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Review Article

Assessing Chemotherapy-Induced Nausea and Vomiting in Breast Cancer Patients in Malaysia: Insights into Quality of Life and Genetic Influences

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Abstract

Background: *Malaysia faces a persistent public health challenge in the form of breast cancer, which affects approximately one in twenty women and accounts for a significant proportion of cancer-related mortality across diverse ethnic groups and age demographics. Despite the advancements in cancer therapeutics, the side effects of chemotherapy, particularly nausea and vomiting, continue to profoundly impact the quality of life of breast cancer patients.*

Objective: *The objective of this scoping review is to explore the prevalence, management practices, and factors contributing to chemotherapy-induced nausea and vomiting (CINV) among breast cancer patients in Malaysia, with a focus on its implications for patient care and treatment outcomes.*

Methodology: *A systematic search of PubMed, Scopus, and local Malaysian journals was conducted to identify relevant studies. The articles identified were then screened and selected based on predefined inclusion criteria. Key themes related to CINV prevalence, management strategies, and patient outcomes were extracted and synthesized.*

Findings: *The review's findings underscore the prominence of nausea and vomiting as major side effects of breast cancer chemotherapy, leading to complications such as poor treatment adherence and suboptimal response rates. The analysis indicates that current management practices within Malaysia's healthcare system are inadequate in alleviating the severity of CINV or enhancing patients' quality of life. Furthermore, the multiethnic composition of the Malaysian population introduces genetic variations that influence drug metabolism, resulting in disparities in treatment efficacy and tolerability.*

Conclusion: *The findings underscore the critical impact of CINV on the quality of life of breast cancer patients, highlighting the necessity for a re-evaluation of existing treatment guidelines and the development of customized strategies tailored to the Malaysian population. Enhancing CINV prevention and management practices has the potential to markedly improve patient health outcomes and treatment success.*

Keywords: *Breast Cancer, Malaysia, Chemotherapy-Induced Nausea and Vomiting, Quality of Life, Genetic Variations.*

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Introduction

Among women, breast cancer accounts for 14% of all cancer-related fatalities and 23% of all new cancer cases each year, making it a significant burden on healthcare systems worldwide (Ibrahim et al., 2012; Jemal et al., 2011). This disease disproportionately affects developing nations, accounting for over 60% of fatalities and 50% of new cases. A global perspective reveals that the incidence rate is highest in North America, Northern Europe, Northern Africa, and Australia and New Zealand; it is intermediate in South America and Northern Africa; and it is relatively low in Asia, Central Africa, and Southern Africa. The disparities in breast cancer incidence can be attributed to various factors, including reproductive and hormonal influences, as well as the accessibility of screening programs (Dahlui et al., 2011; Ibrahim et al., 2012; Jemal et al., 2011; World Health Organization, 2008).

Despite the ongoing rise in incidence, there has been a decline in breast cancer fatality rates. From 1971 to 2007, the number of individuals who have survived breast cancer increased fourfold, from three million to over twelve million (Aapro, 2004). Despite the strides made in treatment outcomes, a significant proportion of patients undergoing chemotherapy continue to encounter adverse effects, including nausea, vomiting, diarrhea, anemia, leucopenia, neutropenia, and thrombocytopenia. Chemotherapy-induced nausea and vomiting, in particular, persist as debilitating side effects despite efforts to prevent and alleviate them (Aapro, 2004).

These symptoms can be particularly challenging to manage, often resulting in significant discomfort and impaired quality of life for patients undergoing cancer treatment. The inadequate management of these symptoms can lead to a reduction in patients' appetite and thirst, which, in turn, can compromise treatment efficacy, increase the risk of mortality and morbidity, and escalate healthcare expenditures (Aapro, 2004). A novel approach to managing these symptoms involves the combination of corticosteroids and 5-HT3 (serotonin3)-receptor antagonists, with the objective of enhancing therapeutic efficacy.

In Malaysia, these challenges are exacerbated by the unique healthcare and cultural context. The country's multiethnic composition, encompassing Malay, Chinese, Indian, and indigenous communities, introduces variations in genetic predispositions, treatment responses, and healthcare access. The disparities in healthcare access between rural and urban areas, compounded by disparities in health literacy, further complicate the management of CINV. The limited availability of specialized cancer care and antiemetic medications, in conjunction with cultural perceptions regarding cancer and its treatment, can also influence patients' decisions regarding treatment-seeking and adherence.

Despite the proliferation of research on breast cancer and its treatment, a comprehensive review study focusing on Malaysia has not been conducted to date. The primary objective of this article is to provide an overview of clinical studies investigating the risk factors for nausea and vomiting in breast cancer patients in Malaysia. We further aim to explore the approaches employed in preventing and treating these significant side effects through personalized therapy and effective treatment guidelines.

Methods

This scoping review was conducted to synthesize evidence on chemotherapy-induced nausea and vomiting (CINV) among breast cancer patients in Malaysia, with a particular focus on genetic influences, treatment efficacy, and quality of life. The review followed a systematic approach to ensure the inclusion of relevant studies and comprehensive coverage of the topic. The synthesis of findings was methodically conducted on the basis of nine studies that met predefined inclusion criteria. These criteria included studies conducted in Malaysia, with a primary focus on breast cancer-related CINV, and addressing genetic influences, treatment efficacy, or quality of life. Studies conducted outside of Malaysia or lacking specific relevance to CINV in breast cancer patients were excluded from the review.

Search Strategy

A comprehensive search of peer-reviewed articles was conducted across databases, including PubMed, Scopus, and Google Scholar. A combination of keywords, including "chemotherapy-induced nausea and vomiting," "breast cancer," "Malaysia," and "genetic polymorphism," was employed to identify relevant studies. To ensure comprehensive coverage, manual searches of references from selected articles were also performed.

Data Extraction

The data extracted from the selected studies included the study design, sample characteristics, focus on genetic influences, quality of life measures, and antiemetic treatment protocols. A particular emphasis was placed on the identification of gaps in current practices and the highlighting of genetic variations across Malaysia's multiethnic population.

Analysis

The findings from the included studies were summarized and synthesized narratively to provide insights into the prevalence, management, and impact of CINV on breast cancer patients' quality of life. The analysis placed particular emphasis on the role of

genetic factors in determining the efficacy of antiemetic treatments and the variability in treatment outcomes.

Findings

Despite the implementation of preventive healthcare initiatives, the incidence of breast cancer continues to increase in Asia. A notable variation in breast cancer incidence rates is observed among Asian countries. For instance, the rate in Singapore is 54 per 100,000, whereas in Iran it is 21.4, in Turkey it is 24.1, in Malaysia it is 34.84, and in Jordan it is 48 (Ahmadian & Samah, 2013). A comprehensive review of the literature reveals that Korea had the highest breast cancer death rate during the mid-1980s to the mid-1990s, with China and Japan following closely behind (Ahmadian & Samah, 2013; Bloechl-Daum et al., 2006; Bray et al., 2004; Harirchi et al., 2004; Hisham & Yip, 2004; Petro-Nustus & Mikhail, 2002; Secginli & Nahcivan, 2006). A comprehensive assessment indicates that de novo metastatic cancer is two to three times more prevalent in Asian women (10-25% vs. 2% to 1% in European and American women). Furthermore, metastases in Asian women are frequently more substantial in size and encompass multiple sites (Miao et al., 2014).

A significant challenge in addressing this issue is the limited accessibility to mammography screenings in many Asian countries. Recent data indicates that 12% of South Asian women, 25% of Turkish women, and less than 10% of women in China, Iran, and the UAE undergo mammography (Ahmadian & Samah, 2013; Schwartz et al., 2008).

Breast Cancer in Malaysia

In Malaysia, breast cancer is the most prevalent form of cancer among women, accounting for 26.5% of all malignancies in 2008. The nation's population, estimated at 28.3 million, is a heterogeneous blend of Malay, Chinese, and Indian ethnic groups. The following cancers are in order of prevalence: cervical (12.6%), colorectal (9.9%), lung (5.8%), and ovarian (5.4%). The breast cancer incidence rate in Malaysia is higher than in neighboring countries like Thailand and Indonesia (Mallick & Cheen, 2013). A study by Yusuf et al. (2013) revealed that 32.1% of all diagnosed cancers in Malaysian females are breast cancers, with 58.2% of these cases detected in their early stages and 42.0% in their later stages (Yusuf et al., 2013; Zainal Ariffin & Nor Saleha, 2011). This type of cancer accounts for approximately 11% of all recorded fatalities among Malaysian women and is the primary cause of cancer-related mortality (Chin Chye et al., 2008; Hadi et al., 2010; Yusuf et al., 2013). Among Malaysia's three primary ethnic groups, the Chinese had the highest incidence rate of 38.1 per 100,000, followed by the Indians at 33.7 per 100,000, and the Malays at 25.4 per 100,000 (Chin Chye et al., 2008; Hassan & Yusoff, 2011; Yusuf et al., 2013; Zainal Ariffin & Nor Saleha, 2011). The varying rates of occurrence among ethnic groups may be explained by differences in lifestyle, nutrition, genetics, and reproductive factors such as sexual behavior, age at which a woman becomes pregnant, and breastfeeding habits (Hadi et al., 2010). The Malay population exhibits the lowest incidence of the disease, yet they also demonstrate the lowest survival rate, as the disease often manifests at a later stage and with larger tumors (Ibrahim et al., 2012; Mujar et al., 2013; Taib et al., 2011; Yip et al., 2006; Yusuf et al., 2013).

Chemotherapy-Induced Nausea and Vomiting (CINV)

Chemotherapy presents considerable challenges for cancer patients due to its associated debilitating side effects, including nausea and vomiting, which can occasionally exceed the impact of the underlying disease (Mustian et al., 2011). CINV stands as a prime example of the deleterious side effects that can profoundly impact the quality of life (QOL) of breast cancer patients. It can have detrimental effects on patients' mental and physical well-being. The propensity for CINV varies according to the specific chemotherapy regimen employed, with certain regimens demonstrating a higher risk than others (Grunberg et al., 2013). The emetogenic risk associated with the majority of chemotherapeutic agents employed in the treatment of breast cancer ranges from low to moderate. Despite the utilization of various antiemetic medications, the prevalence of CINV among patients remains persistently high, ranging from 40% to 75% (Booth et al., 2007; Choi et al., 2005; Hesketh, 2005; Kottschade et al., 2016; O'Shaughnessy, 2003). The most efficacious antiemetic medications are 5-HT3 and NK-1 receptor antagonists (Grunberg et al., 2013). A plethora of studies have investigated nausea and vomiting induced by cancer therapy; however, few prospective observational studies have exclusively focused on breast cancer treatment and the associated risk factors for these side effects in these patients (Hesketh, 2005). The majority of research in this field has primarily examined the effects of CINV on patients' QOL, with limited studies specifically addressing solid cancer patients (Booth et al., 2007; Choi et al., 2005; Hesketh, 2005; O'Shaughnessy, 2003; Rhodes & McDaniel, 2001).

This review encompasses a total of nine studies (four cross-sectional, three observational, one descriptive study, and one case report) that investigate the occurrence of Chemotherapy-Induced Nausea and Vomiting (CINV) among breast cancer patients in Malaysia.

To evaluate the treatment of acute CINV, Dewan et al. (2010) enrolled 35 breast cancer patients based in

Kuala Lumpur in a prospective research study. Participants were interviewed within five days following their most recent chemotherapy treatment for breast cancer. The majority of the participants were female (71.4%) and Malay (63%). The ages of the participants ranged from 51 to 60 years (34%). The administration of granisetron and dexamethasone, in conjunction, over a five-day period, resulted in a 50% reduction in nausea and an 87.5% reduction in vomiting, both in the acute and delayed stages. Furthermore, at the conclusion of chemotherapy, patients who received a five-day combination of dexamethasone and metoclopramide exhibited an 18.5% reduction in emesis control compared to those who received the alternative combination. Furthermore, the addition of granisetron to dexamethasone post-chemotherapy resulted in complete control of nausea and vomiting. The study by Dewan et al. (2010) found a significant correlation between the emetogenic potential of the chemotherapy regimen and the frequency of emesis.

A case report by Gupta et al. (2021) documented the treatment of a Malay woman in her mid-40s diagnosed with cancer of the right breast, who received 110 g of docetaxel and cisplatin. The patient received dexamethasone with granisetron 30 minutes prior to chemotherapy, and no instances of CINV were observed (Gupta et al., 2021).

In 2010, Hassan & Yusoff conducted a longitudinal observational prospective study with 158 breast cancer patients who had three to five days of chemotherapy. The objective of the study was to ascertain the impact of acute chemotherapy-induced nausea and vomiting (CINV) on patients' quality of life and their perceptions of antiemetic protocols. The results of the study indicated that, in comparison with acute CINV and vomiting, delayed CINV exerted a more substantial impact on patients' quality of life (QOL) and control. The authors further noted that patients' perspectives and responses to antiemetic medications appeared to be significantly influenced by genetic variations (Hassan & Yusoff, 2010).

In 2011, researchers in Malaysia embarked on an investigation to ascertain the impact of genetic polymorphism on the antiemetic efficacy of granisetron across the three most prevalent ethnic groups in the nation: Malay, Chinese, and Indian. The study population comprised 158 breast cancer patients, with the majority (93%) undergoing treatment with the FEC (fluorouracil, epirubicin, cyclophosphamide) regimen. The findings of the study indicated that genetic polymorphisms significantly impacted the antiemetic properties of granisetron, particularly due to variant CYP3A4 enzyme activity. The study also underscored the importance of leveraging CYP2D6-specific 5-HT3 receptor antagonists, such as dolasetron and tropisetron, to enhance therapy, particularly in Chinese patients (Lua et al., 2012).

In 2012, a cross-sectional study by Lua et al. was conducted in two public hospitals in northeastern Malaysia to determine the incidence of CINV with antiemetic use and assess its impact on patients' QOL. The study's participants were predominantly of Malaysian ethnicity (92.7%), with a mean age of 49.1 ± 9.6. The majority of patients had stage III cancer and received moderately emetogenic chemotherapy. The study found that a majority of patients experienced nausea (90.2%) and vomiting (29.3%) during or after chemotherapy. Patients who received granisetron, a 5-HT3 receptor antagonist, for two consecutive days reported the drug to be "somewhat useful" (97.6%). Conversely, patients who received a combination of granisetron and corticosteroid (dexamethasone) for four days and experienced CINV rated the experience as "severe." A notable correlation was identified between the presence of moderate to severe nausea and fatigue. Furthermore, patients who experienced vomiting demonstrated worse health-related QOL compared to those who did not (Lua et al., 2012).

A cross-sectional study was conducted at Hospital Melaka in Malaysia, with the objective of investigating the impact of chemotherapy on the quality of life (QOL) of patients diagnosed with breast cancer. The study also examined the influence of confounding variables, including patient age, the stage of cancer, and the presence of comorbidities such as nausea, vomiting, diarrhea, and anorexia. The study population comprised 32 female patients (mean age: 49.7 years) who were administered the FEC regimen. The study found that 46.8% of the patients had stages III and IV of the disease, while approximately half had early-stage breast cancer. The EORTC QLQ-C30 questionnaire was utilized to assess patients' quality of life both prior to and following treatment. The study revealed a substantial decline in QOL following chemotherapy, accompanied by elevated rates of adverse effects, including nausea, vomiting, loss of appetite, and diarrhea. The authors concluded that chemotherapy significantly diminished the QOL of breast cancer patients due to these side effects, emphasizing the need for interventions to improve QOL (Chee Chean et al., 2016).

A similar study by Yusuf et al. included 76 breast cancer patients, predominantly Malays (76.3%) and Chinese (19.7%), in Kelantan, Malaysia. The majority of patients were younger than 50 years old and had advanced-stage breast cancer (31% Stage III and 37.9% Stage IV). The study employed the EORTC QLQ-C30 and QLQ-BR23 questionnaires to assess patients' QOL. While both Malay and Chinese patients exhibited satisfactory QOL, Malay women exhibited comparatively lower QOL scores, attributable to a

higher prevalence of prevalent symptoms such as nausea and vomiting, dyspnea, and constipation (Yusuf et al., 2013).

Noor et al. conducted semi-structured interviews with sixteen breast cancer patients receiving chemotherapy as part of a qualitative descriptive study. The objective of this research was to examine how CINV affects patients' quality of life. A significant proportion of the patient population was in the early stages of the disease and had recently received a breast cancer diagnosis (84.6%). The study found that all patients experienced varying degrees of acute and delayed CINV, which had a negative impact on their eating patterns and daily life activities. The authors underscored the critical nature of CINV, emphasizing its deleterious impact on the QOL of breast cancer patients and underscoring the need for further investigation to elucidate its mechanisms and develop effective mitigation strategies (Lua et al., 2016).

In 2016, a study involving 223 Malaysian breast cancer patients from diverse ethnic backgrounds (Malay, Chinese, Indian, and others) evaluated QOL using the EORTC QLQ-C30 and QLQ-BR23 questionnaires. The majority of patients were diagnosed with advanced-stage disease (Stage III and IV) with a mean age of 52.4 years. Patients aged 50 years and above exhibited enhanced QOL, characterized by a reduced prevalence of specific symptoms, including nausea and vomiting, diarrhea, constipation, and alopecia, resulting from systemic therapy. The study highlighted the detrimental impact of nausea and vomiting on patients' QOL during chemotherapy (Ganesh et al., 2016).

Genetic Effects on Chemotherapy-Induced Nausea and Vomiting

Pharmacokinetic and pharmacodynamic differences are therapeutically significant due to individual variations in drug metabolism, which are impacted by both heredity and exogenous factors, including the environment, nutrition, and concurrent drug therapy (Gross et al., 1999; Ruzilawati et al., 2007). Significant alterations in medication metabolism are predominantly attributable to alterations in cytochrome P450 (CYP) enzymes. The CYP3A subfamily, comprising CYP3A4, CYP3A5, CYP3A7, and CYP3A47, is responsible for over 50% of the drug metabolisms in clinical use. The variations in CYP3A4 activity can be attributed to different CYP3A4 alleles (Ruzilawati et al., 2007). The metabolism of 5-HT3 receptor antagonists, such as dolasetron and tropisetron, is predominantly associated with the CYP2D6 subgroup. In contrast, granisetron is metabolized by the CYP3A43 subgroup, while ondansetron is metabolized by CYP2D6, CYP1A2, CYP3A4, and CYP2E1. Notwithstanding, 5-HT3 receptor antagonists demonstrate a suboptimal response in a substantial proportion of cancer patients. A significant factor contributing to interindividual variations in medication pharmacological reactions is genetic polymorphisms in enzymes, such as the hepatic cytochrome P-450 enzyme subfamily (Kaiser et al., 2002).

A recent longitudinal prospective observational study was conducted in Malaysia among breast cancer patients to elucidate the effect of genetic polymorphism, specifically in CYP3A4, on the antiemetic efficacy of granisetron across the three major ethnic groups (Malay, Chinese, and Indian). Patients were closely monitored for the incidence of nausea and vomiting during the initial 24 hours of chemotherapy administration and subsequently 3 to 5 days later. The majority of the patients were of Chinese descent (63.9%) and had breast cancer in its early stages (79.7%). The treatment regimens employed included FEC (93%), CAF (3.8%), and CMF (3.2%). Prior to the administration of any pharmaceutical agent to a patient, a 5-HT3 antagonist (granisetron) and dexamethasone were administered. Following treatment, metoclopramide and dexamethasone were administered. Acute and delayed CINV occurred in 45 Chinese individuals, but the Malay patients exhibited a reduced incidence of CINV. The study's findings underscore the potential of CYP3A4 mutations to influence the antiemetic efficacy of granisetron, offering a novel perspective on the influence of ethnicity on CINV management. To mitigate the occurrence of CINV, the study recommended that Chinese breast cancer patients opt for 5-HT3 receptor antagonists, such as tropisetron and dolasetron, given their primary metabolic processing via CYP2D6 (Hassan & Yusoff, 2011).

Conclusion

This review underscores the persistent challenges associated with chemotherapy-induced nausea and vomiting (CINV) among breast cancer patients in Malaysia, with its deleterious impact on their quality of life. Addressing this issue necessitates the adaptation of antiemetic treatment protocols to account for genetic variations among the country's multiethnic population. Malaysian healthcare providers are strongly encouraged to adopt patient-centered approaches that incorporate pharmacogenetic testing to optimize antiemetic therapies, ensuring more effective management of CINV. Furthermore, the enhancement of healthcare infrastructure is imperative, involving the augmentation of access to supportive care services, the dissemination of patient education on CINV management, and the promotion of adherence to evidence-based guidelines. Future research should concentrate on identifying specific barriers to care and developing targeted interventions to improve outcomes for breast cancer patients.

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