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ORIGINAL RESEARCH

A STUDY ON THE EVALUATION OF CLINICAL RESPONSE TO THE NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

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ABSTRACT

BACKGROUND

In this study, we wanted to evaluate the clinical/pathological response of primary tumours and lymph nodes to neoadjuvant chemotherapy and assess the tumour involvement of resected margin.

MATERIALS AND METHODS

This was a prospective study conducted from July 2019 to June 2021 among female patients with breast lumps attending the Surgery OPD in the MKCG medical college and hospital, Berhampur.

RESULTS

Response to neoadjuvant chemotherapy (NACT) is more in triple-negative tumours compared to hormone receptor-positive tumours where endocrine therapy along with chemotherapy

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plays a major role. NACT could downstage the disease to make the inoperable tumour to operable one and to plan breast conservation for an operable disease.

CONCLUSION

Patients who show a better response to chemotherapy are shown to have a good prognosis. Patients who did not respond to NACT or who showed disease progression during NACT were predicted to have a poor prognosis compared to those who had shown objective response to NACT. NACT also made it possible to resect locally advanced diseases with tumour-free margin in most cases. The nodal status of the patient is an important prognostic factor as clinically nodal negative patients have better response than clinical nodal positive patients.

KEYWORDS

Neo Adjuvant Chemotherapy, Locally Advanced Breast Cancer

INTRODUCTION

Neoadjuvant chemotherapy is the primary chemotherapy given to the patient before surgery or radiotherapy. This has been used for the treatment of LABC. With the development and testing of increasingly effective agents particularly anthracyclines, dramatic responses had been seen in a significant proportion of patients.[1,2] Thus leading to an interest in breast conservation treatment(BCT) in larger tumours and the use of neoadjuvant chemotherapy in less advanced operable breast cancer.[3,4]

Aims and Objectives

1. To evaluate the clinical/pathological response of primary tumours and lymph nodes to neoadjuvant chemotherapy.
2. To assess the tumour involvement of resected margin

MATERIALS AND METHODS

This was a prospective study conducted from July 2019 to June 2021 among female patients with breast lumps attending the Surgery OPD in the MKCG medical college and hospital, Berhampur.

Inclusion Criteria

1. Patients with breast tumours with size >5 cm with a mobile axillary lymph node.
2. Patients with breast tumours of any size with skin fixity.
3. Patients with breast tumours of any size with an ipsilateral fixed axillary lymph node.
4. Patients with breast tumours of any size with chest wall fixity.

Exclusion Criteria

1. Patients with bilateral breast cancer
2. Patients with inflammatory breast cancer.
3. Patients with multiple masses in a single breast.
4. Pregnant females with breast cancer.
5. Patients with severe hepatic, renal or cardiac dysfunction.
6. Patients who were not willing for the study.

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7. Patients with clinical evidence of distant metastasis.
8. Patients with other proven malignancies
9. Patients with recurrent breast cancer.

Study Procedure

All the female patients with a breast lump to surgery OPD were examined and subjected to CORE NEEDLE BIOPSY (CNB). Patients with biopsy-proven LABC were admitted to the surgery inpatient ward.

Patients after admission were evaluated clinically with a detailed history of them along with a physical examination of the breast and axilla, systemic examination of the cardiovascular system, respiratory system, and kidney function by using haematological and biochemical tests along with 2D Echocardiogram.

Patients of reproductive age were subjected to a urine pregnancy test to know their active pregnancy status.

Patients were subjected to imaging studies like mammography, Ultrasonogram of breast and axilla, MRI Breast and Axilla, High-resolution computed tomography (HRCT) Chest, and Contrast-enhanced computed tomography (CECT) abdomen, Non-contrast computed tomography (NCCT) Brain to assess the loco regional disease and distant metastasis. Then the initial values obtained from the physical examination, mammogram, ultrasonogram, MRI and CNB were noted and kept as baseline values before initiating neoadjuvant chemotherapy.

Then the patients were subjected to 4 cycles of neoadjuvant chemotherapy. After 4 weeks from completion of the last cycle of neoadjuvant chemotherapy, the patients were assessed for response clinically by doing a physical examination of the breast and axilla, ultrasonogram of the breast and axilla, mammography and MRI.

The pathological response was assessed after a histopathological study of the resected primary tumour and regional lymph nodes after the surgery or in the case of patients who did not undergo surgery. CNB of the breast and FNAC of the lymph node were done to assess the pathological response.

The clinical response rates were calculated by comparing the post-chemotherapy value with pre-chemotherapy baseline values.

The patients were followed up for 6 months after the surgery or recorded a complete pathological response. It was done once in 2 weeks for the first month and once monthly for the next 2 months and the final visit was at the end of the 6^{th} month with the first check-up done after 14 days post-operation. A total of 5 follow-up check-ups were done.

RESULTS

Stage	**No. of patients**	**Percentage**
Stage IIIA	26	45
Stage IIIB	32	55
Stage IIIC	--	--
Patient characteristics	**Number of patients**	**Percentage**
Age		

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< 50 years > =50 years	28 30-	48% 52%
Molecular Types of Breast Cancer		
Molecular type	**No. of patients**	**Percentage**
Luminal A	13	22%
Luminal B HER2-positive	15	26%
HER2-positive Non luminal	9	15%
Triple-negative	21	37%
Clinical response of the patients		
Clinical response	**Number of patients**	**Percentage**
Clinical complete response	14	24
Clinical partial		
response	25	43
No response or stabledisease	11	19
Progressive		
Disease Total patients	8 58	14 100
Table 1		

In the current study, after following the inclusion and exclusion criteria, 58 patients were enrolled, and all of these patients had locally advanced breast cancer. Based on the TNM stage grouping, the patients were categorized into 3 groups under stage III. Out of 58 patients, 15 patients (45%) were categorized under stage IIIA, 18 patients (55%) were categorized under stage IIIB. There were no patients under stage IIIC.

Out of the 58 subjects enrolled, 28 patients (48%) were less than 50 years of age group. 30 patients (52%) were aged above 50 years.

Out of 58 patients, 13 patients (22%) were luminal A, 15 patients (26%) were Luminal B Her 2 positive, 9 patients (15%) were HER 2 positive Non-luminal and 21 patients (37%) were Triple negative.

Evaluation of the clinical response of primary tumours and lymph nodes was one of the primary objectives of the study. The product of the two greatest perpendicular diameters was measured both manually and using ultrasonogram before and after every cycle of neoadjuvant chemotherapy as defined by criteria.

The clinical response of 58 patients was observed and recorded. Out of the 58 patients, the overall objective clinical response of 67% was observed. Complete clinical response of 14 patients (24%) was noted. Partial clinical response was noted in 25 patients (46%). No response (<50% response) was observed in 11 patients (19%). However, 8 patients (14%) showed progressive disease. Out of the 8 patients, 3 of them had developed supraclavicular node, 4 patients developed vertebral metastasis and 1 patient developed cerebral metastasis.

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Stage	No. of patients with clinical response				Percentage of clinical response			
	CCR	CPR	NR	PD	CCR	CPR	NR	PD
Stage IIIA	11	8	5	2	42	31	19	8
Stage IIIB	3	17	6	6	9	53	19	19

Table 2

Compares clinical response of patients categorized under different groups of stage III. A total of 26 patients were categorized under stage IIIA. Among the 26 patients, complete clinical response was observed in 11 patients (42%), and partial clinical response was seen in 8 patients (31%). 5 patients (19%) showed no response. Progressive disease was seen in 2 patients (8%).

Among the 32 patients grouped under stage IIIB, 3 patients (9%) showed a complete clinical response, 17 patients (53%) showed a partial clinical response, no response was detected in 6 patients (19%), and progressive disease was observed in 6 patients (19%).

Molecular type	Total patients	CCR		CPR		CNR		PD	
Luminal A	13	3	23%	4	30%	4	30%	2	17%
Luminal B HER2-positive	15	-	-	9	60	3	20	3	20
HER2-positive Non luminal	9	3	33	3	33	1	12	2	22
Triple negative	21	8	38	9	43	3	14	1	5

Table 3

Out of 13 patients, luminal A complete clinical response was observed in 3 patients (23%), and partial clinical response was seen in 4 patients (30%) and 4 patients (30%) showed no response. Progressive disease was seen in 2 patients (17%).

Out of 15 patients, Luminal B Her 2 positive complete clinical response was observed in none of the patients, and partial clinical responses were seen in 9 patients (60%). 3 patients (20%) showed no response. Progressive disease was seen in 3 patients (20%).

Out of 09 patients, HER 2 positive Non-luminal complete clinical response was observed in 3 patients (33%), and partial clinical response was seen in 3 patients (33%). 1 patient (12%) showed no response. Progressive disease was seen in 2 patients (22%).

Out of 21 patients, Triple-negative complete clinical response was observed in 8 patients (38%), and partial clinical response was seen in 9 patients (43%). 3 patients (14%) showed no response. Progressive disease was seen in 1 patient (05%).

Out of the 54 patients operated, 12 patients (23%) showed pathological complete response (PCR) and the remaining 42 patients showed invasive tumour cells (PINV) in the specimen. 4 patients were not operated on and received radiotherapy for vertebral metastasis.

Out of the 26 patients grouped under stage IIIA, 8 patients (30%) showed complete pathological response and 18 patients were pathological non-responders (70%). Out of 32 patients included under the stage IIIB, 4 patients were not operated on and received radiotherapy for vertebral metastasis. Then from 28 patients who underwent surgery, 4 (14%)

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showed complete pathological response and 24 (86%) patients were pathological non-responders (77%).

Out of 13 patients of luminal A-type, pathological complete response was observed in 2 patients (15%), and invasive cells were seen in 9 patients (70%) and 2 patients (15%) were not operated on due to vertebral metastasis.

Out of 15 patients with luminal B Her-2 positive types, pathological complete response was observed in none of the patients, invasive cells were seen in 13 patients (87%) and 2 patients (13%) were not operated on due to vertebral metastasis. Out of 9 patients of Her 2 positive non-luminal type, pathological complete response was observed in 2 patients (22%), and invasive cells were seen in 7 patients (78%).

Out of 21 patients with triple-negative type, pathological complete response was observed in 7 patients (33%), and invasive cells were seen in 14 patients (67%).

Von Minckwitz et al conducted a study which showed PCR with respect to molecular subtypes showing PCR rates of 6%, 10%, 28%, and 37% in types luminal A, luminal B her 2 positive, non-luminal Her2 positive and triple-negative respectively.

Out of 58 patients, 54 patients had undergone surgery with 4 patients in stage IIIB undergoing radiotherapy and did not undergo surgery. There were 25 (96%) patients with resected margins free of the tumour out of 26 patients operated on in stage IIIA. Among 28 patients who underwent surgery in stage IIIB, 26 (92%) were found to have resected margins free of tumour. Hence overall tumour-free resected margins of 94% were detected in our study.

Out of the 58 patients, 9 patients were clinical node-negative (cN-ve) and the remaining 49 patients were clinical node-positive (cN+ve)

Nodal Status	No. of Patients	PCR	Percentage
Clinical node negative (cN-ve)	09	03	33%
Clinical node positive (cN+ve)	49	09	18%

Table 4

Out of the 09 patients with the clinical node-negative (cN-ve), 03 patients (33%) showed pathological complete response.

Out of the 49 patients with the clinical node-positive, (cN+ve) 09 patients (18%) showed pathological complete response.

Stage	No of Patients	No patients with Metastasis	Follow up Period	Response of the Patientwith Metastasis to NACT	
				Clinical	Pathological
Stage III A	26	1	5 months	CNR	PINV
Stage III B	32	1	4 months	CPR	PINV

Table 5

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During the follow-up period, 1 patient in stage IIIA who was assessedto have clinical no response/ histopathologically invasive cell, was detected to have pulmonary metastasis after 5 months.

Another patient categorized under stage IIIB was detected to have cerebral metastasis after 4 months; this patient had clinical partial response/ histopathologically invasive cell.

It was evident from the above-mentioned facts in our study that patients, who had a complete clinical response, had a comparably goodprognosis than those patients who showed a partial or no response to neoadjuvant chemotherapy.

DISCUSSION

In similar studies conducted by Maraz B, Boross G, Cyanti et al., an overall objective response of 60%, complete clinical response of 4%, and partialclinical response of 56% had been reported. In their study, there were no progressive diseases observed after neoadjuvant chemotherapy.[5]

Allassas, Choq, Burton et al conducted a study at Louisiana state university health science on the complete clinical response, and partial response, minimal residual disease and no change were reported to be 22%, 33%, 29% and 15% respectively.[6]

In our study, the percentage of complete responses was higher for the patients in stage IIIA than for the patients in stage IIIB. In a similar study conducted by Hortobogyi, Ames and Ruzdar et al, in the Department of Medical Oncology, in Anderson Hospital, Houston, it was reported that complete clinical response after neoadjuvant chemotherapy was better for a patient in stage IIIA than for patients in stage IIIB.[7]

The GeparTrio trial found that NACT with docetaxel, doxorubicin and cyclophosphamide (TAC) produced a PCR of 21% (Papademetriou et al, 2010).[8]

A similar study conducted by Allassus, chuq, Burton et al, had reported tumour free resected margins of 92% in patients with LABC in stage III after neoadjuvant chemotherapy.[9]

A study conducted by mamtani et al showed PCR rates of 49% for nodal-positive breast cancer.[10]

Y.W. Moon Rha et al in their study showed that those patients with a good response to neoadjuvant chemotherapy had a good prognosis.[11] Gajdas and Tarttar et al concluded in their study, that patients with a complete pathological and clinical response were observed to have good prognosis than those patients with partial or no clinical response and those who had invasive cells on HPE of their resected specimens.[12]

CONCLUSION

Response to neoadjuvant chemotherapy (NACT) is more in triple-negative tumours compared to hormone receptor-positive tumours where endocrine therapy along with chemotherapy plays a major role. NACT could downstage the disease to make the inoperable tumour to operable one and to plan breast conservation for an operable disease. Patients who show a better response to chemotherapy are shown to have a good prognosis. Patients who did not respond to NACT or who showed disease progression during NACT were predicted to have a poor prognosis compared to those who had shown objective response to NACT. NACT also made it possible to resect locally advanced diseases with tumour-free margins in most cases.

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The nodal status of the patient is an important prognostic factor as clinically nodal negative patients have better response than clinical nodal positive patients.

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