RESEARCH COMMUNICATION

Negative Impact of Chemotherapy on Breast Cancer Patients QOL - Utility of Antiemetic Treatment Guidelines and the Role of Race

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Abstract

Introduction: Chemotherapy-induced nausea and vomiting (CINV) is one of the most important worries of cancer patients. Although not life-threatening, it has a great negative impact on quality of life (QOL). Objective: The aim of this study was to determine the impact of CINV (i.e., acute and delayed) on breast cancer patients QOL and to discern opinions related with antiemetic guidelines used dependent on the three main races in Malaysia (Malay, Chinese, Indian). Methods: In this longitudinal prospective observational study, 158 breast cancer patients treated with chemotherapy were interviewed and valid questionnaires (MANE and ONEM) were used to report the impact of CINV on their QOL within the first 24 hours and after 3 to 5 days of chemotherapy treatment. Results: The main result was that delayed CINV has an impact on QOL greater than acute CINV. The impact of nausea was reportedly higher than that of vomiting. Also differences in race i.e., genetic polymorphisms (pharmacogenomics) influenced the utility of antiemetic treatments and patients opinions. Conclusion: Based on the results of our study a new guideline for antiemetic treatment should be used to reduce the impact of CINV on QOL, taking into account variation in genetic polymorphisms among the three races in Malaysia.

Keywords: CINV - acute - delayed - QOL - genetic polymorphisms - races - Malaysia

Asian Pacific J Cancer Prev, **11**, 1523-1527

Introduction

Chemotherapy induced nausea and vomiting (CINV) both represent major problems that cancer patients may face. The distressing effects represent a substantial negative impact on all aspects of patients quality of life (QOL). Moreover even their families and caregivers can also be effected by this negative impact of CINV (Schnell, 2003).

Despite the presence of wide range of antiemetic treatments, CINV still has a great effect on cancer patients QOL (Grunberg, 2004). Also antiemetic treatments have a limited effect in reducing delayed nausea and vomiting than acute nausea and vomiting. Despite the use of antiemetic treatment including $5HT_3$ about 40-75% of cancer patients still suffered from delayed CINV, and it still remains as the significant cause for chemotherapy related morbidity (Bloechl-Daum et al., 2006; Cohen et al., 2007). Cohen et al., (2007) also mentioned that there are few studies that had looked for the development, impact and frequency of delayed nausea and vomiting but only very few of these studies that worked on occurrence of CINV has been published. Also it has been mentioned that the risk effect of delayed emesis on cancer patients is less well described (Lindley et al., 2005). Cohen et al., (2007) also mentioned that the impact of poorly controlled nausea and vomiting on the QOL of the general population of patients receiving emetogenic chemotherapy is not well-reported. Moreover many of the new antiemetic guidelines produced by ASCO, MASCC and NCCN mainly focused on the antiemetic treatment for acute and delayed emesis caused by cisplatin, while there is less consistence in specifying antiemetics recommended for treatment or prevention of delayed emesis due to anthracyclines, cyclophosphamide, carboplatin and other combination (Cohen et al., 2007).

The principal aim of the present study was to examine whether it is possible to discern such a negative impact of CINV on breast cancer patients QOL, to look at the opinion of breast cancer patients on the usefulness of antiemetic treatment i.e., to evaluate whether the Malaysian antiemetic guideline used in Penang Hospital are useful based on breast cancer patients point of view. The major emphasis of our study is on the three chemotherapy regimens used in breast cancer treatment which are cyclophosphamide, adriamycin and 5-flurouracil (CAF), cyclophosphamide, methotrexate and 5-flurouracil (CMF) and cyclophosphamide, epirubicin and 5-flurouracil (CEF). Hence the main emetogenic chemotherapy in all the regimens is cyclophosphamide which is characterized by causing emesis with considerably delay form with latency period in the development of acute emesis and

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it has a different mechanism in causing vomiting from other chemotherapeutics (Hesketh, 2005; Das Gupta et al., 2007). In addition genetic polymorphism could cause the unresponsiveness of the patient to different and potent antiemetic treatments used (Hesketh, 2005). Even though there are numerous number of studies evaluating the impact of CINV on cancer patients QOL, but this issue receive less attention in Malaysia. Also this study tries to discern whether race differences (i.e., genetic polymorphism, pharmacogenomics) will have an effect on the usefulness of the antiemetic guidelines and on patients opinions about usefulness.

Materials and Methods

Patients

This is a longitudinal prospective observational study, conducted in a government hospital on Penang island i.e., Penang General Hospital which is the biggest public hospital in Penang. Penang island is located in the northwest of Malaysia and is separated from the west-coast of Malaysia by five kilometer channel. The approval for this study was given by one of the research institute under the National Institutes of Health (NIH). These are the Institute for Medical Research (IMR), Clinical Research Centre (CRC), Institute of Public Health (IPH), Institute for Health Management (IHM), Institute for Health Systems Research (IHSR), and Institute for Health Behavioral Research (IHBR). Approved was also issued by Ministry of Health Malaysia (MOH). All mentioned above are with accordance with the declaration of Helsinki.

This current study tries to distinguish the impact of delayed nausea and vomiting on breast cancer patients QOL. Secondly to determine the usefulness of antiemetic guidelines used in Penang Hospital based on views from breast cancer patients of the three races in Malaysia since pharmacologically it has been significantly proven that these three ethnic groups are phonotypical and genotypical variant from each others (Yang et al., 2004; Ruzilawati et al., 2007). This study was conducted among adult patient (≥18 years old) with breast cancer, regardless of tumor stage admitted to wards C11 or C19 in Penang Hospital and were treated with chemotherapy only. These patients were monitored till the cessation of their chemotherapy administration or until a maximum of 1 cycle of chemotherapy treatment completed. During this stage all the required data were collected by direct interview (person-to-person) and from patients files for information related with demographic data and clinical data. The direct interview helped in the collection of accurate data which are amenable to qualitative methodology. This direct interview was carried out after getting the patients consent. Data collection sheet used was structured interview form containing mixed questions developed based on standardized questions from a global standard model which is The Morrow Assessment of Nausea and Emesis (MANE). The reliability of the questionnaire used by this study was tested by using Person and Cronbach's alpha test after a pilot study on 40 breast cancer patients who suffered from nausea and vomiting. The results showed that it was reliable since its Cranbach's alpha was high (0.910). While the validity of its face and content was conducted by exploring the opinion of a panel of expert and consultant in Penang Hospital. This study involved patients admitted to the oncology ward (C11 or C19) in Penang Hospital during this study period. The sample size for this study was calculated by using the PS: power and sample size program (Ruzilawati et al., 2007), with a standard calculation at a significant level of 0.05 and confidence interval 95%. The sample size required for this study with power of 95% was 158 breast cancer patients. In this study, breast cancer patients treated with chemotherapy were monitored and data on information related with QOL before receiving chemotherapy and within 24 hours after chemotherapy were collected. The patients were then followed up after 3 to 5 days of chemotherapy treatment to collect information related to delayed QOL. The data collected in this part of the study includes the patients race (Malay, Chinese, Indian), QOL data before and after receiving chemotherapy.

Statistical Analysis

Data collected include categorical data which was un normally distributed and some are continues data. This was confirmed with the Statistical Package of Social Science (SPSS) software program version 15. Continuous data are related with scores of QOL resulted from computing the scores of each part of the questionnaire to get the final score for QOL. Thus non parametric and parametric tests were used to analyze them. The data were entered into the SPSS® software program version 15 for analysis. The type of statistical test used were Wilcoxon test and Chi square test for the categorical data and Linear regression test for continues data. For Wilcoxon test the main parameters for significance depend on $P < 0.05$, positive and negative rank. As for Chi square test, this depend on the frequency for each variable and the result is considered significant when P value < 0.05. While for Linear regression the parameters $P < 0.05$ is considered significant and r for correlation so the highest r value means the highest correlation. The power for this study was more than 95%.

Results

Patient Characteristics

Demographic data are shown in Table 1. All the breast cancer patients (n=158) were women. The majority were Chinese, mean age was 52.4 years and majority (n=53; 33.5%) were between 50-59 years old. Almost all the patients were treated with cyclophosphamide + epirubicin + 5-flurouracil (FEC). All the patients were treated with a combination of granisetron (Kytril®) plus dexamethasone as pre-chemotherapy antiemetic and metoclopramide plus dexamethasone tables as post-chemotherapy antiemetics. All the 158 patients had a valid diary data for one cycle only and all of them completed the diary data for one cycle.

Prevalence of CINV

Majority of the patients (n=47; 29.8%) suffered from acute and delayed CINV followed by those who neither showed acute nor delayed CINV (n=23; 14.5%) and then

Table 1. Characteristics of the Breast Cancer Patients

Demographic data	Value
Female (gender)	158 (100%)
Mean age (range)	52.4 years (26–73 years)
Race	
Chinese	101 (63.9%)
Malay	35 (22.2%)
Indian	22 (13.9%)
Current chemotherapy	
FEC	147 (93%)
CAF	6 (3.8%)
CMF	5 (3.2%)

Table 2. Prevalence of Chemotherapy Induce Nausea and Vomiting (CINV) Within

Type of CINV	Number	Percentage
Acute CINV+ Delay CINV	47	29.8
No Acute CINV+ No Delay CINV	23	14.5
Only Delay CINV	17	10.8
Acute Nausea+ Delay CINV	13	8.2
Acute Nausea+ Delay Nausea	8	5.1
Only Acute Nausea	8	5.1
Acute Vomiting+ Delay CINV	7	4.4
Acute Nausea+ Delay Vomiting	7	4.4
Only Delay Vomiting	6	3.8
Acute CINV + Delay Vomiting	5	3.2
Acute CINV+ Delay Nausea	5	3.2
Only Delay Nausea	5	3.2
Acute Vomiting+ Delay Vomiting	4	2.5
Only Acute Vomiting	2	1.3
Acute Vomiting+ Delay Nausea	1	0.6
Total	158	100

breast cancer patients (n=158)

Table 3. Impact of CINV on Breast Cancer Patients QOL

	Acute			Delayed		
Parameters	Neg	Pos	P value*	Neg	Pos	P value*
Nausea						
Appetite	0	99	0.00	0	125	0.00
Sleep	0	79	0.048	0	111	0.00
Activities	0	83	0.00	0	112	0.00
Social	0	80	0.016	0	112	0.00
Enjoyment	0	86	0.00	0	113	0.00
Vomiting						
Appetite	0	93	0.00	0	117	0.00
Sleep	0	68	0.056	0	89	0.00
Activities	0	74	0.044	0	92	0.00
Social	0	71	0.051	0	90	0.00
Enjoyment	0	79	0.048	0	90	0.00

Neg, negative rank, before chemotherapy > after chemotherapy; Pos, positive rank, after chemotherapy > before; * Wilcoxon signed-rank test

those who suffered from delay CINV (n=17; 10.8%). There are also patients who did not show neither acute nor delayed CINV, but the majority of the 158 patients suffered from either acute or delayed or both of CINV. These results are clearly shown in Table 2.

Effect of CINV on QOL

The results of Wilcoxon test show that the measured QOL before chemotherapy (i.e., before nausea and vomiting incidence) were higher than the QOL after chemotherapy (i.e., after incidence of nausea and vomiting) for both acute and delayed nausea and vomiting. Both have a negative impact on patients QOL. The results show that delayed CINV have a higher negative impact on breast cancer patients QOL than acute CINV. Moreover the results showed that delayed nausea has a higher negative impact on QOL than that of vomiting, this was confirmed by looking at the positive rank. The positive rank for QOL before and after the incidence of delayed nausea higher than that seen before and after the incidence of delayed vomiting. Also the results show that the majority of the differences between QOL before and after incidence of acute and delayed CINV were high. These results are clarified in Tables 3A and 3B.

Association and Correlation Between Acute and Delayed CINV With QOL

According to the results of linear regression test, there is a significant association between severity of acute and delayed nausea with impact of acute and delayed nausea on patients QOL. These results were confirmed depending on ANOVA test result which showed a significant association for acute (P= 0.027) and for delayed (P= 0.00) nausea, this ANOVA test result is a part of Linear regression test result. Also the result of the Coefficients showed significant association for acute (t=4.378, P= 0.034) and for delayed (t=6.574, P= 0.00) nausea. In addition, the results showed that there is a significant correlation between severity of acute and delayed nausea with impact of acute and delayed nausea on QOL, since P= 0.038 for acute and P= 0.00 for delayed. While, the type of the correlation is a positive correlation since r= 0.311 for acute and r= 0.466 for delayed nausea respectively. This means that when the severity of acute and delayed nausea increases then the effect of acute and delayed nausea on patients QOL will increase too. The correlation and association of delayed nausea is higher than acute nausea. This means the effect of delayed nausea has a higher negative impact than acute nausea on QOL.

The result of linear regression test showed a significant association exist between severity of acute and delayed vomiting with vomiting effect on QOL, since ANOVA test showed P=0.047 for acute and P=0.00 for delayed vomiting. Also the result of the Coefficients shows significant association since t=3.472, P=0.04 for acute and t=5.628, P=0.00 for delayed vomiting.

While for correlation, the results show that there is a significant correlation between severity of acute and delayed vomiting with impact of delayed nausea on QOL since P=0.048 for acute and P=0.00 for delayed vomiting. The type of the correlation is a positive correlation since r=0.236 for acute and r=0.411 for delayed vomiting. This means that when the severity of delayed nausea increases then the effect of delayed nausea will increase too. The correlation and association of delayed vomiting is higher than acute vomiting which means the effect of delayed vomiting has a higher negative impact than acute vomiting on QOL. Also it is clear that acute and delayed nausea both have a higher negative impact effect on breast cancer patients than acute and delayed vomiting. All these results are shown in Table 4.

Table 4. The Association and Correlation of Severity of Acute and Delayed of CINV with Impact Effect of Acute and Delayed CINV on Breast Cancer QOL

Risk Factor	Dependent	Test		*P*
Severity of acute nausea	Acute nausea effect	Linear Regression		0.027
Severity of delay nausea	Delayed nausea effect	Linear Regression		0.00
Severity of acute vomiting	Delayed vomiting	Linear Regression		0.047
Severity of delayed vomiting	Delayed vomiting	Linear Regression		0.00
Risk Factor	Dependent	Test	*r*	*P*
Severity of acute nausea	Acute nausea	Correlation	0.311	0.038
Severity of delay nausea	Delayed nausea	Correlation	0.466	0.00
Severity of acute vomiting	Acute vomiting	Correlation	0.236	0.048
Severity of delayed vomiting	Delayed vomiting	Correlation	0.411	0.00

Association between Race and Opinion of Antiemetic Usefulness

The results of Chi-square test show a strong association between race and opinion of usefulness of antiemetic against acute and delayed CINV. Since the *P* values for all variables were 0.00. This simply mean that the race play a risky role in case of effectiveness of antiemetic control on CINV and negative impact on QOL.

Discussion

This is a longitudinal prospective observational study considered as the first study in Malaysia that is looking to distinguish the impact of acute and delayed CINV on breast cancer patients QOL. As mentioned by Bloechl-Daum et al., (2006), it is somewhat clear from self–evident that nausea and vomiting that happened after receiving chemotherapy have a deterioration effect i.e., negative impact on cancer patients QOL. However information from prospective clinical trials to prove and assess this negative impact of CINV on QOL are still scanty. Thus any information from any observational clinical study will help in choosing of suitable antiemetic treatment to be used (Bloechl-Daum et al., 2006). It is obvious from the results of this observational study that both acute and delayed CINV have a negative impact on breast cancer patients QOL. Moreover it is obvious that the delayed CINV has a higher negative impact on QOL than the acute CINV. Delayed nausea has a great negative impact on cancer patients QOL than acute nausea. Also nausea seems to have a higher negative impact on QOL than vomiting. In addition, the effect on the QOL is higher in delayed than acute vomiting (Table3).

The first point of CINV effect on QOL was explained by Neymark and Crott (2005) who mentioned that nausea, vomiting and the symptoms associated with them are considered as very distressing on cancer patients, in addition both have a serious negative impact on cancer patients QOL (Neymark and Crott, 2005). While the second point i.e., nausea have a greater effect on QOL than vomiting was mentioned by Rogers (2009) who indicated that nausea has a higher negative impact on cancer patients QOL than vomiting. Also Rogers (2009) mentioned that the delayed CINV has a negative impact on cancer patients QOL greater than acute CINV (Rogers, 2009). All of these could be due to inadequate control of CINV (Neymark and Crott, 2005). In addition Rogers (2009) confirmed this by mentioning that when antiemetic treatment was used at least 70%-80% of CINV incidence can be prevented (Neymark and Crott, 2005; Rogers, 2009). This has been confirmed by the results of our prospective study since the majority of the patients specifically the Chinese (since they represent the major race in this study) were discontented with the antiemetic treatment used to prevent CINV. According to Chi-square test result, there is a strong association between race and opinions about usefulness of the antiemetic treatments. Despite all the patients receiving granisetron (Kytril®) plus dexamethasone as pre-chemotherapy antiemetic and metoclopramide plus dexamethasone tables as post-chemotherapy antiemetic they were still contented with the treatment. Even though the treatment guidelines are in accordance with the Malaysian guideline and many global guidelines and is considered as a very effective antiemetic treatment (Grunberg, 2004; Bloechl-Daum et al., 2006). The most probable explanation for this is the genetic polymorphism between the three races (Malay, Chinese and Indians) which could result in an alteration in granisetron (Kytril®) metabolism by CYP3A4 enzyme (Rais et al., 2006). As mentioned by Huang and his colleague (Huang et al., 2003), Chinese specifically those suffering from breast cancer have high concentration of CYP3A4. Since the majority of the breast cancer patients in this prospective study were Chinese (n=101; 63.9%), they could be having high concentration of metabolizing enzyme. This will lead to rapid metabolism of granisetron and a reduced or diminished of granisetron antiemetic action. This hence could explain the insufficient antiemetic action and the discontented among the Chinese cancer patients in this study. Beside that it has been proven by Ruzilawati et al. (2007) that the Malay race has a mutation in alleles which will effects on CYP3A4 enzyme action and Rais et al., (2006) on the other hand reported the absence of CYP3A4 and other alleles within the Indian race (Rais et al., 2006; Ruzilawati et al., 2007). Hence this genetic polymorphism results in adequate action and control for CINV specifically acute CINV. As mentioned by Grunberg (2004) when acute CINV is completely controlled by using 5-HT_3 receptor antagonist plus dexamethasone, then more than 92% of delayed CINV will be completely controlled too (Grunberg, 2004). This point is also confirmed by Molassiotis and his colleague that there is an association between acute CINV and delayed CINV, so the failure to control acute nausea and vomiting will lead to failure in controlling the delayed one too (Molassiotis et al., 2002).

According to the results of our study, the delayed CINV

incidence is higher in the Chinese race then the others two races. The main reason would be the poor control of metoclopramide (Maxolon®) plus dexamethasone tablets used to control delayed phase. This has been pointed out by Molassiotis et al., (2002) who indicated that the antiemetic effect of metoclopramide plus dexamethasone against delayed nausea and vomiting is unsatisfactory.

Based on the results of our study a new guideline for antiemetic treatments should be used in order to reduce the impact of acute and delayed CINV on breast cancer patients QOL, and the new guideline should take into account the genetic polymorphism for the three races in Malaysia.

Acknowledgement

We want to declare that this study does not have any conflict of interest.

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