ORIGINAL RESEARCH

Relationship between tumour size and response to neoadjuvant chemotherapy among breast cancer patients in a tertiary center in Nigeria

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Abstract

Background

Tumour biology, physiologic features such as growth fraction and physical features such as size may influence response of breast cancer to neoadjuvant chemotherapy. Molecular biology is an established basis for predicting response and selecting neoadjuvant chemotherapy. Whether physical characteristics such as size should influence chemotherapy regimen is inconclusive and has not been adequately studied in developing countries.

Aim

To determine the relationship between breast tumour size and response to neoadjuvant chemotherapy and hence define the role of tumour size during selection of neoadjuvant chemotherapy regimen for locally advanced breast cancer.

Method: Records of women managed at the University of Ilorin Teaching Hospital, Ilorin Nigeria, with neoadjuvant chemotherapy (NAC) for locally advanced breast cancer were reviewed between January 2013 and June 2015. Data was analyzed as 2 subgroups; primary tumour ≥100mm as group 1 and primary tumour ≥100mm as group 2. Primary outcome was 50% reduction in tumour size. Comparison was by chi-square test of independence at p value 0.05.

Results

57 records were reviewed (group1=24, group2=33). Majority (37(65%)) were premenopausal. Mean age was 47.9 ± 13.1 (range 28-85). NAC was either taxane or anthracycline based regimen. Median chemotherapy dose was 4 (range 2-6). Widest diameter of tumours was 30mm to 180mm (mean 96 ±3.8mm, median 100mm). Mean tumour diameter for groups 1 and 2 was 7.2 ±1.6mm and 12.2± 2.9mm respectively. 50% reduction in tumour size was 45.8% and 6.0% for groups 1 and 2 respectively (p=0.0001)

Conclusion

There was relationship between breast tumour size and response to neoadjuvant chemotherapy at a cut-off of 10mm. Well-designed prospective studies are required to confirm this relationship.

Introduction

Efforts to improve response of breast tumours to chemotherapy and maximize the benefit-to-adverse events ratio of chemotherapy include molecular subtyping to classify tumours, combined and cyclical use of chemotherapy and surgical de-bulking to stimulate proliferation. Molecular characteristics influence response to neoadjuvant chemotherapy (NAC). Whether physical characteristics such as size will have similar influence and impact type of chemotherapy regimen for breast cancer is inconclusive.

Drawing from understanding of tumour kinesis, NAC is expected to be less active on larger tumours due to lower growth index; hence we expect size of breast tumour to influence response to NAC. Surprisingly, clinical evidence is equivocal on this and other related issues such as correlation of breast tumour size to survival and correlation of breast tumour size to rate of pathologic complete response[1-3]. An early report by Fisher et al suggested that tumour size was an independent predictor of complete response to neoadjuvant chemotherapy[4]. Contrary to intuition, areport by Baron et al on data from 62 institutions in the United States of America did not find significant relationship between tumour size and pathologic complete response to neoadjuvant chemotherapy[1]. In contrast, a report by Goorts et al with data from the nationwide cancer register in Netherlands found that tumour size was an independent predictor of pathologic complete response[2].

Data on NAC is scarce from developing countries where this tool is needed the most because breast cancer patients present late with locally advanced disease[5-9]. In Nigeria, the few available reports show contrasting findings. In 2010, Arowolo et al5 in southwestern Nigeria and Anyanwu et[6] al in eastern Nigeria reported that breast tumour size affected response to chemotherapy. In 2013, a retrospective study from eastern Nigeria by Egwuongu et al upheld a contrary view[7]. Egwuongu et al[7] stated that size was not a determinant of response to NAC.

In developing countries, primary breast cancer tumours in excess of 5cm diameter is the norm. Clinicians in Nigeria and many developing countries frequently face the challenge of making treatment decisions on large tumours sometimes ranging beyond 30cm in diameter and sometimes occupying the whole breast[6,8-10]. Despite this, relationship between size and physical characteristics of tumour and response to NAC has not be adequately studied in these centres and the role of size as a physical factor predicting response to chemotherapy has not been clarified.

Among breast cancer patients presenting with large tumours, sorting probable responders from probable non-responders will help tailor treatment and eliminate inadvertent delays in instituting the most beneficial regimen. Therefore, we reviewed the records of breast cancer patients treated in a

tertiary institution in Nigeria where breast cancer patients presented with large tumour volumes. In this report, we described the relationship between tumour size and response to NAC with the aim of providing information which may impact chemotherapy selection and guide further research.

Method

This was a retrospective study conducted at the General Surgery Division of the Department of Surgery of University of Ilorin teaching Hospital Ilorin, North-central Nigeria. After obtaining ethical clearance, we reviewed the records of women who presented with locally advanced breast cancer and received NAC between January of 2013 and June of 2015. Only records of patients whose diagnosis was confirmed by cytology or histology were included. Records of inflamed, ulcerated and fungating lesions were included because these tumours constituted major treatment challenges in our clinical practice. Records of patients with recurrent lesions were excluded. Data was separated into 2 groups based on size of the primary tumour. Records where tumour size was less than 100mm were placed in group 1 and records where tumour size was at least 100mm were placed in group 2.

We hypothesized that there was at least 50% difference in proportion of patients who achieved 50% reduction in tumour size when tumour ≥100mm were compared with those ≥100mm in widest diameter. Cut-off of 100mm size was used for group separation in this study because previous studies in Nigeria showed conflicting reports based on cut-off value of 100mm7, 11. 50% cut-off was elected because tumours previously reported in the study centre and Nigeria were large5, 7, 10; thus, small changes in tumour size was often not sufficient to advance patient care. Data extracted from eligible records included information about maximum of 6 cycles of NAC. Information beyond the 6th cycle of NAC was excluded. Other information extracted were the age and sex of the patients, and the physical characteristics of the primary tumours.

The comparison between the groups was by chi-square test of independence. The primary tumour characteristics, the types and duration of NAC were presented in descriptive statistics. The significance level was placed at 0.05. Reduction in tumour size based on Response Evaluation Criteria In Solid Tumours (RECIST) was secondary analysis. At the time of this study, treatment of breast cancer was not biologically directed at our centre. Immunohistochemistry was reserved for mastectomy specimen due to cost.

Results

A total of 57 case notes were eligible for analysis (group 1= 24, group 2= 33). All were from female patients and 65% were premenopausal. Mean age was 47.9 ± 13.1(range 28-85). The range of NAC was 2-6 cycles (median 4). Widest diameter of tumours ranged from 30mm to 180mm (median 100mm). The groups' demographics were as presented in table 1. The NAC regimens used were FEC (5-Fluorouracil 600mg/m2, Epirubicin 60mg/m^2, Cyclophosphamide 600mg/m2, or TX (Docetaxel 75mg/m^2, Capecitabine 1000mg/m2 twice daily for 14 days) or TEC (Docetaxel 75mg/m^2, Epirubicin 60mg/m^2, Cyclophosphamide 600mg/m^2). Each regimen was repeated 3-weekly. Among the 57 case notes reviewed, 17 received taxane based agents while 40 received anthracycline based regimen. In group 1, 17 patients received anthracycline based NAC while in group 2, 23 patients received anthracycline based NAC. 50% reduction in tumour size was achieved in 45.8% and 6.0% among the groups 1 and 2 respectively (p= 0.0001). 50% reduction rate for those who received taxane and anthracycline based agents was 54.5% and 21.2% respectively. The overall response by RECIST assessment was as shown in figure 1. Goodness-of-fit analysis for the distribution of RECIST response between the two groups returned p value 0.004 (table 2).

Table 1: Locoregional physical characteristics of breast tumors

	GROUP1 <100mm) n= 24	GROUP 2 ≥ 100mm) n= 33
Age (mean ± SD)	48.5 ± 12.8	47.4 ±13.4
PRIMARY BREAST TUMOR		
min Area(mm)	12	160
Max Area(mm)	84	2250
Mean Area(mm2)	48.9±35.4	37 ±68.1
Min Diameter(mm)	3	10
max Diameter(mm)	8	18
Mean Diameter(mm)	7.2 ± 1.6	12.2 ± 2.9
INDICATION FOR NAC		
Large tumor breast ratio	8	8
Large tumor and fixity	3	2
Large tumor and matted/fixed nodes	4	6
Large and ulcerated tumor	2	5
Large ulcerated tumor and fixed/matted node	3	4
Large fixed tumor and fixed/matted nodes	3	1
Large fixed and ulcerated tumor and matted/fixed node	1	3
Fungating tumor	0	4

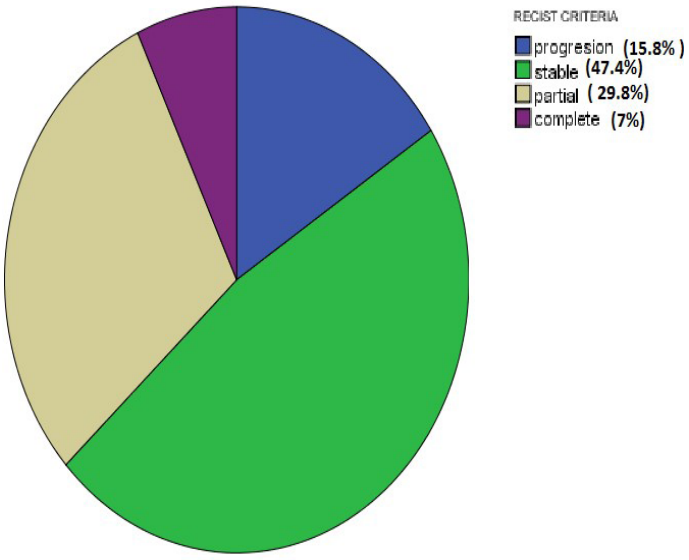

Figure 1: Overall rate of response according to RECIST criteria

Table 2: Frequency of response according to RECIST criteria

	Group 1 (<100mm)	Group 2 (≥100mm)
RECIST		
ASSESSMENT		
Progression	3	6
Stable	7	20
Partial Response	10	7
Complete Response	4	0
		..p=0.004

Discussion

Cytotoxic destroy cancerous cells but they are nonspecific in their mechanism of action; hence, while they can be beneficial in treatment of cancer, they can also cause dangerous adverse events such as bone marrow suppression, cardiotoxicity, infertility and even secondary carcinogenesis. The dangerous adverse effects of chemotherapy propel the continuous efforts to maximize the benefit to risk ratio of these drugs[12].

Most carcinomas of the breast cancer patients in developing countries require neoadjuvant chemotherapy because they present with bulky tumors and large burden of disease. Yet, there has been underreporting of the primary tumor characteristics and response to NAC in these centers. Researchers in South-western Nigeria terminated a phase II clinical trial on capecitabine neoadjuvant chemotherapy with under accrual due to prevalence of fungating, edematous and large tumors which were among their exclusion criteria[11].

In this study, we reviewed the response to chemotherapy of 57 patients who had received NAC and we compared the response of tumors more than ≥100mm (Group 1) with the response in those ≥100mm (Group2). The patients' demographics were similar to previous documentation in Nigeria. Reports of NAC in developed countries suggest response rate ranging from 50-80% with a high rate of complete response. Previous reports by Arowolo et al[5] and Egwuonwu et al[7] in Nigeria were 51% and 74% response rate respectively. This is the first report focusing on the effect of NAC on primary breast tumor in our center and our review revealed that more than 80% of patients benefitted from NAC and 37.8% were either partial or complete response (figure 1). However, the rate of complete and partial response was lower than previously documented in Nigeria[5, 7].

According to RECIST assessment, the numbers of partial and complete response were significantly higher among group 1 (≥100mm) (p = 0.004). In contrast to the findings by Egwuonwu et al[7] and in agreement with Arowolo et al[5],our result showed that response to chemotherapy was related to tumor size.

Most of the studies on NAC in Nigeria employed anthracycline based chemotherapy. Cases in this review received either anthracycline based or taxane based polychemotherapy. Among the 57 records reviewed, 17 received taxane based regimen while 40 received anthracycline based regimen. Exploratory analysis among 33 records where patients had tumors ≥100mm showed that taxanes elicited higher response rates than the anthracycline based chemotherapy (figure 2). However, this finding should be interpreted in the light of limitations of a retrospective design, treatment was not directed by molecular biology and treatment groups were unmatched.

Understanding of the tumor kinesis and mechanism of action of antineoplastic agents is essential in determining expectations from treatment. This will prevent needless exposure to impotent treatments and increase the benefit-to-risk ratio of NAC. This report supports our expectation based on basic understanding that there is a relationship between breast cancer tumour size and response to NAC. This suggests that treatment regimen for management of tumors may vary depending on the tumor size beyond 100mm. Based on the relationship found in this study and in line with previous findings[13], larger tumors may be selected to receive combination of anthracycline and taxane or resectable ones could be considered for "toilet-like" mastectomy to debulk followed by adjuvant chemotherapy and radiotherapy. These suggestions require further studies.

Conclusion

Our study result supported the view that there is a relationship between breast cancer tumor size and response to NAC and there may be a need to stratify treatment beyond 100mm primary tumor size. Properly designed prospective clinical trials blocking confounding variables should be conducted to shed more light on this issue and to provide guidelines for decision making in the management of large breast tumors in developing countries.

Conflict of Interest

The authors disclose no conflict of interest.

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