ORIGINAL ARTICLE

HEALTH-RELATED QUALITY OF LIFE PROFILE IN RELATION TO CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING AMONG BREAST CANCER PATIENTS

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Abstract

Objective: **Despite the availability of modern anti-emetics, chemotherapy-induced nausea and vomiting (CINV) symptoms remain distressing to a high number of cancer patients. This study intended to (1) describe the incidence of CINV and anti-emetic usage; (2) assess the health-related quality of life (HRQoL) and correlate its components with *Global Health Status*; (3) evaluate HRQoL status in relation to CINV among breast cancer patients receiving chemotherapy. *Methods:* A cross sectional study was conducted in two government hospitals located in the East Coast of Peninsular Malaysia (Terengganu, Kelantan). The Morrow Assessment of Nausea and Emesis Follow-up (MANE-FU) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) were administered. Descriptive statistics and non-parametric tests were employed (SPSS 16). *Results:* Respondents included 41 female patients (age = 49 ± 9.6 years; Malay = 92.7%; no family history of breast cancer = 68.3% and on moderately emetogenic chemotherapy = 97.6%). Majority of patients experienced nausea during or after chemotherapy (90.2%) and rated it as 'severe'. Most patients had taken anti-emetic (87.8%) and considered it 'somewhat useful'. The median score for *Global Health Status* was 50 (IqR= 16.7). *Emotional Functioning, Fatigue and Pain* correlated fairly with HRQoL (r_s= +0.435; -0.417; -0.387 respectively). Patients with 'a lot' and 'moderate' nausea displayed significantly more fatigue compared to those with little nausea (p=0.029). Those who experienced vomiting reported worse HRQoL profile compared to those who did not (p=0.011). *Conclusion:* These findings generally ascertained that CINV remains poorly controlled and significantly interferes with HRQoL, providing rooms for improvements in therapeutic intervention. *ASEAN Journal of Psychiatry, Vol. 13(1): January – June: XX XX.***

Keywords: Health-related Quality of Life, Chemotherapy-induced Nausea and Vomiting (CINV), Breast Cancer.

Introduction

Cancer is a leading cause of death worldwide, accounting for 7.4 million deaths or approximately 13% of all deaths worldwide in 2004. This number is projected to continue rising, with an estimated 12 million deaths in 2030 [1]. Low and middle income countries were most affected as 70% of deaths from cancer have been reported in this region.

Expectedly, cancer is currently one of the main health problems afflicting Malaysia. Among the major causes of medically certified deaths in Malaysia, cancer ranked the third. Data from the National Cancer Registry in year 2006 reported that a total of 21,773 cancer cases were diagnosed among Malaysians and breast cancer was the most important cancer among population regardless of sex in Peninsular Malaysia [2].

Essentially, chemotherapy is an important treatment in cancer care but this modality is well-known to be liable to a range of dose-related toxic effects. Among these adverse effects, chemotherapy-induced nausea and vomiting (CINV) have been commonly rated as the most unpleasant and distressing side effects of this particular treatment [3,4]. The symptoms may occur within hours after the initiation of chemotherapy treatment (acute) or their appearance may be delayed until after 24 hours (delayed). A learned or conditioned response known as anticipatory CINV could additionally occur prior to the patients' past experience of poorly controlled CINV. Although current anti-emetic treatments have resulted in much improved control of these symptoms particularly during the acute phase, many cancer patients continue to encounter the adverse effects. In a prospective, multinational study [5], health-related quality of life (HRQoL) status of cancer patients experiencing CINV was shown to be unfavourably impaired despite anti-emetic therapy and this occurred even after treatment with only moderately emetogenic chemotherapy regimens.

The burden that CINV places on cancer patients is substantial and its inadequate control has been specifically shown to affect patients' ability to carry out daily activities, hence reducing the HRQoL status [5]. Evidence from another study indicated that more than 90% of Italian cancer patients with both acute and delayed nausea and vomiting claimed that the symptoms affected their daily life [6]. The same finding also reported that even for those who suffered from at least mild nausea, 77% of them experienced an impact on their daily activities. An evaluation on 832 chemotherapy oncology patients' HRQoL indicated that patients with both nausea and vomiting showed significantly worse physical, cognitive and social functioning, global quality of life, fatigue, anorexia, insomnia and dyspnea as compared to those who did not experience the symptoms [7]. Patients with only nausea but no vomiting appeared to have less worsening in functioning and symptoms than those having both symptoms.

Although investigations on HRQoL have been widely practiced among the Western population, such studies are only recently made common in our community-based population [8], particularly among cancer chemotherapy patients. As such, this study was conducted among breast cancer patients receiving chemotherapy with the aims to (1) describe the incidence of CINV, the use of and satisfaction with anti-emetic therapy; (2) assess the HRQoL profile and correlate the subscales with global health status; (3) evaluate HRQoL status in relation to the incidence and severity of CINV.

Methods

A cross-sectional preliminary study using convenient sampling was conducted in two government hospitals located in the East Coast of Peninsular Malaysia. At each centre, standard procedures for nausea and emesis prevention and management were conducted in accordance with the chemotherapy protocol and patient's clinical condition. The respondents included women aged 18 years and above, diagnosed with breast cancer, receiving chemotherapy, gave informed consent, could communicate in the Malay Language (Bahasa Melayu) and understood the study procedure. Excluded from this study were those with other malignancies or patients who were undergoing concurrent radiotherapy. The exclusion criteria also included any type of illness of such severity that prevented patient's full cooperation in the study. Permission to conduct this study was obtained from the Ministry of Health (MOH) Research and Ethics Committee (MREC). Data collection period commenced from March to August 2011.

Two government-run oncology clinics were the selected recruitment sites. Following MREC approval, potential participants were identified by research assistants (RAs) for the study enrolment. Each woman who has been scheduled to receive their subsequent chemotherapy treatment was invited to participate. After providing written consent, patients attained instructions to complete the research tools. The questionnaires were distributed during their ordinary chemotherapy treatment session in which the completion was conducted under the supervision of RAs, and the forms were later collected all at once.

Patients' medical reports were extracted and reviewed to obtain their demographic and medical information including biochemical data, chemotherapy treatment and breast cancer related characteristics. Monthly household income is an exception whereby this information was self-reported by the patients.

CINV were assessed using questions adapted from Morrow Assessment of Nausea and Emesis Follow-up (MANE-FU) [9]. This instrument was an extension from MANE which includes extra questions on symptom occurrence and anti-emetic usage. The MANE scale is a retrospective tool, provided with separate questions in the areas of anticipatory nausea, anticipatory vomiting, post-treatment nausea and post-treatment vomiting. This questionnaire was translated into Malay language for adaptation in this community-based sample. There are a total of 16 items with 2 major domains; nausea and vomiting. In addition, all items were further categorised into five subscales; occurrence- (4 items with *yes/no* response), frequency- (2 items with 7-point Likert scale), duration in hours – (4 items with open-ended response), severity- (4 items with 6-point Likert scale) and antiemetic use (4 items with with *yes/no* response and 4-point Likert scale assessing usefulness). However, the subscale of duration has been excluded after poor responses from the participants complaining that it was hard to recall or determine the duration of CINV episodes. Therefore, a total of 12 items were answered by the patients.

The validity and reliability of the EORTC QLQ-C30 in measuring the HRQoL of cancer patients in multi-cultural clinical research settings have been reported by Aaronson and colleagues [10]. It was designed to be cancer-specific, multi-dimensional in structure, appropriate for self-administration, applicable across a range of cultural settings and suitable for use with additional site- or treatment specific modules. The translated and validated version of EORTC QLQ-C30 in the Malay language [11] was employed in this study. This questionnaire contains 30 items including five functional scales (physical, emotional, cognitive, social and role), three symptom scales (fatigue, pain, and nausea/vomiting), a global health scale and six single items assessing symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea) and financial impact of the disease. Items were scored and scales were constructed using the recommended procedures. The raw scores were linearly transformed to obtain standard scores in the range of 0-100 for each of the scales and single items. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/ healthy level of functioning and a high score for the global health status represents a better HRQoL. On the other hand, a lower score for symptom domains and single items indicated fewer symptoms, hence better HRQoL.

Statistical analysis

The Statistical Package for the Social Science (SPSS, Version 16.0, 2007) was used for data compilation and statistical analysis. Descriptive statistics were used to assess the incidence of CINV, anti-emetic usage and HRQoL profile. Initial normality test carried out utilizing the HRQoL score as dependent variable showed that normality requirements were violated (Shapiro-Wilk test = $p<0.05$; data was positively skewed). Therefore, in assessing the subsequent objectives, non-parametric correlation was performed to evaluate the association between two

numerical variables (expressed as Spearman's r_s) and Mann-Whitney U test was carried out to test for differences between groups (continuous data). The probability of committing type-1 error was set at 5% level.

Results

In a period of six months, a total of 41 female respondents participated. Participants' age ranged from 24 to 68 years (mean = 49.1 ± 9.6). Majority were Malays, married, unemployed or housewives, and completed secondary school education. Over half of the respondents could be considered as newly diagnosed (≤ 1 years after diagnosis) with no family history of malignancy. Patients were predominantly in Stage Three and receiving moderately emetogenic chemotherapy. Nearly all the patients (97.6%) received a 5-HT_3 antagonist (granisetron) which was administered commonly for two days. This anti-emetic therapy is usually supplemented by a corticosteroid (dexamethasone) (75.6%) for four days (concurrently administered). Patients' demographics and clinical characteristics are presented in Table 1.

Table 1. Patients demographics and clinical characteristics

Characteristics	Frequency *n*=41	Percentage (%)
Age (mean ± sd*)	49.1 ± 9.6 years	
Ethnicity		
Malay	38	92.7
Chinese	3	7.3
Marital Status		
Married	31	75.6
Single/ widowed	10	24.4
Education level		
Never attended school	4	9.8
Primary	5	12.2
Secondary	26	63.4
Tertiary	6	14.6
Occupation		
Employed	19	46.3
Housewife/ Unemployed	22	53.7
Monthly household income		
<RM 1000	11	26.8
≥RM 1000	30	63.2
BMI (mean ± sd*)	25.3 ± 4.5 kg/m^2	
Years after diagnosis		
≤ 1 years	30	73.2
> 1 years	11	26.8
Family history of malignancy		
Yes	12	29.3
No	29	70.7
Stages of breast cancer		
1 & 2	19	46.3
3 & 4	22	53.7
Chemotherapy emetogenicity		
Moderately	40	97.6
Highly	1	2.4
Anti-emetic medication**		
5-HT_3 antagonist	40	97.6
Corticosteroids	31	75.6

**sd= standard deviation*
***Combination possible, percentage > 100%*

Despite the administration of antiemetic therapy, 90.2% of breast cancer patients continued to experience nausea during or after chemotherapy, whereas vomiting was reported by 12% of patients (Table 2). Almost half of those reported to have nausea rated the intensity as 'severe' during its worst with no time more severe as any other. Out of 12 patients who experienced vomiting, 11 considered their symptom to be severe at its worst, which mostly occurred within 12 hours after chemotherapy administration. Concerning anticipatory CINV, a lower percentage of patients reported this event (17%), with over half recorded to have mild nausea (57.1%). The use of oral anti-emetic was reported by 87.8% of patients and the majority expressed their satisfaction with this

pharmacological therapy as being 'somewhat useful' (Figure 1).

Table 2. Prevalence of nausea and vomiting during or after chemotherapy

Symptom	Nausea, n (%)		Vomiting, n (%)	
Occurrence	Yes	No	Yes	No
	37 (90.2)	4 (9.8)	12 (29.3)	29 (70.7)
Severity				
Little	14 (37.8)		-	
Moderate	5 (13.5)	-	1 (8.3)	-
A lot / severe	18 (48.7)		11 (91.7)	
Duration				
0-12 hours post-chemotherapy	14 (37.8)		7 (58.3)	
12-24 hours post-chemotherapy	4 (10.8)		1 (8.3)	
No specific time	19 (51.4)	-	4 (33.4)	-

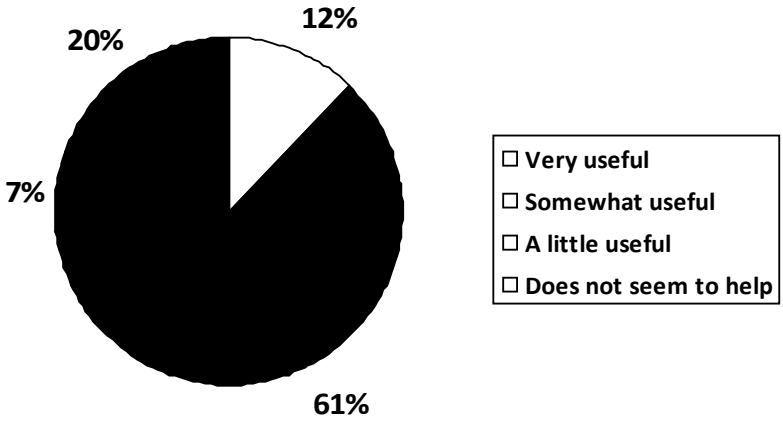

Figure 1. Patients' satisfaction with the use of anti-emetic

Table 3 reports the responses to the EORTC QLQ-C30 for all patients as well as their association with *Global Health Status*. The median score for *Global Health Status* for breast cancer patients who were receiving chemotherapy treatment was 50.0 (IqR= 16.7). *Social Functioning* subscale emerged as the best functional outcome but lowest scores were noted for *Role* and *Emotional Functioning*. This cohort also suffered from fatigue and *pain* ($p<0.05$) while other symptoms seemed to have negligible to little effects. The least impairments were reported with regard to *Nausea and Vomiting*, *Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea* and *Financial Difficulties*. Results of univariate analysis indicated that *Emotional, Fatigue* and *Pain* were linearly and fairly correlated with HRQoL. Patients with better emotional status experienced better HRQoL whereas *Fatigue* and *Pain* were inversely correlated with HRQoL.

Table 3. Median and interquartile range (IqR) of EORTC QLQ-C30 subscale scores and their correlation with global health status

Scale/Item	Median	IqR	Correlation coefficient	p-value
***Global health status *Functioning**	50	16.7	-	
Physical functioning	80.0	14.5	0.068	0.671
Role functioning	67	33.3	0.271	0.086
Emotional functioning	67	66.7	0.435	**0.005**
Cognitive functioning	83	25.0	0.103	0.520
Social functioning	100	0.0	0.057	0.723
†**Symptoms/items**				
Fatigue	33	30.5	-0.417	**0.007**
Nausea and Vomiting	0	0.0	-0.150	0.348
Pain	33	33.3	-0.387	**0.012**
Dyspnoea	0	0.0	-0.208	0.192
Insomnia	0	66.7	-0.301	0.055
Appetite loss	0	33.3	-0.274	0.083
Constipation	0	33.3	0.199	0.213
Diarrhoea	0	0.0	0.027	0.867
Financial difficulties	0	0.0	-0.144	0.370

***** *Score range 0-100 = higher score indicates better HRQoL*
† *Score range 0-100 = higher score indicates worse HRQoL*

For univariate analysis, only the severity of nausea and the occurrence of vomiting were available due to balance number in each group. Patients with 'a lot' and 'moderate' nausea reported significantly more fatigue compared to those with little nausea (Table 4). Patients with little nausea displayed better HRQoL mainly in *Global Health Status, Role, Emotional and Cognitive Functioning* ($p>0.05$). In addition, patients who experienced vomiting reported lower HRQoL than those who did not ($p=0.011$). However, decrement in emotional and cognitive function was observed among patients who experienced vomiting.

Table 4. Comparison of HRQoL subscales by CINV (incidence / severity)

	Mean Rank (Median)					
	Severity of nausea			Vomiting occurrences		
	Little	Moderate and a lot	p-value	Yes	No	p-value
***Global health status**	23.1 (67)	16.5 (50)	0.056	14.1 (50)	23.9 (50)	**0.011**
***Functioning**						
Physical functioning	20.1 (80)	18.3 (80)	0.624	22.0 (83)	20.6 (80)	0.728
Role functioning	20.5 (75)	18.1 (67)	0.502	21.9 (67)	20.6 (67)	0.731
Emotional functioning	21.5 (75)	17.5 (67)	0.271	17.6 (45)	22.4 (66)	0.239
Cognitive functioning	22.2 (100)	17.0 (83)	0.128	17.9 (83)	22.3 (100)	0.245
Social functioning	18.2 (100)	19.5 (-)	0.200	21.5 (-)	20.8 (100)	0.520
†**Symptoms / items**						
Fatigue	14.1 (28)	21.9 (44)	**0.029**	22.3 (33)	20.5 (33)	0.642
Nausea and Vomiting	19.4 (0)	18.7 (0)	0.802	20.3 (0)	21.3 (0)	0.751
Pain	15.3 (33)	21.2 (33)	0.090	22.3 (33)	20.5 (33)	0.643
Dyspnoea	18.2 (100)	19.5 (100)	0.523	21.7 (0)	20.7 (0)	0.692
Insomnia	18.3 (0)	19.4 (0)	0.730	22.4 (17)	20.4 (0)	0.603
Appetite loss	18.0 (0)	19.6 (0)	0.574	22.3 (0)	20.5 (0)	0.589
Constipation	19.4 (0)	18.8 (0)	0.854	22.7 (0)	20.3 (0)	0.493
Diarrhoea	20.9 (0)	17.8 (0)	0.214	21.9 (0)	20.6 (0)	0.647
Financial difficulties	18.9 (0)	19.1 (0)	0.942	18.5 (0)	22.0 (0)	0.221

** Score range 0-100 = higher score indicates better HRQoL*
† Score range 0-100 = higher score indicates worse HRQoL

Discussion

The study results demonstrate that a significant proportion of patients remain to suffer CINV even after usual anti-emetics management. This finding was slightly higher than the previous studies involving a larger number of patients (n=124) whereby 70% of the oncology patients receiving moderately ematogenic chemotherapy experienced either nausea or emesis or both [12]. Although a smaller proportion of the patients claimed to have vomited, majority still experienced severe nausea. A study showed that the incidence of nausea was reported to have actually increased despite reduction in the incidence of vomiting when antiemetic treatment (5-HT_3 antagonist and corticosteroids) was administered [13]. Adequate control of CINV might have been compromised due to the fact that antiemetic treatment regimens are actually influenced by several risk factors such as ematogenicity of chemotherapeutic agents as well as patients-related risk factors. Patients treated with the high risk emetic agent, elderly, women and people with previous CINV experience possessed higher risk towards CINV [14]. In response to the nature of breast cancer itself which affected mostly women, this trait may have indirectly marked up the incidence of CINV events in our samples. The incidence and severity of CINV among this sample

population indicate that there is still room for improvement towards better control of CINV perhaps through the introduction of complementary medicine. Even so, most of the patients have taken oral anti-emetic medications and perceived them as rather beneficial in managing their symptoms.

The psychological impact of breast cancer has also received considerable attention. Many studies have shown that psychological distress impaired HRQoL particularly with regard to emotional functioning, mental health, social functioning and consequently the overall quality of life [15]. The diagnosis of the disease, fears and concerns regarding death and disease recurrence, impairment of body image, and alteration of femininity, sexuality and attractiveness have very much contributed to this psychological distress [16-18]. Apart from that, difficulties in concentration have been identified as a significant stressor following cancer treatment [19]. Nausea and vomiting could be one possible stressor in which their presence and severity could weaken patients' concentration and subsequently may influence their individual role and function. Qualitative research has revealed that women with cancer experienced cognitive difficulties which affect their functioning at home and at work [20]. In our sample, the lowest scores were recorded for *Emotional and Role Functioning* and these findings were possibly associated with the psychological impacts. However, it is of interest that social functioning appeared as the best domain which was supported by the fact that patients received unconditionally substantial support from their family and friends [21].

Consistent with a previous study [15], emotional, fatigue and pain were largely associated with HRQoL. Byar et al. [22] reported that during adjuvant breast cancer chemotherapy treatments, fatigue level were moderately intense, compromising HRQoL level. The symptom distress including increased severity of nausea at the time of treatment and at midpoints of chemotherapy cycle has been noted to intensify fatigue level [22]. Other than that, an analysis of 1,957 breast cancer survivors after one to five years of diagnosis found that depression and pain were the strongest predictors of fatigue [23]. In our study, patients were mostly affected by fatigue and pain but the other symptoms possessed negligible to little effects included nausea and vomiting. It is noted that majority of them were receiving the adjuvant chemotherapy following surgery treatments making them more liable to treatment side-effects [15] such as fatigue and pain. Considering our cross-sectional study design whereby the assessment was completed prior to chemotherapy treatment, minimal detection of symptoms was expected since the adverse effects were usually most intense during the first 3 days after chemotherapy [5]. This could be the reason why only minor impairments were reported with regard to nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation and diarrhoea. Apart from that, patients who experienced vomiting exhibited lower HRQoL than those who did not suggesting possible close association between the occurrence of vomiting and HRQoL status. A previous study involving larger number of patients (n=832) reported similar outcomes in which the differences in HRQoL between patients with and without vomiting were significantly substantial mainly with regard to *Social*, *Cognitive Functioning* and *Global Health Status* [24]. However, it is important to point out that not all of the deterioration in HRQoL is largely attributable to nausea and vomiting considering that the presence of these symptoms could also have been contributed by other effects of chemotherapy and possibly physiological changes of the underlying disease itself.

Nonetheless, our study findings should be interpreted in light of several methodological limitations. One potential limitation might be caused by restricted patients recruitment at only two study centres (convenience sampling) which might therefore not be entirely representative of all chemotherapy breast cancer patients. Still, our study sample had generated evidence on CINV in relation to HRQoL profile. Another possible drawback involves the homogeneity of study sample in terms of cancer diagnosis. The findings are

therefore not necessarily generalizable to the other types of malignancy. Despite these limitations, our preliminary study has generally ascertained that CINV remains poorly controlled and significantly interferes with HRQoL particularly among chemotherapy breast cancer patients. Larger studies in multiple oncology settings could substantiate these early findings, hence providing patients-centred solutions for evidence-based selection of optimal treatments in the future.

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