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Four versus Six Cycles of Neoadjuvant Chemotherapy in Premenopausal Women

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ABSTRACT

Background: Breast cancer in Nigeria occurs mainly in premenopausal women and is seen at an advanced stage of the disease resulting in its poor survival rate. Achieving local disease control in Locally Advanced Breast Cancers (LABC) affecting premenopausal women remains a challenge. Neoadjuvant Chemotherapy (NAC) is the standard of care for LABC. Although response after the initial cycles is maximal, toxicity, however is profound after the fourth cycle.

Objective: To determine the reductions in size of a primary tumour, and adverse effect profiles when 4 and 6 cycles of NAC are used in premenopausal women with clinically confirmed LABC in FETHA.

Methodology: This was a twelve-month prospective, comparative randomised study of premenopausal women with histologically confirmed and clinically diagnosed LABC at FETHA. Patients were randomized into two groups (A and B). Group A received four cycles, and group B received six cycles of NAC. Cyclophosphamide and Adriamycin were administered as NAC. Observed effects were documented. Data collected were demographics, primary tumour size at the onset of NAC, difference in primary tumour size between cycles in each group, difference in tumour size three weeks after the fourth or the sixth cycle of NAC, difference in the values of the hematological profiles between cycles in each group, and other non-hematological toxicities.

Data was analysed using Statistical Package for Social Sciences (SPSS) Version 20. Continuous data were presented as means and standard deviation while categorical data were presented as frequencies and percentages. Students T test and Chi square tests were used to compare continuous and categorical data repectively.Statistical significance was set at P less than 0.05.

Result: Thirty-six patients were recruited into groups A and B; 18 patients in each group. The mean age for groups A and B were 39.50 ± 4.37 years and 36.89 ± 4.75 years. The mean reduction in size of the primary tumour at the end of NAC in groups A and B were 7.78 ± 5.24cm and 8.07 ± 7.04cm (P= 0.899). Maximum response was noted after the first and second cycles in both groups of the study. The mean percentage response of the primary tumour at the end of NAC for groups A and B were 37.80 ± 24.89% and 38.16 ± 45.86% respectively (P= 0.977).

The mean reduction in absolute neutrophil count (ANC) at the end of NAC in groups A and B were 0.48 × 103/mm^3 and 1.31 × 103/mm^3 respectively with a p value of 0.002. Alopecia was the most common adverse effect. Fever occurred more in patients that received six cycles.

Conclusion: No significant size reduction was noted after the fifth and sixth cycles of NAC. Four cycles of NAC achieved reduction of the primary tumour size similar to six cycles. Adverse effects occurred more when six cycles were given.

Keywords: Neoadjuvant Chemotherapy; Locally Advanced Breast Cancer; Premenopausal women

INTRODUCTION

Breast cancer in Nigeria occurs mainly in premenopausal women and is seen at an advanced stage of the disease resulting in its poor survival rate. Neoadjuvant chemotherapy can achieve local disease control in locally advanced breast cancer in premenopausal women.[1,2]

Neoadjuvant Chemotherapy (NAC) is the use of cytotoxic agents as the first treatment modality before definitive loco-regional therapy.[1,2] This has become a valuable strategy in the multimodality treatment approach to breast cancer. NAC achieves tumour down staging benefits, improves respectability, prognosticates tumor chemo responsiveness, tackles micro-metastasis early and may enable breast conservation surgery (BCS).[1,2,3-6]

Locally Advanced Breast Cancer (LABC) is a subset of breast cancer characterized by the most advanced breast tumours in the absence of distant metastasis. This includes patients with;

1. Primary tumours: larger than 5.0cm (T3), involving the chest wall (T4a), the skin (T4b), both skin and chest wall (T4c).
2. Lymph nodes: fixed axillary (N2), ipsilateral internal mammary and supraclavicular/infraclavicular (N3) lymph nodes involvement.
3. Inflammatory breast cancer (T4d).

Thus, all stage III disease and a subset of stage IIB (T3N0M0) are considered LABC.[3,7]

Breast cancer continues to be a significant problem worldwide,[1] as up to one million cases are diagnosed annually with North America and Europe having the highest burden of the disease8. Sub-Saharan Africa on the other hand has a low incidence.[8] In 2012, the estimated global incidence of breast cancer is 1.7million.[8] It is the most common cancer among women in most parts of the world including Nigeria.[1,2] In Nigeria, breast cancer has now

replaced cervical cancer as the commonest female malignancy with prevalence ranging between 10 per cent to 42 per cent.[2,8-11]

Despite higher incidence rates, breast cancer deaths are lower among white women than African American women.[12] In Nigeria, the estimated mortality in 2012 was 13,960.[9]
Breast cancer in sub-Sahara African women is characterized by young age at presentation, occurring about a decade earlier than patients in western countries.[1,8,12] In Nigeria, the disease is mainly premenopausal, seen mostly at stage III of the disease and with poor treatment outcome. Achieving local disease control in LABC in this category of patients remains a challenge.[1,2,13]

NAC is the standard of care for women with locally advanced, inflammatory or inoperable primary breast cancer.[14,15] The tumour down staging benefit of NAC reported from developed countries has resulted in more Breast Conservative Surgery [BCS] and reduced loco-regional recurrence.[5,16] In Nigeria and Sub-Saharan Africa, rate of BCS is negligible[2,17] when compared to developed countries.[2,5,17] Mastectomy continues to be the available surgical treatment modality despite the fact that this procedure is often resented.[18]

Majority of breast cancer patients in Nigeria are premenopausal,[2] therefore, NAC would be more appropriate for these patients than neoadjuvant hormonal therapy. This is because premenopausal breast cancers are predominantly hormone receptor negative.[1,2,8]
Currently, anthracycline-based NAC is widely studied, and it results in at least 50% tumour shrinkage in more than 75% of cases.[2]

Oncologists have varying recommended number of cycles for NAC. Chemotherapeutic drugs are expensive and in Nigeria, most patients fund their health care out-of-pocket. This study may serve as a frame-work for the adoption of a hospital protocol that considers benefits-cost implications in favour of the patients.
Most studies on NAC in breast cancer used the same number of cycles for all the patients studied, and their percentage responses were calculated. This study seeks to clarify patients' responses with respect to the difference in reductions in size of the primary tumour when 4 or 6 cycles of NAC are used.
Studies have reported several adverse effects of NAC. This study also seeks to determine the cycle at which the toxicities may become unacceptable while its down-staging benefits are considered. The study is therefore aimed at determining any difference in primary tumour reduction and adverse effects when 4 and 6 cycles of NAC are used.

PATIENTS, MATERIALS AND METHODS

Ethical approval was obtained from the Hospital Research and Ethics Committee. The details of treatment including complications of chemotherapy were explained to individual patients. It was a one year prospective comparative randomized study carried out at Federal Teaching Hospital, Abakaliki (FETHA), a tertiary health institution located

in Abakaliki, Ebonyi State, and South East Nigeria. FETHA is the only university teaching hospital in Ebonyi State. This hospital serves as a referral centre for patients in Ebonyi state and neighboring states; Enugu, Benue, Cross river, and Abia states. Abakaliki is the state capital, and the largest commercial centre in Ebonyi state. The majority of the population of Abakaliki and other parts of Ebonyi state are farmers, undergraduates, few civil and public servants. The population is, therefore, majorly poor.

All pre-menopausal patients presenting at FETHA with clinically, and histologically confirmed LABC were included in the study. They include those with stage III [A, B and C] breast cancer and T3N0M0 subset of stage IIB who have not received any form of intervention except biopsy/histology. Exclusion criteria included; all pre-menopausal patients with evidence of distant metastasis demonstrable before onset of NAC, patients who did not give consent to be part of the study or withdrew their consent anytime during the study, post-menopausal patients with breast cancers, patients with cardiac problems as determined by two dimensional echocardiography (2D Echo) and/or electrocardiography (ECG), and recurrent breast cancers.

Selected patients underwent staging work-up which included: complete history and thorough physical examination including examination of the breasts, a chest X-ray, and abdominal ultrasound scan. An initial assessment of the size and the local extent of the tumours were determined and recorded. The primary breast tumour was measured in its two greatest diameters using a breast caliper. The sum of the two greatest diameters was documented as the size of the primary tumour for each patient in every cycle of NAC for both groups. Before initiation of NAC, a Full Blood Count (FBC) to include platelet count, liver function test, serum electrolyte, urea and creatinine, 2D Echo and ECG were done to ensure patients' fitness for chemotherapy. Also, the Body Surface Area (BSA) was calculated from height in centimeter and weight in kilogram.

Before each cycle of CA chemotherapy, hematological indices and BSA were assessed. To qualify to receive chemotherapy, each patient is expected to have Hb of $\geq$ 10g/dl, WBC of $\geq 2500/mm^3$ with absolute neutrophil count of $\geq 1000/mm^3$ and platelet count of $\geq 150{,}000/mm^3$.

Breast and regional lymph node assessment were done before each cycle of chemotherapy. Histological confirmation of the breast cancer was performed after obtaining a core biopsy. Group A received four cycles and group B six cycles. The patients were randomized to either of these groups by balloting. An anthracycline-based regimen was used. The CA regimen consisting of Cyclophosphamide $600mg/m^2$ and Adriamycin $60mg/m^2$ was given. The cyclophosphamide was given as bolus injection in a free-flowing intravenous line or as an infusion and the adriamycin was given as an infusion. IV ondansetron 8mg, IV dexamethasone 8mg and IV metochlopromide 10mg stat were given as pre-medications. Post-medications were tabs hematinics for 2weeks, tab ondansetrone 4mg tds, tab metochlopromide 10mg tds and tab dexamethasone 4mg tds for 3days. The cycle of CA was repeated at three-weekly intervals. Each patient received either four or six cycles of CA. NAC was terminated three weeks after the last cycle.

The difference in sizes between two cycles of NAC was documented as the response of the primary tumour to the preceding NAC. The response to the last doses in both groups was measured three weeks after. Response to treatment was also assessed using a modification of the Response Evaluation Criteria In Solid Tumour (RECIST) methodology.

The values of the PCV, platelet count, WBC count, and ANC at each cycle for both groups were noted. These results were obtained two weeks after the previous NAC for both groups. The differences between cycles were documented for analysis.

Evidence of non-hematological toxicities like alopecia, vomiting, diarrhea, fever, weakness, and xerostomia was sought and recorded at the next clinic visit after each NAC cycle. Significant early toxic effects (occurring before visit) were obtained by phone calls from the patients. The total number of patients that had each of the adverse effects was tallied at the end of NAC. The other adverse effects were recorded as the patients complained.

Data was analyzed using the SPSS statistical software (Statistical Package for Social Sciences, SPSS Inc. Norman H. Nie, Dale H. Bent, and C. Hadlai Hull. S Wacker Drive No 1100 Chicago, IL 60606 USA) version 20. Data were expressed as percentage, mean, standard deviation, and in tables or figures where appropriate. Test of significance was done using simple T-test for continuous variables and chi-square test for categorical variables. P value of <0.05 was considered statistically significant and conclusion drawn from it.

RESULTS

5.1 Patients' flow

During the study period,, a total of 51 patients with LABC were assessed for randomization. A total of 15 patients were excluded (13 postmenopausal and 2 premenopausal women with cardiac disease). Thus, 36 patients were recruited into two groups; randomized into group A (18 patients) who received four cycles of NAC and group B (18 patients) that received six cycles of NAC.

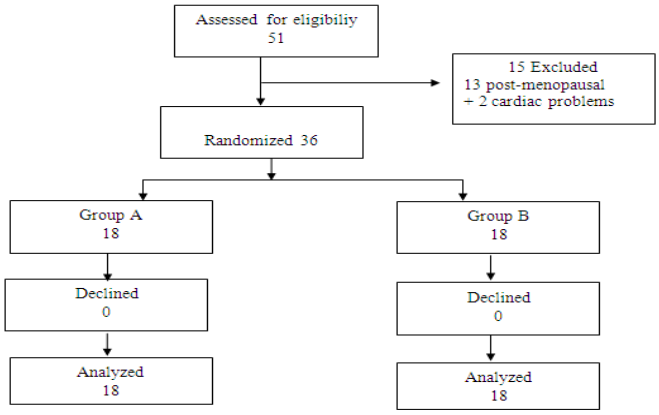

Figure 1: Patients' flow in the study.

The mean age for patients in group A was 39.5 +-4.37 while in group B was 36.89+-4.75 (*P*=0.095)

The age range of patients in group A was 33 - 49 years with a mean age of 39.50 ± 4.37 years. The age range for group B was 33 – 45years with a mean age of 36.89 ± 4.75 years. As shown in Table 1. The weight, height and body surface area for both groups were matched and no statistical difference was found: P values >0.05 as shown in Table

Table 1: Comparison of mean age, weight, height and body surface area amongst study groups.

Parameters	Group A (Four cycles)	Group B (Six cycles)	T test	P value
Age (years)	39.50±4.37	36.89±4.75	1.716	0.095
Weight (kg)	57.39±12.15	62.94±8.74	1.575	0.125
Height (m)	1.54±0.09	1.54±0.05	0.085	0.933
Body Surface Area (kg cm)	1.56±0.19	1.65±0.18	1.44	0.159

Two-thirds of patients in this study presented with breast lump only while one-third presented with both breast lump and ipsilateral axillary lump. Thirteen patients (72.2%) and 11 patients (61.1%) in group A and group B respectively presented with breast mass only while 5 patients (27.8%) and 7 patients (38.9%) respectively presented with breast mass plus ipsilateral axillary mass. Thirteen patients (72.2%) and 15 patients (83.3%) in group A and B respectively discovered their lumps themselves. Nine patients (50%) in group A and 11 patients (61.1%) in group B had their lumps in the left breast while 9 patients (50%) in group A and 7 patients (38.9%) in group B had their lumps in the right breast. No statistical difference was found in the symptoms of the patients, reasons for presentation and location of the mass; p values > 0.05.

All the patients in both groups had stage III disease. The core biopsy result of all the patients showed invasive ductal carcinoma.

The mean size of the primary tumour (at the onset of NAC) for groups A and B was 18.92 ± 6.54cm and 20.52 ± 11.15cm respectively; p = 1.139 as shown in Figure 1. A reduction in the mean size of the primary tumour was noted in both groups at the end of NAC as shown in Table 2. When compared cycle to cycle between group A and group B, the mean reduction in size of the primary tumour after each cycle was not statistically significant, p values > 0.05 (Table 2). Maximum reduction in size was noted after the first and second cycles in both groups of the study as shown in Figure 2. By the fifth and sixth cycles in group B, the mean reduction in sizes was 0.01cm and 0.02cm respectively as shown in Figure 2. The mean total reduction in size of the primary tumor after NAC in groups A and B was 7.78(±5.24)cm and 8.07(±7.04)cm respectively, p value = 0.899 as shown in Table 2. The mean percentage response for group A and B was 37.8% and 38.2% respectively (P=0.977) as shown in Table 2. This shows that majority of the patients had at least a partial response to the NAC irrespective of the number of cycles given. One patient (5.6%) and 2 patients (11.1%) within groups A and B respectively had complete disappearance of the primary tumour. This occurred before NAC 4 in both groups. Clinical responses for groups A and B were 43.4% and 49.3% respectively. None had stable or progressive disease.

Table 2: Primary Tumor Response (mean of total reduction in the sum of the widest diameters in cm and mean of percentage response) after NAC.

Parameter	Group A (Four cycles)	Group B(Six cycles)	T-test	P-value
Mean total reduction in size (cm) after NAC	7.78±5.24	8.07±7.04	0.127	0.899
Mean primary tumor size pre-NAC	18.92±6.54	20.52±11.15	----	1.139
Mean primary tumor size post-NAC	11.14±5.43	12.44±9.14	----	0.607
Mean % response after NAC	37.8±24.9	38.2±45.9	-0.29	0.977

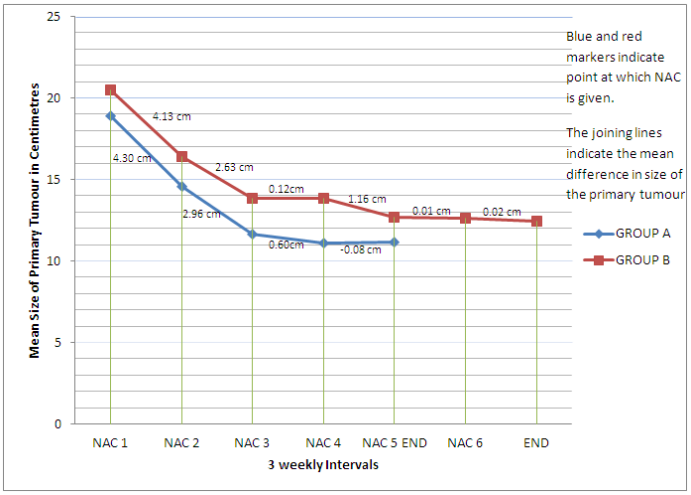

Figure 2: Shows the mean size of the primary tumour and the mean reduction in size during NAC.

A total of 16 patients (88.9%) and 17 patients (94.4%) in groups A and B respectively had a drop in PCV after NAC. Thirteen patients (72.2%) and 15 patients (83.3%) in groups A and B had a drop in platelet count after NAC. All the patients in both groups had a drop in WBC count after NAC. Three patients (16.7%) and 8 patients (44.4%) in groups A and B respectively had a drop in ANC after NAC. The mean changes in PCV, WBC, and platelet counts after each cycle and at the end of NAC in both groups were not statistically significant, $p > 0.05$ as shown in Table 3. The mean reduction in ANC at the end of NAC in both groups were 0.48 × 103/mm3 and 1.31 × 103/mm^3 respectively, P= 0.002 as shown in Table 3.

Table 3: Hematological toxicities (mean total reduction in PCV, Platelet count, WBC, and ANC) after NAC.

Mean total drop after NAC	Group A(Four cycles)	Group B(Six cycles)	T-test	P-value
PCV (%)	-6.17±4.46	-6.83±4.33	0.455	0.652
Platelet count (×10^3/mm^3)	-76.28±103.17	-128.44±83.09	1.671	0.104
WBC count (×10^3/mm^3)	-2.11±1.89	-3.03±1.26	1.714	0.096
ANC (×10^3/mm^3)	-0.48±0.63	-1.31±0.86	3.308	0.002

Across all groups, hair loss was noted to be the most common adverse effect, followed by dry mouth and darkened skin. Thirteen patients (72.2%) in group A and 15 patients (83.3%) in group B. Three patients (16.7%) in group A and 9 patients (50%) in group B had fever at the end of NAC, p value 0.038 as shown in Table 4.

Table 4: Non-hematological toxicities after NAC **.**

Parameter	Group A(Four cycles)	Group B(Six cycles)	Chi^2	P-value
Hair loss	13	15	0.16	0.686
Dry mouth	9	7	0.11	0.737
Darkened nails	7	6	0.12	0.732
Diarrhea	6	5	0.13	0.721
Weakness	3	4	0.17	0.678
Fever	3	9	3.13	0.038

DISCUSSION

The mean age of the patients in this study was 39.5 years and 36.9 years for groups A and B respectively. This is slightly different from a similar study done in Nnewi, South Eastern Nigeria where 42.1 years was reported as the mean age in pre-menopausal women.[2] This shows that more young women are becoming aware of the problems with breast cancers. In Western Nigeria, where over two-thirds of patients studied were premenopausal, the mean age was 48years.[19] The mean age in our study was lower because all the patients were premenopausal women.

RECIST criterion was used to assess individual patient's response to chemotherapy.[20] The size of the primary tumor in this study, like in RECIST model, was the sum of the widest diameter of the targeted tumor. The mean size of the primary tumor at the onset of NAC in groups A and B were 18.92cm and 20.52cm respectively. The difference in size was not statistically significant. The response was independent of initial size and subsequent sizes of the tumor during NAC. The results of this study show a very slight further reduction by 0.29cm of the primary tumor size after NAC in group B, but this was not statistically significant. Chintamani et al.[21] and Egwuonwu et al.,[2] in a similar study, grouped their patients into different sizes, and noted that the response to NAC does not depend on the size of the tumour. Gajdos et al.[22] and Moon et al.[23] noted that primary tumors less than 5cm and 10cm respectively had better response to NAC. These findings may be as a result of grouping of the patients into just two groups and the larger sample size used in both studies.

The mean percentage responses (clinical response) in both groups A and B in this study after NAC were 37.8% and 38.2% respectively which was not statistically significant. This shows that the majority of patients in this study had clinical partial response and it is not dependent on the number of cycles given. This is similar to the finding by Egwuonwu et al.[2] where the majority of their patients had greater than 30% reduction in tumor size at the end of the chemotherapy.[2] Hence, when more cycles were given, no significant increase in the overall percentage response of the primary tumor to the chemotherapy was observed. Anyanwu et al.,[7]in a similar study, found that 89% of

patients had partial response after NAC. The higher value obtained could be due to the 20% bench mark for partial response. Complete clinical response occurred in 3 patients (8.3%) in this study and as such, making them probably eligible for breast conserving surgery. This finding is not too different from similar study done in Nnewi where 12.9% of the patients had complete clinical response.[2] The study has demonstrated that NAC leads to a reduction in tumor size, thus downstages breast cancers. Moon et al.,[23],Fisher et al.[24] and Rastogi et al.[25]found that 25.6%, 36%, and 40% respectively, had complete clinical response. The higher values may be due to the smaller sized primary tumours in their works.

It was also noted in this study that maximum responses occurred in the first and second cycles. This finding is consistent with a study by Egwuonwu, et al in Nnewi, South Eastern Nigeria.[8] There is need for a larger population-based study to confirm this finding. It will desirably result in the use of less than four cycles for NAC. This will be cost effective for LABC patients.

Sixteen patients (88.9%) and 17 patients (94.4%) in groups A and B respectively, had a drop in PCV after NAC. Thirteen patients (72.2) in group A and 15 patient (83.3%) in group B had a drop in platelet count after NAC. All the patients in both groups had a drop in WBC count after NAC. The drops in PCV, platelet, and WBC counts were not significant for both groups when compared cycle to cycle. The reductions in the hematological profiles were minimal. This is in agreement with a work by Anyanwu et al.[7] The drop in the hematological indices noted did not require blood transfusion, or admission for its correction. Rather, the patients were given double dose hematinics, and the cycle of NAC deferred by 1 to 2 weeks.

Egwuonwu et al.[2] also found that the most common reason for deferring NAC was hematologic toxicity seen in 75% of their patients with leucopenia being the most common.[2] This agrees with the findings in this study where all the patients had a drop in WBC count.

The significant hematological toxicity noted in this study was reduction in ANC (neutropenia) that occurred after the third cycle in both groups. The number of patients with neutropenia increased with each additional cycle of NAC, being more in patients that had 6 cycles. This could be as a result of the cumulative effect of the drug at the end of six cycles. The mean drop in ANC from this study was less than 20% of the bench mark (moderate leucopenia), and the patients were managed by deferment of that cycle for 1 to 2 weeks. None of them received Granulocyte Colony Stimulating factor(C-GSF) besides not being available in FETHA. In the study by Egwuonwu et al.,[2] none of his patients with leucopenia developed septic complications and none received G-CSF also.[2]

The non-hematological adverse effects noted in this study include alopecia, diarrhea, darkening of nails, xerostomia, weakness, and fever. It was noted that the majority of patients from both arms of the study had alopecia. It is the most common adverse effect of anthracycline-based chemotherapy.[1] In this study, 13 patients (72.2%) and 15 patients (83.3%) in groups A and B respectively, had alopecia after NAC. Egwuonwu et al.[1] and Chintamani, et al.[21] noted alopecia in 51.6% and 60% respectively. The higher value in group B of this study could be the effects of the fifth and sixth cycles of NAC. However, Clegg-Lamptey, et al.[17] and Fisher, et al.[24] noted alopecia in all

their patients. The differences in these studies could just be individual study and population differences. Moreover, they all showed that alopecia is a very common adverse effect of anthracyclines.

Significant in this study was fever which occurred more in those that received six cycles (50% of the patients at the end of NAC). This correlates strongly with the neutropenia that was more in group B of the study. The fever occurred after the third cycle and persisted with each subsequent cycle of NAC despite negative malaria parasite test result. However, the febrile neutropenia was not significant enough to admit the patients into the wards for treatment. The patients were given antibiotics and antipyretics for two weeks during which they had their chemotherapy deferred.

The other non-hematological adverse effects noted in this study were mild. This is supported by the works done by other authors.[1,7,23] The cumulative adverse effects were noted to be more with the group that received six cycles. The total adverse effects were more than the number of patients. This is because most patients had more than one adverse effect, and some of these effects persisted during the study.
The non-hematological adverse effects from this study were generally tolerable by the patients and there was no need for termination of NAC.

CONCLUSION

NAC was effective in down-staging breast cancers mostly at the initial cycles. Administering six cycles of chemotherapy does not result in any significant down staging benefit over four cycles. Adverse effects abound though most are tolerable. The most serious adverse effect was febrile neutropenia which was noted mostly in those that had six cycles.

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