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Research Article

TO DETERMINE THE COMPLETE PATHOLOGICAL RESPONSE RATE AFTER NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER

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A B S T R A C T

Background: In breast cancer after administration of NACT ultimately negative results for residual cancer is defined as pathological complete response (pCR). Patients with subtype; positive for low-grade estrogen receptor (ER) and negative human epidermal growth factor receptor 2 (HER2), have poor survival rate.
Objective: To determine the complete pathological response rate after neoadjuvant chemotherapy in breast cancers patients at a tertiary care hospital.
Material and Methods: This prospective cohort study was conducted at Department of Medical Oncology Jinnah Postgraduate Medical Center, Karachi from June 2016 to June 2017. All patients received injection Doxorubicin 60mg/m2 IV day 1 and Cyclophosphamide 600mg/m2 IV on day1. Cycle repeated every 21 days for 4 cycles, followed by injection Paclitaxel 80mg/m2 via 1-hour IV infusion weekly for 12 weeks, followed by surgery. During chemotherapy patients were followed up to manage any adverse effect of chemotherapy. Descriptive statistics were calculated. Chi square test were applied to see the association of outcome.
Results: There were significant response observed with high rate of complete response (n=16, 61.5%) in patients with T3 stage of breast cancer. Complete response was similar in ER and PR positive patients that is 29%. Similarly, response to therapy coincided in ER and PR negative patients that is 27%. Complete response was higher (34%) in HER2 patients while in HER2 negative showed in 26%, with no statistically significance (p-value= 0.45).
Conclusion: NACT in breast cancer reduce the tumor burden and considerably good therapeutic option to achieve the complete pathological response. In our study we found that complete pathological response rate of 31.3% after NACT in locally advanced breast cancer.

INTRODUCTION

In early breast cancer neoadjuvant chemotherapy (NACT) is adopted to administer as an option for patients,1 prior to removal of tumor with the aim of improving the surgical safety with minimizing the extent of surgery.1,2 Consequently NACT has improved the rate of surgeries, preserving the breast.2

In breast cancer patients administration of NACT ultimately negative results for residual cancer is defined as pathological complete response(pCR). A study reported only 22% achievement of pCR in patient undergone treatment with NACT. 3 Patients with subtype; positive for low-grade estrogen receptor (ER) and negative human epidermal growth factor receptor 2 (HER2), have poor survival rate.4-12

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Studiess showed patient with positive for low-grade estrogen receptor (ER) negative, human epidermal growth factor receptor 2 (HER2) positive and negative progesterone receptor (PR) status, these may increase the chances to achieve the pathological complete response to NACT.3-7,13,14 Patients if identified through HER2, ER, and PR NACT can be offered to achieve the pCR and also beneficiary to offer the patient tailored therapy, with possibility to attain the outcome via breast preserving surgery. But clinician currently is unable to find out the patients but can make rough inference through HER2, ER and PR as favorable factor for response identification. However further contributing factors are needed to make correct inference. Tumor size is another contributing factor to estimate the pCR to NACT. Studies reported the small size and good indicator of pathological complete response.15 While another study the opposite results, inverse relation between degree of response and initial tumor size (>3cm).16 Tumor grades evaluation is an important

determinant of disease prognosis. NACT selection and treatment depend on tumor grade and molecular subtypes.17

NACT excluded mastectomy in about 25% of patients, while <5% of patient receiving therapy still required mastectomy due to disease progression. 18NACT is currently been used for reducing the large tumor, inoperable tumor and locally advanced breast cancer, to avoid mastectomy.19

Aim of this study is to investigate the response in breast cancer patients undergoing NACT, tumor size, and tumor grades. It is also investigated pCR as marker for disease free survival and overall survival.

MATERIAL & METHODS

This prospective cohort study was conducted at Department of Medical Oncology Jinnah Postgraduate Medical Center, Karachi from June 2016 to June 2017. The study was approved by institutional ethical review board. Informed consent was also taken. A total of 84 patients were enrolled out of which 1 patient was dead. So a total of 83 alive patients were enrolled for this study. Purposive sampling technique was applied. All the patients over 16 years of age, histo- pathologically confirmed locally advanced carcinoma Of breast (Stage III & IV), stage IV non- metastatic having no other malignancy, performance status PS (0 to 1), patients having echocardiogram with ejection fraction >55%, and with normal hepatic renal function were included in the study. Previously treated (surgery/chemo-radiotherapy) patients, having ejection fraction <55% by echocardiogram were excluded. All patients received injection Doxorubicin 60mg/m2 IV day 1 and Cyclophosphamide 600mg/m2 IV on day1. Cycle repeated every 21 days for 4 cycles, followed by injection Paclitaxel 80mg/m2 via 1-hour IV infusion weekly for 12 weeks. All cycles are supported with myeloid growth factor (GCSF).and followed by surgery. During chemotherapy patients were followed up in OPD weekly to manage any adverse effect of chemotherapy and to asses any sign of progression of disease, blood chemistry, hematological derangement. Data were recorded on a predesigned Proforma. Data were compiled and analyzed using SPSS. Descriptive statistics were calculated. Chi square test were applied to see the association of outcome.

RESULTS

The Table-1 showed the frequency distribution of demographics and the Table-2 represented the frequency distribution of basic characteristics. The Table-3 presented the frequency distribution of diagnostic procedures performed. In our cohort of 83 patients, the mean age was 44.80±10.39 years and duration of chemotherapy was 6.57±1.56 months. The descriptive statistics of these parameters are presented in Table-4. As far as response are concerned the results showed that complete pathological response was observed in 31.3% cases, partial response was observed in 54.2% cases, no response was observed in 9.6% patients. The detailed results are also presented in Table-5.

The response was further compared with the demographic parameters and basic characteristics. The results showed that no significant association was observed. The detailed results are presented in Table-6. There were significant response observed with high rate of complete response (n=16, 61.5%) in patients with T3 stage of breast cancer. There was only one patient with T4 stage who did not responded to NACT, while none of non-responder to NACT with T1, T2, T3 stage group. Complete response was similar in ER and PR positive patients that is 29%. Similarly, response to therapy coincided in ER and PR negative patients that is 27%. Complete response was higher (34%) in HER2 patients while in HER2 negative showed in 26%, with no statistically significance (p-value= 0.45). Complete, partial, and no response to NACT with or without HER2, ER and PR are shown in Table-7.

Table 1 Frequency distribution of demographic

Description	n (%)
Age	
≤44	41(49.4)
>44	42(50.6)
Occupation	
House Wife	81(97.6)
Labour	1(1.2)
Student	1(1.2)
Resident	
Sindh	75(90.4)
Punjab	4(4.8)
Balochistan	4(4.8)
Side of cancer	
Left	44(53)
Right	39(47)

Table 2 Frequency distribution of basic characteristics

Description	n (%)
Histology	
Invasive Ductal Carcinoma	54(65.1)
Infiltrating	29(34.9)
Grade	
II	60(72.3)
III	23(27.7)
ER Status	
Not Conducted	12(14.5)
Negative	26(31.3)
Positive	45(54.2)
PR Status	
Not Conducted	12(14.5)
Negative	40(48.2)
Positive	31(37.3)
HER2 Neu Status	
Not Conducted	14(16.9)
Negative	34(41.0)
Positive	35(42.2)
TNM Stages	
III	63(75.9)
IV	20(24.1)
T Stage	
T1	1(1.2)
T2	5(6.0)
T3	59(71.1)
T4	18(21.7)
N Stage	
N1	38(45.8)
N2	33(39.8)
N3	7(8.4)
N	3(3.6)
Nx	2(2.4)

Table 3 Frequency distribution of diagnostics procedures performed

Description	n (%)
Echo	
Yes	78(94.0)
No	5(6.0)
Bone Scanning	
Yes	81(97.6)
No	2(2.4)
Ultrasound	
Yes	10(12.0)
No	73(88.0)
Mammography	
Yes	48(57.8)

Table 4 Descriptive statistics of age and duration of chemotherapy

	Age (years)	Duration of Chemotherapy (months)
n	83	83
Mean	44.8	6.57
SD	10.3	1.56
Minimum	26	3
Maximum	69	12

Table 5 Frequency distribution of responses

Description	n (%)
Complete Response	26(31.3)
Partial Response	45(54.2)
No Response	8(9.6)
Lost To Follow Up	1(1.2)
Expired	1(1.2)
Switch To 2nd Chemo	2(2.4)

Table 6 Association of response with demographic and baseline characteristics

	Response Achieved n=83						
	Complete Response 26(31.3)	Partial Response 45(54.2)	No Response 8(9.6)	lost to follow up 1(1.2)	Expired 1(1.2)	switch to 2nd chemo 2(2.4)	P-value
Age n(%)							0.521**
≤44	14(53.8)	21(46.7)	3(37.5)	0(0)	1(100)	2(100)	
>44	12(46.2)	24(53.3)	5(62.5)	1(100)	0(0)	0(0)	
Occupation n(%)							0.365**
House Wife	24(92.3)	45(100)	8(100)	1(100)	1(100)	2(100)	
Labour	1(3.8)	0(0)	0(0)	0(0)	0(0)	0(0)	
Student	1(3.8)	0(0)	0(0)	0(0)	0(0)	0(0)	
Resident n(%)							0.962**
Sindh	23(88.5)	40(88.9)	8(100)	1(100)	1(100)	2(100)	
Punjab	2(7.7)	2(4.4)	0(0)	0(0)	0(0)	0(0)	
Balochistan	1(3.8)	3(6.7)	0(0)	0(0)	0(0)	0(0)	
Side of cancer n(%)							0.499**
Left	14(53.8)	25(55.6)	3(37.5)	0(0)	0(0)	2(100)	
Right	12(46.2)	20(44.4)	5(62.5)	1(100)	1(100)	0(0)	
Histology n(%)							0.324**
Invasive Ductal Carcinoma	15(57.7)	31(68.9)	6(75)	1(100)	1(100)	0(0)	
Infiltrating	11(42.3)	14(31.1)	2(25)	0(0)	0(0)	2(100)	
Grade n(%)							0.123**
II	19(73.1)	33(73.3)	7(87.5)	0(0)	1(100)	0(0)	
III	7(26.9)	12(26.7)	1(12.5)	1(!00)	0(0)	2(100)	

Table 7 Association of response with NACT

Response	Positive			Negative			p-value
	Complete response n(%)	Partial response n(%)	No response n(%)	Complete response n(%)	Partial response n(%)	No response n(%)	
Estrogen Receptor	13/45(29)	24/45(53)	6/45(13)	7/26(27)	17/26(65)	2/26(7.6)	0.12
Progesterone receptor	9/31(29)	17/31(55)	5/31(16)	11/40(27.5)	24/40(60)	3/40(7.5)	0.089
HER2	12/35(34)	18/35(51)	5/35(14)	9/34(26)	19/34(56)	3/34(9)	0.455

DISCUSSION

In our cohort study NACT offered to 83 patients, out of them 71(85.5%) achieved complete pathological response or partial response and 8(9.6%) patients showed no response. This is comparable to a study conducted by Caudle AS showed partial or complete response in 91% patients, stable disease in 6%, and progressed disease in 35% receiving one regimen.[20] The average age of our cohort was 44.8±10.39) years while study by McFarland Dc observe patients with mean age of 51.14±13.1).[21]

Patient grouped according to complete pathological response 26(31%), partial response 45(54%) and no response 8(9.6%) then patients achieved high rate of response than study conducted by Alawad AA, which showed complete response in only seven percent patients, partial response in 17.3% patients. Our study showed no significant difference in response rate on the basis of disease stage which is similar to Alawad AA study.[22]

In our study 54% patients were ER positive, 37% were PR positive and 42% patients were HER2 positive, while 29% patients were hormone receptor, 38% were HER2 positive in McFarland Dc study.[21] In our study complete response was observe in 34% HER2 Positive group while 29 percent was observed in ER and PR Positive groups. McFerland study reported in term of Pathological response, achieved in 12.1% hormone receptor positive, 41.9% in HER2 positive patients. By breast cancer subtype, pCR rates were as follows: hormone receptor positive only 12.1%, HER2 positive 41.9%, and TNBC 21.6%.[21]

Colleoni *et al.*[23] and other studies[24-26] have reported a better clinical and pathological response and pCR for ER-negative as compare to those patients who were ER-positive. This might be associated with proliferation of tumor cell in ER negative patients.

There was small number of patients to analyze significant association between clinical and pathological response to NACT. Our study showed improved response to therapy. Larger studies and long term follow up is required to evaluate the response and incidence of local recurrence after neoadjuvant chemotherapy.[27]

In our study 45 patients showed partial response and 8 patients did not respond to NACT, only 1 patient expired, out of 8 non responders only two patients were switched to 2nd chemotherapy. Those patients with progressed disease on NACT have poor prognosis, these patients require other therapeutic option to improve the outcome. Identification of non responsiveness to therapy prompts switch to other chemotherapeutic option or surgery. Gepar Trio trial studied the impact of other chemotherapy in patients who did not show response to neoadjuvant chemotherapy.[28]

Clouth B et al.[29] Study has proposed radiotherapy for breast conservation in patients who achieved complete clinical response to prevent the risk of recurrence of cancer as there is a study conducted by Jacquillat *et al*,[30] there was 6% patients showed disease recurrence, who were treated with NACT. Post NACT evaluation of the size of tumor is vital to decide the type and extent of therapy or surgery. Residual disease assessment after NACT is helpful in selecting the patients for breast conservation surgery.[31] Imaging techniques like mammography, ultrasonography

may provide information about the status of progression of the disease.32 Study by Cross *et al*. has shown the tumor size reduction on MRI scan correlates with extent of disease.[33]

CONCLUSION

In conclusion, NACT in breast cancer reduce the tumor burden, considerably good therapeutic option to achieve the complete pathological response and to improve the quality of life with breast conservative surgery in significant number of patients.

Conflict Of Interest

This study has no conflict of interest to declare by any author.

References

1. Kaufmann M, von Minckwitz G, Bear HD. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: New perspectives 2006. *Ann Oncol* 18:1927-34.
2. Kaufmann M, von Minckwitz G, Mamounas EP, Cameron D, Carey LA, Cristofanilli M *et al*. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. *Ann Surg Oncol*. 2012;19(5):1508-16.
3. Cortazar P, Geyer CE. Jr Pathological complete response in neoadjuvant treatment of breast cancer. *Ann Surg Oncol*. 2015;22(5):1441-46.
4. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N *et al*. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164-72.
5. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr*. 2001;30:96-102.
6. Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B *et al*. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 21(22):4165–74.
7. Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, *et al*.Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol*. 2008;26(8):1275-81.
8. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, *et al*. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30(15):1796-1804.
9. Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU,*et al*. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. *J Clin Oncol*. 2005;23(36):9304-11.
10. Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, *et al*. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol*. 2007;25(28):4414-22.
11. Rouzier R, Extra JM, Klijanienko J, Falcou MC, Asselain B, Vincent-Salomon A, *et al*. Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. *J Clin Oncol*. 2002;20(5):1304-10.
12. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol*. 1998;16(8):2672-85.
13. Beaver JA, Amiri-Kordestani L, Charlab R, Chen W, Palmby T, Tilley A, *et al*. FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor- positive, HER2-negative metastatic breast cancer. *Clin Cancer Res*. 2015;21(21):4760-66.
14. von Minckwitz G, Untch M, Nuesch E, Loibl S, Kaufmann M, Kummel S, *et al*. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. *Breast Cancer Res Treat*. 2011;125(1):145-56.
15. Gajdos C, Tartter PI, Estabrook A, Gistrak MA, Jaffer S, Bleiweiss IJ. Relationship of clinical and pathologic response to neoadjuvant chemotherapy and outcome of locally advanced breast cancer. *J Surg Oncol*. 2002;80(1):4-11.
16. Bonadonna G, Veronesi U, Brambilla C, Ferrari L, Luini A, Greco M, *et al*. Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. *J Natl Cancer Inst*. 1990; 82(19):1539-45.
17. Schneeweiss A, Katretchko J, Sinn HP. Only grading has independent impact on breast cancer survival after adjustment for pathological response to preoperative chemotherapy. *Anticancer Drugs* 2004; 15(2): 127-35.
18. Mieog JS, Van der Hage JA, Van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. *Br J Surg* 2007; 94(10): 1189-1200.
19. Rouzier R, Perou CM, Symmans WF. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 2005; 11: 5678-85.
20. Caudle AS, Gonzalez-Angulo AM, Hunt KK, Pusztai L, Kuerer HM, Mittendorf EA, *et al*. Impact of progression during neoadjuvant chemotherapy on surgical management of breast cancer. *Annals of surgical oncology*. 2011; 18(4):932-8.
21. McFarland DC, Naikan J, Rozenblit M, Mandeli J, Bleiweiss I, Tiersten A. Changes in pathological complete response rates after neoadjuvant chemotherapy for breast carcinoma over five years. *Journal of oncology*. 2016 Jun 13; 2016.
22. Alawad AA. Evaluation of clinical and pathological response after two cycles of neoadjuvant chemotherapy on sudanese patients with locally advanced breast cancer. *Ethiopian journal of health sciences*. 2014;24(1):15-20.

23. Colleoni M, Minchella I, Mazzarol G, Nole F, Peruzzoti G, Rocca A *et al*. Response to primary chemotherapy in breast cancer patients with tumours not expressing estrogen and progesterone receptors. *Ann Oncol* 2000; 11: 1057-59.
24. Jacquillat C, Weil M, Baillet F, Borel C, Auclerc G, de Maublanc M *et al*. Results of neoadjuvant chemotherapy and radiation therapy in the breast conserving treatment of 250 patients with all stages of infiltatrative breast cancer. *Cancer* 1990; 66: 119-29.
25. MacGrogan G, Mauriac L, Durand M, Bonichon F, Trojani M, de Mascarel I *et al*. Primary chemotherapy in breast invasive carcinoma: predictive value of immunohistochemical detection of hormone receptors, p53, c-erbB2, MiB1, pS2 and GSTpi. *Br J Cancer* 1996; 74: 1458-65.
26. Daidone MG, Veneroni S, Benini E, Tomasic G, Coradini D, Mastore M *et al*. Biological markers as indicators of response to primary and adjuvant chemotherapy in breast cancer. *Int J Cancer* 1999; 84: 580–86
27. Mauriac L, MacGrogan G, Avril A, Durand M, Floquet A, Debled M *et al*. Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with 124-month median follow-up. Institut Bergonie Bordeaux Groupe Sein (IBBGS). *Ann Oncol* 1999; 10: 47-52.
28. Von Minckwitz G, Kummel S, Vogel P. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. *J Natl Cancer Inst.* 2008; 100:542–51.
29. 29. Clouth B, Chandrasekharan S, Inwang R, Smith S, Davidson N, Sauven P. The surgical management of patients who achieve a complete pathological response after primary chemotherapy for locally advanced breast cancer. *Eur J Surg Oncol*. 2007;33(8):961-6.
30. Waljee JF, Newman LA. Neoadjuvant systemic therapy and the surgical management of breast cancer. *Surg Clin North Am*. 2007;87(2):399-415, ix.
31. Chong HY, Taib NA, Rampal S, Saad M, Bustam AZ, Yip CH. Treatment options for locally advanced breast cancer--experience in an Asian tertiary hospital. *Asian Pac J Cancer Prev*. 2010;11(4):913-7.
32. Jorgensen J, Cold S, Kamby C. [Primary inoperable breast cancer]. Ugeskr Laeger. 2007; 169(37):3091-3.
33. Londero V, Bazzocchi M, Del Frate C, Puglisi F, Di Loreto C, Francescutti G, *et al*. Locally advanced breast cancer: comparison of mammography, sonography and MR imaging in evaluation of residual disease in women receiving neoadjuvant chemotherapy. *Eur Radiol*. 2004;14(8):1371-9.

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