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Response To Neoadjuvant Chemotherapy In Triple Negative Breast Cancer Following 4 Cycles Of Ac Followed By 4 Cycles Of Taxanes Vs 4 Cycles Of Ac With Cisplatin Followed By 4 Cycles Of Taxane

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I. Introduction:

Breast cancer a devastating illness for tens of thousands of women around the world. Most common non-skin cancer in women worldwide with an estimated 1.68 million new cases, breast cancer make it a leading cause of death in women aged 35 to 55 years. Accounts for 23% of all cancers in women and responsible for 20% of cancer related death in women. In India, it is the most common cancer reported from urban cancer registries, for about 30% of all cancers in females. Triple-negative breast cancer (TNBC) is defined by the lack of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (Her2*neu*) expression and associated with aggressive clinical course and poor prognosis.Patients with TNBC derive no benefit from molecularly targeted treatments such as endocrine therapy or trastuzumab, because they lack the appropriate targets for these drugs. Although TNBC is characterized by aggressive behavior, it is particularly sensitive to cytotoxic chemotherapy (the so-called 'triple negative paradox') [19]. In the neoadjuvant setting, TNBC patients have higher response rates to standardchemotherapy when compared with women affected by hormone receptor-positive breast cancer. Approximately 30%–40% of TNBC patients achieve a pathological complete response (pCR) after standard anthracycline plus cyclophosphamide- and taxanebased neoadjuvant chemotherapy. The achievement of pCR in TNBC patients has a strong prognostic value, larger than in other breast cancer subtypes. Therefore, neoadjuvant chemotherapyis currently considered the preferred approach for the majority of TNBC patients with early-stage disease.Platinum agents (i.e. carboplatin and cisplatin) are cytotoxic DNA damaging compounds leading to DNA strand breaks and possible consequent cell apoptosis; this peculiar mechanism ofaction makes them specially active in cancer cells with DNA repairdeficiency such as those harbouring deleterious mutations in the BRCA genes. Based on the biological rationale for a heightened susceptibility of TNBC to DNA-damaging compounds, several trials have investigated the possible role of platinum agents as a treatment option in TNBC patients. Although some of these studies have suggested a possible benefit for platinum-based neoadjuvant chemotherapy in TNBC patients .The primary goal of this study is to assess the efficacy of cisplatin as neoadjuvant chemotherapy in TNBC based on the pathologic complete response [pCR]), progression free survival (PFS), site-specific distribution of recurrence, post recurrence survival (PRS), and overall survival (OS).

II. Aim Of The Study

The aim of this study is to assess the response to neoadjuvant chemotherapy in TNBCfollowing 4 cycles of AC with Cisplatin followed by 4 cycles of Taxanes versus 4 cycles of AC followed by 4 cycles of taxanes to study the efficacy of cisplatin as neoadjuvant chemotherapy in TNBC based on the pathologic complete response[pCR].

III. Materials And Methods

This study was carried out in the Department of Surgery, Government Rajaji Hospital Madurai, during the period August 2017 to November 2019 in collaboration with Department of Medical Oncology, Government Rajaji Hospital, Madurai.

The patients presenting with inoperable triple negative breast cancer with M0(no metastasis) in GRH Madurai will be recruited for this study.

Following consent, a questionnaire will be filled to record the patient's demographic data, duration of disease, symptoms, & treatment history.

Patients coming to GRH, Madurai with lump breast cancer are evaluated based on receptor status , USG Abdomen ,USG breast ,FNAC breast , trucut biopsy from the lump, skeletal survey ,routine blood investigations are done. Patient are categorised under TRIPLE NEGATIVE BREAST carcinoma based on their investigation reports.
Patients are divided into group A and group B regimen. Regimen A (4 CYCLES OF AC FOLLOWED BY 4 CYCLES OF TAXANES) and Regimen B(4 CYCLES OF AC WITH CISPLATIN FOLLOWED BY 4 CYCLES OF TAXANES) will be given to the group of patients accordingly. Response to the treatment is assessed based on the tumour size, nodal status, staging and MRI.

CRITERIA FOR PATIENT SELECTION:
INCLUSION CRITERIA:

1. Female patients who are >18 years of age
2. Patients consented for inclusion in the study according to designated proforma.
3. The tumor must be invasive carcinoma of the breast on histologic examination.
4. No clinical evidence of metastasis.
5. The tumor must have been determined to be HER2-negative.
6. The tumor must have been determined to be ER- and PR-negative,
5. Bone marrow function Hb: ≥ 10.0 g/dL ANC: ≥ 1,500/µL Platelet count: ≥ 10×10^4 /µL
6. Renal function Creatinine: ≤ 1.5 × UNL or Creatine clearance (Ccr) >50 ml/min
7. Hepatic function Total Bilirubin: ≤ 1.5 × UNL AST/ALT: ≤ 2.5 × UNL 10) Ability and willingness to comply with the study visits, treatment, testing, and with the protocol, as per investigator's judgment

EXCLUSION CRITERIA:

1. Any prior systemic treatment for primary invasive breast cancer
2. Evidence of metastatic breast cancer.
3. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder or uncontrolled infection.
4. Pregnant or breastfeeding women.
5. Patients unwilling for the study.

By above mentioned inclusion and exclusion criteria **60** patients had been enrolled for the study. All the women enrolled in the study were subjected to the following protocol. They had been explained about the chemotherapy regimen and insisted to attend chemotherapy regimen regularly. They had been told about surgical and radiation therapy following the neoadjuvant chemotherapy.
Patients are divided into group A(cases) and group B (control) regimen.

- **Regimen A (4 CYCLES OF AC WITH CISPLATIN FOLLOWED BY 4 CYCLES OF TAXANES**)
- **Regimen B(4 CYCLES OF AC FOLLOWED BY 4 CYCLES OF TAXANES**) will be given to the group of patients accordingly.
- Response to the treatment is assessed based on the tumour size, nodal status, staging by MRI.

REGIMEN A (CASE)

4 CYCLES OF AC (Anthracyclines cyclophosphamide) with Cisplatin

⇩

MRM (Modified Radical Mastectomy)

⇩

4 CYCLES OF TAXANES

REGIMEN B (CONTROL)

4 CYCLES OF AC (Anthracyclines cyclophosphamide)

⇩

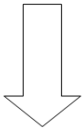
MRM (Modified Radical Mastectomy)

⇩

4 CYCLES OF TAXANES
Response to the treatment is assessed based on the tumour size, nodal status, staging by MRI.

BEFORE CHEMOTHERAPY

Clinical examination	Tumour size(cms)	Nodal status (N)
USG Breast		
MRI		
TNM staging		



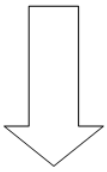
4 cycles of neoadjuvant chemotherapy

AFTER 4 CYCLES OF CHEMOTHERAPY

Clinical examination	Tumour size(cms)	Nodal status (N)
USG Breast		
MRI		
TNM staging		

HPE REPORT FOLLOWING MRM

Tumour size(cms)	Nodal status (N)	Pathological TNM staging



NEO ADJUVANT CHEMOTHERAPY REGIMEN:

INJ CYCLOPHOSPHAMIDE**:** an alkylating agent given as 600mg/m2 of body surface area.
INJ DOXORUBICIN**:** an anthracyclin antibiotic administered in the dose of 50mg/ m2 of the body surface area.
INJ CISPLATIN: an alkylating agent under platinum group given as 30mg/m2 of body surface area.

INJ PACLITAXEL: dose administered 80mg/m2 of body surface area.

8mg of inj Ondansetron (5HT3 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.
To rule out the toxic side effects, complete hemogram and liver function tests were done, the patients with intractable toxicity like uncontrolled vomiting, myelosuppression, cerebellar ataxia, cardiomyopathy, were withdrawn from the chemotherapy regimen and were subjected to surgical intervention. Modified radical mastectomy (MRM) was done for these patients.
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.

MODIFIED RADICAL MASTECTOMY (MRM)
AUCHINCLASS :
Procedure:
1) Patient was positioned on the operative table in the supine position with rolled sheet under the ipsilateral hemithorax so as to allow the motion of arm without limitation.
2) Incision was ideally made transversely from lateral border of sternum to just below anterior axillary fold. This incision included the nipple areola complex 5 cms skin around the lesion and the scar of the previous biopsy if any.
3) Skin flap was elevated in the plane between the subcutaneous fat and the mammary fat. Initially cephalic flap was raised upto subclavius muscle. Pectoralis fascia was dissected from pectoralis muscle in the plane parallel to the course of the muscle bundle. Perforators of the lateral thoracic and anterior intercostal arteries were ligated.
4) Lateral flap was elevated upto anterior border of lattismus dorsi.
5) Inferior flap was raised to upto 3 cms below inframammary fold. After elevating the breast from the chest wall, the breast was attached only to the axilla.
6) Axillary vein was identified at lateral axillary space while anterior border of lattismus dorsi was dissected from inferior to superior direction.
7) Shoulder was abducted and arm was extended to facilitate the dissection of inferior and lateral margin of pectoralis major. Pectoralis major was retracted to identify the pectoralis minor.Inter pectoral nodes were removed preserving the medial pectoral nerve.
8) Loose areolar tissue at the junction of the axillary vein with the anterior margin of lattismus dorsi was swept inferiorly to include the lateral group of axillary nodes, thoraco dorsal vessels and nerve were preserved. Subscapular group of nodes between the thoraco dorsal nerve and chest wall, were dissected enbloc.
9) Central group of nodes were dissected enbloc along with pectoral group, and the Long thoracic nerve of Bell was preserved.
10) After removal of specimen hemostasis was obtained. Two vacuum drains, one for the flap and the another for the axilla were inserted.
11) Skin closure by vertical mattress technique with 2-0 ethilon.

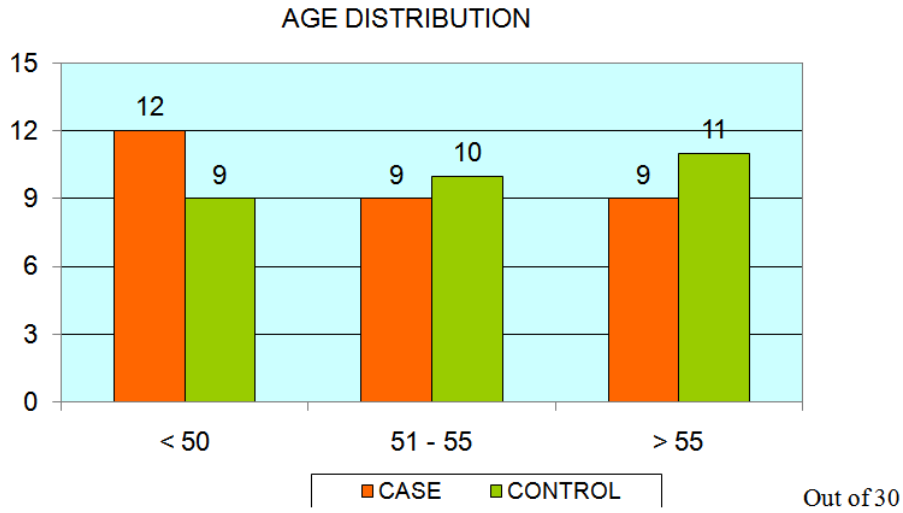
ASSESSMENT OF PATHOLOGIC RESPONSE:
Mastectomy specimens from the patients who underwent MRM were sent for histopathological assessment. In histo pathological examination the following factors were studied.
1. The presence of tumour cells.
2. Whether resected margins were free of tumour
3. Status of lymph node metastasis.

Depending on the pathologic response the patient was categorized into two groups

PATHOLOGICAL COMPLETE RESPONSE (PCR): No tumour cells were detected in the resected specimen.
PATHOLOGICAL NON RESPONDERS (PINV): Presence of tumour cells in the resected specimen.
FOLLOW UP:
In the first two years after surgery , the patients were seen atleast once in every 6 months. In the following 3 years they were followed up for every 6 to 12 months.
The minimum requirement for follow up were, physical examination, locoregional evaluation, performance scale assessment, mammography, MRI, usg breast.

IV. Results

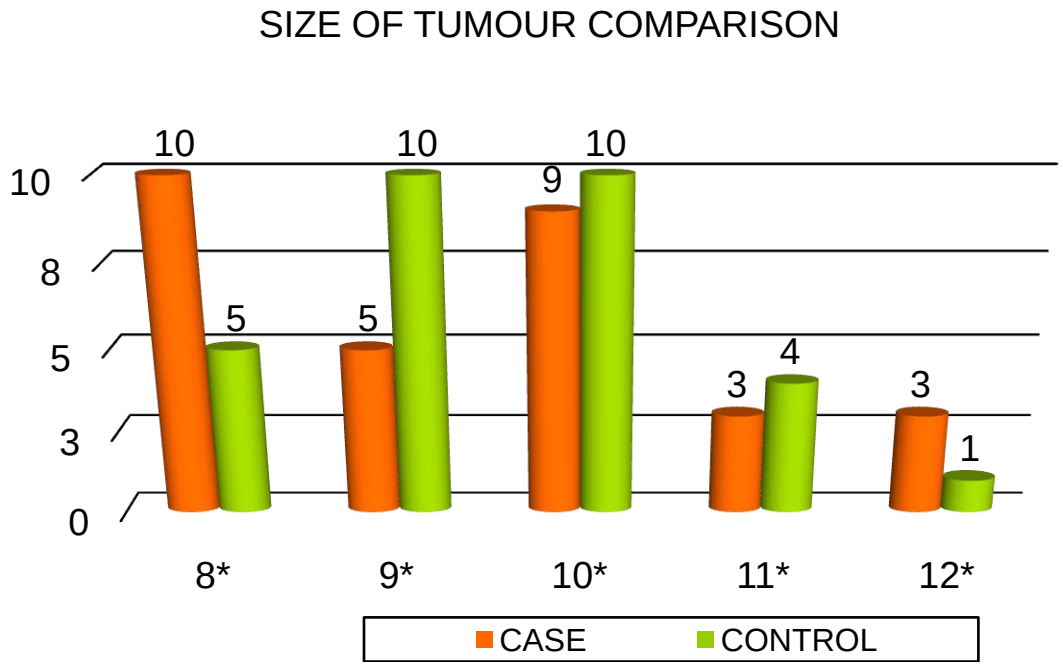
AGE	CASE	CONTROL
< 50	12	9
51 - 55	9	10
> 55	9	11
TOTAL	30	30
Mean	52.633	53.7
SD	4.832	4.669



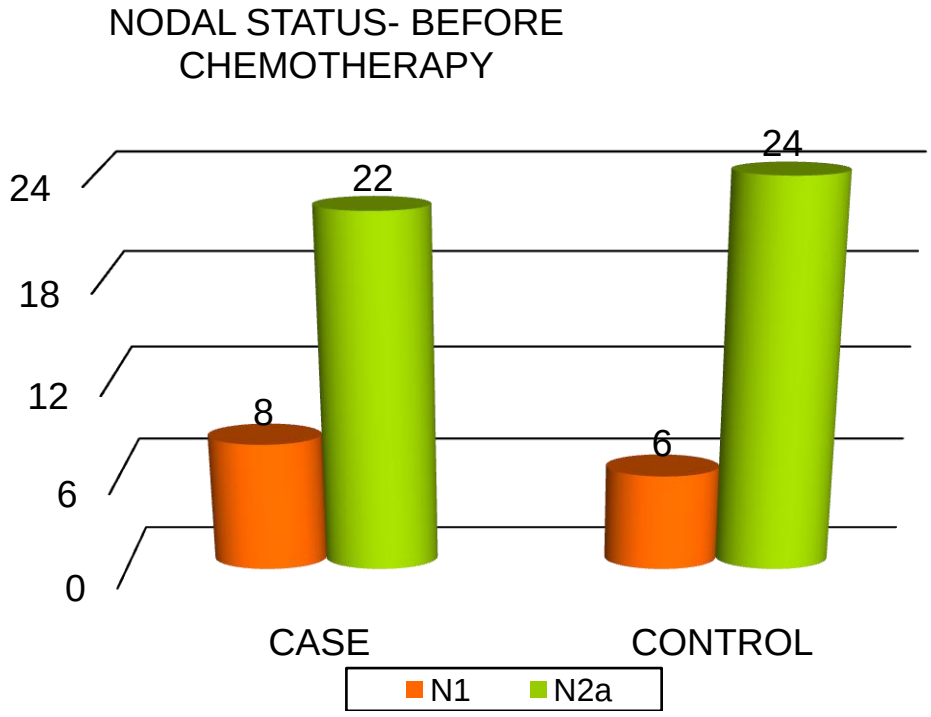
Out of 30 patients in case group, 12 patients in case group belong to less than 50 age group, 9 patients in case group belong to age group 51 to 55 years and rest of the patients (9 patients) belong to age group more than 55 years.

Before neoadjuvant chemotherapy		
size of tumor(cm) app~	CASE	CONTROL
8*	10	5
9*	5	10
10*	9	10
11*	3	4
12*	3	1
TOTAL	30	30

Among 30 patients in study group, 10 of them belong to tumour size 8 cms approximately, and 9 of them belong to tumour size 10 cms app, remaining 9 belong to 9-12 cms. Pre chemotherapy size was assessed and tabulated , to assess the post chemotherapy response.

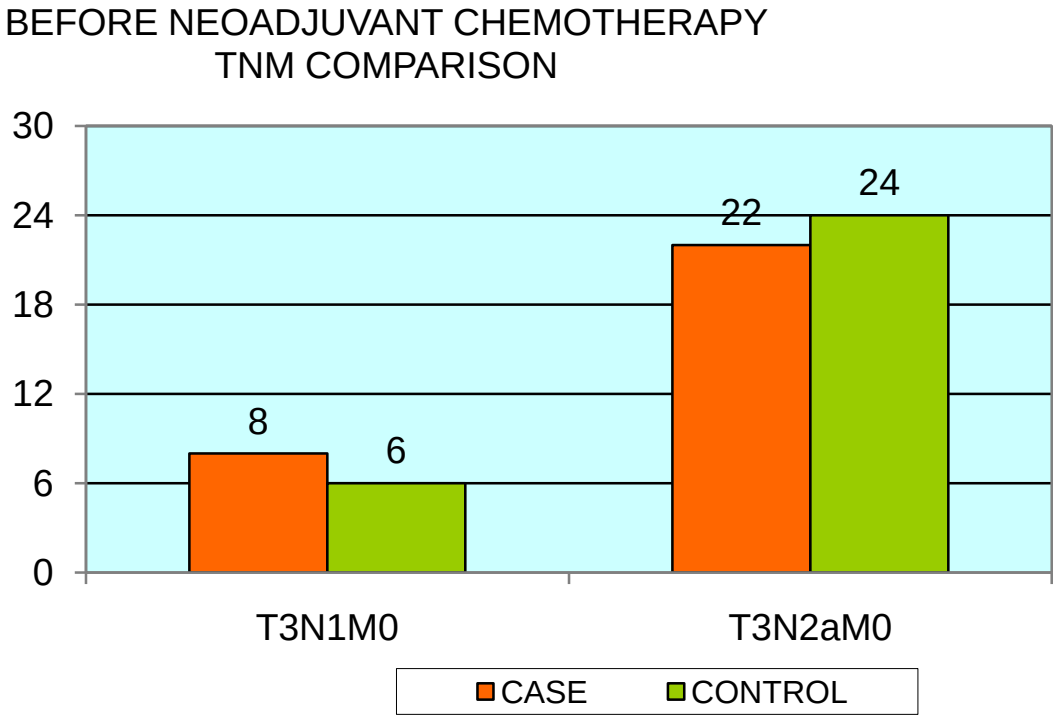


Before neoadjuvant chemotherapy		
Nodal status	CASE	CONTROL
N1	8	6
N2a	22	24
TOTAL	30	30



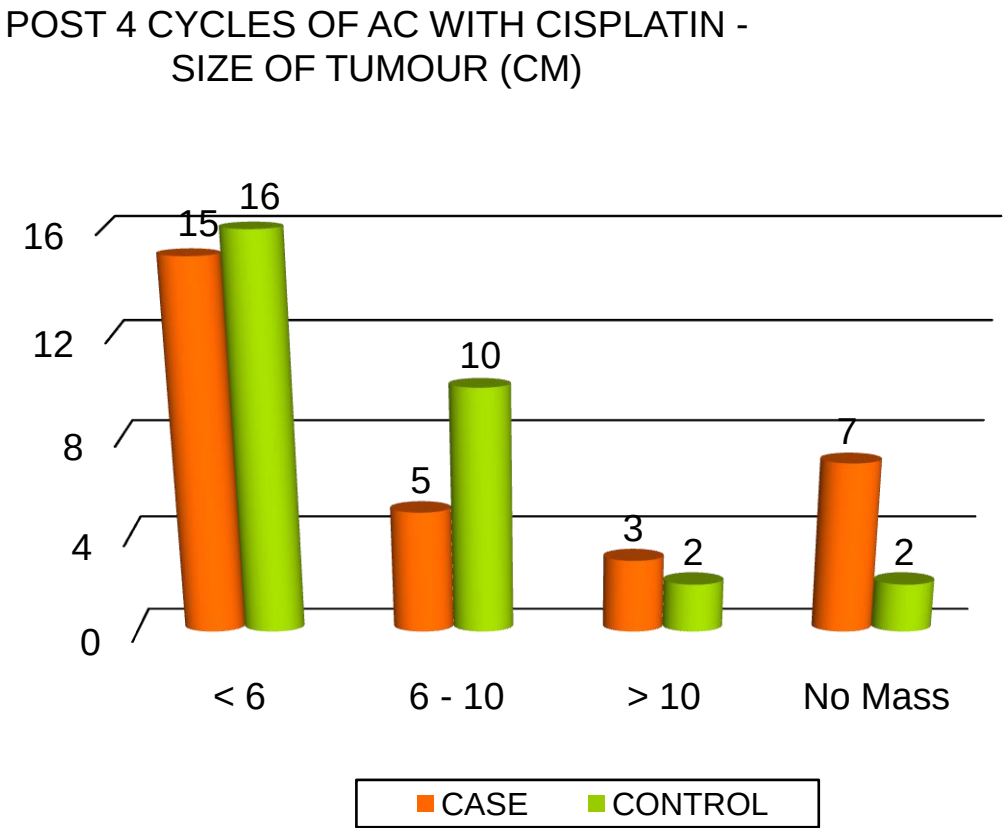
As this study is conducted among LABC patients, case and control group are selected as they belong to approximately equal nodal status as depicted in the bar chart.

	Before neoadjuvant chemotherapy		
	TNM	CASE	CONTROL
	T3N1M0	8	6
	T3N2aM0	22	24
	TOTAL	30	30



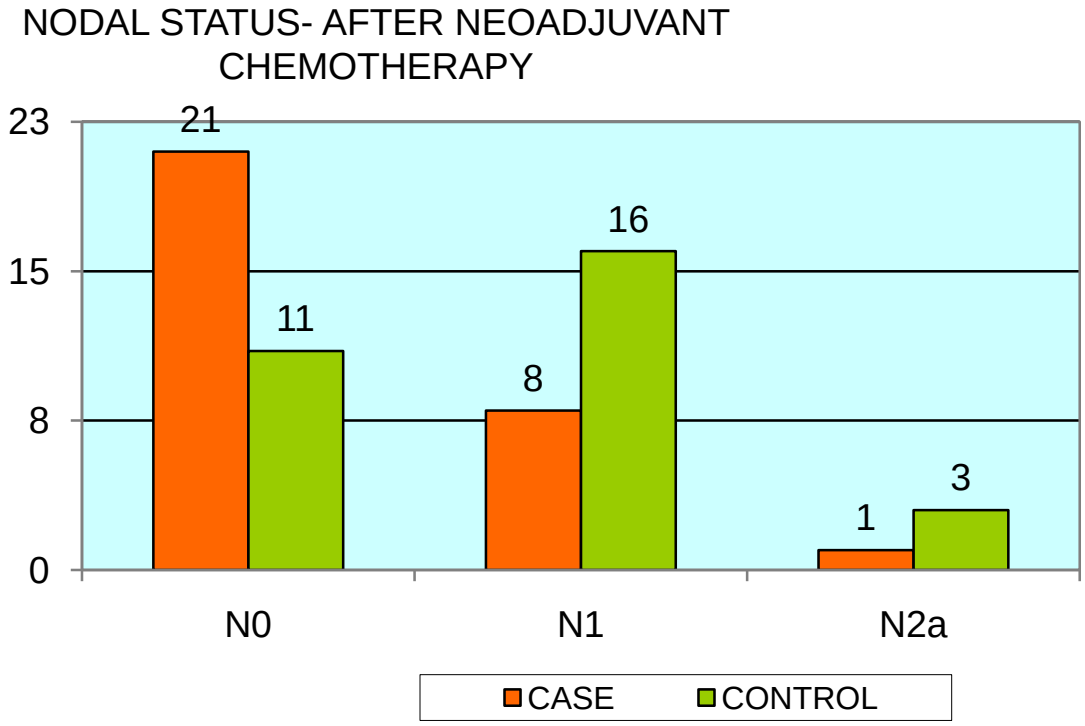
Patients were chosen in a way nearly 22 patients in case group and 24 patients in control group belongs to T3N2aM0 stage and 8 patients in case group and 6 patients in control group belongs to T3N1M0 stage, so that both study group will have patients with equal disease staging.

	Post 4 cycles of AC with cisplatin		
	Size of tumor(cm)	CASE	CONTROL
	< 6	17	13
	6 - 10	6	10
	> 10	0	5
	No Mass	7	2
	TOTAL	30	30
	P'value	0.025 Significant	



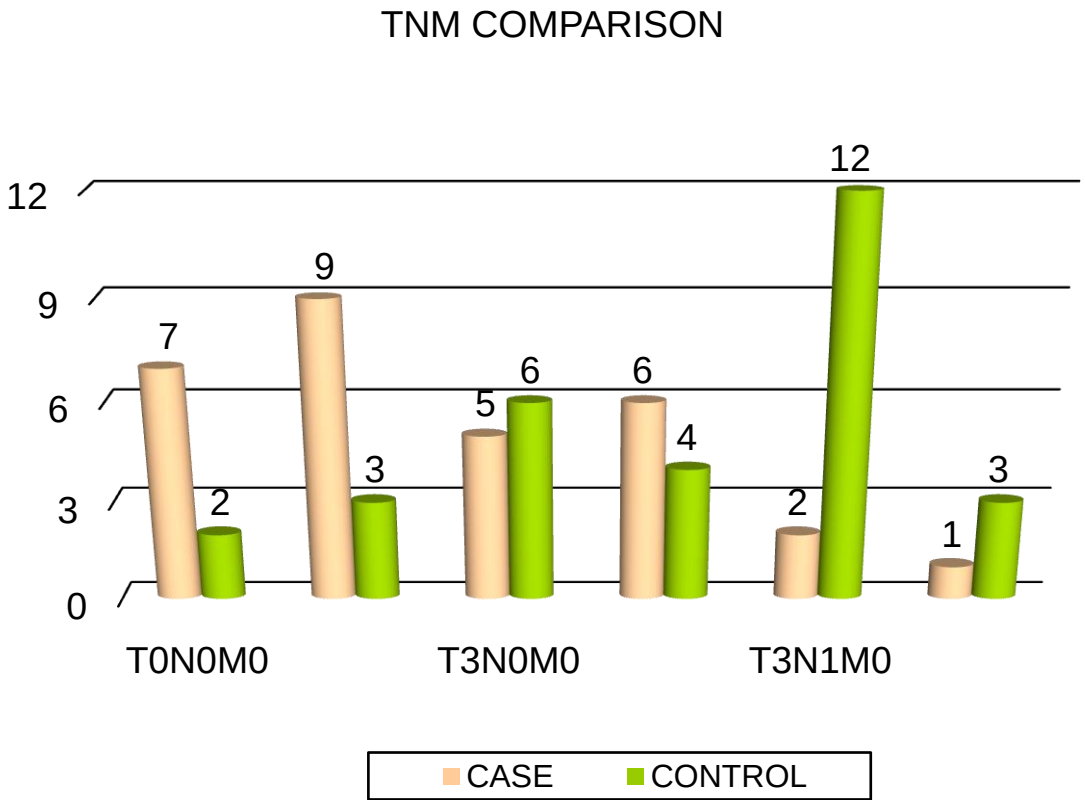
Out of 30 patients in case group who received cisplatin, 7 patients showed complete response with no detectable mass after 4 cycles of AC with Cisplatin which accounts for 23.3%. p value for this response is 0.025 which is significant and implying that cisplatin has good response in tumour regression.

	Post 4 cycles of AC with cisplatin		
	nodal status	CASE	CONTROL
	N0	21	11
	N1	8	16
	N2a	1	3
	TOTAL	30	30
	P'value	0.034 Significant	

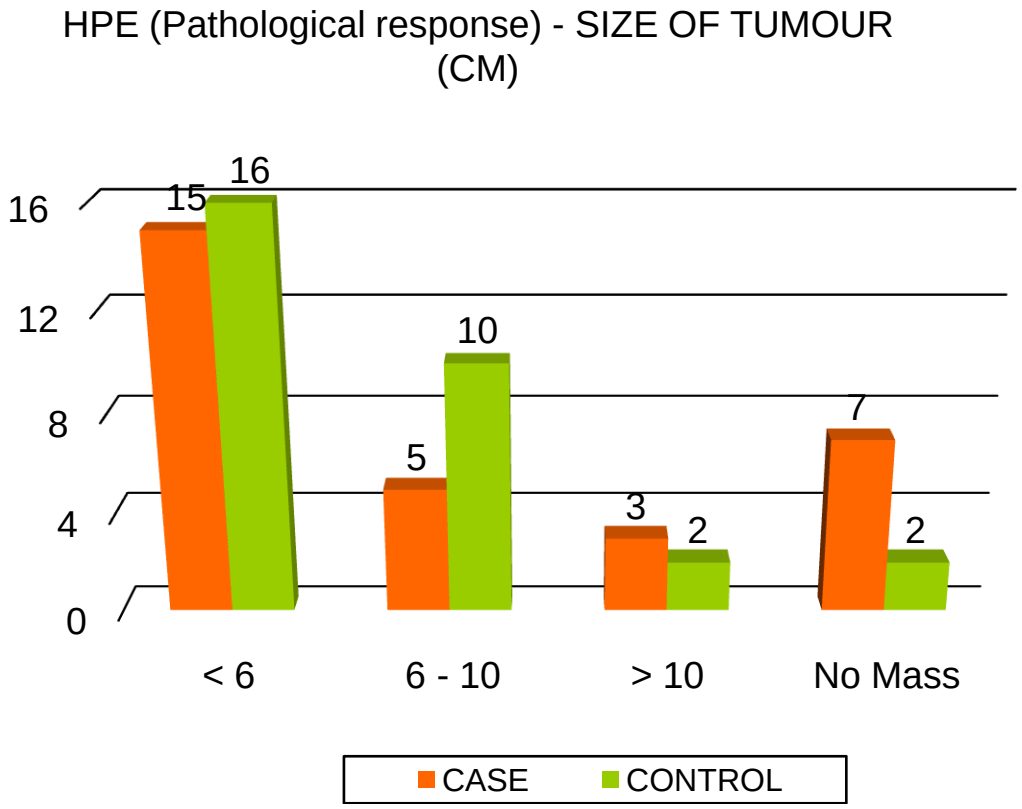


According to nodal status after receiving chemotherapy nearly 21 patients in case group falls under N0 status, which accounts for 70%. p value for nodal response is 0.034 which is significant. Nearly 22 patients in case group belong to N2a status prior to neoadjuvant chemotherapy out of which only one patient stay back in N2a status, remaining 21 patients were downstaged with cisplatin therapy.

	Post 4 cycles of AC with cisplatin		
	TNM	CASE	CONTROL
	T0N0M0	7	2
	T2N0M0	9	3
	T3N0M0	5	6
	T2N1M0	6	4
	T3N1M0	2	12
	T3N2aM0	1	3
	TOTAL	30	30
	P'value	0.013 Significant	

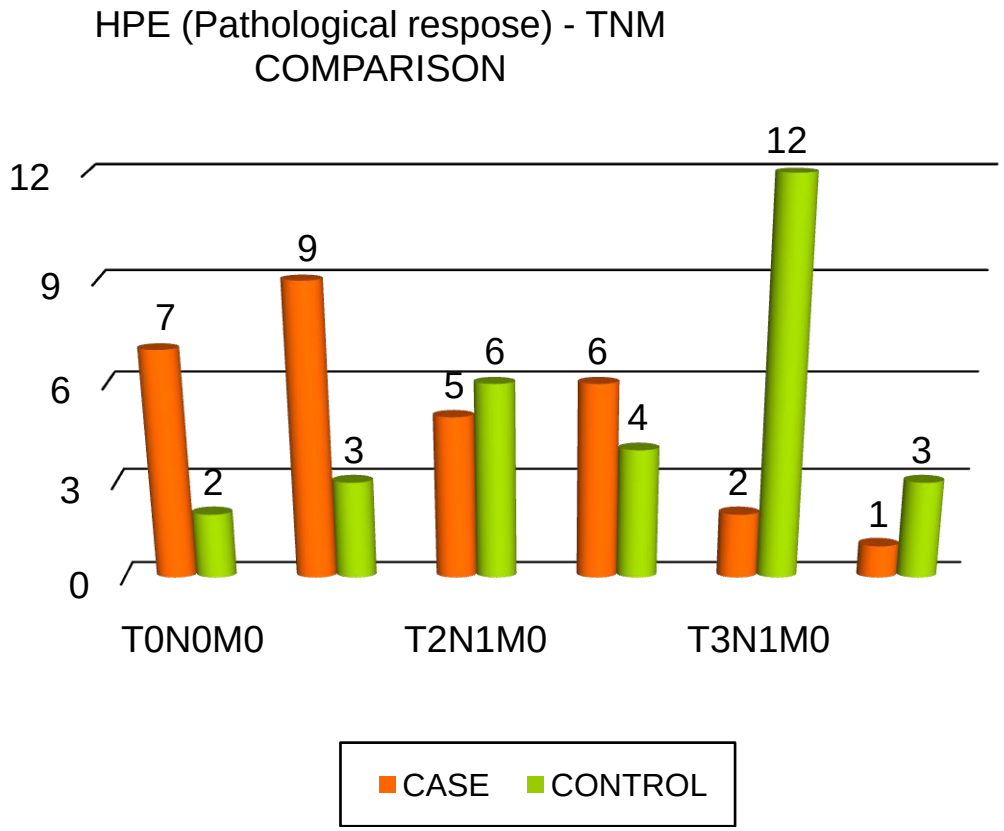


	HPE (Pathological response)		
	Size of tumor(cm)approximately	CASE	CONTROL
	< 6	17	13
	6 - 10	6	10
	> 10	0	5
	No Mass	7	2
	TOTAL	30	30
	P'value	0.025 Significant	



Post operative histopathology report correlates with post chemotherapy clinical assessment of tumour size which is proven through no detectable tumour in HPE for 7 patients in case group. p value is 0.025 which is significant.

	HPE (Pathological response)		
	TNM	CASE	CONTROL
	T0N0M0	7	2
	T2N0M0	9	3
	T2N1M0	5	6
	T3N0M0	6	4
	T3N1M0	2	12
	T3N2aM0	1	3
	TOTAL	30	30
	P'value	0.013 Significant	



Out of 30 patients in control group, 19 patients stayed back in T3 status even after neoadjuvant chemotherapy, but only 9 patients in case group retained in T3 status, which shows addition cisplatin to neoadjuvant chemotherapy has significant role in downstaging of the tumour.

V. Discussion

REGIMEN A (CASES)

Patient characteristics	***Number of patients***	***Percentage***
Age		
< 50 years	12	40%
> 50 years	18	60%
Stage III	30	100%
Total		
Tumour size		
< 10cm	15	50%
>10cm	15	50%
Axillary node status		
N1	8	26.67%
N2	22	73.33%

In the current study, after following the inclusion and exclusion criteria, 30 patients were enrolled under case group (regimen A), and the remaining 30 patients were enrolled under control group (regimen B), all these patients were having locally advanced breast cancer.

The above table summarizes the patient characteristics and the clinical features. Out of the 30 subjects enrolled, 12 (40%) patients were less than 50 year age group and 18 patients (60%) were aged above 50 years. Among 30

patients grouped under case group,15 patients (50%) had tumour size less than 10 cms and 15 patients (50%) had tumour size more than 10 cms.

In the study group of 30 patients under case group(regimen A), all of them had palpable axillary node.Single node was palpable in 8 patients (26.67%). Remaining 22 patients(73.33%) had axillary node status of more than one node palpable.

REGIMEN A (CASE GROUP)

Clinical response	**Number of patients**	**Percentage**
Clinical complete Response	7	23.33
Clinical partial Response	19	63.33
No response or stable Disease	3	10
Progressive Disease	1	3.33

REGIMEN B (CONTROL GROUP)

Clinical response	**Number of patients**	**Percentage**
Clinical complete Response	2	6.67
Clinical partial Response	15	50
No response or stable Disease	9	30
Progressive Disease	4	13.33

Evaluation of the clinical response of primary tumour and lymph node to neoadjuvant cisplatin regimen A (cases) compared with regimen B(control) was one of the primary objective of study. The product of two greatest perpendicular diameter was measured both manually (clinically) and using ultrasonogram & MRI before and after every cycle of Neoadjuvant chemotherapy as defined by criteria.

The clinical response of 30 patients under case study was observed and recorded.

Out of the 30 patients in case group the overall objective clinical response of 86.66% was observed. Complete clinical response of 23.33% (7 Patients) was noted, Partial clinical response was noted in 19 among 30 patients (63.33%). No response(<50% response)was observed in 3 patients (10%). However 1 patient(3.33%) showed progressive disease and developed vertebral metastasis post- MRM.

In similar studies conducted by Aguilar Martinez et al[122] showed an over all objective response of 86.3% was observed. In their study there were no progressive disease observed after Neoadjuvant chemotherapy.

B. Sirohi et al conducted a study in Breast unit, Royal Marsden NHS foundation Trust, London which showed an overall clinical response of 88% was observed[123].

In our study, percentage of complete clinical response(23.33%) was higher for patients in case group than the percentage of complete clinical response(6.67%) for the patients in control group. In similar studies conducted by Aguilar Martinez et al[122] and B. Sirohi et al, it was reported that complete clinical response after platinum based compond added to the standard Neoadjuvant chemotherapy in TNBC was better. This correlated with the present study.

The second objective in our study was to evaluate the pathological response of the primary tumour and lymph node to preoperative chemotherapy. The pathological response was classified into 2 categories, namely pathological complete response and PINV(invasive cells seen). PCR constituted a group of patients who showed no invasive cells detected.Second group consisted of patients who were termed pathological non responders. (PINV), since their mastectomy specimen showed invasive cells on Histopathological examination.

Case group (regimenA)

Pathological response	***No of patients***	***% of pathological Response***
Pathological complete response (PCR)	7	23.33
PINV (pathological non responders)	23	76.67
PINV (pathological non responders)		

In the present study, 7 patients (23.33%), showed complete pathological response after cisplatin neoadjuvant chemotherapy. Invasive cells were detected in the mastectomy specimen of 23 patients on HPE (76.67%).

Control group (regimen B)

Pathological response	***No of patients***	***% of pathological Response***
Pathological complete response (PCR)	2	6.67%
PINV (pathological non responders)	28	93.33%
PINV (pathological non responders)		

In control group (regimen B), 2 patients (6.67%), showed complete pathological response after standard neoadjuvant chemotherapy. Invasive cells were detected in the mastectomy specimen of 28 patients on HPE (93.33%).

From the study it was confirmed that the pathological complete response in case group (23.33%) was better than control group (6.67%).

In similar study conducted by Daniel P. Silver et al [124] , it was reported that complete pathological response (28%) after platinum based compond added to the standard Neoadjuvant chemotherapy in TNBC was better. This correlated with the present study.

VI. Conclusion

From this study it is evident that cisplatin based neoadjuvant chemotherapy in locally advanced triple negative breast cancer

1) Showed a significant increased pCR rates in patients at the cost of worse haematological toxicities.
2) Downstage the disease so as to make the inoperable tumour to operable one.
3) It also provides an opportunity to analyze biological markers as predictors of response to CT.

Bibliography

[1]. Clive peedell concise clinical oncology-Ist edition, page No. 144
[2]. Guinee VF: epidemiology of breast cancer in Blind KI, Copeland EM, (III edition) the breast: Comprehensive management of Benign and Malignant disease. Philadelphia WB Saunder 1998 P 339
[3]. Jemal A, Murray et al Cancer statistics 2003, CA Cancer Journal Clin. 53:5, 2003
[4]. Cancer Incidences in Rural Delhi - 2004-05. Asian Pacific Journal of Cancer Prevention. 2010;11(1):73–8.
[5]. Chopra R. The Indian Scene. J ClinOncol. 2001 Sep 15;19(suppl_1):106s–111.
[6]. WHO Health Situation in South East Asia region. NewDelhi 1994- 1996.
[7]. WHO Health situation in south East Asian region, NewDelhi 1998- 2000.
[8]. Hortobagyi, strom EA et al: Treatment of LABC: disease of Breast IInd Edition.

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