ORIGINAL ARTICLE

Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

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ABSTRACT

Objective: To assess the response to Neoadjuvant Chemotherapy (NAC) in Locally Advanced Breast Cancer (LABC) in terms of pathological response, overall survival and feasibility of breast conservation surgery.
Study Design: Case series.
Place and Duration of Study: King Fahad Medical City (KFMC), Riyadh, from January 2009 to July 2012.
Methodology: All patients of LABC who received NAC and underwent surgery were included. All these patients received the GORG001 regimen (FEC+Docetaxal+Cisplatin+/-Herceptin). After chemotherapy patients were offered surgery either Modified Radical Mastectomy (MRM) or Breast Conservation Surgery (BCS) +Radiotherapy. Patients were then followed to exclude local or distant metastasis. Results were described in percentage.
Results: The median age at the time of diagnosis was 46.8 years. While complete response was achieved in 24 (44.4%) patients, 14 (25.9%) of the patients had partial response and 16 (29.6%) progressed clinically. Surgery was performed in these patients after NAC. Forty (74%) patients had MRM, 14 (25.9%) had BCS; all had axillary lymph node dissection. Invasive ductal carcinoma accounted for 92% of cases. Vascular invasion was present in 12 (22%) of the patients. Estrogen / progesterone receptor positivity was 61%. Thirty nine percent of the patients were Her2 positive. On an average, follow-up of 4 - 51 months in the MRM group, one patient had resection margin (deep) positive and was treated with adjuvant therapy. While in the BCS group after 3 - 26 months of follow-up, one patient had resection margin positive (medial margin) and underwent MRM, while no patient had local or distant metastasis in both the groups.
Conclusion: NAC caused down staging of disease in LABC making more conservative surgery feasible. BCC should be considered as an option for treatment of LABC, however, longer follow-up is recommended.

Key Words: *Breast cancer. Breast conservation surgery. Neoadjuvant therapy.*

INTRODUCTION

Breast cancer is one of the most common carcinomas and is the major cause of cancer mortality among women between 30 - 60 years of age.[1] Locally advanced breast cancer is a heterogeneous clinical entity that includes patients with large ≥ 5 cm primary breast tumors or T4 tumors with chest wall involvement, skin edema, including *peau d' orange* appearance or ulceration of the skin, or inflammatory cancer and/or extensive clinical lymph node involvement as defined by the N2 and N3 categories from the American Joint Committee on cancer TNM classification system.[2] Five-year survival for stage-III breast cancer is approximately 50%, compared with 87% for stage-I.[3]

Although the incidence of LABC has decreased significantly in countries with enhanced resources due to widespread education and screening programmes,[4,5] it remains a daily encounter for surgeons and oncologists in the developing countries. The incidence is 33% in Peru, 40% in KSA, 50 - 70% in India and 77% in Malaysia.[4-7]

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Neoadjuvant Chemotherapy (NACT) was introduced in the 1970s and has become accepted as a standard of treatment for locally advanced breast cancer.[8] Neoadjuvant Chemotherapy (NACT) is administered with the intention to either convert inoperable Locally Advanced Breast Cancer (LABC) to operable state or to downgrade resection from mastectomy to breast conservation surgery.[9]

Although the effectiveness of therapy can be assessed according to clinical, radiological, or pathological response, the period of Disease-Free Survival (DFS) or the Overall Survival (OS); the Pathological Complete Response (PCR) is the most predictive parameter for survival.[9,10] The PCR is considered when there is complete eradication of locoregional disease.

The objective of this study was to assess the response to NAC in LABC in terms of pathological response, overall survival and feasibility of BC surgery.

METHODOLOGY

A retrospective review of all patients of LABC who received both neoadjuvant chemotherapy and underwent surgery at King Fahad Medical City (KFMC), Riyadh, between January 2009 and July 2012 was made. A formal approval was taken from the Institutional Review Board of KFMC prior to data collection. Patients, who were pregnant at presentation, had metastatic or bilateral diseases were excluded from the study.

The patients were staged according to TNM staging system proposed by American Joint Committee on Cancer (AJCC). All stage IIB (T3N0), III disease, and inflammatory breast cancer (T4d) patients were considered to have LABC. All the patients were assessed by triple assessment. Bilateral mammography and ultrasound breast were performed in all patients. Histopathological diagnosis was done by core biopsy. Estrogen and progesterone receptors and Her2 status was determined on pre-treatment biopsy by immuno-histochemistry (IHC). Hormone receptor status was considered positive if ≥ 10% of tumor cells stained for ER and/or PR. Her2 status was assessed by Hercep Test. FISH was carried out on all tumors with Hercep Test +2; tumors with a score of +3 by IHC or gene amplification by FISH were considered as Her2 positive. Tumours were measured both clinically and radio-logically before the treatment. Prior to NAC distant metastases were excluded by CT chest and abdomen and bone scans. Complete blood counts, liver and renal function tests were obtained. Echocardiography was also done as a baseline for all patients and repeated every 3 monthly for patients receiving Herceptin as per departmental guidelines.

A total of 54 patients were included after excluding 2 patients who received Aromatase inhibitors as NAC. All other patients received combined chemotherapy with anthracyclines i.e. 4 cycles (q21 days) of FEC i.e. 5 - Fluorouracil (500 mg/m^2), Epirubicin (100 mg/m^2) and Cyclophosphamide (500 mg/m^2) followed by 4 cycles (q21 days) of Docetaxal (75 mg/m^2) +Cisplatin (75 mg/m^2)+/-Herceptin depending upon the Her 2 status (GORG001 regimen).

All patients had clinical and radiological assessment of the tumor size and lymph node status before and after completing chemotherapy. A Complete Response (CR) was defined as complete disappearance of the tumor while PCR was defined as complete clinical and pathological resolution of the tumor. Partial Response (PR) is defined as 30% decrease in larger diameter of the tumor size. Progressive disease was defined as at least 20% increase in the tumor size or appearance of new metastasis (according to RECIST criteria).

All patients eventually underwent either modified radical mastectomy or breast conserving surgery with axillary lymph node dissection. The surgical procedure under-taken was based upon patients' choice, tumor-to-breast size and clinical response to NAC. Contraindications to breast conservation surgery included multifocal disease, previous irradiation to the breast, patient refusal and positive surgical margins.

The histological type of the tumor, the size of the invasive component, the grade of the tumor and the number positive of lymph nodes were all recorded. The median dissected lymph node number was 13. The estrogen (ER) and progesterone receptor (PR) status and c-erbB-2 expression were also assessed. Following surgery, adjuvant systemic therapy was given as needed. Radiotherapy was applied to all patients who had breast conserving surgery. Hormone therapy was given to patients with positive hormone receptors. Patients were followed-up regularly afterward. Disease Free Survival (DFS) was defined as being free of cancer relapse. Statistical Package for Social Sciences (SPSS) version 13.0 was used for statistical analysis. Frequency and percentage were calculated for categorical variables while mean and standard deviation were calculated for numerical variables.

RESULTS

A total of 54 patients were included in the study after excluding 2 patients who received aromatase inhibitors. The median age of the patients at the time of diagnosis was 46.8 years (range: 29 - 77 years). Thirty eight patients (70.3%) were older than 40 years. Thirty-two (59.2%) patients were premenopausal at the time of diagnosis.

Invasive ductal carcinoma accounted for 50 (92.6%) of cases while 2 (3.7%) patients had invasive lobular carcinoma and mucinous carcinoma each. Lympho-vascular invasion were present in 66.6%. Thirty three (61.1%) patients were ER/PR positive and 21 (38.9%) were ER/PR negative. Expression of c-erb-B2 was detected in 21 (38.9%) of the patients. Thirty (55.6%) patients had grade-II tumors while the remaining 24 (44.4%) were grade-III.

The tumor size (T) at presentation was T2 = 18 (33.3%), T3 = 27 (50%). T4 = 9 (16.6%) respectively. The nodal status being N0 = 16 (29.6 %), N1 = 28 (51.8%) and N2 = 10 (18.5%) respectively. Accordingly 22 (40.7%) patients had stage II-B disease, 23 (42.6%) had stage III-A disease and 9 (16.6%) had stage III-B disease respectively.

While 24 patients (44.4%) had Complete Response (CR), 14 (25.9%) of the patients had partial response to neoadjuvant chemotherapy. While 16 (29.6%) patients had poor response to chemotherapy. Two patients developed febrile neutropenia. There was no severe cardiac toxicity, or any other serious adverse events. Complete pathological response (PCR) was achieved in 18 (33.33%) patients (Figure 1).

Surgery was performed in all the patients after NAC; 40 (74.07%) patients had modified radical mastectomy (MRM), 14 (25.9%) had breast conservation surgery (BCS); all had Axillary lymph node dissection. All patients undergoing breast conservation surgery were given adjuvant radiotherapy. All the patients with receptor positive cancer were given hormone therapy.

The mean follow-up period was 15 months (range: 3 - 26

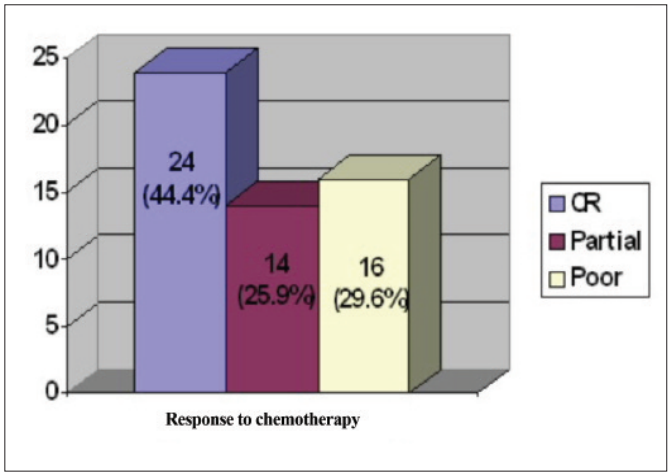

Figure 1: Response to chemotherapy.

Table I: Comparison of BCS vs. MRM groups.

	Total patients	Mean age (years)	Positive resection margins	Recurrence	Mean FU (months)
BCS	14 (25.9%)	47.1 (32-70)	1 (7.7%)	0	15 (3-26)
MRM	40 (74.07%)	47.7 (33-77)	1 (3.1%)	0	16.1 (4-51)

months) in the patients undergoing breast conservation surgery and 16.1 months (range: 4 - 51 months) for the patients having modified radical mastectomy respectively (Table I). One patient among the BCS group had positive resection margins and was treated with MRM. One patient in the MRM group had positive resection margin and was treated with adjuvant radiotherapy. No patient in either groups had local or distant metastasis.

The most common toxicity criteria following neoadjuvant chemotherapy among our patients was fatigue (40 patients; 74.07%) followed by grade 2 alopecia (38 patients; 70.7%). Athralgia and myalgia were developed in 8 patients (14.8%) whereas febrile neutropenia occurred in only 3 patients (5.5%). All patients completed the treatment protocol without interruption of treatment. There were no pneumonitis, and no severe cardiac toxicity occurred among the patients in this study.

DISCUSSION

LABC encompasses a heterogeneous collection of breast neoplasia with widely different clinical and biological characteristics. NACT has an established role in management of this group of patients.[11] It provides appropriate local control, the possibility of breast conservation therapy and increased survival rate in patients with LABC.

The overall response to chemotherapy in this study was 70%, partial = 14 (25.9%) and complete response = 24 (44.4%). Several other studies have shown a similar overall objective response of the primary tumor in patients with locally advanced breast cancer ranging from 71 to 87%.[12-14] On the other hand, the present results are much higher than that reported by Yadav *et al*. who found that only 23% showed response to neoadjuvant chemotherapy.[23] Another study by Tamer *et al*. in 2010 also showed much lesser overall response rates to neoadjuvant chemotherapy 54.5%; (CR 3% and PR 51.5%) and Kim *et al*. also reported that the overall response rate to neoadjuvant chemotherapy is 60% (4% CR and 56% PR) respectively.[15,16]

Complete pathological response (PCR) is considered as a biological marker of survival outcomes. In this study, 18 patients (33.3%) had (PCR). Similar results were reported by Moneer *et al*. who reported a (PCR) of 25% and Al-Tweigeri *et al*. who reported PCR to be 30.5% respectively.[17,19] The presently reported result is much better than that of BalaBasak *et al*. who reported (PCR) of 4%.[18]

Several studies have documented the feasibility and safety of breast conservation for locally advanced breast cancer after pre-operative chemotherapy. Breast conservation is possible in 27 - 90% of patients after pre-operative chemotherapy.[20,21] In this study, 14 patients (25.9%) underwent BCT after neoadjuvant chemotherapy. Similar results were reported by other authors. Danforth *et al*. conducted their study on 126 patients with locally advanced breast cancer who received neoadjuvant chemotherapy. They found that 42 (33%) of them were downstaged to the extent that breast conservation surgery became a feasible technique for them.[22] In another study, Yadav *et al*. reported that 23% of patients with locally advanced breast cancer are good candidates for breast conservation surgery after neoadjuvant chemotherapy provided that they are carefully selected.[23]

The rate of positive margins was 7.7% in this study (1 patient among the BCT group). However, El-Sayed *et al*. reported a much higher rate of positive surgical margins 19.4% (7 out of 36 patients).[24] While Mittra *et al*. reported a much lower rate where only 2.4% of patients with BCS showed positive margins.[25] This difference may be explained by large number of patients in their study (726 patients) than in this study (54 patients).

CONCLUSION

NAC causes down staging of disease in LABC making more conservative surgery feasible. BCT should be considered as an option for treatment of LABC, however, more follow-up is recommended.

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