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Pathologic Complete Response Following Neoadjuvant Chemotherapy for Breast Cancer in a Nigerian Cohort

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ABSTRACT

Background: Pathologic complete response (pCR) following neoadjuvant chemotherapy (NAC) is a marker for important clinical outcomes in the management of breast cancer. In Nigeria where the majority of patients are candidates for NAC, there is limited data on pCR following NAC. This study evaluated the pCR rate in a cohort of Nigerian patients.

Methods: A retrospective review of patients who had NAC and mastectomy for breast cancer between 2017 and 2022. Relevant baseline clinicopathological and treatment data were obtained. pCR was defined as the absence of invasive cancer with or without in situ disease in the breast. The relationship between receptor status, type of chemotherapy and pCR was evaluated.

Results: One hundred and sixty six of the 250 patients who had mastectomy during the period had NAC and were eligible for analysis. The mean age was 50.1±11.1, and the majority had stage 3 disease. The overall (pCR) rate was 19.9%, with the latter part of the study corresponding to the period with increased use of taxanes, having higher pCR (35.9% in 2022 vs 7.4% in 2017, p=0.024). Patients with HER 2 positive/Hormone receptor negative (HER 2+/HR-), HER 2+/HR+ and triple-negative disease had significantly higher pCR than those with HR+/HER 2 negative disease (38.9%, 30.8%, 24.5% and 6.5% respectively, p=0.03).

Conclusion: NAC resulted in pCR in about one-fifth of the entire cohort, particularly those with potentially aggressive HER 2+ and triple-negative disease. The use of taxanes was associated with higher pCR rates.

INTRODUCTION

The discovery of potent systemic therapies and a better understanding of the biological profile of breast cancer have significantly changed the treatment landscape over the years. The use of chemotherapy in the management of breast cancer has been demonstrated to have equivalent effects when administered in the adjuvant or neoadjuvant setting.[1] The bias for neoadjuvant chemotherapy (NAC), however, lies in the opportunity it provides to measure the effect of treatment while the tumor is in situ.[2] The NSABP-18 trial demonstrated that patients

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who achieved pathologic complete response after NAC had better disease-free and overall survival relative to those who did not.[3] In addition, the use of NAC increased the chances of achieving breast conservation with a better quality of life.[4] NAC also provides a unique opportunity to deescalate axillary surgery in node-positive patients who become node-negative after chemotherapy.[5] The downstream effect of this is the avoidance of the morbidity associated with axillary lymph node dissection, which can be quite disabling for some patients. The use of NAC also provides a unique opportunity for testing the efficacy of new agents by evaluating their effect on tumor size.[2]

NAC is recommended in many clinical scenarios such as in patients with large tumors, node-positive disease, and patients with inflammatory breast cancer.[6] It is also recommended in patients with early-stage triple-negative and HER 2 positive diseases, given the higher response rates reported in these categories of patients.[7,8] Globally, several studies have evaluated pCR rates following NAC with varying results ranging from rates as low as 10.1% to 74.2%.[9] The heterogeneity in the reported rates might reflect differences in patient population and study design. However, much of the data available on the subject is from Europe, America, and some from Asia, with very scanty representation from Africa.[9] The global variations in the biological pattern of breast cancer presentation and the marked differences in terms of access to care and system support suggest the need to provide contextual data on the subject. An earlier study comparing the use of NAC between Nigerian patients with locally advanced breast cancer (LABC) and a cohort of American patients showed some disparity with lower rates in the Nigerian cohort.[10]

In this study, we evaluated the pCR rate in patients who had undergone mastectomy following NAC in a Nigerian tertiary institution.

METHODS

This was a retrospective review of patients who had mastectomy at a Nigerian tertiary hospital. From the pathology records, the histopathology reports of patients who had undergone mastectomy between 2017-2022, were evaluated. The data was matched with clinical data from a prospectively maintained institutional database containing patients' clinical and treatment details. Only patients who had received neoadjuvant chemotherapy were included in the study. Patients who had undergone lump excisional biopsy for diagnosis prior to the commencement of neoadjuvant chemotherapy were excluded.

Details of the patients' baseline clinicopathological data were obtained. This included age at presentation, tumor size, stage, clinical stage, immunohistochemistry, number and type of chemotherapy received, and the pathological diagnosis of the mastectomy specimen. The institutional practice with respect to choice of treatment was based on the recommendations of the National Comprehensive Cancer Network (NCCN) guidelines, which takes into consideration the clinical stage and immunohistochemistry. In instances where immunohistochemistry was unavailable or the recommended medications were unavailable or unaffordable, the managing physician discretionally prescribed based on clinical experience, availability and affordability by the patient.

Pathologic evaluation was done by eight certified pathologists in service during the study period, guided by the standard grossing protocol for handling mastectomy specimens in the post-NAC setting by the Royal College of Pathologists UK. Identification of the tumor bed in patients who had a complete clinical response at the time of mastectomy was achieved by identifying the area that best correlated with pre-treatment clinical and radiological findings. A detailed description of the tumor bed was provided, with sutures placed by the surgeon to mark the corresponding area. In the last three years of this review, the practice of clip placement was introduced into our institution. These were manually sought for during grossing and correlated with the clinical and radiological description to identify the tumor bed. The practice in our institution is to slice specimens serially into 0.5-1cm sections. At least a cross-section from the identified tumor bed is submitted for histologic evaluation. The extent of sampling depends on the size of the specimen. Residual cancer burden is currently not routine in our practice, and was not determined in this study. Pathologic response in this study was limited to the breast, defined as the absence of invasive cancer or the presence of in situ disease without any invasion (ypT0, ypTis).[11,12] Response in the axillary lymph nodes was not assessed. The overall pathologic response rate was determined using the total number of patients who had received chemotherapy as the denominator. The association between age at presentation, stage, immunohistochemistry, type of chemotherapy, and the year of the study was determined using the chi-square test.

RESULTS

Patient characteristics

During the period of the review, 250 patients had mastectomy for breast cancer. Of these, 172 patients (68.8%) received neoadjuvant chemotherapy. Six patients who had undergone excisional biopsy before commencement of NAC were excluded. The final

analysis included 166 patients aged 27-84 years with a mean age of 50.1±11.1 years. The majority had stage 3 disease (88%). Invasive ductal carcinoma of no special type was the commonest pathologic type in this study (95%). Immunohistochemistry was performed in 115 patients (69.3%) of which 53 (32%) were triple negative (Table 1).

The majority (120,72.9%) received anthracycline-based combinations only, while 46 patients (27.9%) received taxane in addition to anthracycline combinations. Taxane usage steadily increased from 3.7% of the total number of patients seen in in 2017 to 64.1% of the total number of patients who received NAC in 2022 (Figure 1). The mean number of chemotherapy cycles received was 5±2. Ten of the 31 patients who were HER 2 positive (32.2%) received targeted therapy in addition to chemotherapy, while others received only chemotherapy.

Pathologic complete response

Overall, 33 out of the 166 patients (19.9%) had pathologic complete response. There was a significantly higher response rate in the latter part of the study, corresponding to the period of increased taxane usage, with an overall response rate of 35.9% in 2022, accounting for 45.2% of all patients who had pathologic complete response (Table 2).

Table 1. Patient characteristics

Variables	N(166)	%
Age (in years)	Mean±SD-50.3±11.1 yrs.	
Clinical Stage		
1	3	1.8
2	14	8.4
3	146	88
Unknown	3	1.8
Pathological type		
Invasive ductal carcinoma	151	91
No special type	11	6.6
Metaplastic carcinoma	3	1.8
Mucinuous carcinoma	1	0.6
Invasive lobular carcinoma		
Immunohistochemistry		
HR+,HER 2-	31	18.7
HER 2+/HR+	13	7.8
HER 2+/HR-	18	10.8
Triple Negative	53	32
Unknown	51	30.7
Type of chemotherapy		
Anthracycline based combination	120	72.3
Taxane containing combination	46	27.7

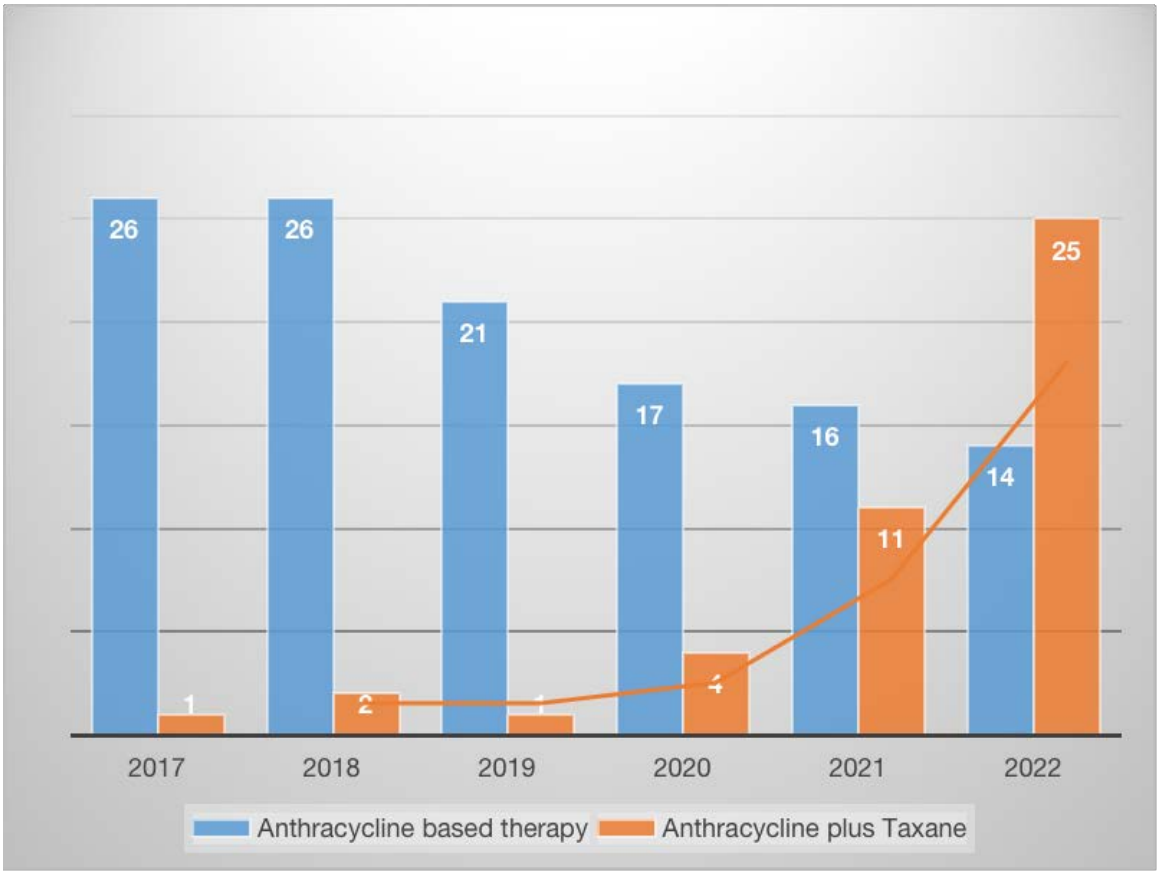

Figure 1. Increased Taxane use over time

Table 2. Pathologic complete response

Variables	N(165)	%	P value
Overall pathologic complete response	33	19.9	
Pathologic response per year of study			0.008
2017	2/27	7.4	
2018	3/28	10.7	
2019	1/22	4.5	
2020	4/21	19	
2021	8/27	29.6	
2022	14/39	35.9	
Pathologic response rate based on receptor type			0.03
	2/31	6.5	
HR+/HER 2-	13/53	24.5	
Triple Negative	4/13	30.8	
HER 2+/HR+	7/18	38.9	
HER 2+/HR-	7/51	13.7	
Unknown			
Pathologic response based on chemotherapy combination			0.001
Anthracycline based combination	14/120	11.8	
Taxane containing combination	18/46	39.1	

Pathologic complete response based on immunohistochemistry status showed a response rate of 6.7% for HR+,HER 2-, 23.9% for triple negative, 27.8% for HER 2+/HR+, and 30.8% for HER 2+/HR- cases (p=0.024). Patients who received Taxanes as part of their chemotherapy combination had significantly higher pathologic complete response rates compared to those who did not (39.1% vs 11.8%, p=0.001). Based on immunohistochemistry, the use of taxanes was associated with higher pCR rate in all biological subtypes, although this was statistically significant only among patients who were HER 2+/HR- (p=0.009, figure 3). Patients who had pathologic complete response received 5.6±2.1 cycles of chemotherapy while those who did not this response had 4.8±2.4 cycles, although this was not statistically significant (p=0.11). Age and clinical stage were not significantly associated with pCR in this cohort (p=0.19, 0.89 respectively).

DISCUSSION

This study retrospectively evaluated the pattern of response to neoadjuvant chemotherapy in a cohort of Nigerian breast cancer patients who had received pre-operative chemotherapy prior to mastectomy. Our review showed an overall pathologic response rate of 19.9% with the best responses recorded among patients who were HER 2 positive and triple negative, and those who had received taxanes as part of their chemotherapy combination.

Table 3. Pathologic response based on biology and chemotherapy type

Biological subtype	Pathologic complete response rate		P value
	Anthracycline n (%)	Taxane n (%)	
HR+/HER 2-	0/22(0)	2/7(22)	0.07
Triple Negative	7/34(20.6)	6/19(31.6)	0.37
HER 2+/HR+	1/7(14.3)	3/6(50)	0.26
HER 2+/HR-	1/10(10)	6/8(75)	0.009

There is considerable variation in literature regarding pCR rate following NAC depending on the period and the location of the study.[13-15] Expectedly, earlier studies reported lower rates compared to more recent reports, presumably due to the rapidly improving landscape of systematic therapy and targeted agents. Our finding compares with a metanalysis including 2895 patients from 52 studies which reported an overall pCR of 21.1%. Although this metanalysis did not include any study from sub-Saharan Africa, our finding falls within the range of what was reported. This might suggest that breast cancer in black women might not be as resistant to treatment as it is perceived, given the right approach to treatment. This is further substantiated by the significant improvement in pCR with the addition of taxanes to the chemotherapy regimen. This is in keeping with observations from the NSABP-B27 trial which showed that the addition of taxanes to doxorubicin and cyclophosphamide significantly increased the rate of pCR from 13% to 26%.[3]

While there is some variation in the actual figures, it is generally known that there is differential response to chemotherapy based on receptor subtype.[16,17] This study is one of the few to examine this subject in the Nigerian context. In line with global observations, patients with HER 2 positive and triple-negative disease had the best response in this review. This is quite instructive in the Nigerian setting given the high prevalence of triple-negative breast cancer.[18] Although quite aggressive, the possibility of complete response in about a quarter of patients is an incentive to consider it for all patients in this category, in line with current practices. The improvement in response rate associated with the introduction of taxanes might suggest that the poorer outcomes observed in patients from sub-Saharan Africa (SSA) might be more related to concordance with contemporary treatment than it is to biology.

An important observation from this study is the identification of potential areas of intervention.

Access to immunohistochemistry services is the bedrock of correct therapeutic decision-making in today's world of breast cancer care. In this study, more than a quarter of the patients did not undergo immunohistochemistry. While this is a significant improvement over past reports[19], there is a need to make the service routine for all patients. The lack of routine access to this important diagnostic service in many Nigerian institutions significantly hampers the opportunity to maximize the benefits of NAC. International agencies willing to support breast cancer treatment in low and middle-income countries (LMICs) as well as local authorities, should consider this as one of their priority areas for intervention. Another key area of intervention noted in this study is the need to promote access to chemotherapeutic agents. As highlighted, the last three years of the review witnessed higher pCR rates corresponding to increased use of taxanes. Towards the end of 2019, the Federal Ministry of Health of Nigeria in conjunction with the Clinton Health Access Initiative, American Cancer Society, Pfizer and other organizations, launched a Chemotherapy Access Programme (CAP), which provided quality chemotherapeutic drugs, at subsidized rates to selected tertiary hospitals in Nigeria.[20] This initiative might have contributed to the higher rates of taxane usage in the last three years of the study. We recommend that such an initiative be sustained, and the scope expanded across all institutions involved in cancer care.

The significance of pCR after NAC has been previously highlighted in the literature. It is a surrogate for survival, and it increases the possibility of breast conservation.[21] For Nigerian patients who are predominantly triple negative and also commonly present with locally advanced diasease[22], both of which are indications for NAC, the use of NAC provides a unique opportunity for breast-conservation which is currently not commonly practiced. The fear of mastectomy and its psychosocial impact, in a society where breast cancer stigmatization is rife[23], justifies the need to push for de-escalation strategies in the management of breast cancer in the Nigerian context. This may encourage affected women to present early for treatment. Since most patients do not qualify for upfront breast conservation due to late-stage disease, the use of NAC holds the key to achieving this goal, provided there is good response and access to adjuvant radiotherapy.

This retrospective study is the first step in evaluating the impact of NAC in our practice. It is unique in that it provides data on pCR which is not available in most sub-Saharan series assessing response to NAC. Our findings are capable of guiding local practice and designing future interventions. It, however, has some limitations which we do acknowledge. of the main limitation is the retrospective design which limits the inclusion of some important clinical variables in the analysis. Data on immunohistochemistry was available in 69.3% of patients; therefore, the pattern of response based on receptor subtype should be interpreted within these limits. This study also did not assess response in the axillary lymph nodes, as only a few patients with clinically node-positive disease underwent axillary lymph node biopsy for pathological confirmation. The relationship between pCR and survival was not assessed in this study, thus limiting our ability to determine the clinical impact of the response observed in this study. These deficiencies are being addressed in a prospective study which is currently underway.

CONCLUSION

Neoadjuvant chemotherapy is beneficial to an appreciable number of breast cancer patients in this Nigerian cohort, particularly those with potentially aggressive receptor-positive and all triple-negative disease. We found the use of taxanes of significant benefit and thus recommend its use in line with treatment guidelines.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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ETHICAL CONSIDERATIONS

Informed consent was obtained from the patients included in the database and ethical approval was obtained from the ethics and research committee of the institution.

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