THE EFFECT OF NEUTROPENIA ON THE DELIVERY OF CHEMOTHERAPY IN BREAST CANCER PATIENTS AT KORLE BU TEACHING HOSPITAL IN ACCRA, GHANA

Nsaful J[1, *], Dakubo JC[2], Nartey ET[3], Clegg-Lamptey JN[2]

[1] Department of Surgery, Korle Bu Teaching Hospital, Accra, Ghana; [2]Department of Surgery, University of Ghana Medical School, College of Health Sciences, University of Ghana, Accra, Ghana; [3]Centre for Tropical Clinical Pharmacology and Therapeutics, University of Ghana Medical School, College of Health Sciences, University of Ghana, Accra, Ghana

Abstract

***Introduction**:* Treatment of breast cancer involves chemotherapy, of which the commonest complication is neutropenia and febrile neutropenia. Neutropenic events interrupt the administration of effective chemotherapy and results in poorer outcomes.

This study evaluates the impact of neutropenia on the effective delivery of anthracycline-based chemotherapy in breast cancer patients and identifies those at risk of neutropenic events.

Methods: This is a prospective study of one hundred and ninety patients presenting with breast cancer who received both adjuvant and neoadjuvant chemotherapy from January 2013 to July 2014. Patients received cyclophosphamide, doxorubicin and 5-fluorouracil. Data collected included baseline absolute neutrophil count and subsequent absolute neutrophil counts on day 10 and day 20 throughout the course of therapy to identify any neutropaenic events. Univariate logistic regression analysis of age, body surface area and ECOG performance was done to determine factors associated with neutropaenia.

Results: The prevalence of neutropenia was 8.7% and that of febrile neutropenia was 0.24%. Body surface area of < 2 m^2 and first cycle neutropenia were found to be associated with an increased risk of developing neutropenia.

Conclusion: The prevalence of neutropaenia and febrile neutropaenia in this study was relatively low 8.7% and 0.24% respectively. The only factor found to be associated with neutropenic events is a BSA< 2m^2. This study forms a basis for a larger study aimed at identifying predictors and developing a model to predict neutropenia risk in the Ghanaian Population.

Key Words: Neutropenia, breast cancer, chemotherapy, absolute neutrophil count

Background

Breast cancer is the most common malignancy among women and the second most common cancer in the world[1]. About 400 new cases of breast cancer are seen at Korle-Bu Teaching Hospital (KBTH) annually and it is the leading cause (17.4%) of female cancer deaths[2]. Treatment involves combinations of surgery, chemotherapy, radiotherapy, hormone and/or targeted treatment.

Over the past decade there has been a shift towards the anthracycline- (doxorubicin/epirubicin) and taxane-based regimens as these have given better results than cyclophosphamide, methotrexate and 5-Fluorouracil (CMF)[3]. This trend towards the increased use of cyclophosphamide, doxorubicin and 5-Flurouracil (CAF) is also evident from records in the chemotherapy suite at the surgical department of KBTH, where about 92% of breast cancer patients are placed on CAF.

Corresponding Author Josephine Nsaful
Department of Surgery, Korle Bu Teaching Hospital, Accra, Ghana
Tel: 233 206301441
Email Address: josco19@yahoo.com
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The use of chemotherapy in cancer treatment has been on the increase since the early 1990s and, subsequently, its associated complications are also on the increase. Cytotoxics directly affect the bone marrow and damage haematopoietic precursors of the neutrophils resulting in neutropenia. The commonest complications of myelosuppressive chemotherapy are neutropenia and febrile neutropenia. Neutropenia puts chemotherapy patients at risk of severe infections which is a major cause of morbidity and mortality in cancer patients. As such febrile neutropenia is regarded as an oncologic emergency. In the United States, it has been estimated that there is an incidence of >60,000 neutropenic hospitalisations annually, with an average cost of $13,372 per hospitalisation and an associated inpatient mortality rate of 6.8%[4]. Neutropenia is classified as mild if Absolute neutrophil count (ANC) is between 1.0 × 10 9/L and 1.5× 10 9/L, moderate when 0.5 × 10 9/L to 1.0 × 10 9/L and severe when ANC is less than 0.5 × 10 9/L. Agranulocytosis occurs when ANC is less than 0.1× 10 9/L. The risk of infection is increased in severe neutropenia. Neutropenic events are more common with the anthracycline-based regimens than with CMF and also with increasing number of chemotherapy courses. Neutrophil counts drop below baseline value after the first course and recurs in-between courses[5].

Neutropenic events interrupt the delivery of effective chemotherapy with regard to the timing and the dose delivered. There is a relationship between the chemotherapy dose-intensity a patient receives and the clinical outcome of the disease. The standard chemotherapy treatment practice when neutropenia develops includes treatment delays and dose modifications. This compromises optimal dose delivery and is associated with poorer outcomes[6]. The dose-intensity depends on both the dose administered and the timing of administration. Below a critical dose-intensity, a patient may not receive the desired benefit of the therapy. A critical dose-intensity of 85% has been adopted by several institutions following the work of Bonadonna et al.[6]

In a publication from the Radiation Oncology Unit of KBTH of 20 cases of febrile neutropenia, 7 had breast cancer. Documented absolute neutrophil counts (ANCs) ranged from 0 to 0.6 x 10 9/L and mortality occurred in 2 (10%) patients. The use of granulocyte colony stimulating factor (G-CSF) for the patients was limited by funds[7]. This study evaluated the impact of neutropenia on the effective delivery of anthracycline-based chemotherapy in breast cancer patients. It assessed the factors that contributed to neutropenia and febrile neutropenia in breast cancer patients; critical information that could help pre-empt febrile neutropenia by selectively managing patients at risk.

Methods

In a prospective study one hundred and ninety consecutive patients who received both adjuvant and neoadjuvant chemotherapy at the chemotherapy suite of the Department of Surgery at the Korle Bu Teaching Hospital from January 2013 to July 2014 were studied. Patients receiving cyclophosphamide 500mg/m2, doxorubicin 50mg/m2 and 5-fluorouracil 500mg/m2 (CAF) every 21 days for 6 cycles were included. Patients had T1 to T4 tumours with or without axillary lymph node involvement. Excluded were those patients who had metastatic disease, been exposed to previous chemotherapy or had established immunosuppression from other causes.

Data collected included patient demographics, body surface area, chemotherapy regimen, actual dose delivered, timing of administration, baseline absolute neutrophil count (ANC), day 10 and day 20 ANC and any other ANC when chemotherapy was delayed. Neutropenia was defined as ANC < 1.0 × 10 9/L, and febrile neutropenia as ANC < 1.0 × 10 9/L plus fever of ≥ 38oC. Suspected or proven infections, antibiotic or granulocyte colony stimulating factor (G-CSF) use were also documented. Ethical clearance for the study was obtained from the Ethical and Protocol Review Committee of the University of Ghana Medical School [Protocol Identification Number: MS-Et/M.5 – P 4.3/2012-13]. Written informed consent was obtained from all participants and information kept confidential.

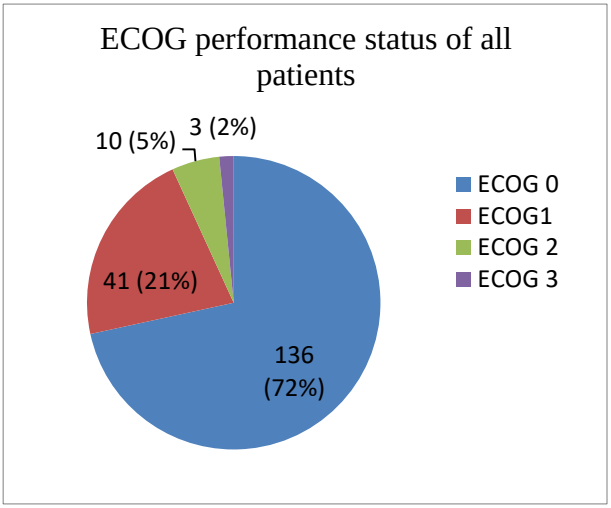
Results

A total of 190 patients (all females) were studied with a median age of 51.5 years [IQR, 42-58]. Their age distribution is shown in Table 1.

Table 1. Age distribution of patients who underwent chemotherapy

Age (yr.) (N=190)	Number (%)
15-24	1 (0.5)
25-34	14 (7.3)
35-44	41 (21.6)
45-54	61 (32.1)
55-64	54 (28.4)
65-74	14 (7.3)
75-84	5 (2.6%)

Fifty-six (29.5%) were younger than 45 years, 115 (60.5%) were between 45 and 64 years, and 19 (10%) were 65 years and older. One hundred and thirty-six patients (71.6%) were classified as Eastern Co-operative Oncology Group (ECOG) status 0, and 41 patients (21.6%) were ECOG status 1 (Fig.1).



ECOG= Eastern Co-operative Oncology Group; BSA= Body surface area; ANC= absolute neutrophil count; OR=odds ratio; CI=confidence interval; *Fisher's exact test

Fig. 1 Eastern Co-operative Oncology Group (ECOG) performance status of the patients

Patients with body surface area (BSA) of <2 m2 constituted 76.8% (n=146) whilst those with BSA of ≥ 2 m2 were 23.2% (n=44). Majority of the patients (99.5%, n=189) had baseline ANC of ≥ 1.0 × 109cells/L. A total of 842 chemotherapy cycles were administered to 190 patients. One hundred and thirty-six patients (71.5%) completed six cycles of chemotherapy. The remaining 54 (28.4%) had a varied number of cycles of CAF. Two patients had their chemotherapeutic drugs changed from CAF to another regimen due to non-

response and 51 patients were either referred to the National Centre for Radiotherapy and Nuclear Medicine (Ghana) for further treatment or defaulted treatment and were lost to this study's follow up. There was one death from respiratory failure as a result of lung metastasis, though she was not metastatic at the start of chemotherapy.

Of the 842 chemotherapy cycles administered, 73 neutropenic events occurred giving a neutropenia incidence of 8.7%. There were only two cases of febrile neutropenia (temperature >38.0 o C), giving a febrile neutropenia incidence of 0.24%.

Table 2 shows the distribution of patients with 1st cycle neutropenia. The prevalence of 1st cycle neutropenia was 9.5% [95% CI, 5.7-14.6] (n=18). Of the 18 patients that developed 1st cycle neutropenia, 10 (55.6%) were aged between 45 and 64 years with 33.3% (n=6) younger than 45 years and only 11.1% (n=2) above 65 years. All the patients were classified as ECOG status 0 (66.7%, n=12) or 1 (33.3%, n=6). Majority of patients with 1st cycle neutropenia had BSA of <2 m2 (94.4%, n=17). In the univariate analysis, age, ECOG, BSA and baseline ANC were not associated with the occurrence of 1st cycle neutropenia (p>0.05), (Table 2).

Table 2. Characteristics of patients who experienced first cycle neutropenia

Characteristic		**1st cycle neutropenia**			
		Yes	No		
		n, %[1]	n, %[1]	**OR [95% CI]**	**p-value**
Age (N=190)					
	45 - 64 years	10 (55.6)	105 (61.0)	0.79 [0.24-2.82]	0.671
	≥65 years	2 (11.1)	17 (9.9)	0.98 [0.09-6.19]	0.982
	<45 years	6 (33.3)	50 (29.1)	1.00	
ECOG (N=190)					
	ECOG 1	6 (33.3)	35 (20.3)	1.77 [0.51-5.54]	0.281
	ECOG 2	0	10 (5.8)	Not estimable	1.000*
	ECOG 3	0	3 (1.7)	Not estimable	1.000*
	ECOG 0	12 (66.7)	124 (72.1)	1.00	
BSA (N=190)					
	< 2 m^2	17 (94.4)	129 (75.0)	5.67 [0.83-242.2]	0.063
	≥ 2 m^2	1 (5.6)	43 (25.0)	1.00	
Baseline ANC (N=190)					
	< 1.0 × 10^9cells/L	0	1 (0.6)	Not estimable	1.000
	≥ 1.0 × 10^9cells/L	18 (100)	171 (99.4)	1.00	

[1]% are column percentages within each super row. ECOG= Eastern Co-operative Oncology Group; BSA=Body surface area; ANC=absolute neutrophil count; OR=odds ratio; CI=confidence interval; *Fisher's exact test

Table 3 shows factors associated with the presence of neutropenia. Fifty out of the 190 patients who were treated developed neutropenia, 26.3% [95% CI, 20.2-33.2]. Thirty-four (68.0%) of them were aged between 45 and 64 years, 13 (26.0%) were younger than 45 years and the remaining 3 (6%) were 65 years and above. Majority (72.0%; n=36) were classified as ECOG status 0, whilst 26% (n=13) were classified as ECOG status 1. All the patients (100%) with neutropenia had baseline ANC of ≥ 1.0 × 10^9cells/L and 94% (n=47) had a BSA of < 2 m^2. In the univariate logistic regression analysis, BSA of < 2m^2 was associated with neutropenia. The odds of patients with BSA of < 2 m^2 experiencing neutropenia was 6.49 [95% CI, 1.90-34.17] times higher compared with patients with BSA of ≥ 2 m^2 (p<0.001). Age, ECOG status and baseline ANC were not associated with neutropenia occurrence.

Ten out of the 18 patients (55.6%) who experienced 1st cycle neutropenia experienced a subsequent neutropenia. The presence of 1st cycle neutropenia was significantly associated with the development of subsequent neutropenia. The odds of experiencing subsequent neutropenia was 5.47 [95% CI, 1.76-17.14] in patients with 1st cycle neutropenia compared with patients who did not experience 1st cycle neutropenia (p<0.001) (Table 4).

The proportion of patients with a baseline ANC <1.5 x 10^9/L was 4.7% [95% CI: 2.2-8.8] (n=9) and of these 55.6% (n=5) patients went on to have a subsequent neutropenia of < 1.0 x 10^9/L at some point during chemotherapy. Analysis shows no association between a baseline ANC <1.5 x 10^9/L and subsequent neutropenia.

Sixty-nine (36.3%) patients experienced a total of 104 treatment delays in the delivery of 842 chemotherapy cycles, implying 12.4% of chemotherapy cycle delays. Eighty-seven (83.7%) of these delays were for up to seven days and the remaining 17 (16.3%) delays were for more than seven days (1 to 4 weeks). Forty-two patients had one delay in the course of treatment, 21 had two delays, 4 had three delays and 2 had four delays.

There were other causes of treatment delay among the patients studied. Apart from neutropenia (70.2%), other causes were infection (7.7%), feeling unwell (6.7%),

financial constraints (4.8%), high blood pressure (3.8%), and anaemia (3.8%). Out of eight clinically diagnosed infections, three were in neutropenic patients. These were respiratory tract infection (3), urinary tract infection (2), sepsis of unknown cause (1) and skin infection/abscess (2). Of the four patients who were anaemic two required blood transfusion as their haemoglobin was less than 8.0g/dl.
G-CSF was used in 3 patients.

Table 3. Characteristics of all patients who developed neutropenia

Characteristic		**Neutropenia**		**OR [95% CI]**	**p-value**
		Yes	No		
		n, %	n, %		
Age (N=190)					
	45 - 64 years	34 (68.0)	81 (57.9)	1.39 [0.63-3.17]	0.383
	≥65 years	3 (6.0)	16 (11.4)	0.62 [0.10-2.71]	0.495
	<45 years	13 (26.0)	43 (30.7)	1.00	
ECOG (N=190)					
	ECOG 1	13 (26.0)	28 (20.0)	1.29 [0.55-2.91]	0.511
	ECOG 2	1 (2.0)	9 (6.4)	0.31 [0.01-2.38]	0.248
	ECOG 3	0	3 (2.1)	Not estimable	0.568*
	ECOG 0	36 (72.0)	100 (71.4)	1.00	
BSA (N=190)					
	< 2 m^2	47 (94.0)	99 (70.7)	6.49 [1.90-34.17]	**<0.001**
	≥ 2 m^2	3 (6.0)	41 (29.3)	1.00	
Baseline ANC (N=190)					
	< 1.0 × 10^9cells/L	0	1 (0.7)	Not estimable	1.000*
	≥ 1.0 × 10^9cells/L	50 (100)	139 (99.3)	1.00	

Table 4. Relationship between the occurrence of first cycle neutropenia and subsequent neutropenia

Characteristic	**Subsequent neutropeania**		**OR [95% CI]**	**p-value**
	Yes	No		
	n, %	n, %		
1st cycle neutropaenia (N=190)				
Yes	10 (23.8)	8 (5.4)	5.47 [1.76-17.14]	**<0.001**
No	32 (76.2)	140 (94.6)	1.00	

OR=odds ratio; CI=confidence interval

Discussion

This study has documented the prevalence of neutropenia in breast cancer patients on chemotherapy in the Korle Bu Teaching hospital and has demonstrated that it leads to ineffective delivery of chemotherapy through delays in administration. Similar to previous publications, the median age of the patients was 51.5 years, a decade less than that of developed countries[2,8,9]. The prevalence of neutropenia was 8.7% with that of febrile neutropenia 0.24%. A 10-year review (1990-2000) of randomised clinical trials found neutropenia grades 3-4 in 1-78% of patients who received CMF and in 3-100% in those who received anthracycline-based therapy[10]. The 2006 ASCO guidelines quoted the incidence of chemotherapy-induced febrile neutropenia in breast cancer as 3-23%[11]. This study therefore reports relatively low rates of neutropaenia and its related complications.

Benign Ethnic Neutropenia (BEN) has been described among people of African descent and is found in otherwise healthy individuals with ANC < 1.5 × 109/L in the absence of other causes of neutropenia. Breast cancer patients in Africa with BEN could have their treatment withheld, delayed or suboptimal doses given if this condition is not recognized. Current evidence however shows that patients with BEN can receive standard doses of chemotherapy safely[12] This fact is corroborated by this study, which found no association between baseline ANC < 1.5 × 109/L on standard dose regimen and subsequent neutropenia.

According to the National Comprehensive Cancer Network (NCCN), the factors which put a patient at high risk of developing febrile neutropenia are previous chemotherapy, pre-existing neutropenia, age >65, concurrent or previous radiotherapy, poor performance status (ECOG>1), co-morbidities, open wounds, active tissue infections and anaemia[13] A systemic review by Lyman et al identified four studies in which a low BSA is an increased risk for febrile neutropenia[14] Advanced age, female sex, poor performance status, poor

nutritional status, and low baseline and first-cycle nadir blood cell count have also been identified as predictors of neutropenic events[15,16]. The current study reports that patients with BSA of < 2 m2 had a higher (6.49 times) chance of developing neutropenia compared with patients with BSA of ≥ 2 m2 as in these publications and can be used as a predictor of neutropenia. However, we did not find an association between age, ECOG status, baseline ANC and neutropenia. The sample size was probably not large enough to detect a significant association in the latter factors. In this analysis, patients who experienced neutropenia after the first cycle of chemotherapy were more likely (5.47 times) to develop subsequent episodes of neutropenia (Table 4). This means that in addition to using BSA as a predictor, once a person did develop first cycle neutropenia there was a significant risk of another episode of neutropenia during the course of treatment. These predictors would provide a guide in selecting patients who would benefit from Granulocyte colony stimulating factor (G-CSF) prophylaxis.

Guidelines for the use of G-CSF recommend primary prophylaxis in patients at a high risk of developing infection only in cancers with about 20% incidence of chemotherapy-induced febrile neutropenia[11] This study found a low neutropenia and febrile neutropenia rate. In this case, primary prophylaxis with G-CSF is not routinely indicated but should be recommended as secondary prophylaxis and be given after an episode of febrile neutropenia or severe or prolonged neutropenia. Combining this with first cycle neutropenia and BSA< 2m2 may further help select those who would benefit from prophylaxis. This more targeted use of G-CSF is known to be more cost effective with fewer risks of its side effects. G-CSF does not prevent neutropenia but improves the rate of recovery of neutropenia and therefore reduces the days of delay in giving anti-cancer treatment while the relative dose intensity (RDI) can be maintained. G-CSF was used in only 3 patients in this study, its use being limited largely by cost since patients had to acquire it from out of pocket purchases.

A reduced dose-intensity below a thresh-hold of 85% compromises outcome. This was popularised in a landmark paper by Bonadonna who found a significantly higher relapse free survival in those who had less than the optimal dose intensity[6]. Similarly, Lyman conducted a nationwide survey and found in addition to dose reductions there were treatment delays ≥7 days in 24.9% of patients, resulting in 55.5% of patients receiving RDI less than the critical 85% [17]. In this study significant proportion of patients (36.3%) experienced treatment delays of up to 4 weeks, with almost 40% of these being delayed more than once. Several causes of treatment delays were found but neutropenia (70.2%) was the commonest cause by far. The delays in administration of chemotherapy are enough to cause a reduction in the RDI. However, this study did not follow up patients to determine the outcomes or overall survival of these patients.

Suboptimal chemotherapy from treatment delays can be improved by interventions aimed at ensuring optimum delivery of chemotherapy, with regard to dose and timing. We believe that targeted prophylaxis would lead to a significant reduction in number and duration of treatment delays. In the study by Lyman, delivery of suboptimal doses was found to have decreased from about two-thirds to a third of the patients from the early 1990s to the late 1990s, and this was attributed to a better physician understanding of chemotherapy dosing and quality of care[17]. There are some validated and yet to be validated models which can be used to predict or assess a person's risk of neutropenic events[18, 19].

Conclusion

The prevalence of neutropaenia and febrile neutropaenia in this study is relatively low 8.7% and 0.24% respectively but when it occurs is a major cause of suboptimal delivery of chemotherapy. The only factors found to be significantly associated with neutropenic events was BSA< 2m2 and first cycle neutropaenia. This study forms a basis for a larger study aimed at identifying predictors and developing a model to predict neutropenia risk in the Ghanaian Population.

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