PREVALENCE AND PREDICTIVE FACTORS OF NEUTROPENIA AMONG PATIENTS WITH BREAST CANCER RECEIVING DOXORUBICIN-CYCLOPHOSPHAMIDE CHEMOTHERAPY AT A CANCER CENTER, SURIN HOSPITAL: A RETROSPECTIVE CASE-CONTROL STUDY

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Abstract

Background: Despite significant advancements in breast cancer treatment with targeted therapy and immunotherapy, chemotherapy remains a crucial component across all stages. Anthracycline-based chemotherapy, while commonly administered, can lead to severe and potentially fatal complications such as febrile neutropenia.

Objectives: This study aimed to investigate the prevalence and predictive factors for developing neutropenia in patients with breast cancer undergoing an anthracycline-based chemotherapy regimen.

Methods: A retrospective case-control study was conducted at the Surin Hospital Cancer Center from January 2020 to December 2022. It focused on patients diagnosed with breast cancer and treated with anthracycline-based chemotherapy, specifically the doxorubicin-cyclophosphamide regimen (AC). Prognostic factors were analyzed using a flexible parametric regression model, employing univariate and multivariate analyses.

Results: A total of 174 eligible patients with confirmed breast cancer who received AC regimen chemotherapy were included; 99.4% were predominantly female, with 21.7% being over 65 and nearly 40% having at least one other health condition. Neutropenia, characterized by a neutrophil count of less than 500 cells/mm^3, was observed among 18% of patients. Of these, 4% developed febrile neutropenia, resulting in two deaths. A multivariate analysis identified two factors, age of 65 years or older (adjusted OR=3.18; 95% CI 1.122-9.013; p=0.029) and an initial absolute neutrophil count less than 3,000 cells/mm^3 (adjusted OR=2.73; 95% CI 1.032-7.204; p=0.043), as independent predictors of neutropenia. Interestingly, the severity of neutropenia did not significantly differ between patients with or without additional health conditions or varying nutritional statuses.

Conclusion: As anticipated, a significant prevalence of neutropenia was observed among individuals with breast cancer, underscoring the critical importance of age and initial neutrophil count in predicting the severity of neutropenic incidents. These findings offer valuable insights for tailoring treatment strategies and optimizing patient care in this clinical context.

Keywords: breast cancer, anthracycline, anticancer treatment, neutropenia

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Introduction

Nowadays, the treatment of breast cancer has advanced significantly with targeted therapy and immunotherapy.[1] However, chemotherapy, mainly an anthracycline-based regimen, remains the cornerstone and is widely utilized across all stages of breast cancer.[1, 2] Nevertheless, certain complications may arise following this treatment, including nausea, vomiting, fatigue, hair loss, mouth sores, and bone marrow suppression,[3] leading to cytopenia and potentially resulting in life-threatening complications such as febrile neutropenia. [4]

In a literature review conducted by Alexandre Chan and colleagues on the 'Incidence of febrile neutropenia among early-stage breast cancer patients receiving anthracycline-based chemotherapy,' it was discovered that early-stage breast cancer (ESBC) patients undergoing anthracycline-based chemotherapy are at moderate risk of developing febrile neutropenia (13.8%).[5] Similarly, a study by Hye Sook Kim and colleagues in Korea found that ESBC patients receiving anthracycline-based chemotherapy are at a high risk of developing febrile neutropenia. [6] Another study by Sun Young Min and colleagues revealed that patients aged 55 years and older with a body surface area (BSA) less than or equal to 1.45 square meters are at a higher risk of developing febrile neutropenia. [7]

According to previous studies, a high prevalence of febrile neutropenia has been consistently reported, and various contributing factors have been identified across multiple studies worldwide. This research explored the prevalence and predictive factors of neutropenia, defined explicitly as a neutrophil count of less than 500 cells/mm³, in breast cancer patients undergoing anthracycline-based chemotherapy. The goal was to refine treatment strategies and enhance patient safety within our real-world clinical context.

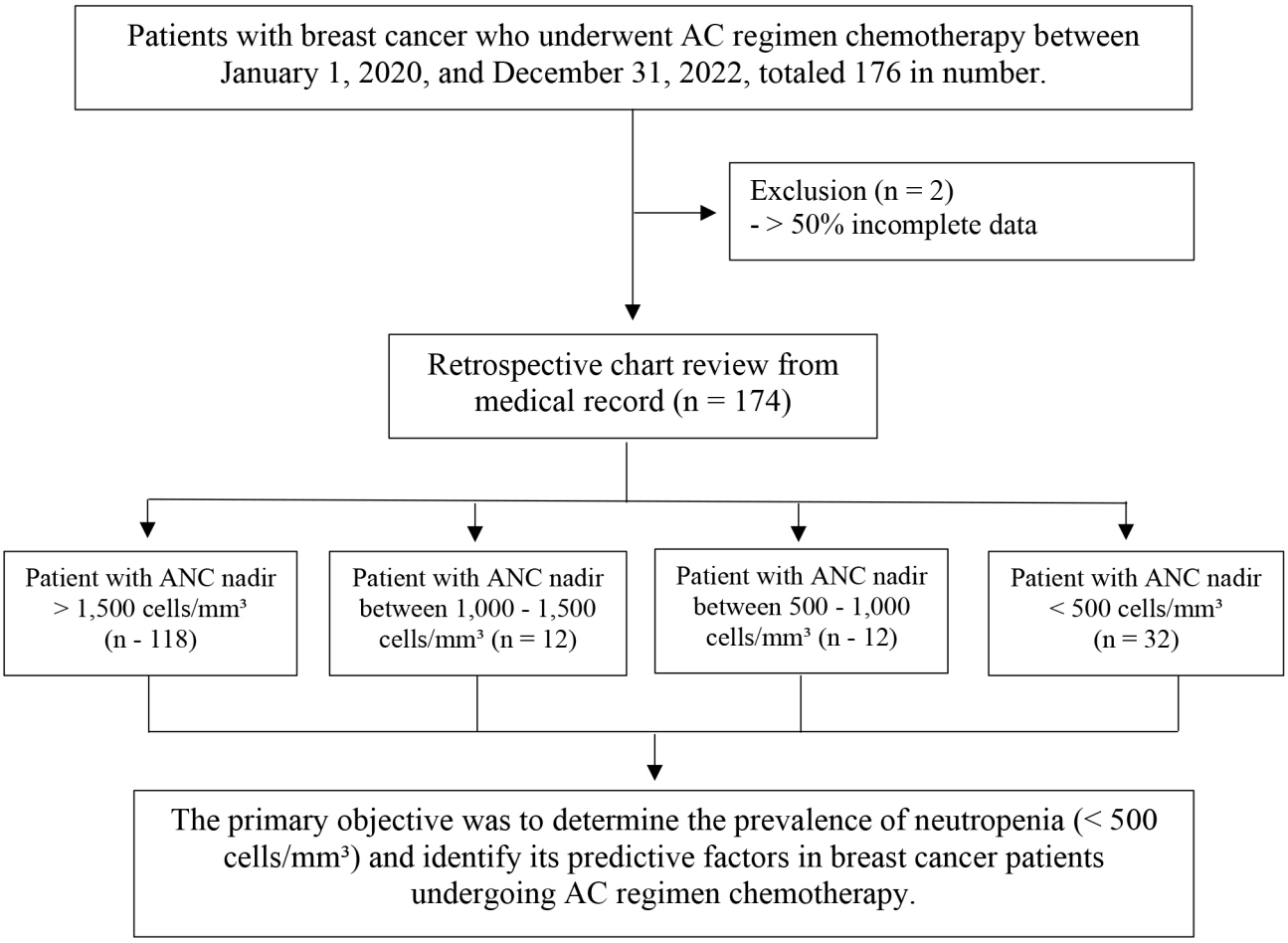

Figure 1. Flow diagram of the retrospective case-control study

Methods

Study design and patients

The study is a retrospective case-control study conducted at the Surin Hospital Cancer Center, with a focus on breast cancer patients aged 18 years or older who underwent treatment with the AC regimen chemotherapy between January 2020 and December 2022. Ethical approval for this study was obtained from the Research Ethics Committee of Surin Hospital (certificate no. 7/2567). Data extraction was performed from the hospital database program, encompassing all patients prescribed at least one cycle of the AC regimen. However, patients with more than 50% incomplete data, those treated with alternative chemotherapy regimens, individuals receiving G-CSF prophylaxis, and patients treated outside Surin Hospital were excluded from the study. **Figure 1** shows the flow diagram of this study.

Outcomes and data collection

Data were obtained from the hospital medical records, which included demographic information, health conditions, and treatment details. The primary objective was to determine the prevalence of neutropenia and identify its predictive factors in breast cancer patients undergoing AC regimen chemotherapy.

Definition

The Eastern Cooperative Oncology Group (ECOG) Performance Status was a scale used to evaluate the functional status of cancer patients, with scores ranging from 0 to 5. A score of 0 signifies full activity, while 5 indicates death. The Common Terminology Criteria for Adverse Events (CTCAE) is a standardized system designed for classifying and grading the severity of adverse events. It is graded from 1 (mild) to 5 (death), with specific criteria tailored for each grade based on the type of adverse event. Neutropenia is defined as a neutrophil count below 500 cells/mm³. Severe neutropenia is characterized by a neutrophil count falling below 100 cells/mm³. Febrile Neutropenia is identified by the presence of fever (body temperature ≥38.3°C) concurrently with neutropenia (absolute neutrophil count <500 cells/mm³) or an expected decline to <500 cells/mm³ within the next 48 hours.

Statistical analysis

Descriptive statistics (mean, median, percentage) were used to analyze numerical and categorical data related to clinical characteristics. Binary logistic regression using univariable and multivariable was employed to analyze the predictive factors for developing neutropenia during AC regimen chemotherapy. A p-value < 0.05 was considered statistically significant. All data were analyzed using IBM - SPSS Statistics version 26.

Results

After conducting a comprehensive review of medical records from January 1, 2020, to December 31, 2022, at Surin Hospital Cancer

Table 1. Patient baseline characteristics (N = 174)

Characteristic	Neutropenia (ANC < 500 cells/mm³) (N = 32), n (%)	No Neutropenia (ANC ≥ 500 cells/mm³) (N = 142), n (%)	*p*-value
Age (year)-Mean (±SD)	57.843 (11.410)	52.042 (11.112)	
Age Group			
Age < 65	20 (62.5%)	116 (81.7%)	0.017
Age > 65	12 (37.5%)	26 (18.3%)	
Female	32 (100.00%)	141 (99.3%)	0.816
BMI < 18.5 Kg/m²	3 (9.4%)	5 (3.5%)	0.164

Table 1. Patient baseline characteristics (N = 174) (Cont.)

Characteristic	Neutropenia (ANC < 500 cells/mm^3) (N = 32), n (%)	No Neutropenia (ANC ≥ 500 cells/mm^3) (N = 142), n (%)	*p*-value
ECOG status			
ECOG 0	22 (68.8%)	110 (77.5%)	0.479
ECOG 1	10 (31.3%)	31 (21.8%)	
ECOG 2	0 (0.0%)	1 (0.7%)	
Non-smoker	32 (100%)	139 (97.9%)	0.541
Non-alcohol drinking	30 (93.8%)	134 (94.4%)	0.580
Comorbidities			
At least one comorbidity disease	13 (40.6%)	55 (38.7%)	0.843
Hypertension	12 (37.5%)	38 (26.8%)	
T2DM	3 (9.4%)	20 (14.1%)	
DLP	2 (6.3%)	17 (12.0%)	
CKD	3 (9.4%)	6 (4.2%)	
CAD	1 (3.1%)	2 (1.4%)	
CVA	0 (0.0%)	3 (2.1%)	
Breast cancer stage			
Stage I	6 (18.8%)	11 (7.7%)	0.115
Stage II	16 (50.0%)	65 (45.8%)	
Stage III	9 (28.1%)	47 (33.1%)	
Stage IV	1 (3.1%)	19 (13.4%)	
Dose of doxorubicin (mg)	Mean (±SD) 90.875 (9.889)	Mean (±SD) 92.693 (8.345)	
Accumulative dose of doxorubicin (mg/m^2)	60	60	
Time to 1st Cycle ChT			
≤ 42 days	12 (37.5%)	87 (61.7%)	0.012
> 42 days	20 (62.5%)	54 (38.3%)	
Dose of anthracycline (mg)	Mean (±SD) 90.875 (9.889)	Mean (±SD) 92.693 (8.345)	
Pre-ChT ANC			
< 3,000 cells/mm^3	10 (31.3%)	19 (13.6%)	0.016
≥ 3,000 cells/mm^3	22 (68.8%)	121 (86.4%)	
Albumin levels before ChT			
≤ 3.5 g/dL	1 (3.1%)	9 (6.5%)	0.406
> 3.5 g/dL	31 (96.9%)	129 (93.5%)	
Hemoglobin (Hb) before ChT			
< 12 g/dL	14 (43.8%)	77 (55.0%)	0.250
≥ 12 g/dL	18 (56.3%)	63 (45.0%)	

Table 1. Patient baseline characteristics (N = 174) (Cont.)

Characteristic	Neutropenia (ANC < 500 cells/mm³) (N = 32), n (%)	No Neutropenia (ANC ≥ 500 cells/mm³) (N = 142), n (%)	*p*-value
Creatinine clearance			
≤ 60 mL/min	3 (9.4%)	8 (5.8%)	0.339
> 60 mL/min	29 (90.6%)	131 (94.2%)	

ANC = absolute neutrophil count, BMI = body mass index, ECOG = The Eastern Cooperative Oncology Group Performance Status, T2DM = type II diabetic mellitus, DLP = dyslipidemia, CKD = chronic kidney disease, CAD = coronary artery disease, CVA = cerebrovascular accident, ChT = chemotherapy

Center. A total of 174 patients with breast cancer underwent anthracycline-based chemotherapy, precisely the doxorubicin-cyclophosphamide regimen (AC). Within this group, most 174 patients (99.8%) were female. The average age of the patients was 58.9 years (SD 13.56), with 33.3% presenting additional underlying medical conditions. Furthermore, 4.6% of the patients were classified as malnourished, defined by a body mass index below 18.5 kg/m².

The collected data were further stratified based on the severity of neutropenia, categorizing patients into two groups according to their neutrophil count. Neutropenia was defined as a neutrophil count of less than 500 cells/mm³, and a separate group included patients with a neutrophil count exceeding 500 cells/mm³. A comprehensive overview of this information is presented in **Table 1**, which shows a detailed distribution based on the severity of the condition. Nonetheless, age and baseline ANC indicated an imbalance among the groups.

Severity of neutropenia and febrile neutropenia in breast cancer patients

From the study, among 174 patients with breast cancer who received AC regimen chemotherapy, most exhibited an ANC nadir >1,500 cells/mm³, comprising 118 patients (67.8%). Additionally, 12 patients (6.9%) had an ANC nadir between 1,000 and 1,500 cells/mm³, 12 patients (6.9%) had an ANC nadir between 500 and 1,000 cells/mm³, and 32 patients (18.4%) had an ANC nadir < 500 cells/mm³. Moreover, 27 patients (15.5%) experienced an ANC of 100-500 cells/mm³, and five patients (2.9%) experienced an ANC<100 cells/mm³. Regrettably, 3.4% of the patients developed febrile neutropenia, resulting in two deaths.

Predictive factors for the severity of neutropenia

The predictive factors for neutropenia severity were analyzed using univariable and multivariable analyses. The factors examined include age over 65 years, BMI < 18.5 kg/m², ECOG status 1-4, comorbidity, presence of both type 2 diabetes mellitus (T2DM) and hypertension (HTN), chronic kidney disease (CKD), cancer stage 3-4, pre-chemotherapy absolute neutrophil count (ANC) less than 3000 cells/mm³, and pre-albumin levels less than or equal to 3.5 g/d.

Using univariable analysis, age over 65 years, pre-chemotherapy ANC <3000 cells/mm³, and hypertension as comorbidity showed significant associations with neutropenia severity, with odds ratios (OR) of 2.34 (p=0.0448), 2.89 (p=0.016), and 8.32 (p=0.003), respectively. Using multivariable analysis, age over 65 years (adjusted OR=3.18, p=0.029) and pre-chemotherapy ANC <3000 cells/mm³ (adjusted OR =2.73, p=0.043) remained significant predictors of neutropenia severity. Other factors did not show significant associations in either univariable or multivariable analyses. **(Table 2)**.

Furthermore, when examining severe neutropenia (ANC<100 cells/mm³) specifically, only one factor was found to have a significant impact in the multivariable analysis, which was pre-chemotherapy ANC below 3,000 cells/mm³ (adjusted OR=8.45; 95% CI 1.165–61.290; p=0.035).

Table 2. Predictive factors for severity of neutropenia using univariable and multivariable analysis

Factors	Odds Ratio	95% CI	*p*-value	Adjusted Odds Ratio	95% CI	*p*-value
Age > 65 years	2.34	1.005 - 5.437	0.045*	3.18	1.122 - 9.013	0.029*
BMI < 18.5 kg/m^2	2.83	0.641 - 12.532	0.153	6.04	0.846 - 43.120	0.073
ECOG 2	1.56	0.671 - 3.637	0.298	1.46	0.564 - 3.806	0.434
Comorbidity	1.08	0.495 - 2.366	0.843	1.28	0.490 - 3.366	0.611
T2DM and HTN	0.95	0.255 - 3.507	0.994	0.85	0.166 - 4.344	0.845
CKD	2.34	0.554 - 9.924	0.235	1.42	0.244 - 8.257	0.697
Cancer stage 3 - 4	0.52	0.231 - 1.185	0.117	0.62	0.355 - 1.095	0.100
Pre-ChT ANC < 3000 cells/mm^3	2.89	1.188 - 7.052	0.016*	2.73	1.032 - 7.204	0.043*
Albumin level before ChT ≤ 3.5 g/dL	0.46	0.057 - 3.787	0.462	0.22	0.017 - 2.889	0.250

ANC = absolute neutrophil count, BMI = body mass index, ECOG = The Eastern Cooperative Oncology Group Performance Status, T2DM = type II diabetic mellitus, HTN = hypertension, CKD = chronic kidney disease, ChT = chemotherapy

*$p < 0.05$ = statistically significant

Discussion

This study reported that AC regimen chemotherapy was linked to a high prevalence of neutropenia in breast cancer patients.[8, 9] Notably, older age and low baseline neutrophil count were the sole independent predictors of neutropenia. These findings align with previous studies reporting similar rates and risk factors for neutropenia in breast cancer patients undergoing AC regimen chemotherapy.[5-7] The prevalence of neutropenia, particularly notable among patients 65 years and older, coupled with a pre-chemotherapy ANC < 3000 cells/mm³, underscores the critical necessity for vigilant monitoring and management within this demographic during chemotherapy.[4] This is paramount, given the potentially life-threatening consequences of severe neutropenia, including fatalities observed in this study due to complications like febrile neutropenia.[10-13]

Age-related factors significantly impact bone marrow recovery in diverse ways. For example, the diminished function of hematopoietic stem cells in the bone marrow, responsible for blood cell production, declines with age. This decline reduces the capacity for bone marrow recovery following injury or stress. Additionally, the overall cellularity of the bone marrow diminishes with age, resulting in fewer hematopoietic and stromal cells available to facilitate recovery and regeneration processes.[14] These findings corroborate our observation of the higher frequency of neutropenic events among patients aged 65 years and above. A pre-chemotherapy ANC lower than 3000 cells/mm³ contributes to neutropenic events, primarily due to the direct impact of chemotherapy on rapidly dividing cells such as blood cells. An ANC lower than 3000 cells/mm³ serves as the cutoff level in this study because ANC < 3000 is considered clinically significant, warranting close monitoring and potential intervention to prevent infections. According to consensus recommendations, it is a clinical threshold for heightened vigilance and potential intervention.[15-16]

Interestingly, the severity of neutropenia did not significantly vary between patients with or without medical comorbidities or differing nutritional statuses. While these factors may impact the overall health and treatment outcomes of breast cancer patients, they may not directly influence the risk of developing severe neutropenia. This suggests that other factors, such as genetic variability, drug interactions, or environment, might play a more significant role

in modulating the chemotherapy response and the development of neutropenia.

Neutropenia is a serious complication that can lead to dose reductions, treatment delays, hospitalizations, infections, and mortality. Therefore, it is crucial to identify patients at a higher risk of developing severe neutropenia and to implement appropriate preventive and therapeutic measures, such as prophylactic granulocyte colony-stimulating factor (G-CSF), antimicrobial agents, or supportive care. Furthermore, it is essential to closely monitor the neutrophil count during chemotherapy and adjust the dose accordingly, especially in older patients or those with a low baseline neutrophil count. Overall, these findings underscore the critical role of age and initial neutrophil count in predicting neutropenia severity among breast cancer patients undergoing AC regimen chemotherapy, offering valuable insights for tailoring treatment strategies and enhancing patient care in clinical settings.

However, this study relies on retrospective data collection, a method prone to gaps in information, potentially impacting the comprehensiveness and precision of the data. Conducted exclusively at the Surin Hospital Cancer Center, the study's findings may not generalize to other contexts or populations due to the unique characteristics of the research setting. Furthermore, inherent limitations of the study design may introduce confounding factors, potentially biasing the results. Therefore, it is imperative to consider these factors when interpreting the findings. Future research should adopt a multicenter approach with more extensive and more diverse samples of breast cancer patients receiving AC regimen chemotherapy to ascertain accurate predictive factors for neutropenia and enhance strategies for its prevention and management. Additionally, exploring the molecular mechanisms and genetic factors underlying neutropenia would provide valuable insights into its pathogenesis and potential therapeutic targets.

Conclusion

A significant prevalence of neutropenia was observed among individuals with breast cancer, underscoring the critical importance of age and initial neutrophil count in predicting the severity of neutropenic incidents. These findings offer valuable insights for tailoring treatment strategies and optimizing patient care in this clinical context.

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