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Original Research Paper

Surgery

AN OBSERVATIONAL STUDY OF CARCINOMA BREAST PATIENTS FOR CORRELATION OF OUTCOME AFTER NEOADJUVANT CHEMOTHERAPY USING CLINICAL AND ULTRASONOGRAPHIC ASSESSMENT

Dr. Anjani Jalaj	M.S.(General Surgery), Professor, Department of Surgery, G.R. Medical College & JAH, Gwalior (M.P.).
Dr. Amit Ojha	MS(General Surgery), Associate Professor, Department of Surgery, G.R. Medical College & JAH, Gwalior (M.P.).
Dr. Mukesh Singh Bhadouria	MS(General Surgery), Senior Resident, Department of Surgery, G.R. Medical College & JAH, Gwalior (M.P.).
Dr. Vishvesh Sharma*	P.G. Student, MS(General Surgery), Department of Surgery, G.R. Medical College & JAH, Gwalior (M.P.). *Corresponding Author

ABSTRACT

Objective: To evaluate the clinico/pathological response to Neoadjuvant CT in the treatment of LABC.

Background: Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths). Breast cancer is the commonest malignancy of females all over the world and the one of the leading cause of death due to malignancy. In India, 75000-80000 new cases of breast cancer are diagnosed annually.

Methods: The method of study consists of Clinical assessment of disease was done by TNM classification. Radiological assessment Imaging of both the breast was done with ultrasonography. Response to chemotherapy was assessed clinically by measuring the size of the tumour and lymph node manually and using ultrasonogram. The product of two greatest diameters were measured before each chemotherapy.

Results: Those patients, who showed a complete/partial clinical response, had a comparably good prognosis than those patients who either showed no response or had disease progression after even NACT. The down-staging of disease was more evident in those patients who received NACT at initial stage during the course of the disease.

Conclusion: NACT plays an important role in clinical trials as it allows more rapid comparison of treatment regimes than can be accomplished in the adjuvant settings.

KEYWORDS : Locally advanced breast cancer, Neoadjuvant chemotherapy

INTRODUCTION

Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths). Breast cancer is the commonest malignancy of females all over the world and the one of the leading cause of death due to malignancy.[1] In India, 75000-80000 new cases of breast cancer are diagnosed annually.[2,3]

Locally advanced breast cancers (LABC) accounts for 10-15% of newly diagnosed breast cancer in United States while 30-60% in India.[4] The target of the NACT is to downsize the large tumours as well as to treat metastatic disease at the earliest. The effect of Neoadjuvant chemotherapy on patient's outcome may depend on the drug or drug combination used as NACT[5]. Various factors affecting complete pathological response to Neoadjuvant chemotherapy such as age, clinical tumour size, menopause status, type of chemotherapy, number of chemotherapy cycles, receptor status, excess of intraductal component and lymphatic and vascular invasion.[6,7]

Physical examination (PE), Ultrasonography (US), and mammography have all been used to assess tumor size in breast cancer patients both before and after Neoadjuvant chemotherapy.

So we have to assess the outcomes after Neoadjuvant chemo therapy based on these parameters and thus identifying the factors affecting outcome in carcinoma breast patients which might be helpful to predicting the progress as well as delay mortality and morbidity.

Perhaps greatest potential advantage of the study is opportunity to observe clinical/ultrasonographic response to treatment and to assess the effect by pathological examination of surgical specimen. Further more if clinical/ultrasonographic/pathological response of primary tumour to Neoadjuvant chemotherapy correlates with or predicts the response of metastasis and the prognosis of the patient such as overall survival[14] Though Neoadjuvant CT in the treatment of LABC had been used in clinical trials for the past 2 decades in the developing world, not many studies have been conducted in developing countries like ours, where LABC constitutes about 50% of cases. Hence this study was planned to evaluate the clinico/pathological response to Neoadjuvant CT in the treatment of LABC.

AIMS AND OBJECTIVES

(1) To study the various outcomes after neoadjuvant chemotherapy in carcinoma breast patients.
(2) To study the various clinical and ultasonographic findings after neoadjuvant chemotherapy in carcinoma breast patients
(3) To correlate the clinical and ultrasonographic findings with various outcomes of neoadjuvant chemotherapy in carcinoma breast patients.

MATERIAL AND METHODS

After obtaining approval from ethical committee the present study entitled **"An Observational study of carcinoma breast patients for correlation of outcome after neoadjuvant chemotherapy using clinical and ultrasonographic assessment"** was conducted on patients admitted in Department of General Surgery, J.A. Group of Hospitals Gwalior during a period from January 2019-January 2020 after taking well informed and written consent from the patient.

Sample Size: 50 Patients

Study Design: Prospective observational study

Source Of Data: Questionnaire and observation of different parameters of patients diagnosed with carcinoma breast attending the Outpatient Department and getting admitted to

Department of surgery& Cancer ward, J.A. Group of hospitals, Gwalior.

Inclusion Criteria:
All female patients of breast carcinoma undergoing neoadjuvant chemotherapy admitted in Department of Surgery, J.A. Group of Hospitals and GRMC, Gwalior.

Exclusion Criteria:
- Patients who have not received neoadjuvant chemotherapy,
- postoperative cases of carcinoma of breast,
- patients having distant metastasis

METHODS:
The method of study consists of **Clinical Assessment** of disease was done by TNM classification. Measurements were repeated before and after neoadjuvant chemotherapy. 38 patients received CAF regimen and 12 received CMF regimen.

Radiological Assessment Imaging of both the breast was done with ultrasonography. Clinical data obtained was recorded on a preprinted proforma before the patient underwent sonological examination.

Statistical Analysis:
Statistical calculations was done by help of Chi –Squared test with degree of significance <5%.

NEO ADJUVANT CHEMOTHERAPY REGIMEN:
The following chemotherapy regimen was given to the patients: **CAF INJ CYCLOPHOSPHAMIDE**[8,9]**:** an alkylating agent given as 800mg/m^2 of body surface area. It was diluted with 500ml of dextrose solution and infused over 3 hours.

INJ DOXORUBICIN[8,9]**:** an anthracyclin antibiotic administered in the dose of 50mg/m^2 of the surface area. Each 10mg was diluted with 5ml of distilled water (70 mg in 35ml) and given as direct i.v over the period of 20 mins.

INJ 5 – FLUOROURACIL[8,9]**:** a pyrimidine analogue administered as 400mg/m^2 it was given as direct i.v. over a period of 5 mins. 8mg of inj Ondansetron ($5HT_3$ Antagonist) and 8mg of inj dexamethasone was given intravenously half an hour before chemotherapy to prevent vomiting. The patient was given another dose of Ondansetron 4 hours later to prevent breakthrough vomiting. Patients were subjected to the above mentioned chemotherapy regimen once in 21 days till maximum response was achieved or till response became plateau or if patients were detected to have intolerable toxicity to the drugs given during chemotherapy.

Every time before the next cycle of chemotherapy was given, the patient was assessed for response to chemotherapy and toxicity to chemotherapy.

ASSESSMENT OF CLINICAL RESPONSE
Response to chemotherapy was assessed clinically by measuring the size of the tumour and lymph node manually and using ultrasonogram. The product of two greatest diameters were measured before each chemotherapy. Chemotherapy was terminated when patient achieved maximum response or response showed a plateau. Based on the response the patients were categorized into 4 groups.

Group I - *Complete Clinical Response*:
Here there was no evidence of measurable tumour or new disease for a specified interval usually 4 weeks.

Group II – *Partial Clinical Response*:
Tumour size decreased 50% or more than 50% determined by two observations not less than 4 weeks apart.

Group III– *No Response* Or *Stable Disease*:
Tumour size decreased less than 50%.

Group IV – *Progressive Disease*:
If 25% or greater increase was seen in the product of one or more measurable lesion or appearance of new lesion, was termed progressive disease.

For each patient the clinical response was assessed and recorded. Depending on the response the patients were subjected to surgery (Breast conservation surgery or Modified Radical Mastectomy) followed by chemotherapy and Radiotherapy.

Surgical Treatment Option:
1)If the clinical and radiological responses were complete breast conservation surgery was considered.
2)If the response was partial and if feasible breast conservation surgery was done or MRM was done.
3)In Stable or progressive disease, modified radical mastectomy with or without reconstruction was considered.
4) If the disease progressed locally with inoperability, preoperative radiotherapy was given followed by reassessment for surgery later.

RESULTS

Table No. 1a : Lump Size Distribution

Lump Size (in cm)	Number of patients (Pre NACT)	Percentage	Number of patients (Post NACT)	Percentage	p value
Up to 5	18	36	35	70	0.0023
6-10	26	52	10	20	
>10	6	12	5	10	

Most Patients in our study presented with lump size ranging between 6 cm and 10 cm. Pre NACT mean size was 6.74 cm. Post NACT the mean lump size was 4.53.The p value was 0.0023. Since the p value is <0.05 therefore the result is statistically significant.

Table No. 1b: Lump Size Distribution (In Ultrasonographic)

Lump Size (in cm)	Number of patients (Pre NACT)	Percentage	Number of patients (Post NACT)	Percentage	p value
Up to 5	16	32%	36	72%	0.0018
6-10	28	56%	08	16%	
>10	06	12%	06	12%	

Most Patients in our study presented with lump size (In Ultrasonography) ranging between 6 cm and 10 cm. Pre NACT mean size was 6.9 cm. Post NACT the mean lump size was 4.6 cm. The p value was 0.0018. Since the p value is <0.05 therefore the result is statistically significant.

Table No. 2 : Co-relation Of Lump Size With Age

Size (in cm)	Number of patients	Age wise distribution		Percentage
Up to 5	18	Up to 45 yrs >45 yrs	11 7	22 14
6-10	26	Up to 45 yrs >45 yrs	7 19	14 38
>10 cm	6	Up to 45 yrs >45 yrs	2 4	4 8

In our study 18 patients (36 %) had lump size less than 5 cm, out of which 22%(11) belonged to age less than 45 years.

26 patients in our study (52 %) had lump size between 6 and 10 cm, out of which 38%(19) belonged to age more than 45 years.
6 patients in our study (12 %) had lump size more than 10 cm, out of which 8%(4) belonged to age more than 45 years.

Table No. 3 : Comparison of Pre NACT and Post NACT Lymph Node Status

Status	Pre NACT	Percentage	Post NACT	Percentage
Palpable	44	88	31	62
Non Palpable	6	12	19	38
Total	50		50	

Prior to NACT 44 patients (88%) had clinically palpable lymph nodes, which decreased to 31 patients(62%) after NACT, i.e 13 patients'(26) lymph nodes became non palpable.

Table No. 4 : Change In Stage After NACT

Stage (as per AJCC 8th edition)	Number Of Patients Pre NACT	Percentage	Number Of Patients Post NACT	Percentage
I	3	6	12	24
IIA	6	12	13	26
IIB	9	18	10	20
IIIA	26	52	09	18
IIIB	6	12	06	12
	50		50	

In our study it was seen that majority of patients had downgrading of the Stage, except for stage IIIB. The number of patients in Stage IIIB remained the same before and after the NACT(12%).

Table No. 5 : Clinical Response

Response	Number of Patients	Percentage
Complete Response	6	12
Partial Response	30	60
No response	11	22
Progressive Disease	3	6

In our study it was seen that majority of patients (60%), 30 patients had partial response of disease to Neo adjuvant chemotherapy. Complete Response was seen in 6 patients (12%) and No Response was seen in 11 patients (22%). However, 3 patients (6 %) had Progressive Disease.

Table No. 6 : Co-relation Of Disease Stage With Clinical Response

Response	Number of Patients	Stage of Disease	Number of Patients	Percentage
Complete Response	6 (12 %)	I	2	33.3
		IIA	1	16.7
		IIB	1	16.7
		IIIA	2	33.3
		IIIB	-	
Partial Response	30 (60 %)	I	-	-
		IIA	5	16.7
		IIB	8	26.7
		IIIA	16	53.3
		IIIB	1	3.3
No response	11 (22%)	I	1	9.1
		IIA	-	-
		IIB	-	-
		IIIA	8	72.7
		IIIB	2	18.2
Progressive Disease	3 (6%)	I	-	-
		IIA	-	-
		IIB	-	-
		IIIA	-	-
		IIIB	3	100

Out of the 6 patients who showed Complete Response 2 patients had Stage I disease, 2 had IIIA disease. Out of the 30 patients who had Partial Response, majority patients (53 %) belonged to Stage IIIA.

Out of the 11 patients who showed No Response, 8 patients (72. %) belonged to Stage IIIA, rest belonged to Stage IIIB.

Progressive Disease was seen exclusively in Stage IIIB patients.

Table No. 7 : Post NACT Management

	Number of patients	Percentage
Surgical (MRM)	45	90
Radiotherapy	5	10

Out of the 50 patients in our study, majority (45) underwent Surgery(MRM) while 5 patients had to undergo palliative radiotherapy for metastasis.

DISCUSSION

NeoAdjuvant Chemotherapy has been known to be beneficial for down-staging the disease of patients in Carcinoma Breast. The mean size of the lump on ultrasonography in our study was 6.9 cm before receiving the NACT. After receiving the NACT the mean lump size on ultrasonography was reduced to 4.6 cm. (p value was 0.0018). When clinical findings were compared with ultrasonography, the lump size measured on USG was slightly larger as compared to the lump size on clinical examination during pre and post NACT stage.

The down-staging of disease was more evident in those patients who received NACT at initial stage during the course of the disease.

Those patients, who showed a complete/partial clinical response, had a comparably good prognosis than those patients who either showed no response or had disease progression after even NACT.

Y.W. Moon Rha[10] et al in their study showed that those patients who showed a good response to NACT had a good overall prognosis. In the study conducted by Gajdas and Tarttar[11] et al, patients with a complete pathological and clinical response were observed to have good prognosis than those patients with partial or no clinical response and than those who had invasive cells on HPE of their resected specimen.

Allassas, choq, Burton[12] et al conducted a study at Lousiana state university health science, the complete clinical response, partial response. Minimal residual disease and no change was reported to be 22% , 33%, 29% and 15% respectively.

In similar studies conducted by Maraz B, Boross G, Cyanti[13] et al there was an overall objective response of 60%, complete clinical response of 4%, partial clinical response of 56% had been reported. In their study there were no progressive disease observed after Neoadjuvant chemotherapy.

Response	Allassas, Choq, Burton[12]	Maraz B, Boross G, Cyanti[13]	Our study
Complete Response	22%	04%	12%
Partial Response	33%,	56%	60%
No Response	29%	40%	22%
Progressive disease	15%	0	6%

CONCLUSION

From this study it was evident that Neoadjuvant Chemotherapy could

- Reduce the size of lump.
- Improve lymph nodal status.
- Downstage the disease so that the tumours which were inoperable tumour prior to the NACT become operable. Also, the tumours which needed Radical Surgical Procedure can now be planned for breast conservation surgeries.
- Patients who did not respond to NACT or who showed disease progression during NACT were predicted to have

poor prognosis compared to those who had shown objective response to neoadjuvant chemotherapy.
- NACT also made it possible to resect locally advanced disease with tumour free margin in most cases.

Thus NACT plays an important role in clinical trials as it allows more rapid comparison of treatment regimes than can be accomplished in the adjuvant settings.

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