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Predictors of Chemotherapy Induced Neutropenia in Patients with Breast Cancer

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ABSTRACT

Objective: Chemotherapy induced neutropenia (CIN) is a common adverse effect of chemotherapy and interferes with optimal dosing. The purpose of this study was to determine the frequency and risk factors of grade 3/4 CIN (absolute neutrophil count <1000/mm^3) in breast cancer patients receiving systemic chemotherapy.

Material and Methods: This single center retrospective study comprised 679 female patients with breast cancer who were treated with anthracycline and/or taxane based or cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy regimens. Patients who received primary prophylaxis with granulocyte-colony stimulating factor were excluded. Demographic and clinical risk factors for grade 3/4 CIN were evaluated with multivariate regression analysis.

Results: The frequency of grade 3/4 CIN was 25.3% and mostly occurred during the first 4 cycles of chemotherapy. In multivariate analysis, stage 4 disease [odds ratio (OR): 3.1], having 2 or more comorbidities (OR: 2.5), and low baseline white blood cell count (<4000/mm^3 *vs.* >10000/mm^3, OR: 7.84) were associated with increased risk for grade 3/4 CIN. Being overweight or obese was found to be protective for the occurrence of grade 3/4 CIN (OR: 0.38 and 0.26, respectively).

Conclusion: Using data from real-world experience, we have identified some risk factors for grade 3/4 CIN, some of which were not included in the current guidelines published for managing CIN. These findings may assist daily clinical practice clinical practice and may provide a rationale for further research in preventing the myelosuppressive side effects of chemotherapy.

Keywords: Breast cancer; chemotherapy; neutropenia

INTRODUCTION

Introduction of chemotherapeutic agents has led to a significant improvement on overall and disease- free survival rates of breast cancer patients.[1] This benefit is particularly evident in subjects who received chemotherapy in planned doses.[2-4] However, some adverse effects of anti-cancer drugs might interfere with optimal dosing and timing of chemotherapy. Chemotherapy induced neutropenia (CIN) is a common adverse effect of chemotherapy.[5] It may also be complicated with fever (febrile neutropenia) and result in increased morbidity, mortality, and healthcare costs.[6] Guidelines published by different groups provided recommendations for the use of prophylactic granulocyte-colony stimulating factors (G-CSF) mainly based on the risk of febrile neutropenia (FN).[7,8] These guidelines combined the treatment-related and patient-related risk factors such as age, disease characteristics, performance status, and comorbidities.[7,8] On the other hand, even in the absence of FN, occurrence of CIN is associated with chemotherapy dose delays and reductions, which may negatively affect outcomes.[9] In line with this, primary prophylaxis with G-CSF was also recommended for patients in whom dose reductions are clearly associated with poorer outcomes.[7] Therefore, it is important to identify risk factors for CIN better. In this single center study, we aimed to determine the incidence and risk

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factors for CIN in female breast cancer patients who received systemic chemotherapy in adjuvant, neoadjuvant, and metastatic settings.

MATERIAL AND METHODS

Study Design and Data Collection

The medical records of breast cancer patients who received systemic chemotherapy in a 7-year period (January 2006-December 2013) at a tertiary-care medical oncology department were retrospectively analyzed. Inclusion criteria were female sex, age ≥18 years, and having received anthracycline and/or taxane based or cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy regimens. The exclusion criteria were as follows: primary prophylaxis with G-CSF for neutropenia; treatment with chemotherapy regimens other than CMF, anthracyclines or taxanes; hepatic or renal insufficiency; documented bone marrow metastasis; missing data for complete blood count within 1 to 4 days prior to any chemotherapy cycle.

Data about demographics [age, weight, body mass index (BMI), number and type of comorbidities], clinicopathological features (stage according to TNM classification, hormone receptor status, human epidermal growth factor receptor (HER)-2/neu positivity), treatment details (type and number of chemotherapy cycles, radiotherapy) and blood count parameters (white blood cell and absolute neutrophil count) were recorded.

Patients were stratified into four main groups according to the type of chemotherapy regimen they received: CMF, anthracycline based only, sequential anthracycline plus taxane, and taxane only. Chemotherapy regimens and doses are summarized in Table 1.

CIN was defined and categorised according to the Common Terminology Criteria for Adverse Events version 4.0. Grade 3 and 4 neutropenia (absolute neutrophil count (ANC) below 1000/mm^3 and 500/mm^3, respectively) were defined as severe neutropenia. Grades of CIN and the chemotherapy cycle during which CIN occurred were determined by using an electronic recording system. All blood counts were performed within 1 to 4 days before each chemotherapy cycle. To exclude the effect of secondary prophylaxis with colony-stimulating factor use and dose reductions in subsequent cycles, the chemotherapy course in which patients first experienced neutropenia was taken into account.

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by Ethics Committee of Hacettepe University (approval number: GO 13/529-12, date: 12.12.2013).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 20.0; IBM Corporation, Armonk, NY, USA). Data from descriptive analysis were expressed as mean ± standard deviation or median (minimum-maximum) as appropriate. Categorical variables were compared with the chi-square test. Student's t-test was used to compare normally distributed continuous data between two groups. The effects of different variables on grade 3/4 CIN risk were calculated in a univariate analysis for each. All variables associated with grade 3/4 CIN with a p value less than 0.25 in univariate analysis, and all predefined clinically important variables (such as disease stage) were included in the multivariable logistic regression model. Collinearity was checked between the variables. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. A p value of <0.05 was considered as significant.

RESULTS

At the beginning of the study, medical records of 1,813 patients were reviewed. After excluding patients who received primary G-CSF prophylaxis (n=505), those treated with chemotherapy regimens other than the predefined protocols (n=55), and those with missing blood count

TABLE 1: Details of chemotherapy regimens used.

CMF: Cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2, 6 cycles, every three weeks.
Anthracycline based only
AC: Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, 2 to 6 cycles, every three weeks. **EC:** Epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2, 4 cycles, every three weeks. **CAF:** Cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, 5-fluorouracil 500 mg/m^2, 3 to 6 cycles, every three weeks. **CEF:** Cyclophosphamide 500 mg/m^2, epirubicin 90 mg/m^2, 5-fluorouracil 500 mg/m^2, 6 cycles, every three weeks.
Sequential anthracycline and taxane
Anthracycline based chemotherapy regimen followed by a taxane; either paclitaxel 80 mg/m^2, 3 to 12 cycles, weekly or docetaxel 100 mg/m^2, 3 to 4 cycles, every 3 weeks.
Taxane only
Paclitaxel 80 mg/m^2, 8 to 18 cycles, weekly or docetaxel 100 mg/m^2, 4 to 8 cycles, every 3 weeks.

data for any of the chemotherapy cycles (n=574), a total of 679 patients were included in the study. Patients who received primary G-CSF prophylaxis were mostly treated with chemotherapy regimens that included a combination of anthracyclines and taxanes, such as docetaxel, doxorubicin and cyclophosphamide (TAC) docetaxel, epirubicin and cyclophosphamide (TEC). Demographic and clinical data of 679 patients are presented in Table 2. Median age at the start of chemotherapy was 48 (20-83) years. Most of the patients had stage 2-3 disease (79.5%) and

TABLE 2: Demographic and clinical characteristics of patients.

	All patients (n=679)	Grade 3-4 CIN (-) (n=507)	Grade 3-4 CIN (+) (n=172)	p
Age, years, median (min-max)	48 (20-83)	47 (21-82)	49 (20-83)	0.07
Age ≥65 years	47 (6.9)	29 (5.7)	18 (10.5)	**0.034**
Body mass index, kg/m²	27.5 (4.9)	28.0 (5.0)	25.9 (4.6)	**<0.001**
Body mass index category				
Underweight (<18.5 kg/m²)	7 (1.0)	5 (1.0)	2 (1.1)	**<0.001**
Normal (18.5-24.9 kg/m²)	216 (31.8)	135 (26.6)	81 (47.1)	
Overweight (25-29.9 kg/m²)	237 (34.9)	185 (36.5)	52 (30.2)	
Obese (≥30 kg/m²)	219 (32.2)	182 (35.9)	37 (21.5)	
Comorbidities				
Hypertension	144 (21.2)	102 (20.1)	42 (24.4)	0.23
Diabetes mellitus	63 (9.3)	46 (9.1)	17 (9.9)	0.76
Hyperlipidemia	23 (3.4)	15 (3.0)	8 (4.7)	0.32
Hypothyroidism	66 (9.7)	44 (8.7)	22 (12.8)	0.13
Number of comorbidities				
0	419 (61.7)	322 (63.5)	97 (56.4)	0.21
1	176 (25.9)	127 (25.0)	49 (28.5)	
≥2	84 (12.4)	58 (11.4)	26 (12.4)	
Stage				
1	79 (11.6)	64 (12.5)	15 (8.7)	0.29
2	360 (53.0)	264 (52.1)	96 (55.8)	
3	180 (26.5)	138 (27.2)	42 (24.4)	
4	60 (8.8)	41 (8.1)	19 (11.0)	
HR positive *	474 (69.8)	354 (70.2)	130 (75.6)	0.18
HER2/neu positive *	196 (29.1)	152 (30.2)	44 (26.2)	0.32
Baseline WBC count/mm³	7500 (2000)	7700 (2000)	6900 (1800)	**<0.001**
Baseline WBC count category				
>10000	85 (12.5)	75 (14.8)	10 (5.8)	**0.003**
8001-10000	154 (22.7)	123 (24.3)	31 (18.0)	
6001-8000	296 (43.6)	210 (41.4)	86 (50.0)	
4001-6000	130 (19.1)	91 (17.9)	39 (22.7)	
≤4000	14 (2.1)	8 (1.6)	6(3.5)	
Chemotherapy regimens used				
Anthracycline based only	345 (50.8)	254 (50.1)	91 (52.9)	0.14
CMF	92 (13.5)	62 (12.2)	30 (17.4)	
Taxane only	13 (1.9)	11 (2.2)	2 (1.2)	
Sequential anthracycline and taxane	229 (33.7)	180 (35.5)	49 (28.5)	

CIN: Chemotherapy induced neutropenia; WBC: White blood cell; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; CMF: Cyclophosphamide, methotrexate, 5- fluorouracil *Hormone receptor and HER2/neu status was not available in 3 and 7 patients, respectively. Values are mean (SD) and n (%) unless indicated otherwise, SD: Standard deviation.

81.1% (n=551) received adjuvant chemotherapy. 68 (10%) and 60 (8.8%) patients received neoadjuvant and palliative chemotherapy, respectively. Five hundred and thirty-two (78.3%) patients had received radiotherapy. The most frequent comorbidities were hypertension, diabetes mellitus, dyslipidemia, and hypothyroidism. Other comorbidities were as follows: hyperthyroidism in 2 (0.3%), papillary thyroid cancer in 3 (0.4%), coronary artery disease in 8 (1.2%), chronic obstructive lung disease or asthma in 18 (2.7%), chronic HBV infection in 7 (1.0%), venous thromboembolism in 3 (0.4%), rheumatoid arthritis in 2 (0.3%), Sjogren's syndrome in 1 (0.2%) and Behçet's disease in 2 (0.3%) patients.

Anthracycline-based-only chemotherapy was most frequently used, followed by sequential anthracycline + taxane regimens. 345 (50.8), 92 (13.5), 13 (1.9) and 229 (33.7) patients received anthracycline based only, CMF, taxane only and sequential anthracycline and taxane regimens, respectively. In the anthracycline based only group, 258 (74.7%) patients received doxorubicin and cyclophosphamide (AC), 85 (24.6%) received cyclophosphamide, doxorubicin and 5-fluorouracil (CAF), 1 patient (0.3%) received cyclophosphamide, epirubicin and 5-fluorouracil (CEF) and 1 patient (0.3%) received epirubicin and cyclophosphamide (EC). In the taxane-only group, 7 patients received paclitaxel and 6 patients received docetaxel. Of 229 patients in sequential anthracycline and taxane group, 102 (44.5%) received AC + paclitaxel, 93 (40.6%) received AC + docetaxel, 23 (10.1%) received CEF + docetaxel, 9 (3.9%) received CAF + docetaxel, 1 (0.4%) received CEF + paclitaxel and 1 (0.4%) received EC + paclitaxel. The median age of patients who received anthracycline-containing regimens was significantly lower than those received received CMF or taxane only (47 *vs.* 52, p<0.001). Patients ≥65 years old more frequently received CMF (59.6% *vs.* 10.1%, p<0.001) and taxane only regimens (6.4% *vs.* 1.6%, p=0.054) than those <65 years. Anthracycline-containing regimens were less frequently used in these patients (34.0% *vs.* 88.3%, p<0.001).

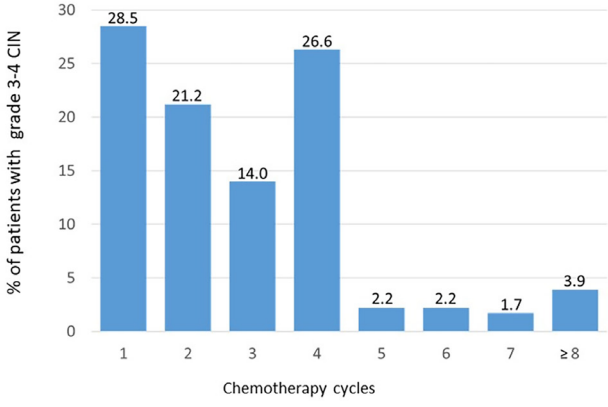

FIGURE 1: Distribution of grade 3-4 neutropenia according to chemotherapy cycles.

CIN: Chemotherapy induced neutropenia

Any grade of CIN (ANC <2000/mm³) occurred in 70.5% of patients (n=479). 140 (29.2%) and 167 (34.9%) patients developed grade 1: (1500≤ ANC <2000/mm³) and grade 2: (1000≤ ANC <1500/mm³) CIN, respectively. The incidence of grade 3/4 CIN in the overall cohort was 25.3% (n=172) (Table 2). Among these patients, grade 3 CIN occurred in 125 (72.7%) and grade 4 CIN occurred in 47 (27.3%) patients. Grade 3/4 CIN occurred mostly during the first four chemotherapy cycles (Figure 1). Grade 3/4 CIN occurred in 26.4%, 32.6%, 15.4% and 21.4% of patients who received anthracycline -based only, CMF, taxane only, and sequential anthracycline and

TABLE 3: Multivariate regression analysis for risk factors of grade 3-4 CIN.

	OR (95% CI)	p
Age ≥65	2.03 (0.96-4.30)	0.06
Hormon receptor positive	1.28 (0.84-1.97)	0.24
Stage		
1	1	Reference
2	1.89 (0.98-3.65)	0.05
3	1.80 (0.85-3.81)	0.12
4	3.10 (1.30-7.34)	**0.010**
Number of comorbidities		
0	1	Reference
1	1.31 (0.84-2.06)	0.22
≥2	2.50 (1.41-4.45)	0.002
Body mass index category		
Normal	1	Reference
Low	0.64 (0.12-3.47)	0.60
Overweight	0.38 (0.24-0.59)	**<0.001**
Obese	0.26 (0.15-0.43)	**<0.001**
Chemotherapy regimen		
Anthracycline based only	1	Reference
CMF	1.01 (0.56-1.82)	0.96
Taxane only	0.69 (0.13-3.53)	0.66
Sequential anthracycline and taxane	0.74 (0.47-1.18)	0.21
Baseline WBC count, mm³		
>10,000	1	Reference
8001-10,000	2.51 (1.11-5.64)	**0.026**
6001-8000	3.96 (1.88-8.33)	**<0.001**
4001-6000	3.74 (1.68-8.34)	**0.001**
≤4000	7.84 (2.11-29.10)	**0.002**

CIN: Chemotherapy induced neutropenia; OR: Odds ratio; CMF: Cyclophosphamide, methotrexate, 5- fluorouracil; WBC: White blood cell, CI: Confidence interval.

taxane regimens, respectively. Among the most frequently used regimens, grade 3/4 CIN incidence was 26.0%, 25.9%, 21.6%, and 21.5% for AC, CAF, AC + paclitaxel and AC + docetaxel regimens, respectively. In 49 patients who received sequential anthracycline and taxane, CIN occurred during the anthracycline phase in 40 (81.6%) patients.

Table 3 shows the results of multivariable logistic regression analyses performed to determine the risk factors independently associated with grade 3/4 CIN. Stage 4 disease [odds ratio (OR): 3.10, 95% confidence interval (CI): 1.30-7.34, compared to stage 1 disease] and having 2 or more comorbidities (OR: 2.50, 95% CI: 1.41-4.45, compared to having no comorbidities) were independently associated with increased risk. Low baseline white blood cell (WBC) count also conferred higher risk for grade 3/4 CIN. As compared to the highest quintile (>10000/mm^3), the lowest quintile (≤4000/mm^3), was associated with an approximately 8-fold increase in the risk of grade 3/4 CIN (OR: 7.84, 95% CI: 2.11-29.10). The model also identified being overweight (OR: 0.38, 95% CI: 0.24-0.59) or obese (OR: 0.26, 95% CI: 0.15-0.43) as protective factors for grade 3/4 CIN.

DISCUSSION

In this study, almost one-fourth of patients with breast cancer developed grade 3-4 CIN in at least one of the chemotherapy cycles. Multivariable logistic regression analysis revealed that advanced disease stage, a higher number of comorbidities, and lower baseline WBC count were independent risk factors for grade 3-4 CIN, whereas being overweight or obese was found to be protective.

The incidence of CIN in patients with breast cancer varies greatly across studies according to the chemotherapy regimens used.[10-15] Schwenkglenks et al.[9] reported a 34% incidence for grade 4 CIN in breast cancer patients. The main difference in that study is that 4% of patients received the TAC regimen, which confers a greater risk for neutropenic events.

Elderly people are considered to be more prone to chemotherapy-related complications possibly due to alterations in renal and hepatic functions and bone marrow reserve. Although both American and European clinical practice guidelines agree on the older age as a risk factor for CIN, data in the literature about this issue have been contradictory.[7,8] Elderly subjects are less frequently involved in studies evaluating adjuvant chemotherapies. It has been shown that only 18% of the patients recruited in the studies sponsored by the National Cancer Institute were over 65 years old.[16,17] Min et al.[15] demonstrated that in breast cancer patients receiving an anthracycline-based chemotherapy regimen, being older than 55 years is associated with an increased risk of FN. However, older age was not identified as a risk factor for FN in two other studies evaluating FN risk in breast cancer patients receiving 5-fluorouracil, epirubicin and cyclophosphamide (FEC) chemotherapy.[18,19] In our cohort, patients over 65 years old more frequently experienced grade 3-4 CIN; however, age was not identified as an independent risk factor in multivariable analysis. This is probably due to the fact that, in our study, patients older than 65 years old more frequently received CMF chemotherapy which carries less risk for CIN than anthracycline-containing regimens.[7]

Advanced disease stage is considered a significant predictor for neutropenic events.[7,20] Poor performance, impaired nutritional status, and cumulative effects previous treatments on bone marrow might be the potential contributors to CIN in patients with advanced disease. In a population-based study, patients with stage 3/4 disease were found to have higher rates of hospitalization due to neutropenia.[21] Similarly, Gianni et al.[22] demonstrated that FN more frequently occurs in patients with advanced disease. In our study, a threefold increased risk of CIN in patients with stage 4 disease supports the previous literature about the impact of disease extension on treatment-related myelotoxicity.

Our results showed that patients with 2 or more comorbidities have a 2.5-fold increased risk of grade 3/4 CIN. Garg et al.[23] reported higher frequency of treatment-related neutropenia and FN along with higher dose reduction and discontinuation rates in breast cancer patients with high comorbidity scores. In a study of 7127 cancer patients, congestive heart failure [hazard ratio (HR): 3.0, 95% CI: 1.3-5.9], osteoarthritis (HR: 2.0, 95% CI: 1.4-2.8), previous cancer history (HR: 3.4, 95% CI: 1.2-7.5) and thyroid disease (HR 1.6, 95% CI: 1.1-2.3) were associated with increased risk of chemotherapy related FN.[24] Vascular comorbidities were identified as risk factors for grade 4 CIN in the INC-EU study.[9] In our analysis, we did not find an increased frequency of any specific comorbidity in patients who developed CIN. Bacrie et al.[18] recently reported a significant association between autoimmune or inflammatory disease and FN in breast cancer patients, most of who did not receive immunosuppressive therapy. We cannot draw any conclusion from our results about the impact of inflammatory comorbidities due to a limited number of patients.

Being overweight or obese has been shown to significantly reduce the risk of CIN in our analysis. Previously, a systematic review of breast cancer patients showed a substantially lower risk for CIN patients with a BMI above 35 kg/m^2.[25] The INC-EU study demonstrated an increased

frequency of grade 4 CIN in patients with lower body weight.[9] Body surface area-based dosing might lead to a higher chemotherapy dose per kilogram of body weight in patients with low body weight. Another possible explanation is that dose-capping strategies might have been used more frequently in overweight and obese patients. Several studies suggested lower survival rates in obese breast cancer patients, than non-obese ones.[26,27] Dose capping in obese subjects is frequently observed in clinical practice, and has the potential to explain these worse outcomes by leading to under-treatment. It might be beneficial to reconsider dosing strategies to achieve maximum benefit from chemotherapy.

In our model, pre-chemotherapy baseline WBC counts strongly predicted grade 3 or 4 CIN, and the risk for patients with WBC <4000/mm^3 was 8 times higher, compared to patients with >10000/mm^3. This finding is consistent with previous studies indicating an association between pretreatment haematological parameters and occurrence of CIN.[9,28,29] Similarly, in another study, low basal white blood cells and absolute neutrophil counts have been shown to predict neutropenic events in patients receiving FEC chemotherapy.[30]

Study Limitations

The retrospective design is the main limitation of this study. Secondly, data about comorbidities were mainly based on patient records, and not systematically evaluated. Although we excluded patients who received primary G-CSF prophylaxis, we were unable to provide data on how many patients received secondary G-CSF prophylaxis in subsequent chemotherapy cycles. Besides, we could not provide information about in how many patients dose-capping strategy was employed. Lack of data regarding metastatic sites in patients with stage IV disease can be considered as another limitation as location of metastases could potentially affect the development of CIN. Lastly, the relatively small sample sizes in the CMF and taxane-only groups may have compromised the statistical power of the comparisons between chemotherapy regimens.

CONCLUSION

In the present study, we have identified some patient-related risk factors for severe CIN using real-world experience from a single-center breast cancer patient cohort. Some of these factors have not been included in the current guidelines published for managing CIN. These findings may assist to daily clinical practice and may provide a rationale for further research in preventing the myelosuppressive side effects of chemotherapy.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by Ethics Committee of Hacettepe University (approval number: GO 13/529-12, date: 12.12.2013).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., S.A., S.Aş., Concept: A.S., S.Aş.,, Design: A.S., S.A., S.Aş., Data Collection or Processing: A.S., S.Aş.,, Analysis or Interpretation: A.S., S.A., S.Aş., Literature Search: A.S., S.A.,, Writing: A.S., S.A., S.Aş., Critical Review: A.S., S.A., S.Aş.

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