IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 3 Ser.17 (March. 2023), PP 33-38
www.iosrjournals.org

An Observational Study on Clinical and Pathological Outcomes ToNeoadjuvant Chemotherapy In Breast Cancer

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Abstract
Aim: *The aim of study is to observe clinical and pathological outcomes to neoadjuvant chemotherapy in breast cancer.*
Methods: *This study was a prospective observational study carried out in thedepartmentofgeneralsurgery,SMS Hospital, Jaipur. Allthepatientsadmittedwithstage II (IIA, IIB), III (IIIA, IIIB, IIIC) were included in the study after obtaining approval from the institutional ethicalcommittee. Clinical response was assessed by RECIST criteria (clinical complete response (cCR), clinicalpartialresponse(cPR),clinicalprogressivedisease(cPD),andclinicalstabledisease(cSD))andpathologicalresponsebyhistopathologicalreport(pCR).Responseofvariousmolecularsubtypeswasnoted.*
Results:*Among50patientsincludedinthestudy,cCRobservedin28%cases,cPRobservedin62%cases while cPD and cSD seen in 4% and 6% cases, respectively. Pathological complete response (pCR)observedin26%cases.Favorableresponseseenwith triple negative (cCR = 55.55%, pCR = 50%) molecularsubtype.*
Conclusions:*It can be concluded that there is definite role of Neoadjuvant chemotherapy in downstaging of tumor. It shows conversion of non-operable cases to operable and creates a way for Breast conservation surgery in early breast cancer as well as locally advanced breast cancer.NACTresultsindownstagingoftumours,thus,help in achieving surgically clear margins and elimination of micrometastases which decreases therecurrenceratesandmorbidity/mortalityofpatients. It also shows that TNBC have better pCR than other molecular subtypes.*

Keywords: *NACT, early breast cancer, locally advanced breast cancer, observational study.*

Date of Submission: 14-03-2023 Date of Acceptance: 30-03-2023

I. Introduction

Breastcanceris one of themostcommonlydiagnosedcancersandthefifthcauseofcancerdeathsintheworld[1].BreastcancerinIndiaaccountsfor14%ofallcancersinwomen.TheincidenceratesinIndiabegintoriseintheearly30sandpeakatages50-64years[2].

Locallyadvancedbreastcancer(LABC) is subset of breast cancer characterizes by the most advanced tumours in absence of distant metastasis..TheUSNationalComprehensive Cancer Network (NCCN) describe LABC as American Joint Committee on Cancer (AJCC)stageIIIbreastcancerthatincludes:tumours>5cm(T3)withregionallymphadenopathy(N1-3),tumoursofanysizewithchestwallorskinorbothinvolvement(T4)irrespectiveoflymphnodestatus,extensivelymphnodes involvement (matted axillary lymph nodes, or any of infra-clavicular, supra-clavicular, or internalmammary)[3].

Neoadjuvant chemotherapy (NACT) has definite role in down stagingtumour which results in conversion of non-operable to operable cases and increases chances of breast conservation surgery in

early breast cancer as well as locally advanced breast cancer[4]. Furthermore, NACT provides the opportunity to discover predictive markers of chemotherapy[4]. Thepathologicalcompleteresponse(pCR)isconsideredabiologicalmarkerforsurvivaloutcomes.ThepCRis consideredwhenthereiscompleteeradicationoflocoregionaldisease[5,6]. Response of axillary lymph node and primary tumour may also differ in different subtype of breast cancer. ThisstudyassessedtumourresponseafterNACTusingclinicalchanges,ResponseEvaluationCriteriainSol idTumors(RECIST)criteriaandpathologicalreport.

The aim of this study is to observe clinical and pathological outcomes to neoadjuvant chemotherapy in Breast cancer.

II. MaterialsandMethods

This study was carried out in the department of General surgery, S.M.S Hospital, affiliated to S.M.S. Medical College, Jaipur, Rajasthan. The study was a prospective observational study and patients were included according to the inclusion criteria and excluded according to exclusion criteria explained in the following paragraphs.

Inclusion Criteria:

1. All the female patients admitted under the department of General Surgery, with diagnosis of breast cancer having tumor size > 2cm or clinically involved axillary nodes.
2. Patients with LABC and those who give consent.

Exclusion Criteria:

1. Patient not willing for study;
2. All cases diagnosed as benign disease of breast;
3. All patients with presence of distant metastasis proved on clinical examination/ investigations.

Afterapplyinginclusionandexclusioncriteria,50patientswereidentifiedforthestudy.Initialstaging workup included clinical examination supplemented by haematological (complete blood count),biochemical(renalandliverfunctiontests),andradiologicalinvestigations(X-ray-chest,skeletalsurvey,andultrasoundabdomen).Computedtomographyandmagneticresonanceimagin gweredonewhereverindicated.Immunohistochemistrywasobtainedforallthepatients.
Patients were subjected to anthracycline-based NACT after the initial assessment was completed.Patients were treated with 4 cycles of AC/EC regime followed by 4 cycles of Taxanes. Most of patients received complete cycles as NACT but few of them operated after 4 or 6 cycles as they developed cCR and received rest of cycles as adjuvant chemotherapy (ACT). As Trastuzumab was not available at our government hospital so we were unable to give it to patients with HER2 overexpression. Surgical specimens were sent for histopathological examination and reports were used to assess response to chemotherapy

Evaluationofneoadjuvantchemotherapyresponse:
ClinicalresponsewasassessedbyRECISTcriteria

Table-1RECIST Criteria

Clinicalcompleteresponse(cCR)	**Nopalpabletumourinthebreastandaxilla**
Clinicalpartialresponse(cPR)	**≥30%reductioninthemaximumdimensionofthetumourmass**
Clinicalprogressivedisease(cPD)	**≥20%increaseinthemaximumdimensionoftumourmass**
Clinicalstabledisease(cSD)	**Whenthechangedoesnotmeetanyoftheothercriteria**

Pathologicalresponsewasassessedbyhistopathology.pCRimpliednoresidualinvasivebreastcancerinthehistopathology specimen of breast and axillary lymph nodes (ypT0/ypTisN0). All comparisons of categoricalvariableswereperformedwiththechi-squaretestwhilecontinuousvariableswerecomparedusingthet-test.

III. Observations and Results

The median age of the patients at the time of diagnosis was 49.58 years (range: 21-75 years). The maximumnumber of patients were in the age group of 41-50 years (46%) followed by 51-

60 years (28%).TheclinicalcharacteristicsarelistedinTable-2.The lump was the most consistent presenting symptom and was present in 100% of the cases. The upper outer quadrant (60%) was the most commonly involved quadrant and the lower inner quadrant (2%) was least involved. The tumour size ranged from 3.5 to 13 cm with a mean size of 5.74 cm. All the patients were lymph node positive at the time of presentation.

Table-

Features	**Numberofpatients**(n=50)
1. Age(years),median(range)	**49.58 (25-79)**
2. Menopausalstatus –	
Premenopausal	**32(64%)**
Post-menopausal	**18(36%)**
3. Lump laterality	
Right	**32(64%)**
Left	**18(36%)**
4. Lumpsize	
<5cm	**11(22%)**
>5cm	**39(78%)**
5. Nodalstatus	
Negative	**0**
Positive	**50(100%)**
6. Clinicalstage	
III A	**18(58.06%)**
III B	**11(35.48%)**
7. Histologicaltype	
Invasiveductalcarcinoma	**46(92%)**
Invasivelobularcarcinoma	**3(6%)**
Others	**1(2%)**
8. Molecularclassification	
LuminalA	**21(42%)**
LuminalB	**6(12%)**
HER2overexpression	**5(10%)**
Triplenegative	**18(36%)**

2Clinicopathological features of patients with Breast cancer

ClinicalresponseinMolecularSubtypes

A clinical response was observed in 90% of the cases subjected to NACT as assessed by RECIST criteriawithclinicalcompleteresponse(cCR)notedin28%cases.58%casesbecameclinicallylymphnode-negativefollowingNACT(pvalue<0.0001)andclinicaldown stagingwasobservedin86%cases(pvalue <0.0001).

Table 3: Clinical response in Molecular Subtypes

Subtype	cCR	cPR	cPD	cSD
LuminalA	4(19.04%)	17(80.95%)	010.00%)	0(0.00%)
LuminalB	0(0.00%)	3(50.00%)	1(16.66%)	2(33%)
HER2overexpression	0(0.00%)	3(60%)	1(20%)	1(20%)
TripleNegative	10(55.5.00%)	8(44.44%)	0(0.00%)	0(0.00%)
Total	**14(28%)**	**31(62%)**	**2(4%)**	**3(6%)**

cCR was observed in a maximum of 55% of the cases of TNBC followed by 19% of cases of Luminal A subtype. No cCR was noted in luminal B subtype and HER2 overexpression. pCR was observed in 22% casesincludedinthestudy.

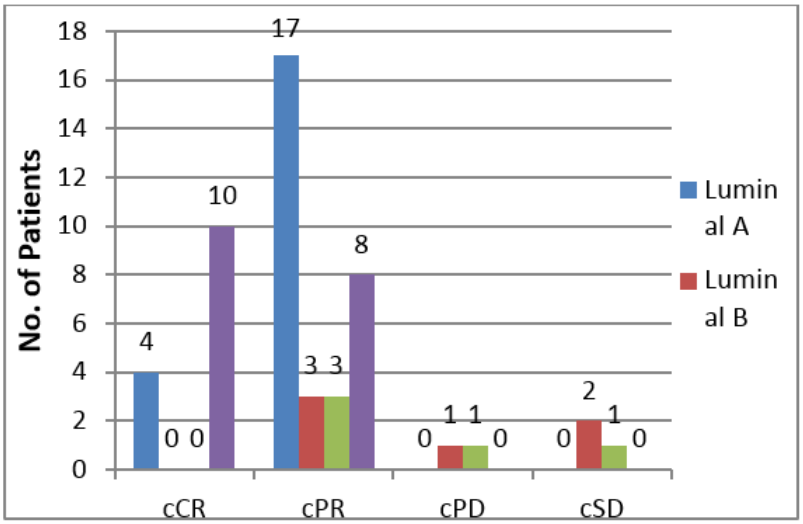

Figure 1:- Clinical response in molecular subtypes

Pathological response in Molecular subtypes

Maximum (50%) pCR was observed in the Triple Negative Breast Cancer followed by 14.28% in the Luminal A. NopCRwasobservedinluminalB and HER2 overexpression subtype (as trastuzumab was not given due to unavailability at our govt. hospital).

Table 4: Pathological Complete Response (pCR) in Molecular Subtypes

Subtype	pCR	NopCR
LuminalA	3(14.28%)	18(80.00%)
LuminalB	0(0.00%)	6(100%)
HER2overexpression	0(0.00%)	5(71.42%)
Triple negative	9 (50%)9(50.00%)	

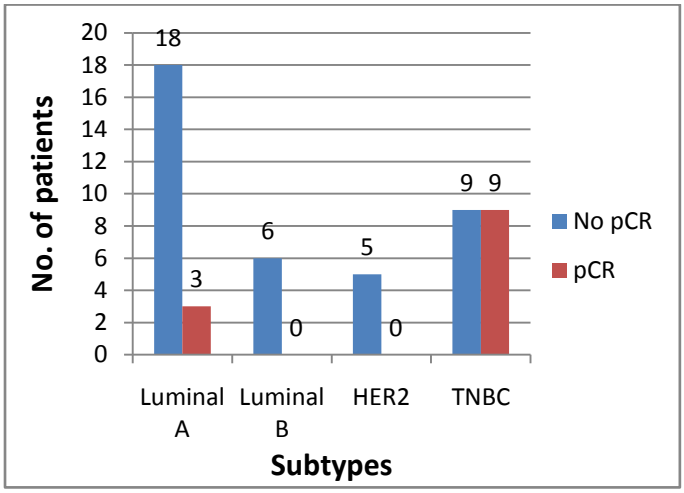

Figure 2: Pathological response in molecular subtypes

IV. Discussion

In LABC as well as early breast cancer, neoadjuvant therapy has become one of the preferred treatment options. Neo-adjuvant systemic therapy integrated into a multimodality program is the established treatment in Operable breast cancer and LABC. Response of Neoadjuvant chemotherapy depends on molecular subtypes of breast cancer which is different in different subtypes. Response of axillary lymph node and primary tumour may also differ in different subtype of breast cancer. But in TNBC usually have better response with NACT as compare to other molecular sub types. pCR of primary tumour and axillary lymph node has definite correlation with overall survival rate.

Neoadjuvant chemotherapy leads tocytoreduction of the primary tumour and regional lymph nodes allowing breast conservation in selectedcases. An additional benefit of this technique is, potentially, eradication of distant microscopic metastases,the presence of which is the most common cause of relapse.

Inourstudy,50patientswereincludedwhohadadiagnosisof early breast cancer and LABCatthetimeofpresentation.Themaximumnumberofpatientswereintheagegroupof41-50years(46%)followedby51-60years (28%)andmeanagewas49.58years.Thisagedistributionofpatientswassimilartoprevious Studies[7,8].Alumpinthebreastwasthecommonestsymptomnoticedin100%casesinourstudywhichwas similartootherstudies[9,10]. Upperouterquadrant (60%)wasthemostcommonlyinvolvedquadrant and the least incidence was found in lower inner quadrant (2%). The tumour size ranged from 3.5 to 13cmwithameansizeof5.74cm.Allthepatientswerelymphnodepositiveatthetimeofpresentation.92% ofpatientshadIDC.

Clinical response to NACT was assessed by calculating the percentage decrease in the volume of the tumour. TheoverallresponsetoNACTinthisstudywas90%withpartialresponseseenin62%casesandcompleteresponse seen in 28% cases which was similar to previous studies [11,12]. 58% of cases becameclinicallylymphnode-negativefollowingNACT(pvalue<0.0001).

The pathological response was assessed by the HPE of the surgical specimen. pCR was noted in 24% cases. Among molecular subtypes, maximum of 50% pCR was observed in triple negative subtype followed by 14.28% cases of Luminal A subtype. No pCR was observed in luminal B subtype and HER2 overexpression.

There are multiple potential reasons that the response to chemotherapy differed by subtype. The triple-negative tumour is basically estrogen/progesterone (ER/PR) negative, and evidence suggests that the negative hormone receptor status is one of the strongest predictive markers associated with the higher likelihood of pCR to NACT [13,14,15] .

Limitations of study: The study was conducted in a single institution and had a small sample size with no provision of trastuzumab for her2 overexpresion subtype.

V. Conclusions

Breast lump is most common presentation of breast cancer with most common stage is T2 or

T3 (LOBC/LABC) in India. LABC is a common presentation of carcinoma breast and the role of NACT has been debated for a long time now. In our study, clinical response (complete plus partial) resulting in a decrease in tumour size was observed in more than 80% cases. Pathological disappearance of the invasive tumour was noted in approximately 20% cases.

Assessment of response of molecular subtypes to NACT suggests that triple- negative breast cancers have better clinicopathological response than luminal subtypes. Hence, molecular subtype determination helps in deciding treatment protocol in patients with early breast cancer and LABC. NACT results in downstaging of tumours, thus, help in achieving surgically clear margins and elimination of micrometastases which decreases the recurrence rates and morbidity/mortality of patients.

AdditionalInformation

Disclosures

Humansubjects: Consentwasobtainedorwaivedbyallparticipantsinthisstudy.InstitutionalEthicsCommittee, SMS Medical College and Attached Hospitals, Jaipur, gave approval for study.

Animal subjects: Allauthorshaveconfirmedthatthisstudydidnotinvolveanimalsubjectsortissue.**Payment/service sinfo:** All authors have declared that no financial support was received from any organization for thesubmittedwork.

Financialrelationships: Allauthorshavedeclaredthattheyhavenofinancialrelationshipsatpresentorwithinthepreviousthreeyearswithanyorganizationsthatmighthaveaninterestinthesubmittedwork.

Otherrelationships: Allauthorshavedeclaredthattherearenootherrelationshipsoractivitiesthatcouldappeartohaveinfluencedthesubmittedwork.

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