Association of creatinine clearance with neutropenia in breast cancer patients undergoing chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide (FAC)

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SUMMARY

Aims: Fluorouracil, doxorubicin, cyclophosphamide protocol (FAC) is a commonly used regimen for breast cancer due to its proven efficacy, acceptable toxicity, high affordability. While hepatic insufficiency dosing for doxorubicin and fluorouracil have been set, there is paucity of data in the literature on how to reduce doses in renal insufficiency. We sought to determine whether there is an association with pre-chemotherapy creatinine clearance, and the occurrence of clinically significant grade 3 to 5 neutropenia during the course of FAC chemotherapy.

Methods: A retrospective study involving chart review from 2009 to June 2012, of breast cancer patients given FAC was conducted. Demographic profile, pre-chemotherapy complete blood count and creatinine clearance (CrCl) were recorded. Occurrence of Grade 3 to 5 neutropenia was the endpoint of the study. Descriptive statistics, one tailed t test, logistic regression analysis were done between the outcome and variables.

Results: A total of 53 patients were included in the study. The mean age of the patients was 49.77 +/- 10.82 years. Patients had an ECOG performance status range of 1 to 3. Patients received mean 5.64 +/- 0.92 cycles of FAC protocol chemotherapy. Pre-treatment chemotherapy WBC was 7.41 +/- 2.68x10^9/L, Hemoglobin was 12.60 +/- 1.16 g/dL, ANC 4656.89 +/- 2379.32. Pre treatment CrCl was 90.79 +/- 31.49 ml/min. Thirteen subjects, or 24.53% developed at least grade 3 neutropenia. Patients who developed neutropenia were significantly different from those who did not in terms of baseline WBC p=0.046 and Weight p=0.0119, CrCl p=0.032. Using logistic regression analysis, only creatinine clearance was a significant predictor of neutropenia. There was an inverse association between creatinine clearance and neutropenia, OR 0.887, 95% confidence interval (CI): 0.808-0.973, p=0.011.

Conclusion: The study revealed that breast cancer patients treated with FAC, there was an inverse association between creatinine clearance and occurrence of neutropenia.

KEY WORDS:
Breast cancer, chemotherapy, creatinine clearance, neutropenia

INTRODUCTION

Breast cancer remains to be the leading malignancy among women in the Philippines, with an estimated 12,262 new cases in 2010[1]. Currently, with the advent of molecular based diagnostics, options for breast cancer treatment ranged from conventional cytotoxic chemotherapy, hormonal therapy, anti HER2neu treatment and now mammalian target of rapamycin (mTOR) treatment. However, cytotoxic chemotherapy remains to be the backbone of treatment in breast cancer. Since the 1980's, anthracyclines in combination with other cytotoxic agents have been considered as the standard in the treatment of breast cancer, whether adjuvant or metastatic[2]. During the 1990's, the addition of taxanes, paclitaxel and docetaxel, to standard chemotherapy, further improved the overall survival of breast cancer patients, but with increased toxicity and cost[3,4,5]. Although newer agents are available here in the Philippines, the combination of doxorubicin, fluorouracil, cyclophosphamide (FAC protocol) is still one of the more commonly used regimen, owing to its proven efficacy and acceptable toxicity[6]. It is also one of the more affordable regimens that an ordinary breast cancer patient can afford. Recently, the Philippine Health Insurance Corporation (Philhealth), the government health insurance, included the doxorubicin, cyclophosphamide with the addition of fluorouracil, in its breast cancer Z package, as a standard treatment protocol for breast cancer[7]. This will further spur its use even with the advent of newer protocols, as most of the indigent breast cancer patients are dependent on Philhealth support.

In cancer chemotherapy, a combination of drugs at optimal doses, such as FAC, is given in multiple cycles, to achieve a better tumor cell kill, and at the same time, limit toxicities, most especially myelosuppresion[8-9]. While keeping the optimum doses is essential in achieving better tumor control, dose adjustment is always necessary in cases of hepatic or renal insufficiency to decrease toxicities. In drugs with narrow therapeutic indices like cytotoxic agents, there is a fine line that divides optimal treatment dose and toxic dose. Although hepatic insufficiency dose adjustments have been set, no renal insufficiency dosing for doxorubicin, and fluorouracil are available[10]. Doxorubicin and fluorouracil are extensively metabolized in the liver, but excreted by the kidneys. Doxorubicin is also excreted in the bile. For

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cyclophosphamide, dosing guidelines have been set, both during renal impairment, and during hemodialysis[11-12]. A study by Hurria *et. al*, among elderly breast cancer patients receiving chemotherapy, showed that decreasing creatinine clearance is associated with an increased hematologic toxicity in the elderly population[13]. Due to the paucity in data as to whether there is an increase in toxicity in breast cancer patients' hematologic profile after chemotherapy with FAC, we sought to determine whether there is an association with pre-chemotherapy creatinine clearance, and the occurrence of clinically significant grade 3 to 5 neutropenia during the course of chemotherapy. Outcome of this study may show that there might be a need for a closer surveillance, exercise more caution with regards to the occurrence of neutropenia, in patients with a deranged creatinine clearance given FAC protocol, and at the same time, provide informed consent to the patient substantiated by local data. To our knowledge, this is the first research in our country dealing with the possible relationship between creatinine clearance and neutropenia in breast cancer patients given FAC protocol.

METHODOLOGY

A retrospective study involving chart review covering the year January 2009 to June of 2012, of all breast cancer patients, with a histopathologic confirmation, and underwent adjuvant, neoadjuvant or palliative chemotherapy with fluorouracil, cyclophosphamide, and doxorubicin (FAC protocol, at 5-Fluoruracil at 500mg/m^2, doxorubicin at 50mg/m^2, and cyclophosphamide at 500mg/m^2 every 21 days) was conducted. Data was obtained from the NKTI medical records section, cross referenced with the Section of Medical Oncology Census logbooks, and records of the NKTI - Ambulatory Chemotherapy Unit. Demographic profile such as age, sex, diagnosis, stage, ECOG performance status, weight, height, Body Mass Index (BMI) blood parameters (done prior to the first cycle of chemotherapy) hemoglobin, platelets, white blood cells (WBC), absolute neutrophil count (ANC) which is derived from the total WBC and %neutrophils and % bands, and creatinine were recorded. Estimated creatinine clearance (CrCl) was computed using the Cockroft-Gault formula. Estrogen, progesterone, and her2neu receptor status, if available, were recorded. Occurrence of chemotherapy induced neutropenia was graded according the National Cancer Institute Criteria for Toxicity version 3. Occurrence of grade 3 to 5 chemotherapy induced neutropenia was the endpoint of the study. Patients given prophylactic fligrastim, those without complete pre-chemotherapy blood, and renal parameters, those with an initial given dose of less than 85% of the planned dose, those with a previous history of cancer or chemotherapy, those with inadequate bone marrow reserve on initial pre-treatment complete blood count, and those with impaired hepatic function, and those known to receive alternative medicines (e.g. herbal medicine) were excluded from the study. Research protocol was approved by the Technical Review Board of the National Kidney and Transplant Institute.

Categorical variables were expressed using descriptive statistics (percentage, range) and continuous variables were expressed as mean +/- standard deviation. To identify the degree of association between each variable against the outcome variable – neutropenia – logistic regression analysis was performed. One tailed t test was used to identify whether there are significant differences in the means of independent variables used (pre-chemotherapy laboratory values, BMI, age, creatinine clearance) for patients with neutropenia from those without. All statistical analyses were carried out using SAS software ver 9(SAS Institute, Cary,NC, USA) at 95% confidence level. P<0.05 was considered significant.

Table I: Demographic Characteristics N=53

Demographic	Characteristics N=53
Age (years)	49.77 +/- 10.82
ECOG performance Status (range)	1-3
Weight (kg)	58.83+/- 11.85
Height (cm)	153.80 +/- 5.36
BMI (kg/m^2)	24.65 +/- 4.12
Estrogen Receptor Status: n (%)	
Positive	26 (49.06%)
Negative	16 (30.19%)
Not Available	11 (20.75%)
Progesterone Receptor Status: n (%)	
Positive	22 (41.51%)
Negative	20 (37.74%)
Not Available	11 (20.75%)
HER2neu Status: n (%)	
Positive	7 (13.21%)
Negative	33 (62.26%)
Not Available	13 (24.53%)
Stage: n (%)	
II	34 (64.15%)
III	9 (16.98%)
IV	10 (18.87%)
Cycles (n)	5.64 +/- 0.92
WBC (x10^9/L)	7.41 +/- 2.68
Hemoglobin (g/dl)	12.60 +/- 1.16
ANC	4656.89 +/- 2379.32
Platelets (x10^9/L)	319.19 +/- 91.89
CrCl (ml/min)	90.79 +/- 31.49

RESULTS

Out of the total 421 breast cancer patients seen at the NKTI-Cancer Unit during the study period, 53 patients fulfilled the inclusion criteria and were included in the study. The mean age of the patients was 49.77 +/- 10.82 years. Patients had an ECOG performance status range of 1 to 3. Mean weight was 58.83+/- 11.85kg, and mean BMI was 24.65 +/- 4.12 kg/m2. Estrogen receptor (ER) status was available in 42 patients (79.25%) with 26 patients having a positive status. There were 22 patients having a positive progesterone status, and 7 patients having a positive HER2neu status. There were 34 patients having stage II disease, 9 patients with stage III disease, and 10 patients with metastatic disease. Patients received mean 5.64 +/- 0.92 cycles of FAC protocol chemotherapy. Pre-treatment chemotherapy WBC was 7.41 +/- 2.68x10^9/L, Hemoglobin was 12.60 +/- 1.16 g/dL, ANC 4656.89 +/- 2379.32. Pre treatment CrCl was 90.79 +/- 31.49 ml/min. Table I.

Among the 53 subjects included in the study, 13 subjects, or 24.53% developed at least grade 3 neutropenia. There was no mortality, or grade 5 neutropenia among the subjects during chemotherapy. Patients who developed neutropenia

Table II: Baseline Clinical Profile and Neutropenic Events

Variable	Mean Value		
	With Neutropenia N=13 (24.53%)	Without Neutropenia N=40 (75.47%)	P value
Age (years)	53.23	48.65	0.138
Weight (kg)	56.32	59.64	0.0119
Height (cm)	153.13	154.03	0.967
BMI (kg/m^2)	23.90	24.89	0.138
Hemoglobin (g/dL)	12.75	12.55	0.325
WBC (x10^9/L)	6.67	7.65	0.046
ANC	3981.2	4876.5	0.109
Platelets (x10^9/L)	286.31	329.88	0.532
CrCl (ml/min)	63.50	99.67	0.032

Table III: Logistic Regression Analysis evaluating the Association between Variables and Outcome - Neutropenia

Variable	Estimate	Odds Ratios (95% Confidence Interval)	P value
Age	-0.0555	0.946 (0.848-1.055)	0.320
ECOG	2.164	8.709 (0.340-222.946)	0.191
Weight	-0.138	0.871 (0.465-1.632)	0.667
Height	0.107	1.113 (0.690-1.795)	0.660
BMI	0.480	1.616 (0.391-6.680)	0.508
Hemoglobin	0.217	1.242 (0.525-2.939)	0.622
WBC	0.514	1.671 (0.072-38.909)	0.749
ANC	-0.00087	0.999 (0.994-1.004)	0.728
Platelets	-0.00652	0.993 (0.981-1.006)	0.313
CrCl	-0.1201	0.887 (0.808-0.973)	0.0111

were significantly different from those who did not in terms of baseline WBC p=0.046, weight p=0.0119 and CrCl p=0.032. Table II

Using logistic regression analysis, only creatinine clearance was a significant predictor of neutropenia. There was an inverse association between creatinine clearance and neutropenia OR 0.887, 95% confidence interval (CI): 0.808-0.973, p=0.011. Table III

DISCUSSION

In adjuvant cancer chemotherapy, proper dosing is critical in achieving optimal tumor control, as there is a dose- response relationship; benefit maybe seen when dose given is the intended dose, or at least 85% or more of intended dose[14]. In the metastatic setting, although dosing is less stringent than the adjuvant setting due to the frequent palliative intent, dose reductions are only done because of intolerable toxicities that may greatly impact quality of life[15]. One of the most dreaded toxicities in chemotherapy is severe neutropenia, including febrile neutropenia. Lyman *et al.* in their review showed that age, performance status, low blood cell counts and chemotherapy dose were all associated with neutropenia[16]. In our study, those who developed neutropenia had a significantly lower baseline mean WBC 6.67x10^9/L, as compared to those who did not, with a baseline WBC value of 7.65 x10^9/L, with a p value of 0.046. Knowing when to reduce dose is critical in preventing toxicities while achieving better patient outcome. The FAC protocol for breast cancer, whether it is used in the adjuvant, or metastatic setting, has acceptable hematologic toxicities, with a grade 3 to 4 neutropenia ranging from 3% to 49.3% %[6,17-19]. While it is proven that taxane based treatments have superior outcomes as compared to the FAC, most especially in node positive, higher stage patients, FAC still has its place in breast cancer treatment, as it has modest efficacy, being at the very least comparable with the cyclophosphamide, methotrexate, fluorouracil(CMF) in terms of outcomes and toxicities, and its more affordable cost[20]. In our study, FAC was given in breast cancer patients both as adjuvant treatment for stage II and III patients, and as palliative treatment for metastatic patients. Although single agent drugs like capecitabine and gemcitabine can be given in the metastatic setting, combination treatment with FAC, FEC (fluorouracil, epirubicin, cyclophosphamide), CMF, AT (doxorubicin, docetaxel), doxorubicin and paclitaxel can likewise be offered[21].

Creatinine clearance has been a commonly used tool as a method to determine renal function of cancer patients, and as a guide for dose reduction in cytotoxic drugs which are known to be nephrotoxic like cisplatin and carboplatin. Unlike dosing guidelines for hepatic dysfunction, there is scarcity of data with regards to dosing guidelines with renal dysfunction, most especially in liver-metabolized cytotoxic drugs like doxorubicin, and fluorouracil[22]. Reduced creatinine clearance was associated with toxicities even in drugs such as irinotecan which is metabolized by the liver[23]. Also, creatinine clearance and performance status are known to be predictors of hematologic toxicity in non platinum chemotherapy regimen in a study by Lheureux[24]. A study by Russo *et. al*, in breast cancer patients treated with anthracyclines and trastuzumab, both of which are not nephrotoxic, likewise showed that a reduced creatinine clearance was a strong predictor for cardiotoxicity[25]. The above data point to a robust role of creatinine clearance in drug toxicity, even if drugs are not metabolized by the renal system.

Our study showed that even in a relatively younger group of patients, given the FAC protocol, those with neutropenia had a lower mean creatinine clearance, as compared to the group without neutropenia, which had a higher level of creatinine clearance. This observation concurs with the studies mentioned above which point to a role for creatinine clearance in drug toxicity. Even if the component drugs of the FAC protocol are extensively metabolized by the hepatic system, drug and metabolite excretion are still highly dependent on renal clearance for drug excretion. It is a common fact that renal clearance is a highly complicated process; in the proximal tubules drug efflux pumps such as the adenosine triphosphate-binding cassette pumps actively excrete drugs, while passive re-absorption occurs in the collecting tubules and distal tubules[26], and a reduced renal function can contribute to altered pharmacodynamic or pharmacokinetic processes, most especially in drugs which have narrow therapeutic indices like cytotoxics[27]. While optimal efficacy is still the primary concern during treatment, it is prudent to exercise more caution and extra vigilance in giving cancer treatment to those with reduced renal function.

CONCLUSION

The study revealed that among breast cancer patients treated with FAC protocol, there was an inverse association between creatinine clearance and the onset of chemotherapy induced neutropenia. This study is limited by its retrospective nature, relatively small sample size, and only one determination of creatinine, which is at baseline. It is recommended that a prospective study be done with serial measurement of creatinine and creatinine clearance alongside with complete blood count during chemotherapy to further strengthen association of renal function and neutropenia.

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