IJPHCS
Open Access: e-Journal

International Journal of Public Health and Clinical Sciences
e-ISSN : 2289-7577. Vol. 4:No. 6
November/December 2017

Incidence of Neutropenia during Chemotherapy Treatment in Breast Cancer Patients at Advanced Medical and Dental Institute (AMDI), Universiti Sains Malaysia, Penang, Malaysia

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ABSTRACT

Background: Neutropenia caused by chemotherapy treatment can frequently lead to severe infection and sometimes life-threatening. It may result in dose reductions, delays or discontinuation of chemotherapy which may subsequently compromise patient outcomes. The aim of this study was to determine the incidence of neutropenia during chemotherapy treatment in breast cancer patients.

Materials and Methods: This was a single-centre, retrospective study conducted in the Advanced Medical and Dental Institute (AMDI), Penang. All breast cancer patients who received chemotherapy treatment from January 2014 to December 2016 were included into the study. Ethical approval was granted by the JEPeM USM.

Result: 155 patients were analysed in this study, with the mean (SD) age of 52.19 (9.46) years. In total, 85 patients (54.8%) manifested neutropenia and sub-categorisation of neutropenia based on severity, showed mild neutropenia (25.8%), moderate neutropenia (12.9%), severe neutropenia (9.0%) and febrile neutropenia (7.1%). Descriptive analysis showed that majority of patients in this study were aged 40 – 59 years (62.6%), overweight (67.1%), postmenopause (60.6%), no family history of breast cancer (85.8%), ductal pathology subtype (94.8%), receptor subtype of Estrogen Receptor or Progesterone Receptor Positive (43.4%), late cancer stage (58.4%), underwent mastectomy surgery (79.3%), received Anthracycline-Taxane Chemotherapy Regimens (66.5%) and received Granulocyte-Colony Stimulating Factor (G-CSF) treatment (67.1%). All breast cancer patients were female in this study.

Conclusion: The incidence of neutropenia in this study centre was 54.8% and was comparable with some of the studies. However, due to different study design of each study, it is quite hard to compare the incidence of neutropenia among all the centres.

Keywords: Neutropenia, breast cancer patients, chemotherapy

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1.0 Introduction

Neutropenia is a condition whereby reduction in the blood absolute neutrophil count (ANC) below 1.5 x 10^9/L (Robert & Justin, 2011). The incidence of neutropenia varies from 16% to 81% among patients who receive chemotherapy treatment (Kim et al., 2016; Ramaswamy et al., 2005). Neutropenia increases patient's susceptibility to infection, thus causing sepsis, which subsequently may require antibiotic therapy, administration of growth factors and in serious cases, may need hospitalisation for urgent evaluation and administration of empiric broad-spectrum antibiotics (Freifeld et al., 2011). Severe neutropenia may lead to treatment delays, chemotherapy dose intensity reduction, sometimes even discontinuation of chemotherapy. This may lead to poor prognosis of the patient (Chan, Chen, Chiang, Tan, & Ng, 2012; Kuderer, Dale, Crawford, Cosler, & Lyman, 2006).

Neutrophil, is a type of white blood cells that play an important role in our defensive system against invading pathogens. Neutrophil cells are produced in bone marrow, contributed to 60 – 70% of the total white blood cells (WBC) and have very short life in blood circulation, roughly 6 – 10 hours (Robert & Justin, 2011). Based on severity, neutropenia is categorised into mild neutropenia (ANC: 1.0 – 1.5 x 10^9/L), moderate neutropenia (ANC: 0.5 – 1.0 x 10^9/L), severe neutropenia (ANC: less than 0.5 x 10^9/L) and febrile neutropenia (FN). FN is the development of fever in a neutropenic patient. A patient would be categorised as FN if his/ her absolute neutrophil count (ANC) is below 1.0 x 10^9/L and having a single oral temperature exceeding 38.3°C or a temperature more than 38°C for over an hour (NCCN, 2016).

Majority of cancer patients will develop neutropenia, mostly due to the myelosuppressive effect of chemotherapy treatment. Chemotherapy drugs or antineoplastic drugs will cause suppression to bone marrow, subsequently lead to decrease in neutrophil cells production and finally end up with neutropenia (Robert & Justin, 2011). 78% of breast cancer patients treated with CMF (Cyclophosphamide, Methotrexate and 5-Flurouracil) has developed neutropenia in a study done by Lyman et al. (Gary H. Lyman, Abella, & Pettengell, 2014). Cancer patients have highest risk of neutropenic event in the first cycle of chemotherapy, which was 50 – 75% (Crawford et al., 2008). Neutropenia also could be due to infiltration of tumour cells into bone marrow, side effect of radiation administration to bone marrow, lymphoproliferative malignancies, autoimmune, hematological disorders, congenital, infections, older age, comorbidities and exposure of multiple cytotoxic chemotherapy drugs (Hassan, Yusoff, & Othman, 2011; Lustberg, 2012; Gary H. Lyman et al., 2014). Most of the studies were more focus on febrile neutropenia, but not the neutropenia in general. Therefore, the study was performed to determine the incidence and severity of neutropenia during chemotherapy treatment in breast cancer patients in this study centre.

2.0 Materials and Methods

This was a single-centre, retrospective record review study conducted at the Advanced Medical and Dental Institute (AMDI), Universiti Sains Malaysia (USM), Penang. AMDI is the clinical service based research centre and referral centre for oncological services.

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All the new breast cancer patients who received chemotherapy treatment, involved all cycles of chemotherapy in AMDI from January 2014 to December 2016 were included into the study. In this study, exclusion criteria were patients with repeat or recurrent breast cancer cases, patients on concurrent chemotherapy and radiotherapy treatment, and patients whose baseline ANC less than 1.5 x 10^9/L (before the initiation of chemotherapy treatment).

A data collection form or called as research proforma was developed to collect information on patient demographics, disease-related and treatment-related information, such as age, gender, body mass index (BMI), receptor subtype, stage of cancer, chemotherapy agent and usage of G-CSF. Data of patients were collected from patient's medical report, Electronic Medical Record (EMR) and Hospital Information System (HIS).

Data entry and statistical analysis were done using Statistical Package for Social Sciences (SPSS) version 22 (IBM SPSS Statistics Version 22). For descriptive statistics, all the numerical data collected were analysed using mean and standard deviation (SD). Data were tested and have a normal distribution hence all the parametric statistical tests were used in this study. For categorical variables, the frequencies were explored and percentage were calculated.

3.0 Result

3.1 Demographic factors

A total of 335 new breast cancer patients received chemotherapy treatment at AMDI from January 2014 to December 2016. A total of 155 patients met the inclusion criteria and selected into the study. All patients were female and the mean (SD) age was 52.19 (9.46) years. Based on demographic factors, majority of patients were aged between 40 – 59 years (97 patients, 62.6%) and overweight with BMI more than 23kg/m^2 (104 patients, 67.1%). Majority of patients had no family history of breast cancer (133 patients, 85.8%) and 94 patients (60.6%) were postmenopausal (Table I).

Table 1: Distribution of demographic factors

Characteristics	**Total (n=155)** **n (%)**
Age (year)*	52.19 (9.46)
< 40 years	15 (9.7)
40 – 59 years	97 (62.6)
≥ 60 years	43 (27.7)
Gender	
Female	155 (100.0)
Male	0 (0.0)
BMI	
Underweight	9 (5.8)

Normal	42 (27.1)
Overweight	104 (67.1)
Menopausal Status	
Yes	94 (60.6)
No	61 (39.4)
Family History of Breast Cancer	
Yes	22 (14.2)
No	133 (85.8)

BMI = body mass index

*Expressed as mean (SD)

3.2 Disease-related factors

Table 2: Distribution of disease-related factors

Characteristics	**n (%)**
Pathology Subtype (n=155)	
Ductal	147 (94.8)
Lobular	8 (5.2)
Receptor Subtype (n=152)	
ER- or PR- Positive	66 (43.4)
HER2- Positive	23 (15.1)
Triple Negative	48 (31.6)
ER- or PR- Positive, HER2- Positive	15 (9.9)
Stage of Cancer (n=154)	
Early Cancer	**64 (41.6)**
Stage I	6 (3.9)
Stage II	58 (37.7)
Late Cancer	**90 (58.4)**
Stage III	47 (30.5)
Stage IV	43 (27.9)

ER=estrogen receptor, PR=progesterone receptor, HER2=human epidermal growth factor receptor 2

In relation to disease-related factors, 94.8% of pathology subtype were ductal subtype and the most common seen receptor subtype was ER- or PR- positive (66 patients, 43.4%). Stage of cancer has been grouped into early and late cancer in this present study. Stage II of early cancer has the highest number of patients (58 patients, 37.7%).

3.2.1 Treatment-related factors

Table 3: Distribution of treatment-related factors

Characteristics	Total (n=155) n (%)
Type of Surgery	
Breast-Conserving	24 (15.5)
Mastectomy	123 (79.3)
No Surgery	8 (5.2)
Chemotherapy Agent	
Anthracycline-Based	29 (18.7)
Taxane-Based	23 (14.8)
Anthracycline-Taxane Regimens	103 (66.5)
Usage of G-CSF	
No	51 (32.9)
Yes	104 (67.1)
Prophylactic G-CSF	56 (36.1)
Therapeutic G-CSF	48 (31.0)

G-CSF=granulocyte colony stimulating factor

During chemotherapy treatment, 54.8% (85/155) patients have developed neutropenia. Sub-categorisation of neutropenia based on severity showed 25.8% (40/155) of patients experienced mild neutropenia, 12.9% (20/155) were moderate neutropenia and 9.0% (14/155) of patients had severe neutropenia. However, febrile neutropenia contributed to 7.1% (11/155) of total neutropenia incidence in the present study.

3.2.2 Incidence of neutropenia

Table 4: Incidence of neutropenia and sub-category of neutropenia

Characteristics	Neutropenia n (%)	No neutropenia n (%)
All cases	**85 (54.8)**	**70 (45.2)**
Sub-category of Neutropenia		
Mild neutropenia	40 (25.8)	
Moderate neutropenia	20 (12.9)	
Severe neutropenia	14 (9.0)	
Febrile neutropenia	11 (7.1)	

During chemotherapy treatment, 54.8% (85/155) patients have developed neutropenia. Sub-categorisation of neutropenia based on severity showed 25.8% (40/155) of patients experienced mild neutropenia, 12.9% (20/155) were moderate neutropenia and 9.0% (14/155) of patients had severe neutropenia. However, febrile neutropenia contributed to 7.1% (11/155) of total neutropenia incidence in the present study.

4.0 Discussion

This study showed that 54.8% or 85 out of 155 breast cancer patients who underwent chemotherapy treatment have developed neutropenia. The severity of neutropenia (based on 100% calculation), showed that 47.1% were mild neutropenia (40/85), followed by moderate neutropenia (23.5%, 20/85) and severe neutropenia (16.5%, 14/85). This finding was almost similar with the study conducted in Brazil. The Gynecologic Oncology and Mastology Outpatient Centre of the Teaching Hospital of the Ribeirão Preto Faculty of Medicine have demonstrated 63.3% of their study breast cancer patients have developed neutropenia during their chemotherapy treatment. In the prospective study, they have classified the severity of neutropenia into grade I (9.5%), grade II (46.5%), grade III (31.9%) and grade IV (12.1%). Grade II, III and IV is equivalent with mild, moderate and severe neutropenia respectively (Nascimento, Andrade, Oliveira, Almeida, & Gozzo, 2014). Another study conducted in Tianjin Medical University Cancer Institute and Hospital, China reported the incidence of neutropenia in early-stage breast cancer in their study centre was 52.5%. They have categorised severity of neutropenia into mild (ANC: 1.0 – 2.0 x 10^9/L) and severe neutropenia (ANC: 0.0 – 1.0 x 10^9/L), with the incidence of 79.0% (139/176) and 21.0% (37/176) respectively (Han et al., 2012). Due to different study models, therefore direct comparison of neutropenia incidence was difficult to carry out.

The incidence of FN during chemotherapy treatment in present study was 12.9% (11/85). This finding was comparable with a study conducted in Singapore regarding the incidence of FN among Asian Early Stage Breast Cancer (ESBC). It has reported 13.8% of patients have developed FN and majority have developed FN in the first treatment cycle (Chan et al., 2012). Another prospective study conducted in the United Kingdom (UK) also reported a similar FN incidence of 12% (Leonard, Miles, Thomas, & Nussey, 2003). FN is considered as medical emergency and need immediate treatment or hospitalisation for antibiotics administration. Therefore, patients with FN were frequently experienced treatment delays or dose reductions, which subsequently affect the patient's outcome (Gary H Lyman, 2009).

There were various range of FN incidence during chemotherapy treatment reported by previous studies. Two clinical trials on adjuvant doxorubicin/ cyclophosphamide (AC) chemotherapy, which were ECOG 1199 and CALBG 40101 trials, reported FN incidence of 6.5% and 6.0% respectively (Shulman et al., 2014; Sparano et al., 2008). However, another trials on adjuvant sequential doxorubicin/ cyclophosphamide and docetaxel (AC-D) chemotherapy reported an FN incidence of 7.7% (Eiermann et al., 2011). Previous studies have revealed that the incidence of FN in randomized control trials were relatively lower than clinical practice. This could be due to well patient selection before inclusion into the trial (Chan et al., 2012). Besides that, chemotherapies were often administered with growth factors in many clinical trials to reduce incidence of FN (Gary H. Lyman et al., 2014).

Development of neutropenia during chemotherapy were caused by multifactorial risks (Gary H. Lyman, 2006). Myelosuppressive effect of chemotherapy drugs and the condition of

patients were the common factors (Koutras & Kalofonos, 2008). Therefore, clinical practice guidelines recommend to assess the risk factors for estimating overall risk of FN (Aapro et al., 2010).

Our study has several limitations that common to all retrospective studies, such as selection bias due to absence of randomisation and missing data. This study has small sample size, high drop-out rate and was conducted in a single institution. Present study included all types of chemotherapy agents used in the institution. Therefore, for future study, it is recommended to conduct prospective study with larger pool of sample size involve multi-centre and identify specific chemotherapy agent to determine the actual incidence of neutropenia caused by the chemotherapy agent during treatment in breast cancer patients.

5.0 Conclusion and recommendation

In conclusion, the incidence of neutropenia during chemotherapy treatment in breast cancer patients this study centre was 54.8%. The sub-categorisation of neutropenia based on severity were mild neutropenia (25.8%), moderate neutropenia (12.9%), severe neutropenia (9.0%) and febrile neutropenia (7.1%). This finding was comparable with some of the previous studies. However, due to different study design of each study, it is quite hard to compare the incidence of neutropenia among all the centres.

Acknowledgement

This study was approved by the JEPeM USM (Jawatankuasa Etika Penyelidikan Manusia) with Project Registration No. USM/JEPeM/16120541.

We would like to thank Advanced Medical and Dental Institute, Universiti Sains Malaysia for sponsoring this study. We also would like to express our gratitude to Encik Nizuwan, Dr. Noorsuzana Mohd Shariff and Dr. Rohayu Hami for data analysis assistance and to medical record office staff for their help in retrieval of patient files

Declaration

Author(s) declare that authors has no conflicts of interest. The authors alone are responsible for the content and writing of the paper

Authors contribution

Author 1: Data collection and data analysis, Author 2: Developing manuscript, Author 3: Scientific writing.

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