Original Article

Pathological response for neoadjuvant chemotherapy in locally advanced breast cancer at NCI, Sudan: 6 years' experience

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ABSTRACT

Background: Breast cancer is the leading cancer in Sudanese females.

Objectives: This study was done to evaluate the clinical response to neoadjuvant chemotherapy for patients treated at National Cancer Institute (NCI) and to compare it with the published literature.

Methods: This is a retrospective study conducted in National Cancer Institute (NCI), Gezira State, Sudan during the period from April 2005 to August 2011. We studied the data for all patients who have locally advanced breast cancer and treated at NCI during study period. Patients who remained inoperable after treatment were considered as having no response to therapy. Data were introduced and analyzed using SPSS software. Data evaluated includes Patient age, disease stage, chemotherapy regimens, and number of cycles, tumor histology, grade and histopathology after chemotherapy.

Results: A total of 110 patients who received neoadjuvant chemotherapy and fulfilled criteria for inclusion during the period 2005 to 2011 were evaluated.

Majority of patients were between 30-50 years of age (63%). Patients who achieved response and had surgery were 65%. Among those who underwent surgery 22% have complete pathological response. Most of patients who achieved complete histopathological response had six cycles of chemotherapy.

Conclusion: this study demonstrated that neoadjuvant systemic therapy is an accepted approach for women with locally advanced breast cancer for whom immediate surgery is inappropriate, and we achieved results similar to the international literature.

Key words: breast cancer, neoadjuvant, chemotherapy, response, NCI, Sudan.

Breast cancer is the most frequently diagnosed cancer and a second leading cause of cancer death after lung cancer among females worldwide[1].

A number of studies have suggested that there are epidemiological differences between breast cancers among women in Europe and Africa. Risk factors such as menopause, oral contraceptive use, cigarette smoking, and family history of breast cancer have been shown to have different relations to breast cancer among blacks and whites[2].

Breast cancer in African women is characterized by younger age at onset, advanced stage at diagnosis, and consequently poor prognosis[3-5]. In Africa, mastectomy rate is more than 85%, compared to just 30% in Europe[6].

Neoadjuvant systemic therapy is the accepted approach for women with locally advanced breast cancer for whom immediate surgery is inappropriate and is an option for women with operable breast cancer, particularly when, based on tumor size, mastectomy rather than conservative surgery is indicated, and the patient desires an attempt at breast conservation[7-10]. Neoadjuvant chemotherapy was developed in the 1970s with the aim of improving outcomes in patients with locally advanced breast cancer[11-12]. With the development of more effective chemotherapy regimens, including taxane combinations, neoadjuvant chemotherapy now achieves a clinical response rate of 60 to 90 percent and pathologic complete response rates ranging from 10 to 30 percent[13-14].

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Since breast cancer is the most frequent cancer among women in Sudan and patients tend to come at late stage. There is an urgent need to assess response of neoadjuvant chemotherapy and if there is prognostic factor for that response. In this study we are to provide some answers.

Material and methods:

This retrospective study is conducted at NCI, University of Gezira, Wadmedani, Sudan. NCI was established in 1999 as the second cancer center in Sudan to serve the heavy populated States in central Sudan. Most modalities of anticancer treatment are available. Chemotherapy, radiotherapy and hormonal therapy are provided at NCI, while surgery is done in Wadmedani teaching hospital. Targeted therapy is not available in Sudan most probably due to its terribly expensive cost. All breast cancer cases attended NCI for treatment, are seen at the combined breast cancer clinic which was established in 2000. Gezira protocol for breast cancer was adopted in 2004, updated in 2006 and finally, a national breast cancer treatment guideline was adopted in 2010.

According to this protocol; cases with locally advanced tumor (stage IIB and III) will receive neoadjuvant systemic chemotherapy. Patients with stage IIA who present with big tumor relative to breast size and wish to have conservative surgery will also receive neoadjuvant treatment. According to guidelines the first line chemotherapy constitutes of Adriamycin, Cyclophosphamide and 5 Fluorouracil (CAF), patient with potential cardiac problems has methotrexate to substitute Adriamycin (CMF). Taxane (docitaxel and paclitaxel) - based chemotherapy (TAC) is used as second line and for young ladies with high risk tumor characteristics (less than 35years). Patients who shows good clinical response (>75% reduction) undergo breast conservative surgery provided that there are no other indications for mastectomy. Patients who achieve partial response will undergo mastectomy. In both conditions axillary clearance is performed. Patients with less than 25% reduction in tumor size will be considered as non-responders and will have surgery "whenever possible".

After surgery all sample will be submitted to histopathology and report has to include viability of tumor cells (or necrosis), type of histology, grade, lymph vascular-invasion, margin status, number of retrieved lymph nodes and number of involved nodes. American Joint Committee for Cancer staging (AJCC) and Tumor, Lymph node and Metastasis (TNM) is used for staging.

In this retrospective study we searched files of all breast cancer patients who received neoadjuvant systemic chemotherapy (2005-2011) for age, stage, type of chemotherapy given, number of cycles prior to surgery, operability, type surgery performed and histopathological response. Patients who discontinued their treatment, unable to have histopathology after surgery and those with metastatic disease were excluded. Well-structured questionnaire filled from records. Data was introduced and, then analyzed by using statistical package for social sciences; (SPSS).

Results:

Total number of patients who are fulfilling criteria for evaluation
were 110. Majority of patient ages were between 30-50 years (63.6%), while patient over 50 years of age are (27.3%) and patients who are 30 years or less represents 9.1% (table 1). The median age for the study population is 45 years. Almost 94.6% of patients were stage III and 5.4% were stage II. Invasive ductal carcinoma was the dominant histopathology and seen in 90% of cases and lobular carcinoma was seen in 3.6%. Most patients had tumor grade II (48%) or III (47%), while grade 1 was seen in only 5%. Tumor characteristic is shown in table 2. Number of patients treated by CAF regimen were 80.9%, CMF 13.6% and 3.6% received taxane- based chemotherapy regimen (table 3). Some patient responded to total of three cycles or less of chemotherapy (25%) and most of them showed response after four-six cycles (67%) and only 8% received more than six cycles. Good clinical response was achieved in 81%. On the other hand 19% of

patients showed poor response and remained inoperable. From the responders 19% were able to undergo conservative surgery (table 4). Complete pathological response was seen in 22.7%. No single patients from those received more than six cycles showed complete pathological response (figure 1).

Table 1: Age distribution of studied patients. (Total number: 110).

Age distribution	Percentage
21-30	9.1
31-40	30
41-50	33.6
51-60	10.9
61-70	9.1
71-80	6.4
81-90	0.9
Total	100

Table 2: Stage and tumor characteristic prior to treatment of the studied patients

Stage (%)	Histopathology (%)	Grade (%)
I (0)	Ductal (90)	I (4.5)
II (5.4)	Lobular (3.6)	II (48.2)
III (94.6)	Others (6.4)	III (47.3)

Table 3: Different chemotherapy regimen used by the studied patients.

Regimen	Total (%)
CAF/ AC	(63.6)
CMF	(13.6)
TAC	(3.6)
AC	(1.8)
First and second lines	(19.1)

Discussion:

Neoadjuvant chemotherapy is increasingly being used in the management of patients with large operable and locally advanced breast cancers. This treatment is administered in the hope that down-staging might lead to avoid mastectomy, as an *in vivo* measure of chemo-sensitivity, and to enable systemic treatment of occult micrometastatic disease[15].

Table 4: Type of surgery done after treatment of studied patients. (Total number: 110)

Surgery	percentage
Mastectomy	65.5
Conservative	15.5
Inoperable	19.1
Total	100%

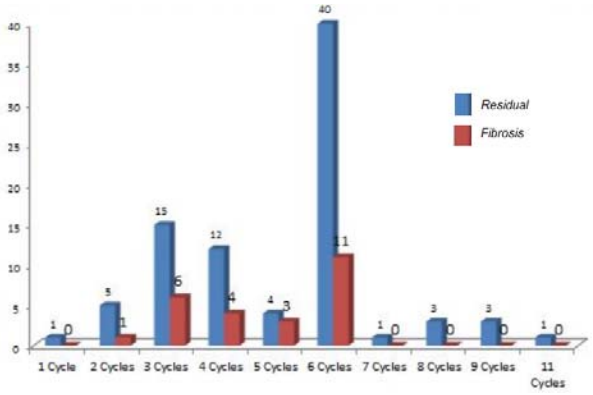

Figure (1): Histopathological response according to number of cycles.
(Residual: viable tumor; Fibrosis: complete histopathological response).

Randomized trials comparing pre-operative and post-operative adjuvant chemotherapy in early breast cancer show similar rates of local control and overall survival (OS), but the mastectomy rate is lower with the pre-operative approach[16].

Existing studies show that the patients who benefit the most from neoadjuvant chemotherapy are those who achieve a pathological complete response (PCR) with no residual microscopic tumour. This is relatively uncommon, occurring in only 3–16% of patients[17,18].

Regarding age group among the study population, 30 – 50 predominated 70 cases (66.6%), the common age in Western studies is found to be 50 years or above.

This observation is consistent with the literature and has been reported in several other studies conducted in sub-Saharan Africa[19, 20]. A higher incidence of breast cancer in younger women has also been observed in women of African descent residing in western countries[21].

The most stage grouping found among the study population was IIIB (53.6%) nearly

equally distributed between negative and positive receptor status, and it seemed to be selected for neoadjuvant therapy, while stage IIIA, IIB and IIA represented only (15.5%), only two cases (1.8%) were found to have bone metastasis while on treatment. Regarding type of chemotherapy, most of patients received CAF regimen (61.8%) according to the adopted protocol. Patients receiving anthracycline-based chemotherapy are more likely to achieve a PCR than those receiving non-anthracycline regimens. NSABP-18 studied anthracycline and non-anthracycline regimens in operable breast cancer anthracycline regimens in favour of 12% reduction of recurrent and 11% reduction of deaths. Addition of taxane to anthracycline had resulted in high pathological complete response (PCR) rate and survival benefits, the cost and availability restricted taxane use previously.

Most of patients received six cycles, followed by those who received three and four cycles, it was found that, response to chemotherapy increases with increasing of cycle's number up to six cycles, further cycles do not affect the response. NSABP-B 27 showed that eight courses of sequential pre-operative chemotherapy are superior to four cycles in term of PCR and DFS. Probably six cycles of an active regimen is sufficient in Neoadjuvant chemotherapy. As a result, guidelines preferred to give all chemotherapy before surgery.

Most of study population underwent mastectomy (65.5%), while those who received conservative treatment were (15.5%) and those of inoperable represented (19.1%). Two of the most influential publications that addressed breast conservation after neoadjuvant chemotherapy were from the two largest randomized trials (NSABP B-18 and EORTC) comparing neoadjuvant chemotherapy with adjuvant chemotherapy for patients with stage II or stage III breast cancer. The conclusion in both studies was that neoadjuvant chemotherapy offered an advantage because breast conservation rates were higher in the neoadjuvant chemotherapy groups[22]. However, it is important to recognize that approximately 60% of the patients enrolled in these studies were considered candidates for breast conservation at the time of diagnosis. This explains the low percentage of breast conservative treatment as most of patients included in the study were initially inoperable.

The finding of this study, concerning response to neoadjuvant systemic chemotherapy, is similar to the data reported in the literature[13,14]. Clinical response rate is 80% while PCR is 22%.

Conclusion:

In management of locally advanced breast cancer using neoadjuvant chemotherapy; this study showed results similar to literature and indicating that CAF regimen may remain equivalent to other new regimens as the first line of treatment. Invasive ductal carcinoma is the predominant histological type of cancer and the most common grade is grade II and III.

Pathological complete response is found to be better among those who received six cycles compared to those who received less cycles. Addition of more than six cycles didn't seem to improve PCR and confirmation of this may need a prospective study with big number of patients.

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