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Research Article

The Response, Operability, and Type of Surgery Following Neoadjuvant Chemotherapy in Sudanese Patients with Locally Advanced Breast Cancer

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Abstract

Background: Neoadjuvant chemotherapy (NACT) treatment has become the standard treatment for locally advanced breast cancer (LABC) in many centers worldwide. **Objectives**: This study evaluates the short-term response of patients with LABC to NACT and its impact on operability and the type of surgery. **Patients and Methods**: This is a descriptive analytical hospital-based study including 147 patients with LABC who were presented to Plastic and Reconstructive Surgery Unit at Soba University hospital (SUH), between January 2012 and December 2014, and were treated with NACT. Clinical and pathological responses to neoadjuvant chemotherapy were evaluated according to Union for International Cancer Control criteria, operability, and the type of surgery performed was also recorded. **Results:** All patients were females, the mean age was 43 ± 7 years, of them 53.7% were pre-menopausal, 51% presented with a breast lump, 19.7% with nipple discharge, and 19% with skin changes and ulceration. The mean initial tumor size was 7 cm ± SD. Following NACT, complete clinical response was reported in 30 patients (20.4%), partial clinical response in 92(62.6%), stable clinical response in 20 (13.6%), and five (3.4%) had progressive clinical response. Initial smaller tumors (size < 5 cm) showed a better clinical response to NACT as 76.7% of complete clinical response was achieved. Pathological complete response was achieved in 25(17%) patients, pathological partial response in 102(74.1%), and pathological stable disease in 13(8.8%). Following NACT, breast conserving surgery was performed in 78(53.1%) patients, Modified Radical Mastectomy in 64(43.5%), 25 of them had Latissimus Dorsi, and five patients were not offered surgery as they developed progressive disease during the study period. **Conclusion:** Following NACT, it was possible to perform surgery in more than 96% of patients with LABC.

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1. Introduction

Neoadjuvant chemotherapy treatment (NACT) is now the standard treatment for locally advanced breast cancer (LABC) in several centers worldwide [1–3]. It reduces the size of the primary tumor, thus offering the option of breast-conserving surgery in patients who couldn't have this advantage before [4]. By down-staging tumors, NACT may likely improve available surgical options.

Numerous randomized clinical trials confirmed the equivalence of Neoadjuvant and adjuvant chemotherapy in terms of disease-free and overall survival rates [5]. Pathological complete response (pCR), which is defined as absence of residual and in-situ disease in the breast and the axillary nodes, has recently emerged as a powerful prognostic marker for overall and disease-free survival following NACT [6, 7]. Attaining a pCR after NACT has been shown by several investigators to be a good marker for improved long-term outcome [8–10].

LABC is not a usual presentation among females in the Western world; however, in Sudan, this stage is not only uncommon, but it also more prevalent among younger patients [11].

2. Objectives

This work aimed to assess the short-term response of Sudanese patients with LABC to NACT and its impact on operability and the types of the surgery performed.

3. Patients and Methods

This is a descriptive analytical hospital-based study. A consecutive one hundred forty-seven (147) patients who were presented with LABC to the Plastic and Reconstructive Surgery Unit at Soba University hospital (SUH) from January 2012 to December 2014 were reviewed. They were assessed initially at SUH and then referred to Radio-isotope Center, Khartoum (RICK) for receiving NACT. The study was approved by the Scientific and Research Committee of Soba University hospital (SUH).

LABC is defined as stage IIIA (To-N2; T1/2-N2; T3-N1/2), stage IIIB (T4, No-2), and stage IIIC disease (any T, N3). Patient with early breast cancer (stage I/II), metastatic breast cancer (stage IV) proven clinically and/or radiologically and those who haven't had regular follow-up during the study period in both RICK and SUH were excluded from study.

According to the national protocol of Neoadjuvant chemotherapy, the aim of the treatment was standardized. For patients with operable lesions and not suitable for breast conserving surgery (BCS), the chemotherapy was delivered until BCS could be performed. For patients with inoperable lesions, the chemotherapy was delivered until curative surgery could be achieved.

The clinical response was assessed at the start, after each two cycles and at the end of the treatment to document and classify the response. Assessment of the clinical response was based on Union for International Cancer control (UICC) criteria with definitions as follows: complete response (CR) = complete clinical resolution of tumor; partial response (PR) = 50% or greater diminution of bi-dimensional tumor; minimal response (MR) = 25% to 50% diminution of tumor; stable disease (SD) = no more than 25% increase or decrease in tumor size; progressive disease (PD) = more than 25% increase in tumor [12].

The pathological response was also assessed. Complete pCR was defined as a complete disappearance of invasive breast cancer in the final histological specimen of the primary tumor. Partial pathological response was defined as a reduction of more than 50% of the initial tumor size, whereas stable pathological disease was defined as a reduction of less than 50% of the initial tumor size, and progressive disease was defined as any increase in initial tumor size during cycles of chemotherapy [12]. Data were processed and analyzed using the SPSS software package (version 21 windows). To determine the statistical significance of differences, the Pearson test was used and probability test (*P*-value) with $p < 0.05$ was considered as significant at 95% confidence interval.

4. Results

One hundred forty-seven (147) patients receiving neoadjuvant chemotherapy for LABC were reviewed. All were females, the mean age of the patients at the time of diagnosis was 43 ± 7 years and 79 patients (53.7%) were pre-menopausal. More than half of the patients (51%) were presented with a breast lump, 29(19.7%) patients had nipple discharge as a chief complaint, whereas 28(19.0%) were presented initially with skin changes and ulcers and 15 patients (10.2%) were presented primarily with axillary changes and swelling. The mean tumor diameter measured clinically before neoadjuvant chemotherapy was 7 ± 3 cm (range 3–15 cm). Tumor stage and nodal status were summarized in (**Tables 1 and 2, respectively)**. No association was found between age and tumor size (*P* = **0.11**); however, a significant association was observed between

age and nodal status (*P* = **0.0002**) with 53% of those aging more than 45 years having a late nodal stage (N2 and N3). Regarding histopathological type of the tumors, 132 patients (88.2%) had invasive ductal carcinoma (IDC) and only 15 patients had invasive lobular carcinoma. Other less common histopathological variants were not reported in this series. Estrogen receptors (ER) showed positivity in 80 patients (54.4%) with 55(68.8%) of those with positive ER being below 45 years of age, and progesterone receptors being positive in 78 patients (45%).

Based on clinical evaluation and echocardiographic findings, patients were classified into three groups. Group A consisted of 52 patients who received 5-Fluorouracil 500mg/m2 I.V, Adiramycin (Doxorubicin) 50mg/m2 I.V, and Cyclophosphamide 500mg/m2 (FAC) for six cycles on a 21-day period, followed by Paclitoxel800 mg/m2 for 12 weeks; group B includes 47 patients who were treated with the 5-Flurouracil 500mg/m2 I.V, epirubricin90mg/m2 I.V, and Cyclophosamide 600mg/m2 (FEC) for four cycles with three weeks off, and then they received Paclitaxel 100mg/m2 for six weeks; group C were patients who received doxorubicin 600mg/m2 Cyclophosamide 600mg/m2 I.V and Taxanes (Doxetaxel) 100mg/m2(TAC) regimen and included patients with cardiac diseases based on echocardiography reports in whom other regimens were contraindicated. In addition, Prednisolone, antiemetic, and antibiotics were given when they were clinically indicated.

Thirty (20.4%) patients achieved a clinical complete response (CR). Complete clinical response (CR) was associated significantly with initial tumor sizes; 56.7% of CR was achieved in patients with tumor stages (T1 and T2 with tumor size < 5 cm). Partial response was observed in 92 (62.6%) patients, while static response was achieved in 20 (13.6%) patients, and five (3.4%) patients had developed a progressive disease (**Table 3**). Clinical response was not found to be affected by the age and tumor histopathology type. Complete pathological response (pCR) was achieved in 25 (17%) patients in whom no residual disease was seen in postoperative pathological specimens. A significant association was found between pCR and nodal disease and negativity of ER ($P < 0.001$ in both) **(Table 4)**.

The type of chemotherapy regimen used was neither found to affect clinical response nor pathological response (*P*-values were 0.196 and 0.087. respectively).

Following NACT, BCS was performed in 78 patients (53.1%) who had sufficient reduction to allow BCS, while 64 (43.5%) patients had modified radical mastectomy, and in 25 patients (39.1%) Latissimus Dorsi flap (LD) was used to close the defect following mastectomy, myo-cutaneous flap in 16 patients and muscle flap in 9 patients. A curative surgery could not be achieved in five patients who had developed a

Table 1: Relation between age with initial tumor size (T stage) (*n* = 147).

Age (years)	Initial tumor Size (T stage)*				
	T1	T2	T3	T4	Total
< 35	1	4	16	5	26
35–45	0	10	21	21	52
> 45	2	13	41	13	69
Total	3	27	78	39	147
Note: *P = 0.11 (> 0.05).					

Table 2: Relation between age with nodal status (N stage) (*n* = 147).

Age (years)	Nodal status (N stage)*				
	No	N1	N2	N3	Total
< 35	0	13	6	7	26
35–45	7	6	32	7	52
> 45	3	29	28	9	69
Total	10	48	66	23	147
Note: *P = 0.0002 (< 0.05).					

Table 3: Association between clinical response and initial tumor size (T stage) (*n* = 147).

	Clinical Response				
	Complete	Partial	Stable	Progressive	Total
Initial tumor size (in cm)* T1 < 2	2	1	0	0	3
T2 2–5	15	10	2	0	17
T3 > 5	12	57	9	0	78
T4 (any size, skin/chest involvement)	1	24	9	5	39
Total	30	92	20	5	147
Note: *P < 0.001.					

Table 4: Association between pathological complete response (pCR) and nodal status and ER status (*n* = 147).

		Pathological Response			
		Complete	Partial	Stable	Total
Nodal Status*	No	7	3	0	10
	N1	10	32	6	48
	N2	5	58	3	66
	N3	3	16	4	23
	Total	25	109	13	147
ER Status**	Positive	3	72	6	83
	Negative	22	37	7	64
	Total	25	109	13	147
Note: *P < 0.001; **P < 0.001.					

progressive disease during the course of neoadjuvant therapy. Hormonal therapy was given to all patients with positive ER receptors.

5. Discussion

NACT permits breast conservation in some patients who would otherwise require mastectomy [12]. The median age of patients in this study was 43 years and 42% of the patients were premenopausal, which is comparable to other reports [13–15].

The average number of NACT cycles ranged from four to six cycles depending on patient's response. However, the literature reported considerable variations in numbers of cycles of chemotherapy that are usually given in neoadjuvant setting [16, 17]. Three regimens of NACT were employed in this study. However, both clinical and pathological responses were not found to be affected by the type of regimen used (*P*-values are 0.196 and 0.087, respectively); this is similar to many series [18, 19], in contradiction to others that showed a better response with Taxanes-based regimens [20, 21].

Complete pathological response (pCR) was achieved in 17%, which is in the range of other series [18, 22], although significant variations exist in pCR values in the literature ranging from 4% to 40% [23–25]. These variations could be attributable to the use of different chemotherapy regimens and or the ethnical and racial differences [26, 27]. Age and family history were not associated with complete pathological response in this series, which is in line with what was reported in the previous studies [28–30]. On the other hand, the authors found an association between the nodal stage and pCR ($P < 0.001$) as the late nodal disease (N2, N3) was associated with poor pathological response, a finding which is similar to what was found by many other workers [30, 31].

Complete clinical response (CR) was achieved in 20.4% of the patients; it was significantly associated with initial tumor size (T stage) as 56.7% of complete clinical response was observed among patients with an initial tumor size of less than 5 cm (T1 and T2) ($P = 0.001$). These findings are in agreement with previous reports that proved better clinical responses with smaller tumors [27, 29]. Clinical response was not found to be affected by the age and tumor histopathology type which is comparable to the previous series [29, 30].

Estrogen receptor (ER) status was associated with a better pCR, as 65% of patients with pCR had a negative ER ($P < 0.001$) in keeping with previous reports [31, 32]; however, this finding disagrees with other reports that found a better pCR with ER-positive tumors [13]. Nevertheless, there is an evidence to suggest that ER-negative

tumors are more likely to achieve better pCR, following NACT in comparison to ER-positive ones, as an inverse relationship exists between ER expression and tumor proliferation; with ER-positive cancers showing a low proliferation rate, whereas ER-negative breast cancers having a high proliferation rate, which is correlated with a better short-term response to NACT [29, 30].

Seventy-eight (53.1%) patients had achieved a sufficient clinical down-staging to allow BCS; these results are quite comparable with other international reports [33–35], but higher than that reported previously in one study from Sudan (33.3%) [13]. In fact, the literature has reported different rates of BCS after NACT ranging from 16% to 80% [15]. These variations could be attributable to the differences in the types of chemotherapy regimens used, the studied population, and the study designs [36]. Nevertheless, there are certain factors that predict eligibility of a conserving surgery after NACT, with the tumor size being the most important one [37]. It is interesting to note that some workers have designed validated nomograms to predict the probability of residual tumor size and eligibility for a conserving surgery after NACT; these nomograms would be useful when counseling patients about treatment options [37].

To appreciate the findings of this study, some limitations have to be addressed; the authors had a short-term follow-up period so they could not assess the mid- and long-term effects of NACT. Besides, the study was conducted in only one center, and further prospective multi-center studies are recommended to ascertain the findings of this study.

6. Conclusion

NACT has shown satisfactory short-term results in Sudanese patients with LABC as it can reduce the tumor size rendering initially inoperable tumors to be operable, and it can also increase the chance of BCS in other patients with operable tumors that were initially not suitable for conserving surgery. Further studies to assess the long-term effects of NACT on disease recurrence and survival rates are recommended.

Conflict of Interest

None declared

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