Neoadjuvant Chemotherapy in Breast Cancer: How Many Courses are Adequate?

Chimezie I. MADUBOGWU

ABSTRACT

Background: Neoadjuvant chemotherapy (NAC) has been found very useful in the treatment of locally advanced breast cancer. The number of chemotherapy cycles given during NAC varied between 4-6 cycles in most studies. **Objectives:** To assess the number of courses of NAC that will show the earliest and most significant reduction in sizes of breast mass. **Methodology:** The size of breast masses and regional lymph nodes in the pre-menopausal women were assessed before each course of chemotherapy and three weeks after the 4th course of NAC. A Doxorubicin containing regimen: cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) was given at 3 weekly intervals. Medication response was evaluated using a modification of the RECIST (Response Evaluation Criteria In Solid Tumours) methodology. The data were analyzed using the SPSS statistical software version 23.0. (Statistical Package for Social Sciences SPSS Inc.). **Results:** Forty-nine patients completed the four courses of neoadjuvant chemotherapy with age range of 24-54years and mean age of 40.92±7.98 years. The initial sizes of the breast masses ranged from 3.0-25.0cm with mean of 9.70±4.33cm. The mean size of the breast masses after 1st, 2nd, 3rd and 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 very significant, Spearman's correlation coefficients rs values of 0.869, 0.667, 0.619 and 0.599 from 1st to 4th course. The patients achieved clinical complete response (cCR) of 0%, 2.0%, 10.2% and 18.4% after the 1st to 4th courses. **Conclusion:** The tumour sizes in pre-menopausal breast cancer showed significant reduction after the first to the fourth courses of neoadjuvant chemotherapy. Chemotherapy regimen should be reviewed after the third course if there is no significant clinical response.

Keywords: Breast cancer, Chemotherapy, Neoadjuvant, Number of courses.

INTRODUCTION

Neoadjuvant chemotherapy (NAC) has been found very useful in the treatment of locally advanced breast cancer. It is equivalent to adjuvant (post-operative) chemotherapy in terms of disease-free and overall survival.[1,2] As a cancer biology research tool, NAC provides a platform for effectively evaluating the safety and efficacy of novel therapeutic drugs while monitoring the tumour's physical and/or biological response. Surgically, the primary goal of NAC is to achieve tumour or nodal down-staging to increase tumour resectability and decrease surgical morbidity. Other indications of NAC

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include: rise in resectability of locally advanced breast cancer and inflammatory breast cancer (stage IIIA-IIIC) and enhances early administration of systemic therapy to individuals at highest risk of systemic occult disease. It increases the feasibility of breast-conserving surgery among women with Stage II-III invasive breast cancer who would otherwise require mastectomy due to unfavourable breast-to-tumour ratio. It also increases the cosmesis of breast-conserving surgery among breast-conserving surgery candidates who might otherwise achieve inferior cosmetic results due to unfavourable breast-to-tumour ratio. Neoadjuvant chemotherapy helps to achieve reduction in the morbidity and extent of axillary surgery in patients with significant axillary lymph node disease.[1,2,3,4,5] It helps to downstage the axillary nodal stage in node-positive patients who might benefit from sentinel node biopsy. Neoadjuvant chemotherapy may be considered an option for anyone for whom adjuvant systemic therapy is indicated.

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 preceded by a taxane (docetaxel or paclitaxel).[6] The number of chemotherapy cycles given during NAC varied between 4-6 cycles in most studies.[7-9] In a survey by Egwuonwu et al.[9] at Nnewi using a combination of Cyclophosphamide, Doxorubicin and 5-Flourouracil, they demonstrated that the use of four courses of doxorubicin-based neoadjuvant chemotherapeutic regimen resulted in tumour down-staging that is equivalent to an entire course of 6 cycles and independent of primary tumour size and disease stage at presentation.

In Nigeria, studies on NAC have been done in some centres.[7,9,10,11,12,13] In all these studies, NAC was found as a reliable means in the multimodal treatment of locally advanced cancer of the breast. This study aims to assess the number of courses of NAC that will show the earliest and most significant reduction in sizes of breast mass. Also to evaluate the degree of breast tumour response to NAC in relation to the initial pre-chemotherapy sizes.

METHODOLOGY

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 obtained from the institutional ethics committee before commencement of the study. 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. The clinical regional lymph node assessment was done before each course of chemotherapy and three weeks after the 4th course of NAC. The regional lymph nodes were graded according to the AJCC (TNM) system of staging of breast cancer.[14] A Doxorubicin containing regimen was used. The regimen: cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) consisted 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.

Medication response was evaluated using a modification of the RECIST (Response Evaluation Criteria In Solid Tumours) methodology.[15] The 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). Furthermore, the primary tumour response was categorized into ≤10 cm and >10 cm to determine their response to NAC.

The data collected were recorded initially in the proforma used for the study. The data were analyzed using the SPSS (Statistical Package for Social Sciences SPSS Inc.).statistical software version 23.0. 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. Nine (18.4%) of the 49 patients have achieved clinical complete response (cCR). 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 r_s 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 ($p<0.00$).

Of the 49 patients, 9 (18.4%) achieved complete clinical response after the 4th course of neoadjuvant chemotherapy. The significant clinical response, a combination of full and partial response, was 37(75.5%) (Table 7). Six out of the nine with complete response have breast masses that were ≤10cm at the pre-chemotherapy stage, while three have masses >10cm (Table 8). Out of 28(57.1%) that achieved partial response, 10 patients had pre-chemotherapy tumour sizes ≤10cm, and 18 had tumour sizes >10cm (Table 8). These showed no statistical significance ($Chi^2=3.458$, $p=0.326$).

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

Pre-chemotherapy size			
Size of breast mass(cm)	Frequency	Percentage frequency	Cumulative Percent
3.0	3	6.1	6.1
4.0	2	4.1	10.2
5.0	2	4.1	14.3
6.0	5	10.2	24.5
7.0	5	10.2	34.7
8.0	4	8.2	42.9
8.5	1	2.0	44.9
9.0	1	2.0	46.9
10.0	8	16.3	63.3
11.0	2	4.1	67.3
11.5	2	4.1	71.4
12.0	4	8.2	79.6
14.0	2	4.1	83.7
15.0	5	10.2	93.9
16.0	1	2.0	95.9
17.0	1	2.0	98.0
25.0	1	2.0	100.0
Total	49	100.0	

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

Size after 1st course			
Size of breast mass(cm)	Frequency	Percentage frequency	Cumulative Percent
2.0	2	4.1	4.1
3.0	3	6.1	10.2
4.0	2	4.1	14.3
5.0	4	8.2	22.4
6.0	9	18.4	40.8
7.0	4	8.2	49.0
7.5	2	4.1	53.1
8.0	6	12.2	65.3
9.0	2	4.1	69.4
9.6	1	2.0	71.4
10.0	2	4.1	75.5
11.0	2	4.1	79.6
12.0	3	6.1	85.7
13.0	1	2.0	87.8
15.0	1	2.0	89.8
16.0	3	6.1	95.9
18.0	1	2.0	98.0
19.0	1	2.0	100.0
Total	49	100.0	

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

Size after 2nd course			
Size of breast mass(cm)	Frequency	Percentage frequency	Cumulative Percent
.0	1	2.0	2.0
1.0	1	2.0	4.1
2.0	4	8.2	12.2
3.0	4	8.2	20.4
4.0	4	8.2	28.6
5.0	6	12.2	40.8
6.0	9	18.4	59.2
6.5	1	2.0	61.2
7.0	4	8.2	69.4
7.5	2	4.1	73.5
8.0	3	6.1	79.6
10.0	5	10.2	89.8
14.0	1	2.0	91.8
15.0	1	2.0	93.9
16.0	1	2.0	95.9
20.0	2	4.1	100.0
Total	49	100.0	

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

Size after 3rd course			
Size of breast mass(cm	Frequency	Percentage frequency	Cumulative Percent
.0	5	10.2	10.2
1.0	3	6.1	16.3
2.0	3	6.1	22.4
3.0	1	2.0	24.5
4.0	7	14.3	38.8
5.0	5	10.2	49.0
6.0	9	18.4	67.3
6.5	2	4.1	71.4
7.0	2	4.1	75.5
7.5	1	2.0	77.6
8.0	1	2.0	79.6
9.0	2	4.1	83.7
10.0	3	6.1	89.8
14.0	1	2.0	91.8
15.0	1	2.0	93.9
16.0	1	2.0	95.9
20.0	1	2.0	98.0
24.0	1	2.0	100.0
Total	49	100.0	

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

Size after 4th course			
Size of breast mass(cm)	Frequency	Percentage frequency	Cumulative Percent
.0	9	18.4	18.4
1.0	1	2.0	20.4
2.0	2	4.1	24.5
3.0	5	10.2	34.7
4.0	4	8.2	42.9
5.0	7	14.3	57.1
6.0	6	12.2	69.4
6.5	1	2.0	71.4
7.0	2	4.1	75.5
7.4	1	2.0	77.6
8.0	1	2.0	79.6
10.0	5	10.2	89.8
14.0	1	2.0	91.8
15.0	1	2.0	93.9
16.0	1	2.0	95.9
20.0	1	2.0	98.0
26.0	1	2.0	100.0
Total	49	100.0	

Table 6: Result of the spearman's ranked correlation analysis **. Correlation is significant at the 0.01 level (2-tailed).
Table 6.
Correlations

			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 4 course (RECIST criteria).

RECIST criteria			
Clinical response(RECIST criteria)	Frequency	Percentage frequency	Cumulative Percent
Complete response	9	18.4	18.4
Partial response>30%	28	57.1	75.5
Stable disease<30%	7	14.3	89.8
Progressive disease>20%	5	10.2	100.0
Total	49	100.0	

DISCUSSION

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 r_s 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.

The optimal timing and duration of neadjuvant chemotherapy has not been clearly defined but a lot of studies has advocated four to six courses.[8,9,16,17] Egwuonwu et al.[9] in their study on locally advanced breast cancer in pre-menopausal women at Nnewi concluded that four courses of anthracycline based regimen was effective for neoadjuvant chemotherapy. They also noted that maximum reduction in tumour size was after the second course. They found out that prescribing six courses of NAC did not confer any significant advantage over the use of four courses in their patient population, but could result in reduced adherence to NAC in the treatment of LABC. They were able to achieve cCR and significant clinical response rate of 12.9% and 74.2% respectively after four courses of CAF chemotherapy. The current study documented cCR of 0%, 2.0%, 10.2% and 18.4% after the first to the fourth courses respectively (Tables 2-5). The index study also showed significant reduction in tumour sizes from the first to the fourth course as shown in the Spearman's correlation coefficients r_s 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). From the findings above in the current study, a review of the chemotherapy regimen is advocated if there is no significant clinical response after maximum of third course of neoadjuvant chemotherapy.

In this study, 9(18.4%) achieved clinical complete response (cCR) after the fourth course of chemotherapy. Of these nine with cCR, six patients had pre-chemotherapy tumour sizes ≤10cm, and the remaining three had tumours >10cm in their widest diameter. Also, out of the 28 patients that achieved partial response, 10 had pre-chemotherapy tumour sizes ≤10cm, and 18 had tumours >10cm (Table 8). Though there seemed to be a marked difference between tumours ≤10cm and ones >10cm in terms of cCR, this did not reflect on the other parameters on the RECIST criteria (Table 8). The significance level test in response to NAC between tumours ≤10cm and ones >10cm showed no statistical significance (Chi^2= 3.458, p=0.326). The finding in the current study agrees with similar work done by Egwuonwu[18], who noted there was no apparent statistically significant correlation between pre-chemotherapy primary neoplasm size and clinical response. This is, however, in contrast to the findings by Arolowo et al.[10] and Olatoke et al.[13], who noted that the numbers of partial and complete responses were significantly higher among groups with pre-chemotherapy tumours ≥10cm.

CONCLUSION

The tumour sizes in pre-menopausal breast cancer showed significant progressive reduction after the first to the fourth courses of neoadjuvant chemotherapy. It also showed cCR of 10.2% and 18.4% after the third and fourth courses respectively. It is therefore advocated that the chemotherapy regimen be reviewed after the third course if there is no significant clinical response. There is also no statistically significant correlation between pre-chemotherapy primary neoplasm size and clinical response.

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