations in

**Table 4.** Comparison of quality of life on day 6 across four cycles: group 1 + 2 + 3 vs. group 4 vs group 5

Cycle No.	Mean scores of group 1 + 2 + 3	Mean scores of group 4	Mean scores of group 5	p value	Mean difference group 1, 2, & 3 vs. group 4	Mean difference group 1, 2, & 3 vs. group 5
Vomiting domain						
Cycle 1	12.76	3.63	6.74	.0097	−9.13 <sup>a</sup>	−6.02
Cycle 2	11.47	5.92	3.32	.0346	−5.55 <sup>a</sup>	−8.15 <sup>a</sup>
Cycle 3	11.79	5.12	2.14	.0065	−6.67 <sup>a</sup>	−9.65 <sup>a</sup>
Cycle 4	8.72	4.46	0.92	.0036	−4.26 <sup>a</sup>	−7.80 <sup>a</sup>
Nausea domain						
Cycle 1	29.21	8.39	17.55	<.0001	−20.82 <sup>a</sup>	−11.66 <sup>a</sup>
Cycle 2	25.24	11.51	6.51	<.0001	−13.73 <sup>a</sup>	−18.73 <sup>a</sup>
Cycle 3	26.05	10.82	6.21	<.0001	−15.23 <sup>a</sup>	−19.84 <sup>a</sup>
Cycle 4	17.09	9.07	4.91	.002	−8.02 <sup>a</sup>	−12.18 <sup>a</sup>

F-statistics.

<sup>a</sup>p value < .05 indicating a difference between the comparison.**Table 5.** Day 6 FLIE-mean scores of previous cycle(s) in relationship to mean scores of subsequent cycle(s)

Cycle	FLIE nausea domain		FLIE vomiting domain	
	Mean score	p value	Mean score	p value
Cycle 1	23.45		10.03	
Cycle 2		<.0001		<.0001
< Cycle 1 mean score	6.87		3.71	
≥ Cycle 1 mean score	36.71		32.08	
Cycle 3		<.0001		<.0001
< Cycle 1 mean score	7.07		3.26	
≥ Cycle 1 mean score	36.87		31.87	
Cycle 4		<.0001		.0137
< Cycle 1 mean score	5.92		3.03	
≥ Cycle 1 mean score	21.48		15.13	
Cycle 2	17.61		8.25	
Cycle 3		<.0001		<.0001
< Cycle 2 mean score	5.60		1.05	
≥ Cycle 2 mean score	49.16		43.05	
Cycle 4		<.0001		<.0001
< Cycle 2 mean score	4.03		1.78	
≥ Cycle 2 mean score	36.15		23.53	
Cycle 3	17.84		7.97	
Cycle 4		<.0001		<.0001
< Cycle 3 mean score	2.76		1.43	
≥ Cycle 3 mean score	36.47		28.47	

Abbreviation: FLIE, Functional Living Index-emesis.

practice on the modification of chemotherapy dosages and the use of rescue medications in different groups across the four cycles of AC chemotherapy. As such, our observations between different groups of patients should be noted with caution. Because QoL assessments were only conducted prior to and five days after AC during a chemotherapy cycle, we were unable to confirm the timing of the peak impact of CINV on patients' QoL. Although the missing data from nonresponding patients who dropped out of the studies might have affected the findings, such likelihood was considered to be low, as the attrition rate over serial assessments was less than 4%.

## CONCLUSION

The current study has demonstrated the impact of CINV on QoL during multiple cycles' assessments. These findings collectively lend support to the notion that optimal control of CINV in the first cycle is an important factor that can improve QoL in not only the first cycle, but throughout multiple cycles of chemotherapy. A better appreciation and acknowledgment of CINV in patients by health care providers will ultimately achieve better control of CINV in the future. QoL improvements from the use of newer antiemetics add further support to similar recommendations in current international antiemetic guidelines.



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## DISCLOSURES

**Winnie Yeo:** CINV Network (C/A), Mundipharma (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

## REFERENCES

- Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med* 2008;358:2482–2494.
- Cohen L, de Moor CA, Eisenberg P et al. Chemotherapy-induced nausea and vomiting—incidence and impact on patient quality of life at community oncology settings. *Supportive Care Cancer* 2007;15:497–503.
- Farrell C, Brearley SG, Pilling M et al. The impact of chemotherapy-related nausea on patients' nutritional status, psychological distress and quality of life. *Support Care Cancer* 2013;21:59–66.
- Ballatori E, Roila F, Ruggeri B et al. The impact of chemotherapy-induced nausea and vomiting on health-related quality of life. *Support Care Cancer* 2007;15:179–185.
- Glaus A, Knipping C, Morant R et al. Chemotherapy-induced nausea and vomiting in routine practice: A European perspective. *Support Care Cancer* 2004;12:708–715.
- Hilarius DL, Kloeg PH, van der Wall E et al. Chemotherapy-induced nausea and vomiting in daily clinical practice: A community hospital-based study. *Support Care Cancer* 2012;20:107–117.
- Haiderali A, Menditto L, Good M et al. Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a U.S. population. *Support Care Cancer* 2011;19:843–851.
- Bloechl-Daum B, Deuson RR, Mavros P et al. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *J Clin Oncol* 2006;24:4472–4478.
- Colagiuri B, Roscoe JA, Morrow GR et al. How do patient expectancies, quality of life, and postchemotherapy nausea interrelate? *Cancer* 2008;113:654–661.
- Pirri C, Bayliss E, Trotter J et al. Nausea still the poor relation in antiemetic therapy? The impact on cancer patients' quality of life and psychological adjustment of nausea, vomiting and appetite loss, individually and concurrently as part of a symptom cluster. *Support Care Cancer* 2013;21:735–748.
- Abunahlah N, Sancar M, Dane F et al. Impact of adherence to antiemetic guidelines on the incidence of chemotherapy-induced nausea and vomiting and quality of life. *Int J Clin Pharm* 2016;38:1464–1476.
- Karhaus M, Oskay-Özcelik G, Wülfing P et al. Real-world evidence of NEPA, netupitant-palonosetron, in chemotherapy-induced nausea and vomiting prevention: effects on quality of life. *Future Oncol* 2020;16:939–953.
- Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. *N Engl J Med* 2000;342:1554–1559.
- Fernández-Ortega P, Caloto MT, Chirveches E et al. Chemotherapy-induced nausea and vomiting in clinical practice: Impact on patients' quality of life. *Support Care Cancer* 2012;20:3141–3148.
- Schnell FM. Chemotherapy-induced nausea and vomiting: The importance of acute antiemetic control. *The Oncologist* 2003;8:187–198.
- 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;113:529–535.
- 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;50:30–38.
- Yeo W, Lau TKH, Kwok CCH et al. NEPA efficacy and tolerability during (neo)adjuvant breast cancer chemotherapy with cyclophosphamide and doxorubicin. *BMJ Support Palliat Care* 2020:bmjcare-2019-002037.
- 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;11:522–527.
- Pirri C, Katris P, Trotter J et al. Risk factors at pretreatment predicting treatment-induced nausea and vomiting in Australian cancer patients: A prospective, longitudinal, observational study. *Support Care Cancer* 2011;19:1549–1563.
- Molassiotis A, Saunders MP, Valle J et al. A prospective observational study of chemotherapy-related nausea and vomiting in routine practice in a UK cancer centre. *Support Care Cancer* 2008;16:201–208.
- Osoba D, Zee B, Pater J et al. Determinants of postchemotherapy nausea and vomiting in patients with cancer. Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1997;15:116–123.
- Grassi L, Berardi MA, Ruffilli F et al. Role of psychosocial variables on chemotherapy-induced nausea and vomiting and health-related quality of life among cancer patients: A European study. *Psychother Psychosom* 2015;84:339–347.