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Assessment of CBC Changes in Breast Cancer Patients Following Treatment with 5-Flourouracil, Adriamycin and Cyclophosphamide (FAC-Protocol) and Adriamycin and Cyclophosphamide (AC-Protocol)

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Research Article

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Abstract

Objective: FAC (5 fluorouracil, Adriamycin and cyclophosphamide) and AC (Adriamycin and cyclophosphamide) protocols have significant anti-tumor activity in patients with breast cancer. Our objective was to evaluate the CBC changes in patients undergoing FAC and AC protocols.

Methodology: A comparative retrospective study was performed to determine CBC changes in breast cancer patients following 5-Flourouracil, Adriamycin and Cyclophosphamide (FAC-Protocol) and Adriamycin and cyclophosphamide (AC-Protocol) among 150 breast cancer patients following 4 cycles of respective protocols. Marital status, surgical history, stages, diagnosis and receptor status were also determined. The parameters under observation were hemoglobin, platelets, MCV, MCHC, RBC's, WBC's, monocytes, lymphocytes, eosinophils and neutrophils. Data was analyzed using SPSS.

Results: FAC and AC protocol influenced the values of CBC in breast cancer patients in different patterns. A mild decrease in the Hemoglobin level and a significant decrease in the value of RBC's and significant increase in the level of MCV was observed in the study population after 4 cycles of both FAC and AC protocols of chemotherapy where most of the parameters such as platelets, MCV, Monocytes, Neutrophils, Eosinophils, Lymphocytes and WBCs remained in the normal range except hemoglobin, MCHC and RBCs by the end of 4th cycle of the therapy.

Conclusion: No significant difference was observed with the CBC changes in both protocols. A frequent investigation of CBC parameters and careful selection of chemotherapy protocol should be done in patients who are prone to CBC disturbances.

Keywords: Breast; Women; Cancer; Protocols; Hemoglobin; Platelets

Introduction

Every year, one million women are diagnosed with breast cancer [1]. Breast cancer is the most common cancer among females and it is estimated that over 1.38 million women suffer from breast cancer according to the 2008 GLOBOCAN of WHO (World Health Organization) [2]. In Asia, Pakistan has the highest rate of breast cancer. Young women also present advanced stage of breast cancer, which has negative effect on prognosis [3]. At some stage of life, 1 in 9 Pakistani women has become the patient of breast cancer [4]. Primary chemotherapy is very beneficial as it leads to prompt tumor shrinkage. It enables the surgeons to use breast-conserving procedures more [5]. In women with large tumors (>5.0 cm), primary chemotherapy can be safely administered. Moreover, it allows breast sparing surgery in a high fraction of patients [6]. TAC (docetaxel, doxorubicin, and cyclophosphamide) was compared in the patients treated with FAC (5-flourouracil, doxorubicin, and cyclophosphamide) with and without primary prophylactic granulocyte colony stimulating factor (G-CSF) resulted in improved quality of life. The neutropenia fever incident was considerably reduced by the addition of G-CSF, associated with TAC chemotherapy. By G-CSF addition the HRQoL of TAC and FAC patients was significantly improved [7]. The efficacy of doxorubicin and methotrexate was compared in combination with IV cyclophosphamide and 5-flourouracil (FAC versus CMF) as adjuvant therapy for operable breast cancer. It was concluded that doxorubicin is more efficient than methotrexate when given in combination with day 1 IV cyclophosphamide and 5-flourouracil as adjuvant therapy in breast cancer patients [8]. Long term follow up study confirmed that FAC regimen reduces the risk of recurrence effectively. Moreover, it's also prolongs the survival of high risk patients. A study was conducted to know the various troublesome side effects experienced by patients who received cyclophosphamide, methotrexate, 5-flourouracil (CMF) in 6 cycles for the treatment of breast cancer. 94 different side effects were reported, alopecia being the most common problem identified. The other problems reported were fatigue, weight gain, and difficulty sleeping and sore eyes. To alleviate these side effects patient education is necessary [9]. CEF (cyclophosphamide, epirubicin and fluorouracil) when compared with CMF (cyclophosphamide, methotrexate and fluorouracil) showed efficacy in terms of overall survival in premenopausal women with axillary lymph node-positive breast cancer [10]. Safety and Efficacy of doxorubicin and paclitaxel (AT) was compared with FAC for the first line therapy in metastatic breast cancer patients. AT was more efficient in response rate, time to progression and overall survival as compare to FAC no unexpected toxicities were reported [11]. Assessment of adjuvant combination chemotherapy after radical mastectomy for primary breast cancer with histologically positive axillary lymph nodes was done. It was compared with the surgery alone. Long term result of this trail of adjuvant chemotherapy was effective for treatment in women having node positive breast cancer [12]. Breast cancer proved fatal in 1983, in U.S to over 37000 women. Hormonal manipulation is effective in receptor positive women who have 50-70 % chance of responding. Newer agents are more beneficial having less morbidity e.g. tamoxifen. Administering more than one chemotherapeutic agent helps to increase the duration of response in comparison with single chemotherapeutic agent. We can say that chemotherapy along with appropriate hormonal treatment prolongs disease-free survival [13]. Only a small fraction of patients are able to get long-term remissions with standard chemotherapy regimens and most patients achieve temporary responses to treatment. More remission consolidation plans are required [14]. Despite well recognized limitations in the grading and reporting system of chemotherapy related anemia, the results of review of literature confirm a relatively high incidence of mild-to-moderate anemia. Clinical data are emerging that suggest that mild-to-moderate chemotherapy-induced anemia results in a perceptible reduction in a patient's quality of life (QOL) and functional capacity [15]. A study aimed at assessing the incidence of Febrile Neutropenia in Korean female breast cancer patients receiving preoperative or postoperative Doxorubicin/Cyclophosphamide followed by Docetaxel chemotherapy, concluded that, The incidence of Febrile neutropenia during AC-D neoadjuvant or adjuvant chemotherapy was higher than expected [16]. The aim of this study was to assess the CBC changes in breast cancer patients following 5-Flourouracil, Adriamycin and Cyclophosphamide (FAC-Protocol) and Adriamycin and cyclophosphamide (AC-Protocol).

Methodology

Study design

A retrospective observational study was performed from July-December 2016 to investigate the safety of chemotherapy by FAC (5-Flourouracil, Adriamycin, Cyclophosphamide) and AC (Adriamycin, Cyclophosphamide) protocols, with reference to chemotherapy induced CBC changes.

Ethical Approval and Consent to Participate

Ethical approval for the study was granted by Punjab University College of Pharmacy Lahore, Pakistan. The purpose of the study was elucidated to the medical director and medical superintendent of concerned oncology section of the hospital and consent letter was approved by the concerned authority.

Study Setting and Time Duration

The data was gathered from oncology department of Mayo Hospital Lahore, Pakistan.

Study Participants

A total of 150 patients were enrolled for the study. Females with breast cancer, having chemotherapy with FAC (5-Flourouracil, Adriamycin, Cyclophosphamide) and AC (Adriamycin and Cyclophosphamide) with any receptor status were included. Females with breast cancer following protocol other than FAC and AC were not included.

Data Collection Procedure

Data for CBC parameters, hormonal status and basic demographics for both chemo protocols was collected from hospital laboratory reports and patients file. CBC Parameters included RBCs, Platelets, MCV, MCHC, Monocytes, Neutrophils, Eosinophils, Lymphocytes, WBCs and Hemoglobin. Hormonal status parameters included HER2, PR and ER. Metastasis, stage of cancer and diagnosis were also noted.

Data Analysis

Data was analyzed using SPSS (Statistical program for social sciences version) Chi-square test was used to compare different demographic characteristics and diagnosis among two protocols. P-value ≤0.05 was kept significant. Descriptive statistics was used to calculate mean and standard deviation of CBC parameters.

Results

Basic Demographics, Diagnosis and Hormonal Properties

Out of total 150 subjects (Females), 109 were on FAC out of which 102 (93.6%) were married and 7(6.4%) were unmarried and remaining 41 were on AC protocol with 40 (97.6%) married and 1(2.4%) unmarried female. Out of total, 64.7% females had undergone surgical process including both the mastectomy and lumpectomy whereas 35.3% female did not show any surgical history. Among the patients on FAC protocol, 60.6 % subjects were with the history of surgery and 39.4% patients had not undergone through any surgical process. And among patients with AC protocol, 75.6% patients showed surgical history whereas 24.4 % patients showed no surgical history. Moreover, receptor status was supported by clinical reports, out of total of the patients, 56.7% female were having receptor status HER2-ve whereas 43.3 were with HER2+ve status. 47.3% female showed -ve status response towards Progesterone hormone while positive receptor status for progesterone was shown by 52.7% of the total female. 44.7% subjects showed negative receptor status towards estrogen hormone whereas 55.3% showed positive response towards estrogen receptor. The FAC and AC receptor status for HER2, PR and ER was shown positive by 41.3%, 51.4% and 54.1% patients and 48.8%, 56.1% and 58.5% patients respectively. While negative receptor status for HER2, PR and ER for FAC and AC was shown by 51.2%, 43.9% and 41.5% and 51.2%, 43.9% and 41.5% respectively. Overall receptor status i.e. Triple negative was shown positive by 28.7% and 71.3% showed negative status towards triple negative status. 72.5% female following FAC showed negative status towards FAC whereas 27.5% were positive for triple negative. According to clinical representation two categories of diagnosis were considered i.e. Invasive ductal carcinoma and invasive lobular carcinoma. Out of total 150 patients 72.0% were having invasive ductal carcinoma while 28% were having invasive lobular carcinoma of the breast. Among patients following FAC 75.2% were diagnosed with invasive ductal carcinoma and 24.8% were diagnosed with invasive lobular carcinoma. While 63.4% patients with AC protocol showed invasive ductal carcinoma and 36.6% showed invasive ductal carcinoma. Three stages of breast cancer were considered 2, 3 and 4.Out of total 30.7%, 50.7% and 18.7% were on stage 2, 3 and 4 respectively. Among FAC 19.5%, 57.9%, 6% were on stage 2, 3 and 4 respectively. Whereas Patients following AC protocol showed 34.9%, 57.9% and 6% for stage 2, 3 and 4 respectively. Metastasis was observed in 40% patients while 60% were free from metastasis. 63.4% following FAC did not show any metastasis while 36.6% patients were having metastasis. Patients following AC protocol showed metastasis in 36.6% and 63.4% of patients. The demographic characteristics, diagnosis and hormonal status with the two protocols are depicted in Table 1.

Marital status				
Married	102(93.6%)	40(97.6%)	142(94.7%)	0.447
Unmarried	7(6.4%)	1(2.4%)	8(5.3%)	
Diagnosis				
Invasive ductal carcinoma	82(75.2%)	26(63.4%)	108(72.0%)	
Invasive lobular carcinoma	27(24.8%)	15(36.6%)	42(28.0%)	0.395
Metastasis				
No	64(58.7%)	26(63.4%)	90(60.0%)	0.709
Yes	45(41.3%)	15(36.6%)	60(40.0%)	
Stage of cancer				
2	38(34.9%)	8(19.5%)	46(30.7%)	
3	49(45%)	27(57.9%)	76(50.7%)	0.069
4	22(20.2%)	6(14.6%)	28(18.7%)	
Surgical History				
Yes	66(60.6%)	31(75.6%)	97(64.7%)	0.124
No	43(39.4%)	10(24.4%)	53(35.3%)	
Hormonal status				
HER2-ve	64(58.7%)	21(51.2%)	85(56.7%)	0.462
HER2+ve	45(41.3%)	20(48.8%)	65(43.3%)	
PR-ve	53(48.6%)	18(43.9%)	71(47.3%)	0.714
PR+ve	56(51.4%)	23(56.1%)	79(52.7%)	
ER-ve	50(45.9%)	17(41.5%)	67(44.7%)	0.714
ER+ve	59(54.1%)	24(58.5%)	83(55.3%)	
Triple negative				
No	79(72.5%)	28(68.3%)	107(71.3%)	0.68
Yes	30(27.5%)	13(31.7%)	43(28.7%)	

Table 1: Basic demographics, diagnosis and hormonal status among two protocols.

Variation of Different CBC Parameters

Table 2 indicates the CBC changes with FAC and AC protocols in women with breast cancer.

Change in Hemoglobin value: Patients following FAC showed decrease in Hb value from cycle 1 to cycle 2 while a little increase was seen in cycle 3 and cycle 4 but overall there is increase in Hb whereas the value remained below normal range i.e. 12-16 g/dl. Patients following AC protocol showed gradual increase in Hb concentration from 1 to cycle 3 but very slightly decreased in cycle 4. Overall, there is increase in Hb whereas the value remained below the normal range. So as a whole there was not much difference in the effects of FAC & AC protocols on the Hb changes among the patients.

Change in Platelets*10^3/µL value: There was rapid decrease in value of platelets in patients following FAC protocol from cycle 1 to cycle 3 and decreased a little bit in cycle 4. Overall the value decreased throughout chemotherapy, but remained within normal range i.e. (150-450 *10^3/µL).There was decrease in value from cycle 1 to cycle 3 in patients with AC protocol then contrary to the effect of FAC, there was increase in value from cycle 3 to cycle 4 but overall response was decrease in platelet count. Whereas the value remained within range throughout chemotherapy.

Change in MCV value: There was increase in value of MCV in patients with FAC protocol from cycle 1 to cycle 3 and then decrease from cycle 3 to cycle 4, overall there is increase in MCV. Whereas the value remained within normal range i.e. (80-99fL). An increase in value of platelets with patients following AC protocol was seen from cycle 1 to cycle 2, decreased from cycle 2 to cycle 3 then again increased from cycle 3 to cycle 4.Overall there is an increase in value of MCV. Whereas value remained within normal range throughout chemotherapy.

Change in MCHC value: Patients following FAC protocol showed an increase in MCHC value from cycle 1 to cycle 3 then decreased in cycle 4. But overall the value is increased .Value remained within normal range i.e. (32-36 g/dl) except cycle 1. Contrary to FAC protocol, an overall decrease in value of MCHC was observed throughout chemotherapy from cycle 1 to cycle 4 in patients following AC protocol. The value remained below normal range in last three cycles.

Change in value of RBC'S*10^6/µL: Increase in value from cycle 1 to cycle 2 was observed in patients with FAC protocol then slightly decrease from cycle 2 to cycle 3 then again slightly increase from cycle 3 to cycle 4 but overall there is an increase in RBC count. Whereas the value remained below the normal range i.e. (4.5-6 *10^3/µL) as contrary to results of FAC protocol, the RBC count decreased throughout chemotherapy from cycle 1 to cycle 4 in patients with AC protocol. An overall decrease in value was observed throughout chemotherapy and remained below normal range.

Change in value of Monocytes (%): Patients following FAC protocol showed decrease in value of monocytes from cycle 1 to cycle 2 then an increase in value from cycle 2 to cycle 4. An overall increase in value of monocytes was observed whereas value remained within normal range throughout i.e. (2-8%). Contrary to FAC protocol, an increase in value of monocytes was observed in AC from cycle 1 to cycle 3 then decreased from cycle 3 to cycle 4.An overall decrease was observed whereas value remained within normal range.

Neutrophils (%): Decrease in value of neutrophils from cycle 1 to cycle 2 was observed in patients following FAC whereas increase in value from cycle 2 to cycle 4. Overall response is decrease in value. Values remained within normal range i.e. (45-70%) throughout chemotherapy whereas the patients following AC showed increase in value of neutrophil from cycle 1 to cycle 2 then decrease from cycle 2 to cycle 3 then increase in value from cycle 3 to cycle 4.An overall increase is observed while values remained in normal range.

Eosinophils (%): Patients following FAC showed decrease in value from cycle 1 to cycle 2 then increase in cycle 3 then decreased in cycle 4. Overall decrease in eosinophils was seen while remained within normal range i.e. (1-4%).Whereas in patients with AC showed an increase in value of eosinophils from cycle 1 to cycle 2 then decrease in cycle 3 and again increase in cycle 4. An overall increase was seen and remained within normal range throughout chemotherapy.

Change in value of Lymphocytes (%): An increase in value of lymphocytes was observed in cycle 1 and 2 then decreased in cycle 3 and 4 in patients following FAC protocol. An overall decrease in lymphocytes was observed. And value remained within normal range i.e. (20-45%).Patients following AC showed decrease in value of lymphocytes from cycle 1 to cycle 4 but remained within normal range.

Change in value of WBC'S*10^3/µL: Patients following FAC showed decrease in value of WBC's from cycle 1 to cycle 3 then increased in cycle 4.Overall the value is decreased but remained within normal range i.e. (4-11 *10^3/µL whereas an increase in value of WBCS was seen from cycle 1 to cycle 2 then decrease from cycle 2 to cycle 3 then again increase from cycle 3 to cycle 4.

Lab values	FAC				AC			
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Hemoglobin(mg/dl)	10.91 ± 2.35	11.25 ± 1.55	11.45 ± 1.34	11.46 ± 0.96	11.10 ± 1.48	11.10 ± 1.87	11.31 ± 1.19	11.55 ± 1.24
Platelets*10^3/µL	316.23 ± 119.14	294.52 ± 124.26	260.66 ± 89.28	257.38 ± 35.70	346.7 ± 118.65	342.11 ± 145.1	328.40 ± 126.33	321.8 ± 134.29
MCV(FL)	81.41 ± 12	82.9 ± 7.5	83.44 ± 7.5	83.87 ± 9.09	81.59 ± 8.64	81.66 ± 9.74	80.83 ± 8.34	87.49 ± 86.82
MCHC(g/dl)	31.58 ± 3.85	32.08 ± 2.88	32.10 ± 2.17	32.10 ± 22.16	39.47 ± 47.45	31.66 ± 2.47	32.05 ± 2.02	32.02 ± 1.49
RBC'S*10^6/µL	4.29 ± 0.70	4.39 ± 0.75	4.36 ± 0.77	4.34 ± 0.71	4.42 ± 0.55	4.28 ± 0.84	4.36 ± 0.60	4.16 ± 0.43

Monocytes (%)	4.21 ± 2.32	3.79 ± 3.04	4.87 ± 3.21	5.73 ± 4.9	4.19 ± 3.05	3.92 ± 1.57	5.85 ± 5.03	5.17 ± 4.62
Neutrophils (%)	61.73 ± 13.34	59.34 ± 15.57	61.60 ± 13.89	61.18 ± 11.68	55.30 ± 16.11	62.19 ± 12.92	57.21 ± 8.51	66.02 ± 5.56
Eosinophils (%)	2.79 ± 1.57	2.72 ± 1.80	3.12 ± 1.89	2.17 ± 1.47	2.27 ± 0.95	2.37 ± 1.59	2.16 ± 0.98	2.17 ± 1.47
Lymphocytes (%)	35.09 ± 64.35	29.78 ± 14.08	28.44 ± 13.30	25.50 ± 10.45	33.78 ± 11.01	29.04 ± 11.29	27.18 ± 10.85	25.36 ± 10.17
WBC'S*10^3/µL	8.30 ± 3.39*	7.69 ± 5.34*	7.58 ± 7.47*	6.42 ± 3.32*	6.94 ± 2.20*	6.96 ± 2.46*	5.80 ± 2.43*	7.31 ± 3.57*

Table 2: Post therapy values of CBC in FAC and AC protocol in breast cancer female.
MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, RBC'S: Red blood cells, WBC'S: White blood cells.

Discussion

Anticancer drugs are used under strict supervision because of their narrow therapeutic window, high toxicity profile, significance of drug interaction and finally to prevent recurrence of painful disease condition [17]. Anticancer drugs affect every tissue of the body because the drug is unable to target the site of tumor [18]. The drugs especially affect vital organs like brain, heart, kidney or liver and those who undergo rapid cell division [19,20]. On the basis of CBC count, Hb value increases but remain below the normal range and a significant decrease in the value of RBC's was seen in both group of patients with FAC and AC protocol which indicates the tendency of patient of getting anemic. There can be multiple underlying causes of anemia in patient with cancer, which can add to the difficulty in the evaluation. It can be due to underlying comorbidities such as bleeding, hemolysis, hereditary disease, renal insufficiency, anemia of chronic disease, or a combination. The malignancy itself can also be a reason. Chemotherapeutic agents may also induce anemia by directly impairing hematopoiesis. An increase in the anemia can also be associated with a greater number of chemotherapy cycles [21]. So measuring the Hb level after fourth cycle can also be a reason of getting below normal range of Hb in patients. A progressive decline with the start of chemotherapy including FAC and AC protocols, was observed in values of platelets, monocytes, neutrophils, lymphocytes and WBC's, although the values were still within the normal range. (Further decreases in values with chemotherapy can lead towards anemia, neutropenia, thrombocytopenia and increase chance of infection). Suppression of hematopoietic system by cytotoxic chemotherapy impairs the host protective and defense mechanisms. Being the first cellular component of the inflammatory response, the Neutrophils are the first line of defense against infection. So, Neutropenia reduces the inflammatory response to infections, allowing multiplication and invasion of pathogenic organisms [22]. But in study population the values of platelets, monocytes, neutrophils, lymphocytes and WBCs were within normal range at the end of four cycles, indicating that the patients were least prone to getting infections as a result of chemotherapy. Whereas there was increase in value of MCHC in patients following FAC protocol, but significant decrease in value which was below the normal range was observed in AC protocol. An increased in value of MCV in both protocols is observed but the values remained within normal range.

Conclusion

5-Flourouracil, Adriamycin and Cyclophosphamide (FAC) protocol and Adriamycin and Cyclophosphamide (AC) protocol both affect the values of Blood cells count in patients with breast cancer in different patterns. A mild decrease in the Hemoglobin level and a significant decrease in the value of RBC's and significant increase in the level of MCV were observed in the study population after the 4 cycles of both FAC and AC protocols of chemotherapy. Whereas most of the parameters remained within normal range i.e. platelets, MCV, Monocytes, Neutrophils, Eosinophils, Lymphocytes and WBCs, except Hemoglobin, MCHC and RBCs by the end of 4th cycle of the therapy. A frequent investigation of these parameters should be done in patients undergoing these two protocols. Future studies demand a more detailed research in a preferably large number of women suffering from breast cancer to optimize the results and evaluate outcomes of two chemo-protocols in Lahore, Pakistan.

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