

การศึกษาเพื่อหาอุบัติการณ์และปัจจัยทำนายที่ส่งผลต่อการเกิดภาวะไข้ร่วมกับภาวะนิวโทรพีเนียต่ำ (Febrile Neutropenia) ในผู้ป่วยมะเร็งเต้านมที่ได้รับเคมีบำบัด สูตร Anthracycline ร่วมกับยา Cyclophosphamide: การศึกษาย้อนหลังที่ศูนย์มะเร็งโรงพยาบาลสุรินทร์

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บทคัดย่อ การรักษามะเร็งเต้านมด้วยยาได้มีการพัฒนาอย่างต่อเนื่อง ทั้งการใช้ยาเคมีบำบัด ยาภูมิคุ้มกัน และยามุ่งเป้า แต่อย่างไรก็ตามยาเคมีบำบัดยังคงมีบทบาทสำคัญในการรักษามะเร็งเต้านมทั้งในระยะเริ่มต้นและระยะลุกลาม โดยเฉพาะอย่างยิ่งยาเคมีบำบัดสูตรที่ประกอบด้วยยา Anthracycline เป็นยาซึ่งมีประสิทธิภาพในการรักษาสูง อย่างไรก็ตามยาสูตรดังกล่าวนี้อาจก่อให้เกิดภาวะแทรกซ้อนที่รุนแรง คือ ภาวะไข้ร่วมกับนิวโทรพีเนียต่ำ (febrile neutropenia; FN) ซึ่งเป็นปัญหาสำคัญที่อาจนำไปสู่ภาวะที่เป็นอันตรายถึงชีวิตได้ ดังนั้นการจัดการภาวะ FN อย่างมีประสิทธิภาพจึงเป็นสิ่งสำคัญยิ่ง เพื่อความปลอดภัยและความสำเร็จในการรักษาผู้ป่วยมะเร็งเต้านม วิธีการศึกษา เป็นการศึกษาย้อนหลังในผู้ป่วยมะเร็งเต้านมที่ได้รับการรักษาด้วยเคมีบำบัดสูตรที่มี Anthracycline ร่วมกับยา cyclophosphamide ตั้งแต่ มกราคม 2563 ถึงธันวาคม 2565 ที่ศูนย์มะเร็งโรงพยาบาลสุรินทร์ วัตถุประสงค์ เพื่อหาอุบัติการณ์และปัจจัยที่ส่งผลต่อการเกิดภาวะนิวโทรพีเนียรุนแรง (severe neutropenia) และภาวะ FN หลังจากได้รับการรักษาด้วยเคมีบำบัดสูตรดังกล่าว ปัจจัยทำนายภาวะดังกล่าว ถูกวิเคราะห์โดยใช้สถิติแบบถดถอย (flexible parametric regression model) ทั้งการวิเคราะห์เชิงเดี่ยวและเชิงพหุ ผลการศึกษา พบว่าจากการศึกษาผู้ป่วยมะเร็งเต้านมจำนวนทั้งสิ้น 174 ราย พบว่าอุบัติการณ์การเกิดภาวะ severe neutropenia (absolute neutrophil count <100 เซลล์/มม³) ร้อยละ 2.9 ของผู้ป่วย และร้อยละ 4 ของผู้ป่วยเกิดภาวะ febrile neutropenia ซึ่งส่งผลให้มีผู้เสียชีวิต 2 ราย การวิเคราะห์เชิงเดี่ยวแสดงให้เห็นว่าภาวะ FN และภาวะ severe neutropenia มีความสัมพันธ์กับผู้ป่วยที่มีอายุมากกว่า 65 ปี มีคะแนน สถานะการทำงาน หรือ ECOG score ที่มากกว่า 1 และมีโรคประจำตัวอย่างน้อยหนึ่งโรค อย่างไรก็ตามในการวิเคราะห์เชิงพหุ พบว่าปัจจัยทำนายสำหรับภาวะ FN และภาวะ severe neutropenia คือ ค่า ANC เริ่มต้นที่ต่ำกว่า 3,000 เซลล์/มม³ (OR 8.449; 95% CI 1.165–61.290; $P=0.035$) การศึกษานี้ชี้ให้เห็นว่าภาวะ FN เป็นภาวะแทรกซ้อนที่สำคัญในการรักษาด้วยเคมีบำบัด สูตรที่มี Anthracycline ในผู้ป่วยมะเร็งเต้านม การตรวจพบค่าจำนวนเซลล์นิวโทรฟิลก่อนเริ่มการรักษาเป็นปัจจัยทำนายที่สำคัญ ซึ่งเน้นย้ำถึงความสำคัญของการตรวจอย่างละเอียดก่อนเริ่มการรักษา รวมทั้งการจัดการเชิงรุกเพื่อลดความเสี่ยงของการเกิดภาวะ FN (วารสารโรคมะเร็ง 2567;44:131-142)

คำสำคัญ: มะเร็งเต้านม แอนทราไซคลิน ความเป็นพิษ ใช้นิวโทรพีเนีย

Exploring Febrile Neutropenia as Non-Cardiac Fatal Toxicities of Anthracycline-Based Chemotherapy: Incidence and Predictive Factors among Breast Cancer Patients – A Retrospective Analysis at Surin Hospital Cancer Center.

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Abstract In the ongoing battle against breast cancer, chemotherapy remains a critical tool alongside immunotherapy and targeted therapy. Anthracycline-based regimens stand out as powerful chemotherapy agents in this fight. However, alongside therapeutic advancements, febrile neutropenia (FN) poses a significant challenge as a potentially fatal non-cardiac toxicity. Attention to managing FN is crucial for the safety and treatment success of breast cancer patients. We conducted a retrospective study from January 2020 to December 2022 at Surin Hospital Cancer Center, focusing on breast cancer patients treated with anthracycline-based chemotherapy. Our objective was to identify incidents and contributing factors to severe neutropenia and FN following chemotherapy. Prognostic factors were analyzed using a flexible parametric regression model in both univariate and multivariate analyses. The result showed that among the 174 eligible breast cancer patients included in the study, severe neutropenia (defined as ANC <100 cells/mm³) occurred in 2.9% of cases, while 4% developed FN, resulting in two deaths. Univariate analysis revealed associations between FN and severe neutropenia with age over 65, higher ECOG performance status scores, and comorbidities. However, in multivariate analysis, only an initial absolute neutrophil count below 3,000 cells/mm³ emerged as an independent predictor of FN (OR 8.449; 95% CI 1.165–61.290; $P=0.035$). Notably, the severity of neutropenia did not significantly vary based on patients' nutritional statuses. In conclusion, the study highlights FN as a significant complication of anthracycline-based chemotherapy in breast cancer patients. The identification of baseline neutrophil count as a predictive factor emphasizes the importance of pre-chemotherapy screening and proactive management strategies to mitigate FN risk and improve patient outcomes. (*Thai Cancer J* 2024;44:131-142)

Keywords: breast cancer, anthracycline, toxicity, febrile neutropenia

Introduction

Breast cancer remains a formidable adversary in the realm of oncology, necessitating a multifaceted approach for effective management. Among the various therapeutic modalities available, chemotherapy continues to play a pivotal role alongside immunotherapy and targeted therapy¹. Anthracycline-based regimens have long been recognized as potent cytotoxic agents, exerting their antineoplastic effects through interference with DNA replication and transcription processes, ultimately leading to tumor cell death. Despite their efficacy, the use of anthracyclines is not devoid of adverse effects, with one of the most concerning being febrile neutropenia (FN)^{2,3}.

Febrile neutropenia, characterized by fever in the setting of neutropenia, represents a significant clinical challenge, particularly in breast cancer patients undergoing anthracycline-based chemotherapy. This complication not only compromises treatment efficacy but also poses a serious threat to patient safety, potentially leading to fatal outcomes⁴⁻⁶. As such, understanding the incidence, predictive factors, and management strategies for FN is paramount in optimizing patient care and treatment outcomes.

In this retrospective analysis conducted at the Surin Hospital Cancer Center, we sought to explore the incidence and predictive factors associated with severe neutropenia and FN among breast cancer patients receiving anthracycline-based chemotherapy. By identifying these factors, we aim to provide insights that can inform clinical practice and facilitate the implementation of proactive management strategies to mitigate the occurrence of FN and improve patient outcomes. Through our investigation, we endeavor to contribute to the ongoing efforts in the fight against breast cancer by enhancing the safety and efficacy of chemotherapy regimens.

Methodology

Study design and study population

This retrospective analysis was conducted at the Surin Hospital Cancer Center from January 2020 to December 2022. The study encompassed breast cancer patients who underwent anthracycline-based chemotherapy during this period. Identification of eligible patients was facilitated through electronic medical records, with stringent eligibility criteria applied to ensure the inclusion of relevant cases. Ethical approval for the study was obtained from the Institutional Review Board (IRB) at Surin Hospital, ensuring compliance with ethical guidelines and maintaining patient confidentiality.

Outcome measures

The main aim of this study was to investigate the frequency of FN and to pinpoint the factors that may predict its occurrence among breast cancer patients undergoing anthracycline-based chemotherapy. Additionally, an important secondary objective was to assess the severity of neutropenia and FN, utilizing the Common Terminology Criteria for Adverse Events (CTCAE) grading system.

Data collection statistical analysis

Demographic information, clinical characteristics, and treatment-related variables were extracted from patient records. Variables of interest included age, gender, Eastern Cooperative Oncology Group (ECOG) performance status scores, comorbidities, baseline absolute neutrophil count, nutritional status, chemotherapy regimen, and occurrence of severe neutropenia and FN.

The sample size for this study, set at 100 participants (N=100), was determined based on previous research conducted by Sun Young and colleagues⁷, incorporating factors such as age over 65. Descriptive statistics were utilized to summarize patient characteristics and outcome measures. Associations between variables were assessed through univariate analysis, employing chi-square tests for categorical variables and t-tests for continuous variables. Subsequently, multivariate analysis was conducted using a flexible parametric regression model to identify independent predictors of severe neutropenia and FN. Odds ratios (ORs) along with 95% confidence intervals (CIs) were calculated to quantify the strength of associations, with statistical significance set at a $P < 0.05$.

Definition

1. Eastern Cooperative Oncology Group (ECOG) Performance Status: A scale utilized to assess the functional status of cancer patients, ranging from 0 to 5, where 0 denotes full activity and 5 indicates death.
2. Common Terminology Criteria for Adverse Events (CTCAE): A standardized system for classifying and grading the severity of adverse events, graded from 1 (mild) to 5 (death) with specific criteria for each grade based on the type of adverse event.
3. Neutropenia: Defined as a neutrophil count of less than 500 cells/mm³.
4. Severe Neutropenia: Classified as a neutrophil count below 100 cells/mm³.
5. Febrile Neutropenia: Defined as fever (body temperature $\geq 38.3^{\circ}\text{C}$) concurrent with neutropenia (absolute neutrophil count < 500 cells/mm³) or an anticipated decline to < 500 cells/mm³ within the next 48 hours.

Result

During the study period, a total of 174 eligible breast cancer patients underwent anthracycline-based chemotherapy at Surin Hospital Cancer Center. The majority of patients were female (99.4%), with a mean age of 58.9 years (SD 13.56). Approximately 21.3% of patients were aged over 65, and nearly 40% had at least one comorbidity. Baseline characteristics, including Eastern Cooperative Oncology Group (ECOG) performance status scores, nutritional status, and baseline absolute neutrophil count, are summarized in Table 1.

Table 1 Patient baseline characteristics (N=174)

Variable	Febrile neutropenia or neutropenia ANC<100 cells/mm ³ (N=8)	No febrile neutropenia ANC≥100 cells/mm ³ (N=166)	P value
Age (Years), Mean (±SD)	64.875 (6.701)	52.542 (11.253)	
Female	8 (100%)	165 (99.4%)	0.954
Age Group			
• Age<65 years	3 (37.5%)	134 (80.7%)	0.012
• Age>65 years	5 (62.5%)	32 (19.3%)	
Stage of Breast Cancer			
• Stage 1	2 (25.0%)	15 (9.0%)	0.375
• Stage 2	4 (50.0%)	77 (46.4%)	
• Stage 3	2 (25.0%)	54 (32.5%)	
• Stage 4	0 (0.0%)	20 (12.0%)	
ER or PR Positive	5 (62.5%)	107 (65.6%)	0.563
HER-2 Positive	4 (50.0%)	76 (46.6%)	0.566
Neoadjuvant or Adjuvant Chemotherapy			
• Neoadjuvant	1 (12.5%)	25 (15.1%)	0.659
• Adjuvant	7 (87.5%)	141 (84.9%)	

Variable	Febrile neutropenia or neutropenia ANC<100 cells/mm ³ (N=8)	No febrile neutropenia ANC≥100 cells/mm ³ (N=166)	P value
Time to chemotherapy			
• ≤42 days	6 (75.0%)	93 (56.4%)	0.255
• >42 days	2 (25.0%)	72 (43.6%)	
Pre-chemotherapy ANC			
• <3,000 cells/mm ³	4 (50.0%)	25 (15.2%)	0.028
• ≥3,000 cells/mm ³	4 (50.0%)	139 (84.8%)	
Dose (mg), Mean (±SD)	88.125 (8.823)	92.785 (8.587)	
BMI			
• <18.5 Kg/m ²	1 (12.5%)	7 (4.2%)	0.319
• ≥18.5 Kg/m ²	7 (87.5%)	159 (95.8%)	
Albumin Levels Before Chemotherapy>3.5 g/dL	7 (87.5%)	153 (94.4%)	0.391
Hemoglobin (Hb) Before Chemotherapy≥12 g/dL	2 (25.0%)	79 (48.2%)	0.180
Creatinine clearance>60 mL/min	6 (75.0%)	154 (94.5%)	0.085
ECOG Status			
• ECOG 0	3 (37.5%)	129 (77.7%)	0.029
• ECOG 1	5 (62.5%)	36 (21.7%)	
• ECOG 2	0 (0.0%)	1 (0.6%)	

Variable	Febrile neutropenia or neutropenia ANC<100 cells/mm ³ (N=8)	No febrile neutropenia ANC≥100 cells/mm ³ (N=166)	P value
Never smoking	8 (100%)	163 (98.2%)	0.868
Non-alcohol drinking	8 (100.0%)	156 (94.0%)	0.617
Comorbidities			
• Hypertension	7 (87.5%)	61 (36.7%)	0.006
• Type 2 diabetic mellitus	6 (75.0%)	44 (26.5%)	
• Dyslipidemia	1 (12.5%)	22 (13.3%)	
• Chronic kidney disease	1 (12.5%)	18 (10.8%)	
• Coronary artery disease	2 (25.0%)	7 (4.2%)	
• Cerebrovascular accident	0 (0.0%)	3 (1.8%)	

Severity of neutropenia and febrile neutropenia in breast cancer patients

From the study, it was observed that among 174 breast cancer patients who received anthracycline-based chemotherapy, the majority exhibited an ANC nadir >1,500 cells/mm³, comprising 118 patients (68%) according to the Common Terminology Criteria for Adverse Events (CTCAE) grading. Additionally, 12 patients (7%) had an ANC nadir between 1,000 and 1,500 cells/mm³, 13 patients (8%) had an ANC nadir between 500 and 1,000 cells/mm³, and 25 patients (14%) had an ANC nadir <500 cells/mm³. Moreover, the study revealed that 6 patients (3%) experienced an ANC<100 cells/mm³, as illustrated in Table 2. Regrettably, 4% of the patients developed FN, resulting in two deaths.

Table 2 Distribute the number of neutropenic and FN patients according to CTCAE severity grading.

Neutropenia Grading	Number of neutropenic patients N (%)	Febrile neutropenia Grading	Number of febrile neutropenic patients N (%)
Grade 1 (ANC LLN - 1,500 cells/mm ³)	16 (9.19%)	-	-
Grade 2 (ANC 1,000 – <1,500 cells/mm ³)	12 (6.89%)	-	-
Grade 3 (ANC 500–1,000 cells/mm ³)	13 (7.47%)	Hospitalization	0 (0%)
Grade 4 (ANC<500 cells/mm ³)	31 (17.82%)	Life-threatening Consequences	4 (2.30%)
Grade 5 (Death)	-	Death	2 (1.15%)

Predictive factors for severity of severe neutropenia and FN

When comparing and analyzing predictive factors for the severity of neutropenia using univariable analysis, it revealed significant associations between FN and severe neutropenia with age over 65, higher ECOG performance status scores, and comorbidities as show in Table 3. However, in multivariate analysis adjusting for potential confounders, only an initial absolute neutrophil count below 3,000 cells/mm³ emerged as an independent predictor of FN (OR 8.449; 95% CI 1.165–61.290; $P=0.035$). Notably, the severity of neutropenia did not significantly vary based on patients' nutritional statuses. Association between FN and chemotherapy regimen: Further analysis explored the association between FN and specific anthracycline-based chemotherapy regimens. While no significant differences were observed in FN incidence between different regimens, there was a trend towards higher FN rates with certain combinations, warranting further investigation in larger cohorts.

Table 3 Predictive factors for severity of severe neutropenia and FN with univariable analysis and multivariable (N=174)

Factor	Odd ratio	P value	Univariable 95% CI	Odd ratio	P value	Multivariable 95% CI
Age>65 years	6.98	0.004	1.585-30.733	5.53	0.083	0.800-38.268
BMI<18.5 kg/m ²	3.24	0.275	0.3450-30.113	8.63	0.141	0.490-151.961
ECOG 2	5.81	0.009	1.326-25.458	4.84	0.108	0.709-33.068
Co-morbidity	12.05	0.004	1.448-100.278	9.69	0.065	0.869-107.888
T2DM and HTN	1.34	0.790	0.155-11.588	3.20	0.379	0.223-51.673
CKD	7.57	0.0010	1.289-44.465	1.04	0.974	0.093-11.705
Cancer stage 3-4	0.41	0.276	0.081-2.113	0.41	0.186	0.107-1.545
Pre CMT ANC <3,000 cells/mm ³	5.56	0.010	1.304-23.699	8.45	0.035	1.165-61.290
Pre albumin ≤3.5 g/dL	2.43	0.415	0.269-21.929	1.57	0.768	0.079-31.119

BMI: Body Mass Index, ECOG; Eastern Cooperative Oncology Group, T2DM; Type 2 Diabetes Mellitus, HTN; Hypertension, CKD; Chronic Kidney Disease, ANC; Absolute Neutrophil Count, and CMT for Chemotherapy

Discussion

The findings from our retrospective analysis shed light on the incidence and predictive factors associated with severe neutropenia and FN in breast cancer patients undergoing anthracycline-based chemotherapy. Our study unveils several important insights that warrant discussion in the context of existing literature and clinical implications.

Firstly, our study uncovered a relatively low incidence of severe neutropenia (2.9%) and FN (4%) among breast cancer patients undergoing anthracycline-based chemotherapy. This incidence falls within the lower range compared to previous studies, which have reported incidences ranging from 8% to 25%. Notably, our study specifically focused on the first cycle of chemotherapy, which may contribute to the observed lower incidence rates. However, when comparing our findings with other retrospective studies, we noted a notably higher incidence of FN reported by Kim et al.⁸, although the reasons for this discrepancy remain unclear. Of particular concern, our analysis revealed that two out of six (33.3%) fatalities in our study were attributed to FN, highlighting its clinical significance and potential consequences in this patient population¹⁰.

Multivariate analysis identified an initial absolute neutrophil count (ANC) below 3,000 cells/mm³ as the only independent predictor of FN, underscoring the importance of baseline neutrophil levels in risk stratification. Although advanced age, higher Eastern Cooperative Oncology Group (ECOG) performance status scores, and comorbidities were associated with FN in univariate analysis, their significance was not maintained in multivariate analysis. This suggests that baseline neutrophil count may serve as a more robust predictor of FN risk, independent of other clinical factors. Undoubtedly, a pre-chemotherapy ANC lower than 3,000 cells/mm³ contributes significantly to neutropenic events, primarily due to the direct impact of chemotherapy on rapidly dividing cells such as blood cells.

The identification of baseline neutrophil count as a predictive factor for FN underscores the potential utility of pre-chemotherapy screening to assess individual patient risk. Close monitoring of neutrophil levels during treatment may facilitate early identification of patients at increased risk of FN, enabling timely intervention and preventive measures. Furthermore, our findings emphasize the importance of proactive management strategies, including the use of granulocyte colony-stimulating factors (G-CSF) and antimicrobial prophylaxis, to mitigate the occurrence of FN and minimize associated morbidity and mortality.

In summary, our study highlights the importance of baseline neutrophil count as a predictive factor for FN and underscores the need for vigilant monitoring and proactive management strategies in breast cancer patients undergoing anthracycline-based chemotherapy to minimize the risk and impact of neutropenic complications.

Limitations and Future Directions

Despite its contributions, our study has several limitations, including its retrospective design and reliance on data from a single center. Additionally, the relatively small sample size may limit the generalizability of our findings. Future studies with larger, multicenter cohorts are warranted to validate our results and further elucidate the complex interplay of factors influencing FN risk in breast cancer patients.

Conclusion

In conclusion, our study highlights the clinical significance of FN as a potentially fatal complication of anthracycline-based chemotherapy in breast cancer patients. The identification of baseline neutrophil count as a predictive factor underscores the importance of pre-chemotherapy screening and proactive management strategies to mitigate FN risk and improve patient outcomes.

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