Chemotherapy-Induced Neutropenia, Anemia and Thrombocytopenia among Filipino Breast Cancer Patients on Adjuvant Chemotherapy

Lou Jorel P. Tia,[1] Arthur Gregory A. Lui,[1] Noel S. Chua[2] and Heinrik Martin Jude S. Strebel[1]

[1]*Section of Medical Oncology, Department of Medicine, College of Medicine and Philippine General Hospital, University of the Philippines Manila*
[2]*Section of Medical Oncology, Department of Medicine, Department of Health-Jose R. Reyes Memorial Medical Center, Manila*

ABSTRACT

Introduction. Cytotoxic chemotherapy places all cancer patients at risk of developing myelosuppression. Different chemotherapy regimens could lead to development of neutropenia, anemia and thrombocytopenia which may lead to delays in facilitating chemotherapy and also may place cancer patients at risk of developing severe complications which may be life threatening. This study determined the incidence of neutropenia, anemia, and thrombocytopenia per cycle of chemotherapy starting after the 1st cycle among non-metastatic breast cancer patients. It also evaluated if age, size of primary tumor, number of positive lymph nodes, IHC result, BMI, co-morbidities and chemotherapy used were associated with the development of neutropenia, anemia and thrombocytopenia during the 1st cycle of chemotherapy; this may help in ascertaining which patients may need more intensive monitoring during subsequent chemotherapy sessions.

Methods. This is a time series study wherein the CBC results starting prior 1st chemotherapy cycle were gathered from medical charts of non-metastatic breast cancer patients receiving cyclophosphamide/ doxorubicin/ docetaxel/ fluororuracil chemotherapy at UP-PGH and JRRMMC Medical Oncology Clinics enrolled under the DOH-NCPAM BCMAP program, from 1 January 2009 to 31 June 2014. Incidence rates of neutropenia, anemia and thrombocytopenia were recorded per cycle of chemotherapy. Severity of myelosuppression was graded based on the Common Toxicity Criteria of the National Cancer Institute Version 2.0. Possible predictors of myelosuppression were assessed focusing on the 1st cycle of chemotherapy where interventions were not yet done. Standard statistical methods were used for the descriptive analysis. Variables were analyzed using the Chi square test and logistic regression; level of significance was at $p<0.05$.

Results. 751 patients were included in the study, who had a total of 3,759 CBC results. The incidence of neutropenia, anemia, thrombocytopenia for all 3,759 CBC results were 3%, 2.3%, and 0.5%, respectively. Among all recorded CBC results only 0.9% had grade 3-4 neutropenia and 0.3% grade 3-4 anemia. There was no severe thrombocytopenia.

After the 1st chemotherapy cycle, the incidence of neutropenia was 4.67% (35 patients), anemia 2.27% (17 patients), and thrombocytopenia 0.8% (6 patients). Of these patients, only 1.17% (9 patients) experienced severe neutropenia and 0.27% (2 patients) experienced grade 3-4 anemia. No patient experienced grade 3-4 thrombocytopenia.

Age, size of primary tumor, number of positive lymph nodes, IHC result, BMI, co-morbidities and chemotherapy used were not associated with risk for myelosupression during the 1st cycle of chemotherapy.

Conclusion. Incidence rates of neutropenia, anemia and thrombocytopenia were minimal in non-metastatic breast cancer patients undergoing cytotoxic chemotherapy, with low rates of severe myelosupression. Myelosuppression from standard doxorubicin/ cyclophosphamide/ docetaxel/ fluorouracil containing chemotherapy regimens can be given to non-metastatic breast cancer patients, completing required number of chemotherapy cycles with nil interruption or delay.

Key Words: myelosuppression, cytotoxic chemotherapy, breast cancer

Introduction

Cytotoxic chemotherapy places all cancer patients at risk of developing myelosuppression,[1-4] which may cause significant morbidity and mortality increasing health care cost. Neutropenia, anemia and thrombocytopenia can cause delays in treatment and at times dose reductions, which may have an impact in the overall outcome of the cancer treatment. Neutropenia, anemia and thrombocytopenia can place cancer patients at risk of developing severe complications which may be life threatening, such as severe infection, cardiovascular complications or active bleeding.

Crawford J et al[5] noted that out of 2962 patients with breast, lung, colorectal, lymphoma and ovarian cancers who initiated chemotherapy, 10.7% experienced febrile neutropenia.

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Corresponding author: Heinrik Martin Jude S. Strebel, MD, MCM(MO)
Section of Medical Oncology
Department of Medicine
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000 Philippines
Tele/Fax: +632 5263775
Email: arik_strebel@yahoo.com

Due to the significant impact of neutropenia to the health, outcome and cost of treatment, the National Comprehensive Cancer Network[6] made a guideline that focused on three aspects that predisposed patients to infections. These are: a) patient-related aspects (age, gender, performance and nutritional status, comorbidities, b) treatment-related aspects (neutropenia, drugs such as anthracyclines, relative dose intensity); c) cancer-related aspects (some cancers, including haematological malignancies and lung cancer, and all cancers at advanced stage). Prophylaxis using CSFs is recommended if the patient is determined to be at high risk (i.e., >20% of developing febrile neutropenia).

Anemia is a common complication of myelosuppressive chemotherapy but is often an over-looked problem in breast cancer patients.[7] Mild to moderate anemia in patients undergoing chemotherapy is often treated conservatively and is usually neglected. Several clinical data[8-9] are suggesting that even mild to moderate anemia causes reduction in the patient's energy level and quality of life.

Thrombocytopenia is also an expected hematologic complication of patients undergoing myelosuppresive chemotherapy. Thrombocytopenia if not addressed could lead to serious complications such as bleeding or worse case scenario intracranial hemorrhage which can be life threatening. There are limited studies[10-11] showing the real incidence of thrombocytopenia during chemotherapy or risk factors to its development. Kuderer et al[10] concluded that patients with a lower BSA and a decreased pre-chemotherapy platelet count had a higher risk of developing thrombocytopenia. Othieno-Abinya et al[11] which included 202 cancer patients noted that thrombocytopenia during chemotherapy was not frequently encountered and complications such as bleeding were easily resolved by platelet transfusion.

Among Filipino patients with non-metastatic breast cancer undergoing chemotherapy, this study evaluates the incidence of neutropenia, thrombocytopenia and anemia, and the variables that may contribute to their development.

Methods

This is a time series study among Filipino women diagnosed to have stage I to III histologically proven breast cancer who underwent at least one cycle of cytotoxic chemotherapy. Included in the study were patients from the medical oncology clinics of the Philippine General Hospital (PGH) and Jose R. Reyes Memorial Medical Center (JRMMC), two of six satellite institutions of the DOH Breast Cancer Management Access Program (DOH-BCMAP), enrolled from 1 January 2009 to 31 June 2014.

The University of the Philippines Manila Research Ethics Board (UPMREB) approved the protocol prior to data collection; data confidentiality was observed.

Age, co-morbidities (hypertension, diabetes mellitus, heart failure/coronary artery disease, chronic kidney disease), body mass index (classified as underweight, normal, overweight), tumor size (<20 mm, >=20mm), axillary node status (positive nodes: 0-3, 3-6, 6-9), ER PR HER2 status, chemotherapy regimen used, were gathered from the medical charts as independent variables.

Records of the chemotherapy sessions per cycle were reviewed. Complete blood counts (CBC) taken after every cycle of chemotherapy were recorded. Dependent variables absolute neutrophil count (ANC), hemoglobin and platelet counts were extracted from the CBC results.

Incidence of neutropenia, anemia and thrombocytopenia was determined among all CBC results. Severity grade based on the Common Toxicity Criteria of the National Cancer Institute Version 2.0. (Table 1) was noted for neutropenia, anemia and thrombocytopenia.

Table 1. Common Toxicity Criteria of the National Cancer Institute Version 2.0

Neutropenia	Anemia	Thrombocytopenia
Grade 1 :1500-2000 cells/mm3	Grade 1: less than the normal limit to 10 g/dl	Grade 1: less than the normal limit to 75,000
Grade 2: 1000-1500 cells/mm3	Grade 2: less than 10g/dl to 8 g/ dl	Grade 2: less than 75,000
Grade 3: 500-1000 cells/mm3	Grade 3: less than 8 g/dl to 6.5 g/dl	Grade 3: less than 50,000
Grade 4: below 500 cells/mm3	Grade 4: less than 6.5 g/dl	Grade 4: less than 10,000

Descriptive statistics was used to describe the patient, disease, treatment profile as well as the incidence of neutropenia, anemia and thrombocytopenia. Variables (age, comorbidities, body mass index, cancer stage, tumor size, axillary node status, ER PR HER2 status, chemotherapy regimen used) hypothesized to affect the *incidence of anemia, neutropenia and thrombocytopenia occurring after the first chemotherapy cycle*, *when no intervention was done to correct the myelosuppression*, were analyzed using logistic regression; a p-value of <0.05 was considered statistically significant. Results were presented as odds ratio with a confidence interval of 95%.

A limitation of the study is the unavailability of some of the CBC results. Those cycles without CBC results were not included in the analysis of the overall result; many of the pre-chemotherapy CBC results were also missing from the charts hence no analysis was done using this data. Mean and SD of platelet counts cannot be accurately computed because a lot of results reported qualitative ordinal variables (increased, adequate, decreased).

When at least grade 2 myelosuppression was noted for a certain patient, granulocyte stimulating factor was routinely given prior to subsequent cycles of chemotherapy. ANC of

less than 1500/ μL was managed with up to 3 doses of filgastrim 300 mcg subcutaneous injection depending on the judgment of the attending physician. The DOH BCPAM program also provided three doses filgastrim support if ordered. Anemia was usually addressed with blood transfusion of PRBC to target a hemoglobin level of >=100 mg/dl prior continuing the next chemotherapy cycle. Thrombocytopenia was managed by giving platelet concentrate to target at least 100,000 /μL prior to chemotherapy. Such interventions were done for chemotherapy cycles preceding the 1st cycle as needed.

Results

There were 751 patients included in the study, with a total of 3,759 CBC results. Majority belonged to the 31-60 year old age group (84%), with a BMI under the normal category (63%). (Table 2)

Table 2. Patient Baseline Characteristics

Patient Demographics	N = 751 Frequency (%)
Age	
• 18-30	8 (1%)
• 31-60	630 (84%)
• 60-70	84 (11%)
• 70 onwards	29 (4%)
BMI	
• Underweight	56 (8%)
• Normal	474 (63%)
• Overweight	168 (22%)
• Obese	53 (7%)

About 90% of the patients had tumor size >20 mm; axillary lymph node metastases was present in 46%; 47% had an ER/PR positive tumor, while 38% had ER/PR negative tumors; HER2 positive was 44% versus HER2 negative of 39%. (Table 3)

Majority of the patients underwent either sequential chemotherapy AC x 4 cycles then T x 4 cycles (37%) and TC x 4 cycles (36%), (Table 5). The mean dose/BSA for adriamycin (A), cyclophosphamide (C), docetaxel (T), fluororuracil (F), methotrexate (M) were 96 mg, 960 mg, 120 mg, 960mg, 64 mg, respectively.

The incidence of neutropenia, anemia, thrombocytopenia for all 3,759 CBC results were 3%, 2.3%, and 0.5%, respectively. Among all recorded CBC results only 0.9% had grade 3-4 neutropenia and 0.3% grade 3-4 anemia. There was no severe thrombocytopenia.

Table 3. Cancer profile

Cancer Profile	N = 751 Frequency (%)
Size of tumor	
• <10 mm	28 (4%)
• >10 mm <20 mm	46 (6%)
• >20 mm	677 (90%)
Node Positive	
• 0 nodes	408 (54%)
• 1-3 nodes	187 (25%)
• 4-6 nodes	90 (12%)
• 7-9 nodes	66 (9%)
ER PR status	
• ER -/ PR –	286 (38%)
• ER +/ PR +	351 (47%)
• ER +/ PR –	93 (12%)
• ER -/ PR +	21 (3%)
Her 2 status	
• Her 2 negative	290 (39%)
• Her 2 equivocal	130 (17%)
• Her 2 positive	331 (44%)

Most patients (64%) did not have any associated co-morbid conditions. (Table 4)

Table 4. Comorbid Conditions

Comorbidities	Frequency (%)
None	552 (64%)
Hypertension	131 (17%)
Diabetes Mellitus	62 (8%)
Chronic Kidney Disease	1 (0.1%)
Coronary Artery Disease/ Heart Failure	5 (0.7%)

After the 1st chemotherapy cycle, the incidence of neutropenia was 4.67% (35 patients), anemia 2.27% (17 patients), and thrombocytopenia 0.8% (6 patients). Of these patients, only 1.17% (9 patients) experienced severe neutropenia and 0.27% (2 patients) experienced grade 3-4 anemia (grade 3-4). No patient experienced grade 3-4 thrombocytopenia. The mean±sd hemoglobin and ANC, for all patients after the 1st chemotherapy cycle were 125±45, 5400±1800, respectively.

Age, size of primary tumor, number of positive lymph nodes, ER/PR/HER2 result, BMI, co-morbidities and chemotherapy used were not associated with risk for myelosupression during the 1st cycle of chemotherapy by logistic regression, (Tables 6A, B, C).

Table 5. Chemotherapeutic regimens

Chemotherapeutic Regimen	Number of patients (%)	After 1st Chemotx Cycle		
		Proportion with anemia	Proportion with neutropenia	Proportion with thrombocytopenia
AC x 4 cycles	102 (14%)	2%	4%	0%
AC->T x 8 cycles	277 (37%)	3%	5%	1%
TC x 4 cycles	270 (36%)	1%	4%	1%
FAC x 6 cycles	89 (12%)	2%	3%	0%
CMF x 6 cycles	16 (1%)	1%	0%	1%

Table 6A. Risk factors associated with neutropenia after the 1st chemotherapy cycle

Factor	Odds Ratio	Std Error	p-value
Age (years)			
30-60	0.6602629	0.5381532	0.611
61-70	1.109437	0.9451659	0.903
over 70	1.834367	1.656403	0.502
Number of lymph node			
1-3 nodes	0.8666114	0.2154038	0.565
4-6 nodes	0.8084028	0.2749896	0.532
7-9 nodes	1.727525	0.5479416	0.085
Size of Primary Tumor			
>10mm <20mm	1.664434	1.084415	0.434
>20mm	1.02064	0.5781121	0.971
ER/PR/HER2			
ER +/ PR +	0.9683835	0.2353535	0.895
ER +/ PR -	0.8469145	0.2859687	0.623
ER -/ PR +	1.664941	0.9460623	0.37
Her2 status			
positive	0.7817307	0.2516719	0.444
equivocal	1.095534	0.2633703	0.704
Drug Regimen			
AC-T	2.480686	2.638435	0.393
TC	3.467569	3.678652	0.241
FAC	3.346506	3.654288	0.269
CMF	4.894179	5.291364	0.142
Comorbidity			
HPN	0.7956162	0.2143034	0.396
DM	0.8987917	0.3134929	0.76
CKD	3.23E-06	0.0023793	0.986
AD/CHF	0.7222566	0.825194	0.776
BMI			
normal	.6805008	.467489	0.575
overweight	.7663074	.5753095	0.723
obese	.1803863	.2214517	0.163

Table 6B. Risk factors associated with anemia after the 1st chemotherapy cycle

Factor	Odds Ratio	Std Error	p-value
Age (years)			
30-60	868727.2	790000000	0.988
61-70	1795301	1630000000	0.987
over 70	2333612	2120000000	0.987
Number of lymph node			
1-3 nodes	0.6538356	0.1959904	0.156
4-6 nodes	1.119218	0.3939572	0.749
7-9 nodes	1.832391	0.632566	0.079
Size of Primary Tumor			
>10mm <20mm	3.156699	2.618517	0.166
>20mm	1.587716	1.206874	0.543
ER/PR/HER2			
ER +/ PR +	0.7168874	0.2051693	0.245
ER +/ PR -	0.7423601	0.2788318	0.428
ER -/ PR +	1.770553	1.034816	0.328
Her2 status			
positive	0.8863129	0.3368303	0.751
equivocal	1.598925	0.4441502	0.091
Drug Regimen			
AC-T	1.836542	1.975319	0.572
TC	2.192136	2.357098	0.465
FAC	1.471823	1.651912	0.731
CMF	3.184069	3.486947	0.29
Comorbidity			
HPN	0.7946447	0.2399021	0.446
DM	0.6080038	0.2701632	0.263
CKD	2.14E-07	0.0005868	0.996
AD/CHF	0.000000698	0.0007823	0.99
BMI			
normal	.361123	.3247357	0.257
overweight	.279624	.2941302	0.226
obese	.2755021	.3819707	0.352

Table 6C. Risk factors for thrombocytopenia after the 1st chemotherapy cycle

Factor	Odds Ratio	Std Error	p-value
Age (years)			
30-60	617646.8	303000000	0.978
61-70	784290.9	385000000	0.978
over 70	748077.8	367000000	0.978
Number of lymph node			
1-3 nodes	1.000174	0.2278185	0.999
4-6 nodes	1.004343	0.3101776	0.989
7-9 nodes	1.605274	0.4915283	0.122
Size of Primary Tumor			
>10mm <20mm	1.96842	1.198777	0.266
>20mm	1.253438	0.6669963	0.671
ER/PR/HER2			
ER +/ PR +	0.8863885	0.2068939	0.605
ER +/ PR -	1.187816	0.3532038	0.563
ER -/ PR +	1.637163	0.8739894	0.356
Her2 status			
positive	0.890377	0.282587	0.714
equivocal	2.116396	0.4817058	0.001
Drug Regimen			
AC-T	2.089059	2.230069	0.49
TC	4.698174	4.989654	0.145
FAC	3.033704	3.307579	0.309
CMF	5.696063	6.14667	0.107
Comorbidity			
HPN	0.9041298	0.2220433	0.682
DM	1.047503	0.3431672	0.887
CKD	3.84E-07	0.0005809	0.992
AD/CHF	0.8237931	0.9613224	0.868
BMI			
normal	1.06e+07	7.89e+10	0.998
overweight	4.54e+07	3.39e+11	0.998
obese	.8228495	7889.006	1.000

Discussion

Myelosuppression in breast cancer patients are common and expected when undergoing the standard adjuvant chemotherapy regimens (adriamycin, docetaxel, cyclophosphamide). Abdul B and Hasan R[12] showed a significant number of early breast cancer patients who experienced myelosuppression while undergoing chemotherapy; the incidence of febrile neutropenia could go as high as 16.7% on the first cycle of chemotherapy. Kirshner J et al[8] indicated a 17% incidence of anemia in early stage breast cancer patients undergoing chemotherapy (adriamycin, cyclophosphamide). Between 20% and 25% of patients with solid tumors or lymphoma who receive chemotherapy develop thrombocytopenia (40,000 platelet cells/μL) and approximately 10% experience platelet counts between 10,000 and 20,000 cells/μL.[13-15]

The results of this study (which also used adriamycin, cyclophosphamide, docetaxel) indicated lower incidence of neutropenia, anemia, thrombocytopenia compared to the findings of other studies[8,12-15] Out of this study's 3,759 CBC results of 751 patients, only 3%, 2.3% and, 0.5% experienced neutropenia, anemia and thrombocytopenia, respectively during chemotherapy. Kirshner et al[8] included 310 stage II-III breast cancer patients treated with adjuvant adriamycin and cyclophosphamide, and found that even before chemotherapy, a significant number (31.3%) of breast cancer

patients were already anemic (hgb<12g/dl) prior to chemotherapy. Patients who were already anemic pre-chemotherapy had higher incidence of severe anemia (hgb<10 g/dl) during chemotherapy. Denison et al[9] noted anemia being present in a significant number of their study's breast cancer patients even before undergoing chemotherapy, and that pre-chemotherapy hemoglobin level was a reliable predictor of developing anemia during chemotherapy.

Kuderer NM et al[10] also noted that the pre-chemotherapy level of hemoglobin and platelet count were good indicators for increased incidence of anemia and thrombocytopenia while undergoing chemotherapy.

Myelosuppression is a major concern in facilitating chemotherapy including difficulty in adhering to the recommended dose per body surface area and the scheduled time of the chemotherapy cylcle. In instances of grade 3-4 myelosuppression, patients end up not receiving or completing the recommended cycle treatment; some end up being hospitalized and moribund.

Several studies[12,16-22] looked into predictors that could help oncologists in determining which patients would benefit from more intensive monitoring; these studies evaluated if patient characteristics such as age, nutritional status, comorbid conditions could affect the incidence of myelosuppression in patients undergoing chemotherapy.

Abdul B and Hasan R[12] studied early stage breast cancer patients undergoing chemotherapy, and indicated that lower platelet count, hemoglobin, and certain genetic defects increased the incidence of febrile neutropenia. The study also checked on age, BMI, tumor characteristics, and chemotherapy regimens however none of these were noted to have a significant impact on the incidence of febrile neutropenia.

Possible predictors of myelosuppression in our study looked into such as age, BMI, comorbidity, tumor size, axillary node status, ER PR Her2 status, and chemotherapy regimen used, were not significantly shown to be associated with the development of myelosuppression during chemotherapy.

In contrast, other studies[16-19] showed that age, nutritional status, comorbid conditions and performance status were reliable predictors of febrile or severe neutropenia during chemotherapy. Chia et al[16] included 7127 breast cancer patients which included mostly early stage breast cancer at a median age of 55 years which was similar to our study population, and noted that those with congestive heart failure, osteoarthritis, previous cancer, and thyroid disorder were associated with increased risk of febrile neutropenia. Takenaka et al[17] which included head and neck cancer patients showed that incidence of febrile neutropenia was highest during the first cycle of chemotherapy and that the addition of fluorouracil to cisplatin and docetaxel were more susceptible to developing febrile neutropenia. Laskey et al[18] with a population of 226 ovarian CA patients, noted that age of >60 years old had a higher risk of developing febrile neutropenia and therefore such age group warranted closer surveillance. Sue Mayor[19] indicated that age, albumin, intensity of chemotherapy, starting ANC, and presence of liver disease were significant risk factors for the development of severe neutropenia and that the more risk factors that were present the greater the risk.

Conclusion

Incidence rates of neutropenia, anemia and thrombocytopenia were minimal among Filipinas with non-metastatic breast cancer patients undergoing cytotoxic chemotherapy, with low rates of severe myelosuppression. Myelosuppression from standard adriamycin/ cyclophosphamide/ docetaxel/ fluorouracil containing chemotherapy regimens can be given to non-metastatic breast cancer patients, completing required number of chemotherapy cycles with nil interruption or delay, but still closely minding whatever myelosuppression will occur and intervene accordingly. Further validation is required to develop risk models to guide physicians on choosing patients which might require more intensive support during chemotherapy.

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