RESEARCH ARTICLE

Taxane and Anthracycline Based Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer : Institutional Experience

Ajay Gogia[1]*, Vinod Raina[1], Suryanarayan Vishnu Deo[2], Nootan Kumar Shukla[2], Bidhu Kalyan Mohanti[3], Daya Nand Sharma[3]

Abstract

Background: The aim of this study was to assess the response rates (clinical and pathological) with docetaxel and epirubicin combination chemotherapy and its effect on outcome. Materials and Methods: We retrospectively analysed locally advanced breast cancer (LABC) patients who received NACT from January 2008 to December 2012 in our tertiary care centre. LABC constituted 37% of all breast cancer cases and 120 patients fulfilled the eligibility criteria. The regimens used for NACT were, six cycles of DEC (docetaxel 75 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 500 mg/m^2 on Day 1, 3 weekly) and a sequential regimen (4 cycles of FEC, 5-flurouracil 600 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 600 mg/m^2 followed by 4 cycles of docetaxel 85 mg/m^2). Results: The median age was 47 years (range 23-72). Ninety six (80 %) had T4 disease and 90% had clinically palpable lymph nodes at diagnosis. The median size of primary tumor at presentation was 5.9 cm. Hormone receptor positivity was seen in 55% and HER2/neu positivity, in 25%. Triple negative breast cancers constituted 25 % of the cases. The overall clinical response rate (complete or partial) was 85% and pathological complete responses were obtained in 15%. Four cases defaulted, 5 patients died of treatment related toxicity and 15% developed febrile neutropenia on DEC. The median duration of follow up was 22 months. The median time to relapse was 20 months and the 3 year relapse free and overall survival rates were 50% and 70% respectively. Conclusions: LABC constituted 37% of all breast cancer cases at our institute. With NACT, pCR was seen in 15% of the cases. Sequential chemotherapy was better tolerated than concurrent anthracyline and taxane chemotherapy with a similar pCR.

Keywords: Breast cnacer - chemotherapy - taxane and anthracycline - response - outcome

Asian Pac J Cancer Prev, **15 (5)**, 1989-1992

Introduction

Breast cancer is the most common cancer among females in India, as per urban cancer registries. The Annual Age Adjusted Rate (AAR) varies from 30 per 100,000 in Mumbai to 33.4 per 100,000 in Delhi (Manoharan et al., 2010). LABC refers to large breast tumors (>5 cm) associated with either skin/ chest wall involvement or with fixed axillary lymph nodes or spread to ipsilateral internal mammary or supraclavicular nodes. It accounts for 10-20% of all breast cancers in the west and the long term outcome is around 60-70% in different series (Giordano, 2003). In India , LABC accounts for 30-35% cases , with a five year survival of not more than 50% (Chopra, 2001).

Neoadjuvant chemotherapy (NACT) is now the standard of care for locally advanced and inflammatory breast cancer. The use of NACT has several advantages, like treatment of micro metastasis and downsizing the tumor which also helps in increasing rates of breast conservation surgery (Mathew et al., 2007). Previous studies have reported superiority of anthracylinee based chemotherapy over CMF (cyclophosphamide, methotrexate and 5- flurouracil) regimen, further, taxanes have been extensively used either alone or in combination with anthracyclines to improve outcome in patients with LABC (Bull et al., 1978; Early Breast Cancer Trialists Collaborative Group, 1998; Yao et al., 2012). The largest study to demonstrate this benefit was the NSABP B27 study, in which, the addition of docetaxel to AC resulted in an improvement of pCR from 14 to 26% (Rastogi et al., 2008). Further, sequential anthracycline-taxane combination has been found to be better than using the same agents concurrently in several studies (Gradishar et al., 2005; Pierga et al., 2010).

There is paucity of data on combination chemotherapy (either sequential or concurrent taxanes and anthracylines) from India (Raina et al., 2007). We conducted a retrospective study of patients with locally advanced breast cancer who have received neoadjuvant chemotherapy at our institution to assess response and survival outcomes.

*[1]Department of Medical Oncology, [2]Surgical Oncology, [3]Radiation Oncology, Dr. B. R. A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India *For correspondence: ajaygogia@gmail.com*

Materials and Methods

The study population consisted of 120 patients with Locally advanced breast carcinoma (LABC), registered over a period of 5 years (January 2008 to December 2012) in the department of Medical Oncology. Patient details were obtained from our computer database as well as case records using ICD code 50. Staging was carried out according to the The American Joint Committee on Cancer (AJCC), 7th edition. Histopathological confirmation of malignancy along with receptor status was required for inclusion into this study. Those patients who had received prior chemotherapy/radiotherapy were excluded. Baseline information regarding demography, clinical stage and hormone receptor status were collected for all those patients who had received at least three cycles of chemotherapy and underwent definitive surgery and radiotherapy. Data for clinical response rates, number of preoperative chemotherapy cycles, type of chemotherapy, and pathological response rates were collected. Clinical complete response was defined as no evidence of a palpable breast mass and nodal disease. Partial response was defined as a reduction of at least 50% in the product of the bi-perpendicular diameters of the breast mass. A reduction of less than 50% or an increase of less than 25% would be classified as stable disease. Progressive disease is an increase of this parameter by more than 25% or clinical or radiological evidence of new disease elsewhere.

Pathological complete response (pCR) is classified as the absence of malignant cells in the resected breast and lymph nodes on histopathological assessment. Surgery was done approximately 4-6 weeks after the last cycle of chemotherapy. Overall survival was calculated from the date of diagnosis till last seen or date of death. Relapse free survival was calculated from the date of surgery till either relapse or date of death or date last seen whichever was earlier. SPSS Version 10.0 software was used for statistical analysis. The t-test/Mann-Whitney test was applied wherever required to compare the continuous variables. For categorical variables, Chi square/Fisher's exact test was used. Survival curves were generated using Kaplan Meier method and survivals compared with log-rank test.

Results

The median age of the whole cohort was 47 years (range 23-72 years). Sixty two patients had right-sided tumors while 58 patients had left-sided tumors. Fifty two patients (43%) were premenopausal. Median duration of symptoms was 6 months (range 1-66 months). Clinical and tumour histological characteristics are summarized in Table 1. A lump was the most common presenting symptom. Skin involvement was present in 80% of the cases. Chemotherapy regimens were used in combination (DEC, docetaxel 75 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2 with growth factor support, 3 weekly) or sequentially (four cycles of FEC, 5-FU 600 mg/m^2, epirubicin 75 mg/m^2 cyclophosphamide 600 mg/m^2 followed by four cycles of docetaxel 85 mg/m^2, 3 weekly). Hormone positive tumors formed 55%, and triple negative disease comprised 25% of the study population. One hundred and fifteen (96%) cases had invasive ductal carcinoma, 3 cases were of invasive lobular carcinoma and 2 cases were metaplastic carcinomas. There were mainly two chemotherapy regimens used and these are summarized in Table 2. Clinical complete or partial response was seen in 83% of the patients. Stable disease was present in 15 (12%) and progressive disease in 5 (4%). Eighteen (15%) patients achieved pathological CR. Patients had ER and PR negative disease had a response rate of 90% and those who were ER or PR positive had a response rate of 70%. However, this difference was not statistically significant, possibly due to the small sample size. The median follow-up was 22 months. The median time to relapse was 20 months and 3 years relapse free survival (RFS)and overall survival (OS) was 50% and 70% respectively. Kaplan-Meier curves illustrating relapse free and overall survival are shown in Figure 1. Relapse free survival was also analyzed according to the ER status, and it was found,that although patients with ER positive

Table 1. Clinico-Pathological Characteristics of Patients

Tumour Characteristics' (n=120)		No. of Patients (%)
Laterality	Right	61 (51)
	Left	59 (49)
Histology	Infiltrating ductal	115 (96)
	Infiltrating lobular	3 (2.5)
	Metaplastic	2 (1.5)
T stage	T2	6 (5)
	T3	18 (15)
	T4	96 (80)
Nodal stage	N0	11 (10)
	N1	39 (31)
	N2	51 (43)
	N3	19 (16)
Hormone profile	Hormone positive (either ER/PR)	66 (55)
	Her2 Neu IHC +++	30 (25)
	TNBC	30 (25)

Table 2. Neoadjuvant Chemotherapy and Response

Chemotherapy		n (%)
Neo-adjuvant	6-Dec	72 (60)
	4FEC-4D	46 (40)
Response to NACT (clinical)		
	Complete response	20 (16.5)
	Partial response	80 (66.5)
	Overall response	100 (83)
	Stable disease	15 (12)
	Progressive disease	5 (4)
Response to NACT (Pathological)		
	Pathological complete response	18 (15)

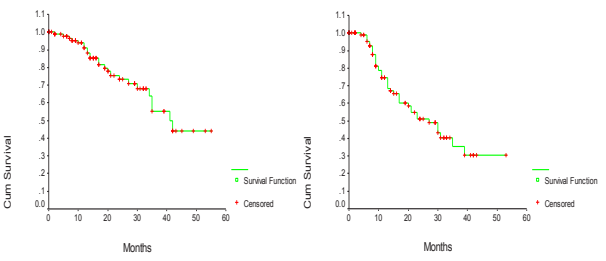

Figure 1. Overall Survival and Relapse Free Survival

Table 3. Salient Features of Published Indian Study

	No. of patients	Period	Study design	NACT used	Results
Deo et al	101	1997-2001	Prospective	Anthracyline based (FEC)	No survival benefit in operable LABC, however good responders had better DFS
Raina V et al	128	1995-2004	Retrospective	Majority anthracycline based (FEC)	pCR rate is 7.8%, ORR 84%. Median DFS and OS 41 months and 101 months respectively
Gupta D et al	91	2000-2007	Retrospective	To compare the anthracyline (FEC)and taxane (D) in NACT	pCR rate higher with docetaxel based NACT, but DFS and OS same
Present study	120	2008-2012	Retrospective	Combination of anthracyline and taxane concurrent and sequential	Pathological complete* response =15% Median relapse free survival=20 months

disease tended to relapse later compared to patients with ER negative disease, this difference was not statistically significant. Thirty four patients died during follow up. Four patients defaulted, 5 died of chemotoxicity and 15% developed febrile neutropenia in concurrent chemotherapy subset.

Discussion

A previous retrospective analysis of LABC from our institute showed that LABC comprises 26% of all breast cancer patients. The median age was 48 years with 43% patients being premenopausal and 63% having ER+ tumors. Deo et al compared neoadjuvant with adjuvant chemotherapy in 101 women with T4b N0-2 disease (Deo et al., 2003). These were randomized to either 3 cycles of CEF before and after surgery or 6 cycles of adjuvant CEF. Although there was an overall response rate of 66% with 3 cycles of neoadjuvant CEF, there was no difference in overall or disease free survival between the two arms. Gupta et al found that docetaxel was better then epirubicin in LABC in terms of pCR (Gupta et al., 2011). In our analysis, LABC constituted 37% of all cancers and NACT was admistered in one third of these. Earlier trials suggest that, anthracyclines as NACT produced pCR rates of 2-13% and there was no difference in DFS and OS with their use. Subsequently, taxanes have been used either alone or with anthracyclines and have shown improved pCR rates, with single agent docetaxel achieving pCR in 16-20% patients (Von Minckwitz et al., 2008). However, mortality and febrile neutropenia ar relatively common (Phua et al., 2012).

Salient features of Indian studies are given in Table 3. The largest trial to substantiate this was the NSABP B27 study in which the addition of docetaxel to AC resulted in improvement of pCR from 14 to 26% (Rastogi et al., 2008). In the NSABP study, however, the addition of taxanes did not have an impact on DFS or OS. The sequential anthracycline-taxane combination has been found to be better than using the same drugs concurrently in several studies (Gradishar et al., 2005; Pierga et al., 2010). The largest study to show the same was Gepar Duo study (German preoperative adriamycin and docetaxel study) in which pCR rates increased from 11%, to 22% when the drugs were used sequentially (Pierga et al., 2010). The GeparTrio trial found, that six cycles of docetaxel, doxorubicin and cyclophosphamide (TAC) produced a pCR of 21% (Papademetriou et al., 2010). The role of epirubicin has also been explored and the concurrent administration of docetaxel, epirubicin and cyclophosphamide (TEC) is considered as effective as the TAC regimen but may have a more favourable toxicity profile (Baltali et al., 2002). In our study we found a pathological CR rate of 15% which was lower than previously reported. This might be due to late presentation and a possibly different biology of disease in our study population.

The usage of trastuzumab as a part of neoadjuvant therapy has become the standard of care in recent years with results of various trials reporting pCR rates as high as 67% in the NOAH study and 43% in the Gepar Quattro study especially those whose tumors are hormone receptor-negative, reflecting the aggressive nature of disease (Gianni et al., 2010; Untch et al., 2010). A pCR after chemotherapy plus HER2-directed therapy is associated with recurrence and survival advantages, likely due to enhanced chemosensitivity of HER2-positive breast cancer cells with concurrent HER2-directed therapy. The prognostic significance of achievement of a pCR with neoadjuvant therapy in HER2-positive patients was confirmed by a 2012 meta-analysis (Cortazar et al., 2012).

Overall, HER2-positive patients who achieved a pCR had superior event-free survival (EFS) compared to those who did not (HR 0.39). In addition of pertuzumab to trastuzumab is emerging based on results from two randomized studies, in which higher pCR rates were seen with the addition of pertuzumab to NACT plus trastuzumab. Further few studies demonstrate higher pCR rates when lapatinib was added to neoadjuvant chemotherapy plus trastuzumab (Baselga et al., 2012; Guarneri et al., 2012; Untch et al., 2012) Although studies suggest that the addition of the angiogenesis inhibitor, bevacizumab, to chemotherapy in patients receiving neoadjuvant treatment can increase pCR rates, it is not clear which patients are most likely to benefit from this approach. In one German trial (GeparQuinto), the pCR rate with the addition of bevacizumab was significantly higher only in patients with hormone receptor-negative disease (von Minckwitz et al., 2008). However, in an NSABP B-40, hormone receptor-positive patients had a significant improvement in pCR with incorporation of bevacizumab.

In CALGB 40603 study (Sikov et al., 2009), there was a significant increase in the pCR rate within the breast was seen in the women who received bevacizumab in TNBC patients (Sikov et al., 2009). In all of these studies, bevacizumab resulted in higher rates of serious (grade 3/4) toxicities, including febrile neutropenia, hypertension, and mucositis. Higher rates of bleeding, thromboembolic events, and post-surgical complications (early and late) were also seen with bevacizumab therapy. Finally, none

of these studies have reported whether the pCR rate with bevacizumab improves survival outcomes.

Initial anthracycline based chemotherapy for four cycles benefits from the crossover to a non-cross-resistant regimen like taxanes and has become a common practice. In the United States, four cycles of doxorubicin and cyclophosphamide (AC) followed by a taxane (12 cycles of weekly paclitaxel or 4 cycle of 3 weekly docetaxel) is commonly used. In Canada and Europe, fluorouracil, epirubicin and cyclophosphamide for 6 cycles is more popular. We use mainly 2 protocols as describe above (6 DEC or 4FEC followed by 4D), but toxicity profile is different in the two regimens. Sequential regimen is well tolerated but in the concurrent regimen there is a 15% incidence of febrile neutropenia despite prophylactic use of growth factors and there were five deaths attributed to this approach.

In conclusion, this study of neoadjuvant chemotherapy in patients with locally advanced breast cancer treated at our centre, showed pCR rates somewhat lower than the published literature. Sequential chemotherapy is better tolerated than the concurrent use of anthracyclines and taxanes, with similar rates of pathological complete response.

References

Baltali E, Altundag MK, Onat DA, et al (2002). Neoadjuvant chemotherapy with Taxotere-epirubicin-5-fluorouracil (TEF) in loco regionally advanced breast cancer: A preliminary report. *Tumori*, **88**, 474-7.

Baselga J, Bradbury I, Eidtmann H, et al (2012). Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet*, **379**, 633-8.

Bull JM, Tormey DC, Li SH (1978). A randomised comparative trial of adriamycine versus methotrexate in combinationdrug therapy. *Cancer*, **41**, 1649-57.

Cortazar P, Zhang L, Untch M, et al (2012). Meta-analysis results from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC). *Cancer Res*, **18**, 72-93.

Chopra R(2001).The Indian scene. *J Clin Oncol*, **19**, 106-11.

Deo SV, Bhutani M, Shukla NK, et al (2003). Randomized trial comparing neoadjuvant vs adjuvant chemotherapy in locally advanced breast cancer (T4bN0-2M0). *J Surg Oncol*, **84**, 192-7.

Early Breast Cancer Trialists Collaborative Group (1998). Polychemotherapy for early breast cancer: an overview of randomised trials. *Lancet*, **352**, 930-42.

Gianni L, Eiermann W, Semiglazov V, et al (2010). Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet*, **375**, 377-84.

Giordano SH (2003). Update on locally advanced breast cancer. *The Oncologist*, **8**, 521-30.

Gradishar WJ, Wedam SB, Jahanzeb M, et al (2005). Neoadjuvant docetaxel followed by adjuvant doxorubicin and cyclophosphamide in patients with stage III breast cancer. *Ann Oncol*, **16**, 1297-304.

Guarneri V, Frassoldati A, Bottini A, et al (2012). Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. *J Clin Oncol*, **30**, 1989-99.

Gupta D, Raina V, Rath GK, et al (2011). Clinical and pathological response rates of docetaxel-based neoadjuvant chemotherapyin locally advanced breast cancer and comparison with anthracycline-based chemotherapies: Eight-year experience from single centre. *Indian J Cancer*, **48**, 410-14.

Manoharan N, Tyagi BB, Raina V (2010). Cancer incidences in rural Delhi-2004-05. *Asian Pac J Cancer Prev*, **11**, 73-7.

Mathew J, Asgeirsson KS, Agrawal A, et al (2007). Neoadjuvant chemotherapy in locally advanced primary breast cancers: The Nottingham experience. *EJSO*, **33**, 972-76.

Papademetriou K, Ardavanis A, Kountourakis P (2010). Neoadjuvant chemotherapy for locally advanced breast cancer:Focus on chemotherapy and biological targeted treatments' armamentarium. *J Thoracic Disease*, **2**, 160-8.

Phua CE, Bustam AZ, Yusof MM, et al (2012). Risk of treatment related death and febrile neutropaenia with taxane-based adjuvant chemotherapy for breast cancer in a middle income country outside a clinical trial setting. *Asian Pac J Cancer Prev*, **13**, 4623-6.

Pierga JY, Delaloge S, Espie M, et al (2010). A multicenter randomized phase II study of sequential epirubicin/ cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER2 status, as primary chemotherapy for localized invasive breast cancer patients. *Breast Cancer Res Treat*, **122**, 429-37.

Raina V, Medhi K, Deo S (2007). Shukla NK, Mohanti BK, Rath GK. Outcome of combined modality treatment of 412 cases of locally advanced breast cancer (LABC): Data from a tertiary cancer center in India. *Breast Cancer Res Treat*, **106**, 1-350

Rastogi P, Anderson SJ, Bear HD, et al (2008). Preoperative chemo-therapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol*, **26**, 778-85.

Sikov WM, Dizon DS, Strenger R, et al (2009). Frequent pathologic complete responses in aggressive stages II to III breast cancers with every-4-week carboplatin and weekly paclitaxel with or without trastuzumab: a Brown University Oncology Group Study. *J Clin Oncol*, **27**, 4693-99.

Sikov W, Berry DA, Perou CM, et al (2013). Impact of the addition of carboplatin (Cb) and/or bevacizumab (B) to neoadjuvant weekly paclitaxel (P) followed by dose-dense AC on pathologic complete response (pCR) rates in triple-negative breast cancer (TNBC): CALGB 40603 (Alliance). San Antonio Breast Cancer Symposium. Abstract, 5-14.

Untch M, Rezai M, Loibl S, et al (2010). Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol*, **28**, 2024-31.

Untch M, Loibl S, Bischoff J, et al (2012). Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol*, **13**, 135-9.

von Minckwitz G, Eidtmann H, Rezai M, et al (2012). Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med*, **366**, 299-309.

Von Minckwitz G, Kummel S, Vogel P, et al (2008). Intensified neo-adjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. *J Natl Cancer Inst*, **100**, 552-62.

Yao X, Hosenpud J, Chitambar CR (2012). A phase ii study of concurrent docetaxel, epirubicin and cyclophosphamide as a neoadjuvant chemotherapy regimen in patients with locally advanced breast cancer. *J Cancer*, **3**, 145-51.