TOLERACE AND TOXICITY TO ANTHRACYCLINE BASED NEOADJUVANT CHEMOTHERAPY IN PREMENOPAUSAL WOMEN WITH BREAST CANCER.

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ABSTRACT:

Background: *Cytotoxic drugs play an important role in the management of breast cancer particularly in pre-menopausal patients and patients with triple negative breast cancer (TNBC). The adverse reactions to chemotherapeutic drugs are wide and varied. These adverse reactions to chemotherapy drugs could be haematologic and non-haematologic.*

Objectives: *The study aims to evaluate the toxicity and tolerance of cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) combination on pre-menopausal women with breast cancer.*

Materials and methods: *A Doxorubicin containing regimen (CAF) consisting of cyclophosphamide 500 mg/m^2, Doxorubicin 50 mg/m^2, and 5-Fluorouracil 500 mg/m^2 all were given on day one. During the course of the cytotoxic drugs, all the side effects both haematological and non-haematological were recorded. The data collected were analyzed using the SPSS statistical software version 23.0. (Statistical Package for Social Sciences SPSS Inc.).*

Results: *Forty-nine patients were recruited with age range 24 to 54 (40.92 ± 7.98) years. Out of 49 patients, 8(16.3%) developed anaemia, 2(4.1%) leucopenia and 3(6.1%) mild thrombocytopenia during neoadjuvant chemotherapy. The majority of the patients, 41 (83.7%), did not produce significant haematologic side effects. Out of a total of 49 patients, 47 (95.9%) developed atleast one non-haematologic side effect during neoadjuvant chemotherapy. The most common side effects were: vomiting, nausea and body weakness at the frequencies of 29 (59.2%), 28 (57.1%) and 24 (50.0%), respectively.*

Conclusion: *The study demonstrated that neoadjuvant CAF chemotherapy was very tolerable by our patients with only minimal haematological and non-haematological toxicities. The recorded toxicities were readily managed by simple measures without need for admission.*

Keywords: *Adverse reactions, neoadjuvant chemotherapy, breast cancer.*

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INTRODUCTION:

The primary goal of Neo-adjuvant chemotherapy (NAC) in breast cancer treatment is to achieve tumour or nodal down-staging, increase tumour resectability and decrease surgical morbidity. [1-5] An overview of breast cancer chemotherapy confirmed the superiority of combination chemotherapy over single agents.[6] Experience over the years shows that combination chemotherapy is more effective than single agents. The combination approach may succeed where single agents fail because, individually, each drug's maximum tolerated doses may be

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insufficient to kill all cancerous cells. In combination therapy, 100% kill may be achieved with tolerable toxicity, as long as the toxicity of the component drugs is non-overlapping. Furthermore, tumours represent a heterogeneous population of cell lineages that vary in sensitivity (and resistance) to chemotherapy. Therefore, a combination therapy approach allows a broader range of coverage. One of the chemotherapy regimen most rigorously assessed consists of Cyclophosphamide, Adriamycin/Doxorubicin and 5-fluorouracil (CAF). Adriamycin and cyclophosphamide (AC) regimen remain the gold standard in neoadjuvant therapy.[7,8] However, several trials have reported increased response rates for taxane-containing regimens,[9,10] although phase III studies have failed to demonstrate an advantage over anthracyclines.[11]

The adverse reactions to chemotherapeutic drugs are wide and varied. Most patients exhibit adverse reactions to chemotherapy drugs which could be haematologic and non-haematologic. Adverse drug reactions from Cyclophosphamide are connected to the cumulative medication dose. They include chemotherapy-induced nausea and vomiting, bone marrow suppression, stomach ache, hemorrhagic cystitis, diarrhoea, alopecia (hair loss), darkening of the skin/nails, or thinning of hair, changes in colour and texture of the hair, lethargy, and profound gonadotoxicity.[12,13] Other side effects may include easy bruising/bleeding, joint pain, mouth sores, slow-healing of existing wounds, a remarkable reduction in the amount of urine or unusual tiredness or weakness. Potential side effects also include infection, leukopenia, bladder toxicity, and cancer.[14] Pulmonary injury appears rare but can present with two clinical patterns: an early, acute pneumonitis and a chronic, progressive fibrosis.[15,16]

Doxorubicin is an anthracycline antibiotic extracted from the bacterium Streptomyces peucetius. Its cytotoxic effect is produced by intercalating with DNA, causing the breakdown of DNA strands, which induces cancer cell apoptosis. Despite being an effective anticancer agent, it causes several crucial side effects like cardiotoxicity, neuropathy, hepatotoxicity, nephrotoxicity, alopecia, typhlitis, myelosuppression, neutropenia, anaemia, thrombocytopenia, nausea, and diarrhea.[17] These adverse effects result mainly from the inability to distinguish between cancer cells and normal cells.[17]

Common side effects of 5-fluorouracil include loss of appetite, inflammation of the mouth, hair loss, skin inflammation, and low blood cell counts.[18,19] Diarrhea is severe and may be dose-limiting and is exacerbated by co-treatment with calcium folinate.[18] Neutropenia tends to peak about 9–14 days after beginning treatment.[18] Thrombocytopenia tends to peak about 7–17 days after the beginning of treatment and tends to recover about 10 days after its peak.[18] Cardiotoxicity is a reasonably common side effect. However, this cardiotoxicity is just angina or symptoms associated with coronary artery spasm, but about 0.55% of those receiving the drug will develop life-threatening cardiotoxicity.[19] Life-threatening cardiotoxicity includes: arrhythmias, ventricular tachycardia and cardiac arrest, secondary to transmural ischaemia.[19]

Despite these numerous side effects recorded in relation to the use of these cytotoxic drugs, they still play an important role in the management of breast cancer particularly in pre-menopausal patients and patients with triple negative breast cancer (TNBC).[20-22] This study aims to evaluate the toxicity and tolerance of cyclophosphamide, doxorubicin and 5-

fluorouracil (CAF) combination on pre-menopausal women with breast cancer.

Materials and methods:

All premenopausal patients manifesting with cytology/histologically confirmed locally advanced breast cancer (LABC), Stage III (A, B and C) breast disease and $T_3N_0M_0$ subset of Stage IIB presenting at the general surgery clinic were recruited. The patients were counseled on the benefits as well as the possible side effects of the neoadjuvant chemotherapy. A written consent was obtained from all eligible patients that accepted to be part of the study. Ethical approval was sort and obtained from the institution's Ethical committee with health research committee assigned number: ETH.C/VOL.1/FN:04/0082.

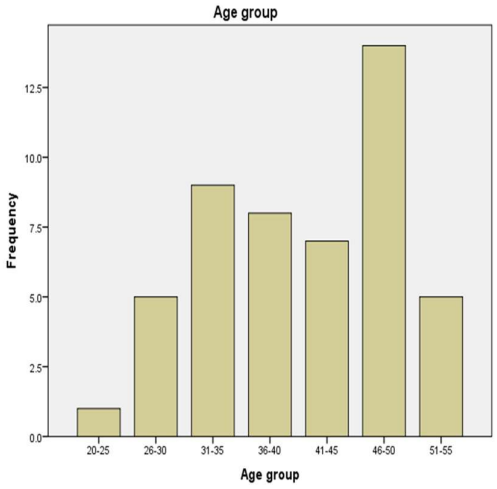
The patients were expected to have a haemoglobin concentration of ≥10 g/dl, white blood cell count of ≥ 2,500/mm^3 with an absolute neutrophil count of ≥1,000/mm^3 and platelet count of ≥100,000/mm^3. All the patients with evidence of metastatic disease were excluded from the study. A Doxorubicin containing regimen (CAF) consisting of cyclophosphamide 500 mg/m^2, Doxorubicin 50 mg/m^2, and 5-Fluorouracil 500 mg/m^2 all were given on day one. The Cyclophosphamide and Fluorouracil were given as bolus injection in a free-flowing intravenous line, and the doxorubicin was given as an infusion. The cycles of the CAF were repeated at 3 weekly intervals. Cycles were deferred if haematologic parameters were inadequate. However, all eligible women who complied (by signing the consent form) were given four courses of CAF.

During the course of the cytotoxic drugs, all the side effects both haematological and non-haematological were recorded and the patients treated as the case required. The data collected were analyzed using the SPSS statistical software version 23.0. (Statistical Package for Social Sciences SPSS Inc.).

RESULTS:

A total of 62 patients were recruited but only 49 were able to complete the four courses of neoadjuvant chemotherapy and are the ones used for the analytical aspect of the study. The age of the study population ranged from 24 to 54 years with a mean of 40.92±7.98 years. The age group distribution of the patients is as shown in figure 1. One (2%) of the patients was within 20-25 years age group; five (10.2%) within 26-30 years; nine (18.4%) within 31-35 years; eight (16.3%) within 36-40 years; seven (14.3%) within 41-45 years; 14 (28.6%) within 46-50 years and five (10.2%) within the 51-55 years age group (Figure 1).

Figure 1: Bar chart showing age group distribution of patient.



Haematologic side effects:

Out of 49 patients, eight (16.3%) developed anaemia during neoadjuvant chemotherapy, with three of the patients requiring blood transfusion. The rest needed 1-2 weeks dose deferment and oral haematinics for correction of the anaemia. Only 2(4.1%) of the patients developed leucopenia, corrected by 1-2 weeks dose deferment. Three (6.1%) of the patients developed mild thrombocytopenia updated

by dose deferment. The majority of the patients, 41 (83.7%), did not produce significant haematologic side effects (Table 1).

Haematologic side effect	Frequency	Percentage frequency
Anaemia	8	16.3
Leucopenia	2	4.1
Thrombocytopenia	3	6.1
Pancytopenia	2	4.1
Nil	41	83.7

Table 1: Frequency distribution of haematologic side effects. Some of the patients had multiple side effects.

Non-haematologic side effects:

Out of a total of 49 patients, only two (4.1%) did not manifest any of the non-haematologic side effects. The remaining 47 (95.9%) of the patients developed atleast one non-haematologic side effect during neoadjuvant chemotherapy. The most common side effects were: vomiting, nausea and body weakness at the frequencies of 29 (59.2%), 28 (57.1%) and 24 (50.0%), respectively (Table 2). All the recorded side effects were mild, and none required hospitalization or dose deferment. Nausea and vomiting were resolved on oral ondansetron therapy. The rest were self-limiting and required no additional measures.

Non-haematologic side effects	Frequency	Percentage frequency
Nil	2	4.1
Nausea	28	57.1
Vomiting	29	59.2
Anorexia	6	12.2
Alopecia	13	26.5
Weakness	24	50.0
Skin Pigmentation	7	14.3

Table 2: Frequency distribution of non-haematologic side effects. Some patients developed multiple side effects.

DISCUSSION:

The toxicity that can follow the administration of chemotherapeutic drugs can broadly be divided into haematologic and non-haematologic side effects. Haematologic side effects usually result from myelosuppressive effects of cytotoxic drugs. Because of their impact on the different stages of the cell cycle, these groups of medicines hinder cell proliferation, especially the rapidly proliferating cells, of which blood cells are one of them. This myelosuppression could affect any formed blood cells, including red blood cells, white blood cells, and platelets, resulting in anaemia, leucopenia, and thrombocytopenia, respectively. Occasionally all the blood cells are affected, giving rise to pancytopenia. In the current study, anaemia was described as a haemoglobin concentration of <10 g/dl, leucopenia as white blood cell count of <2,500/mm^3 or absolute neutrophil count of <1,000/mm^3 and thrombocytopenia as a platelet count of <100,000/mm^3.

In the present study, 8(16.3%) of the patients developed anaemia during neoadjuvant chemotherapy. Three (6.1%) of the patients were severe enough to receive a blood transfusion, while the remaining 5(10.2%) were corrected by oral haematinic and dose deferment (Table 1). Egwuonwu[23], in a similar study at Nnewi, recorded anaemia in 8(25.8%) of his patient's majority of who were treated with haematinic but 3(9.7%) of the patients required admission, blood transfusion and dose deferment of their chemotherapy. The above findings were comparable with that of the current study, which showed that most of the anaemia from chemotherapy could be corrected by haematinic and dose deferment but rarely blood transfusion.

Leucopenia in the present study was seen in only 2(4.1%) of patients. This was readily corrected by 1-2 weeks dose deferment. There was no infective complication and no

need for administration of granulocyte colony-stimulating factor (G-CSF). This is different from the report by Egwuonwu[23], who documented leucopenia in 10(32.3%) of the patients with 5(16.0%) requiring dose deferment but, however, no need for G-CSF. Other similar studies also recorded higher rates of leucopenia: Chintamani et al.[24] recorded 10%, and Moon et al.[25] noted 36.0% with one episode of pneumonia and septic shock with the need to use G-CSF to manage the myelosuppression. In a randomized trial by Broet et al.[26] using CAF regimen, they recorded leucopenia in 25 of their 200 patients (i.e. 12.5%). In EORTC study[27] using 5-Fluorouracil, epirubicin and cyclophosphamide (FEC) regimen, leucopenia was seen in 38 of their 350 patients (i.e. 10.9%). The NSABP B-18 study[1] noted leucopenia in 54(7.2%) out of 748 of their patients using cyclophosphamide and adriamycin/doxorubicin combination.

Thrombocytopenia in the index study was noted in only 3(6.1%) of the patients, with none requiring any further attention. Furthermore, all the involved patients recovered on 1-2 weeks of dose deferment, and no bleeding diathesis was noted in any of the patients. This is lower than the findings by Egwuonwu[23], who recorded thrombocytopenia in 4(12.9%) of his patients, with only 2(6.2%) requiring deferment of their chemotherapy schedule.

Non-haematologic side effects of cytotoxic chemotherapy are wide and varied depending on the agents or regimen used. The commoner side effects that can follow the regimen used in this study, i.e. cyclophosphamide, doxorubicin/Adriamycin and 5-Fluorouracil (CAF) combination, include but are not limited to the following: nausea; vomiting; anorexia; diarrhoea; body weakness; alopecia; cardiotoxicity; skin pigmentation; mucositis; hand-foot syndrome etc. In the current study, 47(95.9%) patients manifested one or more non-haematologic side effects. The recorded side effects in the study were: nausea (57.1%); vomiting (59.2%); anorexia (12.2%); alopecia (26.5%); body weakness (50.0%) and skin pigmentation (14.3%) (Table 2). In this study, vomiting and nausea were the commonest recorded side effects. However, the cases were mild and resolved by oral anti-emetics (ondansetron). No admission was required, and no dose deferment was done. Chintamani et al.[24], in their study among Indian women, noted vomiting in 63.3% of their patients, which correlates with the index study. Egwuonwu[23], in a similar study at Nnewi, noted a lower incidence of vomiting in 38.7% of the patients studied. However, the vomiting was readily controlled by anti-emetics, just like in the index study. Clegg-Lamptey et al.[28] in their study in Ghana using the CAF regimen, noted that nausea and vomiting were seen to a certain extent in all their patients. In all these studies, including the index study, nausea and vomiting were readily controlled by anti-emetics.

Body weakness was a prevalent complication recorded in the current study. This was noted in 24(50.0%) patients and lasted between 2-7 days in most involved patients. The cases of body weakness were self-limiting and required no further treatment. The aetiology of the body weakness could be multifactorial, including anaemia, anorexia with reduced food intake, vomiting, diarrhoea etc. Body weakness though very common in this present study, was not documented in other similar studies.[23,24,28,29]

Alopecia was also a prevalent complication in the index study documented in 13(26.5%) of the cases. The value in this study is low compared to 51.6% reported by Egwuonwu[23] and 60% by Chintamani et al.[24] In EORTC trial[27] using the FEC regimen, they

noted alopecia in 148 out of their 350 patients (42.3%). Wolmark et al.[1], in the NSABP-B18 trial using adriamycin and cyclophosphamide (AC) combination, noted alopecia in 491 of their 748 patients (65.6%). All the above studies recorded a much higher incidence of alopecia compared to the current research. Broet et al.[26], in a randomized control trial using CAF regimen, noted alopecia in 22% of their patients. This is closer to 26.5% documented in the present study. The noted difference may be due to different drug combinations and dosages used in the various studies.

Other documented non-haematologic side effects in the current study were skin pigmentation in 7(14.3%), and anorexia in 6(12.2%) see table 14. Anorexia was mild and transient; therefore required no additional treatment. Skin pigmentation was also not disabling apart from the patients' cosmetic concerns, which were taken care of by counselling. Egwuonwu[23] noted hyper-pigmentation of the hands and feet in 7 (22.6%) of his patients. Cardiotoxicity, one of the documented side effects of the anthracyclines like Doxorubicin/Adriamycin, was not noted in this study or other similar studies using the CAF regimen.[23,24,26,28] In all these studies, the current Electrocardiography (ECG) or Echocardiography, which could detect mild changes in cardiac functions were not done routinely.

CONCLUSION:

The study demonstrated that neoadjuvant CAF chemotherapy was very tolerable by our patients with only minimal haematological and non-haematological toxicities. The recorded toxicities were readily managed by simple measures without need for admission.

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