Effectiveness of Anthracycline Based Neoadjuvant Chemotherapy in Tumour Size Reduction in Pre-Menopausal Women with Locally Advanced Breast Cancer

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ABSTRACT

Background: Neo-adjuvant chemotherapy (NAC) has been demonstrated as a helpful strategy and the standard of care in the multimodal management of locally advanced breast cancer. **Objectives:** This study aims at evaluating the effectiveness of anthracycline based neoadjuvant chemotherapy in down-staging locally advanced breast cancer in pre-menopausal women. **Materials and Methods:** The size of the primary breast tumour was measured initially, after each course of chemotherapy and three weeks after the 4th course of NAC. Four courses of the regimen: cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) were given every three weeks. Medication response was evaluated using a modification of the RECIST methodology. The data were analyzed using the SPSS statistical software version 23.0. (Statistical Package for Social Sciences SPSS Inc.). **Results:** Only 49 patients were able to complete the four courses of neoadjuvant chemotherapy. The age of the study population ranged from 24 to 54 (40.92±7.98) years. The pre-chemotherapy sizes of the breast masses ranged from 3.0-25.0 (9.70±4.33) cm. The mean size of the breast masses after 1st to 4th course were:8.26±4.13cm, 6.72±4.32cm, 6.09±4.97cm and 5.79±5.35cm respectively. The size reduction were significant, Spearman's correlation coefficients S_r values of 0.869, 0.667, 0.619 and 0.599 from 1st to 4th course. Nine (18.4%) of the 49 patients have achieved clinical complete response (cCR) after 4 courses of NAC. **Conclusion:** Neoadjuvant chemotherapy using combined cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) was found to be very effective in the management of locally advanced breast cancer in premenopausal women.

Keywords: Breast cancer, chemotherapy, premenopausal women.

INTRODUCTION

The commonest malignancy affecting women in many parts of the world is breast cancer, with an estimated 2.1 million new patients diagnosed in 2018 worldwide.[1] Breast carcinoma is the commonest diagnosed cancer among women and the leading cause of cancer death.[1] Breast cancer in Nigeria and other developing countries is characterized by the late presentation and poor outcome primarily due to ignorance, superstition, self-

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denial, fear of mastectomy and unavailability of treatment facilities.[2-4] Breast cancer presents a decade earlier in Nigerian women and other black women with worse biological behaviour and poor prognosis.[5-10]

Neo-adjuvant chemotherapy (NAC) has been demonstrated as a helpful strategy and the standard of care in the multimodal management of locally advanced breast cancer in Countries at all levels of development.[11-18] A lot of clinical benefits have been attributed to the use of NAC, which include: tumour down-staging to allow for breast-conserving surgery; improved cosmetic outcome; reduction of surgical dissection of the axilla; allowing enough time for germline mutation test results (i.e. BRCA1/2) that may influence surgical plan; making available individualized post-treatment prognostic information (e.g. pathological complete response, residual cancer burden) for management decisions; allows monitoring of response to treatment at an early stage; permitting time and flexibility to switch therapies if the patient is not responding adequately.[11-18]

Several chemotherapeutic agents have been used in various combinations. The choice of chemotherapeutic agents has since been defined by some guiding factors such as age, hormone receptor status, Her-2 neu status, and the biological nature of the tumour.[19,20-22] Post-menopausal women respond better to hormonal therapy, especially with hormone receptor-positive tumours.[11] Patients with HER-2 neu enriched breast cancers respond better to combinations containing monoclonal antibodies like trastuzumab.[11] While the standard of care for premenopausal women, especially those with Triple-negative breast cancers (TNBC), includes anthracycline-based regimens such as doxorubicin and cyclophosphamide followed or proceeded by a taxane (docetaxel or paclitaxel).[11] The number of chemotherapy cycles given during NAC varied between 4-6 cycles in most studies.[12-14]

Objective: This study aims at evaluating the effectiveness of anthracycline based neoadjuvant chemotherapy in down-staging locally advanced breast cancer in pre-menopausal women.

MATERIALS AND METHODS

This is an interventional cohort study of all consecutive premenopausal female patients presenting in the two general surgery clinics with confirmed locally advanced breast cancer (LABC), Stage IIIA, IIIB and IIIC breast cancer and $T_3N_0M_0$ subset of Stage IIB who had not received any form of intervention except core needle biopsy. The study was carried out over a period of 12 months. Ethical approval was sort and obtained from the Ethical committee of the University Teaching Hospital. The patients were adequately counselled and their written consent obtained.

The staging investigations were done before and after NAC and include chest X-ray, liver function test, abdominopelvic ultrasound scan and X-ray of the bone site if bone pain is present. All premenopausal women with evidence of distant metastasis demonstrable before the onset of NAC or shortly after that (<1 month) were excluded. Before initiation of NAC, a complete blood count was performed, and the body surface area was determined. On each visit, these were repeated for subsequent cycles of chemotherapy.

All eligible patients presenting to the specialist breast clinic were counselled on the benefits of NAC as regards downstaging the primary tumour before mastectomy. 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. With the calliper, the size of the primary breast tumour was measured in its two greatest diameters and recorded before each course of chemotherapy and three weeks after the 4th course of NAC. A Doxorubicin containing regimen was used. The regimen: cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) consisted of cyclophosphamide 500 mg/m^2, Doxorubucin50 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.

Medication response was evaluated using a modification of the RECIST methodology.[23] Response was assessed as a clinical complete response (cCR), this was when there is an absence of residual tumour on examination anytime throughout NAC or by the end of the NAC before loco-regional therapy. Partial response was described as a decline of at least 30% in the greatest diameter of the target tumour. No response (NR) was established as no evidence of a decrease in tumour size or any reduction in the longest diameter of target lesion <30%, or any evidence of the presence of a new lesion (i.e., stable and progressive disease in RECIST methodology).

The data collected were recorded initially in the proforma used for the study. The data were analyzed using the SPSS statistical software version 23.0. (Statistical Package for Social Sciences SPSS Inc.). Simple frequency and graphic statistics, one sample T-test, correlation and ANOVA table were used while evaluating response using RECIST methodology.

RESULTS

A total of 62 patients were recruited into the study after confirmation of breast carcinoma via core needle biopsy of breast masses. Out of the initial 62 patients, 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. Pre-chemotherapy sizes: The pre-chemotherapy sizes of the breast masses ranged from 3.0-25.0cm (Table 1). The mean size of the breast masses was 9.70±4.33cm.

Sizes after 1st course: The dimensions of breast masses after the first neoadjuvant chemotherapy ranged from 2.0-19.0cm (Table 2). The mean size of the breast masses was 8.26±4.13cm. None of the 49 patients had achieved clinical complete response (cCR) according to the RECIST criteria.

Sizes after 2nd course: The dimensions of breast masses after the second course of neoadjuvant chemotherapy ranged from 0-19.0cm (Table 3). The mean size of the breast masses was 6.72±4.32cm. One (2.0%) of the patients had achieved clinical complete response (cCR) according to the RECIST criteria.

Sizes after 3rd course: The dimensions of breast masses after the third course of neoadjuvant chemotherapy ranged from 0-24.0cm (Table 4). The mean size of the breast masses was 6.09±4.97cm. Five (10.2%) of the patients have achieved clinical complete response (cCR) according to the RECIST criteria.

Sizes after 4th course: The dimensions of breast masses after the fourth course of neoadjuvant chemotherapy ranged from 0-26.0cm (Table 5). The mean size of the breast masses was 5.79±5.35cm. Only 5(10.2%) of the patients showed an increase in dimensions of their tumours, i.e. progressive disease.

From table 6, the result of the spearman's ranked correlation analysis shows that the reduction in the sizes from pre-chemotherapy size to the sizes after the first course, second course, third course and fourth course respectively is highly significant. This can be seen from the Spearman's correlation coefficients $\mathbf{S}_r$ values of 0.869, 0.667, 0.619 and 0.599 for the first course, second course, third course and fourth course respectively. This indicates a high level of response of the breast tumours to NAC with CAF.

Nine (18.4%) of the 49 patients have achieved clinical complete response (cCR) according to the RECIST criteria (Table 7). The pre-chemotherapy sizes of the tumours show a significant reduction in sizes after the 4th course of NAC with Pearson's correlation of 0.602 ($p<0.00$).

Table 1: Frequency distribution of size of breast masses pre-chemotherapy.

Size of breast mass(cm)	Frequency	Percentage
3.0	3	6.1
4.0	2	4.1
5.0	2	4.1
6.0	5	10.2
7.0	5	10.2
8.0	4	8.2
8.5	1	2.0
9.0	1	2.0
10.0	8	16.3
11.0	2	4.1
11.5	2	4.1
12.0	4	8.2
14.0	2	4.1
15.0	5	10.2
16.0	1	2.0
17.0	1	2.0
25.0	1	2.0
Total	**49**	**100**

Table 2: Frequency distribution of size of breast masses after 1st course neoadjuvant chemotherapy.

Size of breast mass(cm)	Frequency	frequency
2.0	2	4.1
3.0	3	6.1
4.0	2	4.1
5.0	4	8.2
6.0	9	18.4
7.0	4	8.2
7.5	2	4.1
8.0	6	12.2
9.0	2	4.1
9.6	1	2.0
10.0	2	4.1
11.0	2	4.1
12.0	3	6.1
13.0	1	2.0
15.0	1	2.0
16.0	3	6.1
18.0	1	2.0
19.0	1	2.0
Total	**49**	**100**

Table 3: Frequency distribution of size of breast masses after 2nd course neoadjuvant chemotherapy.

Size of breast mass(cm)	Frequency	frequency
1.0	1	2.0
1.0	1	2.0
2.0	4	8.2
3.0	4	8.2
4.0	4	8.2
5.0	6	18.4
6.0	9	18.4
6.5	1	2.0
7.0	4	8.2
7.5	2	4.1
8.0	3	6.1
10.0	5	10.2
14.0	1	2.0
15.0	1	2.0
16.0	1	2.0
20.0	2	4.1
Total	**49**	**100**

Table 4: Frequency distribution of size of breast masses after 3rd course neoadjuvant chemotherapy.

Size of breast mass(cm)	Frequency	frequency
.0	5	10.2
1.0	3	6.1
2.0	3	6.1
3.0	1	2.0
4.0	7	14.3
5.0	5	10.2
6.0	9	18.4
6.5	2	4.1
7.0	2	4.1
7.5	1	2.0
8.0	1	2.0
9.0	2	4.1
10.0	2	4.1
14.0	1	2.0
15.0	1	2.0
16.0	1	2.0
20.0	1	2.0
24.0	1	2.0
Total	**49**	**100**

Table 5: Frequency distribution of size of breast masses after 4th course neoadjuvant chemotherapy.

Size of breast mass(cm)	Frequency	frequency
.0	9	18.4
1.0	1	2.0
2.0	2	4.1
3.0	5	102
4.0	4	8.2
5.0	7	14.3
6.0	6	12.2
6.5	1	2.0
7.0	2	4.1
7.4	1	2.0
8.0	1	2.0
100	5	102
14.0	1	2.0
15.0	1	2.0
16.0	1	2.0
200	1	2.0
26.0	1	2.0
Total	**49**	**100**

Table 6: Result of the spearman's ranked correlation analysis. Correlation is significant at the 0.01

Corrections

			Pre-chemotherapy size	Size after 1st course	Size after 2nd course	Size after 3rd course	Size after 4th course
Spearman's rho	Pre-chemotherapy size	Correlation Coefficient	1.000	.869**	.667**	.619**	.599**
		Sig. (2-tailed)	.	.000	.000	.000	.000
		N	49	49	49	49	49
	Size after 1st course	Correlation Coefficient	.869**	1.000	.830**	.788**	.764**
		Sig. (2-tailed)	.000	.	.000	.000	.000
		N	49	49	49	49	49
	Size after 2nd course	Correlation Coefficient	.667**	.830**	1.000	.965**	.939**
		Sig. (2-tailed)	.000	.000	.	.000	.000
		N	49	49	49	49	49
	Size after 3rd course	Correlation Coefficient	.619**	.788**	.965**	1.000	.980**
		Sig. (2-tailed)	.000	.000	.000	.	.000
		N	49	49	49	49	49
	Size after 4th course	Correlation Coefficient	.599**	.764**	.939**	.980**	1.000
		Sig. (2-tailed)	.000	.000	.000	.000	.
		N	49	49	49	49	49

Table 7: Frequency distribution of clinical response after 4th course (RECIST criteria

Clinical response (RECIST criteria)	Frequency	frequency
Complete response	9	18.4
Partial response>30%	28	57.1
Stable disease<30%	7	14.3
Progressive disease >20%	5	10.2
Total	**49**	**100**

DISCUSSION

The age of the patients in the current study ranged between 24-54 years with a mean of 40.92±7.98 years. This correlates with a mean of 42.1 years and an age range of 26 to 51 years was documented in a similar study at Nnewi.[24] This is also similar to a mean of 42.8 years and a range of 30-49 years recorded by Anyanwu et al.[12] The similarity of the current study to these two studies is most likely because all the studies were done on premenopausal women. Other studies, including the one done in Shiraz, Iran, noted a mean age of 41.0±8.61 years.[25] The above findings differ from what was documented by Olatoke et al.[26] who recorded an age mean of 47.9±13.1 years with a range of 28-85 years. This difference is obviously due to the inclusion of both pre-and post-menopausal women in their study.

The mean sizes of the breast tumours showed significant reduction with each course of NAC compared to the pre-chemotherapy size. The mean pre-chemotherapy tumour size was 9.70±4.33cm (Range 3.0-25.0 cm) and the mean sizes after NAC were as follows: 8.26±4.13cm (Range 2.0-19.0cm); 6.72±4.32cm (Range 0-19.0cm); 6.09±4.97cm (Range 0-24.0cm) and 5.79±5.35cm (Range 0-26.0cm) after the first to the fourth courses respectively (Tables 1-5). This size reduction showed a positive correlation between the pre-chemotherapy sizes and the sizes after the 4 courses of neoadjuvant chemotherapy. This can be seen from the Spearman's correlation coefficients **(A)**

values of 0.869, 0.667, 0.619 and 0.599 for the first course, second course, third course and fourth course respectively (Table 6). This indicates a high level of response of the breast tumours to NAC with CAF. Anyanwu et al.[12] in their study at Nnewi on premenopausal and perimenopausal patients using a combination of cyclophosphamide, doxorubicin and 5-Fluorouracil (CAF), recorded a pre-chemotherapy tumour size of 13.5cm (Range 7-35cm), which declined steadily to mean of 7cm at the 5 visits. This showed some correlation with the finding in the current study, which also made use of the same chemotherapy regimen.

At the end of the current study, 9 (18.4%) of the patients achieved clinical complete response after the 4th course of neoadjuvant chemotherapy, and significant clinical response was 37(75.5%) according to the modified RECIST criteria (Table 7). The significant clinical response of 75.5% in this study corresponds with the range of 50-89% recorded by several authors in Nigeria.[12,14,19,26] Also, reports of NAC in developed countries suggest significant clinical response rates ranging from 50–80% with a high rate of clinical complete response.[26] Previous reports by Arowolo et al.[19], Egwuonwu et al.[14] and Anyanwu et al.[12] in Nigeria were 51.8%, 74.2% and 89% response rates. The present study also recorded a clinical complete response (cCR) rate of 9(18.4%) (Table 6). The clinical complete response recorded in this study is much higher than 3.6% and 12.9% documented by Anyanwu et al.[12] and Egwuonwu et al.[14] respectively, probably because the current study recruited a slightly larger number of patients than the other two studies. Arolowo et al.[19] noted 6.6% for clinical complete response which is also low compared to the current study. This is probably so because their study used the NAC regimen: Cyclophosphamide, methotrexate, and 5-Fluorouracil (CMF) combination, which has a lower response rate than the CAF regimen used in the current study.[19]

The present study also documented a stable disease rate of 7(14.3%) and a progressive disease rate of 5(10.2%), which could be summed up as no response rate of 12(24.5%) (Table 7). This no response value corresponds to the finding by Egwuonwu et al.[14] who noted no response of 25.8% but lower than 33.9% documented by Arolowo et al.[19] This probably because Arolowo and his team used CMF instead of CAF used by Egwuonwu et al.[14] and the current study. These differences in the responses reported by Arolowo et al.[19] compared with the present study and similar studies further reinforce that the CAF regimen has a superior clinical reaction on breast cancers than CMF.

CONCLUSION

Neoadjuvant chemotherapy using intravenous cyclical combined cyclophosphamide, doxorubicin and 5-flourouracil (CAF) was found to be very effective in the management of locally advanced breast cancer in premenopausal women in our study population. The study recorded very good clinical response with significant reduction in sizes of breast tumours. This will ensure a better prognosis with reduction in the extent of breast surgery and a possibility of breast conserving surgery in some of the cases. This is very encouraging especially in our environment where a majority of the patients with breast cancer present in very advanced stages.

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Ethical approval: The study was approved by the Institutions Ethical Committee.

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