Brief Communication

Chemotherapy-induced febrile neutropenia in patients with breast cancer. *A multivariate risk assessment model for first cycle chemotherapy*

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ABSTRACT

Objectives: To identify factors that increase the risk of developing febrile neutropenia (FN) during the first cycle of chemotherapy in breast cancer patients.

Methods: In this retrospective study, we reviewed the records of 211 patients with confirmed breast cancer treated with chemotherapy at the Princess Norah Oncology Center, King Abdulaziz Medical City, Jeddah, Kingdom of Saudi Arabia between January 2010 and May 2012. Statistical analysis was conducted using descriptive analysis, univariate, and multivariate logistic regressions. A multivariate regression of FN occurrence in the first cycle was developed.

Results: The median age of patients was 48 years. Febrile neutropenia was documented in 43 (20.3%) of 211 patients. Twenty-one (49%) of the 43 patients had FN during the first cycle of chemotherapy. A multivariate logistic regression revealed that age (odds ratio [OR] 1.059, 95% confidence interval [CI]: 1.007-1.114), non-anthracycline and/or taxane-based chemotherapy regimens (OR of 39.488; 95% CI: 4.995-312.187), and neo-adjuvant chemotherapy (OR of 8.282; 95% CI: 1.667-41.152) were the most important independent risk factors of FN.

Conclusion: Identifying risk factors of FN may help to target high-risk patients with granulocyte colony-stimulating factor prophylaxis and reduce FN incidences, with subsequent morbidities and mortalities.

Breast cancer is the most common form of malignancy among women in Saudi Arabia, accounting for 25% of all newly diagnosed female cancers in 2008.[1] During the same period, the age standardized rate was 19.2/100,000 for the female population.[1] Chemotherapy is one of the standard therapies for breast cancer patients. However, it is has been documented that patients treated with such treatment are at risk for developing febrile neutropenia (FN).[2] Febrile neutropenia is a dose limiting hematologic toxicity with a life-threatening complication that occurs with many chemotherapeutic agents used in the treatment of cancer, and is associated with prolonged hospitalization, negative impact on quality of life, substantial morbidity, mortality, and cost.[2,3] Furthermore, clinical literature indicates that neutropenic events most likely occur when patients are treated with full-dose chemotherapy during the first cycle of chemotherapy.[4] Previous studies reported that patient-specific and treatment regimen-specific risk factors predispose cancer patients to neutropenia.[2] Despite this, the number of studies examining the risk of developing neutropenia in cancer patients receiving chemotherapy is limited.[4,5] There is a lack of published studies specifically addressing this issue in patients with breast cancer in Saudi Arabia. The primary objective of the present study is to bridge this knowledge gap by identifying factors that may increase the risk for the development of FN during the first cycle of chemotherapy in patients with breast cancer treated in a single institution in Saudi Arabia. The findings of the study may help reduce neutropenic complications by targeting breast cancer patients who are at high-risk of developing FN with prophylactic granulocyte colony-stimulating factors (G-CSF).

Methods.

Study design and patient selection. This is a single-center retrospective study of 211 adult patients diagnosed with breast cancer at the Princess Norah Oncology Center, King Abdulaziz Medical City, Jeddah, Kingdom of Saudi Arabia between January 2010 and May 2012. All patients with a confirmed tissue diagnosis and treated with curative or palliative-intent chemotherapy were included.

Data collection. Patients' records were used for data collection. Information extracted included demographic factors: age and gender; physical and clinical variables: height, weight, body surface area, and absolute neutrophil count (ANC); co-morbidities; disease characteristics: stage, metastasis; receptor status; human epidermal growth factor receptor 2 (HER2) overexpression; date and cycle number for chemotherapy; types of treatment: surgery, chemotherapy, radiotherapy, and hormonal therapy;

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

intent of chemotherapy (adjuvant, neo-adjuvant, or palliative); menopausal status, use of prophylactic G-CSF.

Chemotherapy agents. All patients were treated with chemotherapy. The chemotherapy regimen administered to each patient was categorized into one of the following mutually exclusive chemotherapy treatment groups: anthracycline-based, taxane-based, anthracycline plus taxane-based, and non-anthracycline and/or taxane chemotherapy, such as vinorelbine and bevacizumab. In addition, data on the chemotherapy cycle and the intent of chemotherapy (curative: adjuvant and neo-adjuvant; palliative) were extracted.

Statistical analysis. Febrile neutropenia is defined as an ANC of $<0.5\times10^9$/L (or $<1.0\times10^9$/L and predicted decline to $<0.5\times10^9$/L over the next 48 hours) with a body temperature of ≥38.3°C orally, or ≥38.0°C orally for ≥1 hour.[6] Descriptive analysis was conducted to describe the patients characteristics.

Categorical variables were compared using Chi-square test or Fisher's exact test as appropriate. Univariate and multivariate logistic regression were used to identify independent risk factors for developing FN in the first cycle of chemotherapy. All variables were first tested in a univariate, and only covariates with $p<0.2$ were subsequently entered into the multivariate logistic regression model. At the multivariate analyses, covariate with p-values of less than 0.05 were considered statistically significant. Data were analyzed using the Statistical Package for Social Sciences software version 20 (SPSS Inc., Chicago, IL, USA).

Results.

Patient characteristics. The characteristics of the 211 patients are reported in (**Table 1**). In total, 21 patients experienced FN (10%) during the first cycle of chemotherapy.

Patients with febrile neutropenia in first cycle. Patients who experienced FN during the first cycle of chemotherapy were all females with a median age of 50 (range: 32-75) and a median body surface area (BSA) of 1.70 (range: 1.21-2.20). Almost half (47.6%) of these patients were postmenopausal, 57% were in stage III, 19% had metastasis, 57.1% had positive estrogen receptor, 52.4% had positive progesterone receptor, and 28.6% had HER2-positive disease. Among patients who developed FN in the first cycle of chemotherapy: 10 (47.65%) had surgery, 18 (85.7%) received adjuvant radiotherapy, and 19 (90.5%) hormonal therapy. A significant p-value was found upon comparison between the patients who developed FN after cycle one and the other patients in relation to the BSA (p=0.038), chemotherapy intent (p=0.046), and the regimen (p=0.014).

Patients who developed FN in cycle one categorized by intent of chemotherapy revealed that 85.7% were curative (adjuvant and neo-adjuvant), and 14.3% palliative. More than half of the FN (57.1%) occurred in patients who received neo-adjuvant chemotherapy. Among the patients who developed FN in cycle one: 42.9% were treated with taxane-based chemotherapy, 33.3% with anthracycline-based, and 4.8% with taxane plus anthracycline. The rest (19%) had non-anthracycline/taxane chemotherapies. Two (9.5%) of the patients who had FN in cycle one received primary prophylaxis G-CSF (filgrastim).

Table 1 - The characteristics features of 211 patients with breast cancer.

Characteristics	FN in cycle one		No FN in cycle one		*P*-value
	n (%)				
Number of patients	21	(10.0)	190	(90.0)	
Demographic factors					
Age (years)					
Median (range)	50	(32-75)	48	(23-79)	0.808
Gender					
Female	21	(100.0)	188	(98.9)	1.00
Male	0	(0.0)	2	(1.1)	
Menopausal status*					0.107
Premenopausal	7	(33.3)	115	(60.5)	
Postmenopausal	10	(47.6)	64	(33.7)	
Unknown status	4	(19.1)	11	(5.8)	
Body surface area					
Median (range)	1.70	(1.21-2.20)	1.80	(1.21-2.34)	0.038
Disease characteristics*					
Breast cancer stage					0.409
I	0	(0.0)	8	(4.2)	
II	5	(23.8)	56	(29.5)	
III	12	(57.1)	67	(35.3)	
IV	4	(19.0)	48	(25.3)	
Estrogen receptor (+)	12	(57.1)	128	(67.4)	0.423
Progesterone receptor (+)	11	(52.4)	111	(58.4)	0.682
HER2 (+)	6	(28.6)	60	(31.6)	0.872
Intent of chemotherapy*					0.046
Adjuvant	6	(28.6)	83	(43.7)	
Neo-adjuvant	12	(57.1)	51	(26.8)	
Palliative	3	(14.3)	44	(23.15)	
Use of prophylactic G-CSF*					0.544
No	18	(85.7)	18	(9.5)	
Filgrastim	2	(9.5)	2	(1.1)	
Pegfilgrastim	0	(0.0)	2	(1.1)	
Chemotherapy regimen					0.014
Anthracycline-based	7	(33.3)	83	(43.7)	
Taxane-Based	9	(42.85)	83	(43.7)	
Taxane/anthracycline	1	(4.8)	20	(10.5)	
Others	4	(19.0)	4	(2.1)	

G-CSF- granulocyte colony-stimulating factors, FN- fiber neutropenia, HER2 - human epidermal growth factor receptor 2

Several demographic, clinical, and treatment characteristics were investigated for association with FN using a univariate logistic regression. Age, menopausal, BSA, status of estrogen receptor, status of progesterone receptor, and the first chemotherapy received met the inclusion criteria. These covariates were included in a multivariate logistic to model the risk factors for developing FN in breast cancer patients in cycle one. The results are reported in **Table 2**. Age was positively related to the risk of developing FN in the first cycle (odds ratio [OR] of 1.059; 95% confidence interval [CI]: 1.007-1.114). After adjusting for other covariates, the risk for developing FN in the first cycle was positively associated for patients treated with chemotherapy agents other than anthracycline and/or taxane-based. These patients were 39 times more likely to experience FN in the first cycle than patients treated with anthracycline-based (OR of 39.488; 95% CI: 4.995-312.187). Similarly, neo-adjuvant treatment intention had a higher risk of chemotherapy-induced neutropenia than those whose treatment intention was palliative (OR of 8.282; 95% CI: 1.667-41.1).

Discussion. Febrile neutropenia is a life-threatening complication of chemotherapy. Approximately one-fifth of breast cancer patients treated with chemotherapy in our institution between January 2010 and May 2012 experienced FN during the course of their chemotherapy treatment, and almost half of them had FN during the first cycle. This finding is consistent with reports in the literature that neutropenic events occur most frequently during the first cycle of chemotherapy.[4]

Several risk factors have been reported in the literature.[7] These factors can be classified as chemotherapy-related factors (related to the type of chemotherapy and the intent of therapy), patient-related factors, and disease-specific factors (related to the cancer type and its extent).[8] For the chemotherapy-related factors, the 20% cut-off risk of FN was adopted by the American Society for Clinical Oncologists and the European Organization for Research and Treatment of Cancer as an acceptable and cost-effective indication for primary prophylactic use of colony-stimulating factors (CSF). From the chemotherapy point of view, patients can be classified as being at high-risk (>20%), intermediate-risk (10-20%), or low-risk (<10%) according the chemotherapy potential of inducing FN in chemotherapy-naïve patients. Among breast cancer regimens, taxotere, adriamycin, and cyclophosphamide and dose dense doxorubicin and cyclophosphamide followed by paclitaxl are known to be associated with more than 20% risk of FN.

However, none of the cancer treatment guidelines have addressed the patient-related factors and their relation to the risk of developing FN, and hence, whether they need primary CSF prophylaxis. Lyman et al[8] in their review, tried to identify risk factors for chemotherapy-induced FN, and to develop a risk-model to predict the risk of chemotherapy-induced FN. They identified several patient-related factors; among these factors age was identified as an important independent risk factor. Other patient-related factors include performance status, co-morbidities (liver, kidney, and heart diseases), laboratory abnormalities (pretreatment white blood cells, hemoglobin level <12 g/dL, albumin <35 g/L, and lactate dehydrogenase higher than normal).

Comparison of patients who developed FN during the first cycle of chemotherapy and those who did not revealed similar median age and median body surface area. In the present study, more than half of patients who developed FN in cycle one were in stage III, the group of patients most likely considered candidates for neo-adjuvant chemotherapies, since approximately

Table 2 - Chemotherapy-induced neutropenia in patients with breast cancer.

Variables	Multivariate logistic regression			95% confidence interval	
Predictors	**Beta coefficient**	***P*-value**	**Odds ratio**	**Lower**	**Upper**
Age	0.075	0.025	1.059	1.007	1.114
Chemotherapy regimen*			0.006		
Taxane-based	0.832	0.159	2.297	0.723	7.304
Taxane/anthracycline	-0.027	0.981	0.973	0.105	9.023
Others	3.676	0.000	39.488	4.995	312.187
***Intent of chemotherapy**†*			0.004		
Adjuvant	0.280	0.734	1.324	0.263	6.663
Neo-adjuvant	2.114	0.010	8.282	1.667	41.152

*For chemotherapy regimen, the reference is anthracycline-based; †For intent of chemotherapy, the reference is palliative. OR - odds ratio, CI - confidence interval

60% of the patients who developed FN in the first cycle received neo-adjuvant chemotherapy. There was no statistically significant difference in the distributional pattern of patients with co-morbidities, metastasis, and HER2 overexpression between patients who developed FN and those who did not. The number of patients who were treated with surgery, radiotherapy, hormonal, and prophylactic G-CSF were similar between the 2 groups.

The present study identified patient-specific and regimen-specific risk factors. Age was found to be an important and independent patient-specific risk factor for developing FN during the first cycle of chemotherapy. This finding suggests that older patients with breast cancer have greater risk of experiencing FN when starting chemotherapy. Similarly, this study has demonstrated that patients treated with chemotherapy agents other than anthracycline and/or taxane-based regimens have higher odds of experiencing FN during the first cycle compared with those treated with anthracycline-based. This finding might be explained by the fact that non-anthracycline and/or taxane regimens are usually considered as treatment options in later lines of treatments after failure of multiple prior lines of chemotherapies (including prior anthracycline, or taxane regimens), which means that bone marrow function in these patients might not be optimal to start with. Other indications for non-anthracycline/taxane-based regimens might include those patients who have poor general condition at presentation, which might exclude them from treatment with more aggressive taxane and/or anthracycline-based regimens.

The current study revealed that chemotherapy-induced neutropenia is a major risk factor when the intent of chemotherapy is curative and even greater risk when the treatment is neo-adjuvant. Comparison of chemotherapy intent showed that breast cancer patients treated with neo-adjuvant intent have higher risk of developing FN than patients whose treatment intention was palliative. This finding may be explained by the fact that younger cancer patients treated with curative-intent intervention are likely to receive intensive chemotherapy where dose modification is less tolerated as the aim is cure, and hence, they might develop FN compared with palliative-intent patients. Unlike curative-intent, if the intent of chemotherapy is palliative, then the goal is to improve symptoms and quality of life, prolong survival, while minimizing toxicities such FN, and hence selection of chemotherapy regimens and doses with a less toxic profile is an important treatment decision.[9]

Our study has a few limitations. The design of the present study is single-center and retrospective, and caution is therefore needed when interpreting the findings. In total, 6 patients were treated with prophylactic G-CSF and this number is very small to provide any meaningful results related to the effectiveness of G-CSF in reducing the risk of FN in breast cancer patients. However, the use of primary G-CSF prophylaxis had been proved to be beneficial to prevent FN, FN-related hospitalization, and use of IV antibiotics in breast cancer patients treated with docetaxel.[10] In a meta-analysis,[11] primary G-CSF use reduced the risk of FN, infection-related death, and early deaths during chemotherapy. It also showed improvement in relative dose-intensity of chemotherapy delivered.

In conclusion, almost one-fifth of breast cancer patients treated with chemotherapy in our institution experience neutropenia during the first cycle of chemotherapy. Patients who developed FN in cycle one of chemotherapy, and those who did not had similar demographic and clinical characteristics. Despite this, age was found to be an important patient-specific risk factor for developing FN in our study population. Thus, chemotherapy treatment decisions should reflect this reality. Our study recommends the use of G-CSF prophylactic treatment to target patients at high-risk of developing FN. This strategy may help reduce prolonged hospitalization, and the negative impact on quality of life, and cost associated with FN. Further prospective studies are required to validate these findings, and to test the value and cost-effectiveness of using primary G-CSF prophylaxis in high-risk patients identified by a predicting risk-model.

Received 4th November 2013. Accepted 1st April 2014.

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