Med Oncol (2010) 27:454–458
DOI 10.1007/s12032-009-9233-9

ORIGINAL PAPER

# Neoadjuvant chemotherapy for locally advanced breast cancer: a single center experience

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Received: 7 April 2009 / Accepted: 8 May 2009 / Published online: 2 June 2009


**Abstract** Neoadjuvant chemotherapy (NAC) is one of the treatment options for patients with locally advanced breast cancer (LABC). Preoperative chemotherapy potentially may reduce the extent of the surgery and offers the opportunity to assess the chemosensitivity of the tumor in vivo. Herein, we evaluated the results of NAC in Turkish LABC patients. We retrospectively analyzed 73 LABC patients. Anthracycline/taxane-based chemotherapy regimens were administered. Patients were stratified according to age, menopausal status, type of surgery, response to the treatment, histopathological properties, and survival. After 3–6 cycles of chemotherapy, patients were re-staged radiologically and surgery was performed in operable patients. Adjuvant chemotherapy was administered as needed. The median age was 45 (29–93) at the time of diagnosis. Sixteen percentage of patients were younger than 35 years of age and 45.2% were premenopausal. Median follow-up time was 20.2 months. Sixty-seven out of 73 patients responded to therapy (89%). Breast conserving surgery was possible in the 15% of the patients. In histopathological analysis, lymph node invasion was detected in 85%. The estrogen (ER) and progesterone (PR) receptor were positive in 78.1% and c-erb-B2 was positive in 17.5% of patients. The median disease-free survival (DFS) was 44 months (SE: 9; %95 CI: 27.1–60.8), overall survival (OS) was not reached at the time of analysis. Three-year DFS and OS were 58% and 91.9%, respectively. In a multivariate Cox regression analyses; no demographic or pathologic prognostic parameter predicted overall survival. In recent years, NAC in breast cancer has become a viable treatment option for patients with LABC. NAC is not commonly applied in Turkey. The response rate to NAC in Turkish breast cancer patients is encouragingly high. Broader efforts should be made to evaluate breast cancer patients preoperatively at tumor boards for proper treatment sequence.

**Keywords** Neoadjuvant chemotherapy · Breast cancer · Locally advanced

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## Introduction

Neoadjuvant chemotherapy (NAC) is administered with the intention to either convert inoperable locally advanced breast cancer (LABC) to operable state or to downgrade resection from mastectomy to breast sparing surgery [1–3]. Because of the tumor size, involvement of regional lymph nodes, extension of the tumor to the chest wall or to the skin; primary resection is difficult in LABC. Also, there is high risk for local recurrence or distant metastasis [3, 4].

Consequently, LABC have poor prognosis [4]. Therefore, while the stage II breast cancer has a 10-year survival rate of 60%, stage III breast cancer survival rate is a dismal 30%.

Preoperative chemotherapy reduces the size of primary tumor and the number of positive lymph nodes in more than 80% of cases [5]. The other aim of NAC is to increase the rate of breast conservation surgery which has less morbidity compared to total breast removal [1, 6]. At the time of diagnosis, there may be occult metastasis so that preoperative chemotherapy can prevent progression at these metastatic foci and increase chances of survival [7]. Furthermore, preoperative chemotherapy facilitates monitoring of tumor response in vivo, so that when there is resistance to a specific chemotherapy another cytostatic agent may be administered [1, 6, 8].

Although the effectiveness of therapy can be assessed according to clinical, radiological, or pathological response, the period of disease-free survival (DFS) or the overall survival (OS); the pathological complete response (pCR) is the most predictive parameter for survival [7]. The pCR is considered when there is complete eradication of locoregional disease [8]. Residual disease in the axilla after NAC has been associated with poor prognosis [4].

There is no standard NAC regimen. Taxanes or an anthracycline-based regimen could be used as monotherapy or in combination [7]. Immunohistochemical markers, estrogen, and progesterone receptor status, c-erb-B2 expression may predict the response to NAC [8]. In this study, we retrospectively reviewed results of NAC in patients with LABC.

## Patients and methods

Seventy-three patients with LABC, treated with NAC between 2004 and 2008 in Dr. Lutfi Kirdar Education and Research Hospital, Department of Medical Oncology were retrospectively evaluated. The patients are staged according to TNM staging system proposed by American Joint Committee on Cancer (AJCC). All stage IIB (T3N0), III disease, and inflammatory breast cancer (T4d) patients considered to have LABC [4]. Mammography was performed in all patients. Histopathological diagnosis was done by tru-cut biopsy in majority of the patients. Tumors were measured both clinically and radiologically before the treatment. All patients had T3 or T4 tumors and 58 out of 73 patients had clinically palpable fixed axillary lymph nodes. Prior to NAC distant metastases excluded by chest X-ray, abdominal ultrasound, and bone scans. Complete blood counts, liver and renal functions tests were obtained. Combined chemotherapy with anthracycline [AC: doxorubicin, cyclophosphamide/EC: epirubucin, cyclophosphamide/CEF: cyclophosphamide, epirubucin-5-Fluorouracil (5-FU)] and taxanes-based regimens (TAC: docetaxel, doxorubicin, cyclophosphamide/TE: docetaxel, epirubucin) were given preoperatively for 3–6 cycles. Patients with axillary lymph node involvement and without any serious comorbidity received taxane-based regimen. All patients eventually underwent either modified radical mastectomy or breast conserving surgery with axillary lymph node sampling. The surgical procedure decided upon patients' choice, tumor-to-breast size, clinical response to NAC, clinically involved axillary lymph nodes. The histological type of the tumor, the size of the invasive component, the grade of the tumor, and the rate of lymph node involvement recorded. The median dissected lymph node number was 13. A pCR was defined as no residual invasive tumor in the surgical specimen. The estrogen (ER) and progesterone receptor (PR) status and c-erbB-2 expression were also assessed. Following surgery, adjuvant systemic therapy was given as needed. Radiotherapy is applied to all patients who had breast conserving surgery or who had any axillary lymph node involvement. Hormonotherapy were given to patients with positive hormone receptors. Patients were followed-up regularly afterward. OS was defined as the time from diagnosis of cancer to the death related or unrelated the breast cancer. DFS was defined as being free of cancer relapse. Pathologic partial response (pPR) defined as residual invasive disease after chemotherapy (according to RECIST criteria 30% decrease in larger diameter of the tumor size). Progressive disease was defined as at least 20% increase the tumor size or appearance of new metastasis [10].

### Statistical methods

Statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA) software. Descriptive parameters are quoted as mean ± SD with 95% confidence intervals (CI). A Cox regression analysis was used to evaluate the relationship between prognostic factors and the median survival. DFS was defined as the time from breast surgery to disease progression or recurrence or to the date of death or last known contact. DFS was measured with Kaplan–Meier analysis. $P$ values $\leq 0.05$ were accepted as statistically significant.

## Results

The median age of the patients at the time of diagnosis was 45 years (range: 29–93). Sixty-one patients were older than 35 (84%). Thirty-three patients were premenopausal (45%) at the time of diagnosis. The median number of NAC cycle was 3. Anthracycline-based NAC (AC-EC-CEF) were given to 80% and taxane-based regimens were given to the

20% of patients for 3–6 cycles. While pCR was achieved in 3 (4%) patients, 85% of the patients had partial responses. Although 8 patients (11%) were progressed clinically, others were clinical complete or partial responders.

There was no grade 3–4 toxicity in patients with NAC. Non-hematological toxicities were grade 1–2 and most common were alopecia and asthenia followed by nausea, arthromyalgia, and stomatitis which occurred in less than 4% of patients. Only grade 3–4 hematological toxicity was neutropenia and observed in 2 patients. No dose reduction was required because of myelotoxicity. Dose reduction because of febrile neutropenia occurred in 1 patient after 2 cycles of TAC regimen. There was no severe cardiac toxicity, thrombocytopenia, or any other serious adverse events.

Surgery was performed in 89% of patients after NAC; 54 patients had modified radical mastectomy, 9 had breast conservation surgery, all had axillary lymph node dissection. Breast conservation surgery with sentinel lymph node sampling only was performed in 2 patients. Distant metastases were detected in 8 patients during NAC, and no surgery carried out. Invasive ductal carcinoma accounted for 91% of cases, invasive lobular carcinoma 3%, mixed carcinoma 3%, and medullar carcinoma 3%. Vascular and perineural invasion were present in 71% and 67% of the cases, respectively. In all three patients who had pCR, pre NAC lymph node status was N1. The median number of metastatically involved lymph node was 3 and the median tumor size was 3.5. Either ER or PR positivity rate were 69% and 69%, respectively. The expression of c-erb-B2 was detected in 18% of the patients.

Total 55 of patients who underwent BCS (8 patients) or had axillary lymph node involvement after surgery were given radiotherapy (73%). All the patients with receptor positive cancer (70%) were given hormonotherapy.

The median follow-up period was 20.2 months (range: 1–129 months). DFS for 1 and 3 years were 84% and 58%, respectively. The median DFS time was 44 months [95% CI (27.1–60.8) SE:86], (Fig. 1) OS for 1 and 3 years were 98% and 91%, respectively, the median OS had not been reached at the time of analysis (Fig. 2). In a multivariate analysis, there were no evidence of any relation between survival and any of the following: age, menopausal status, tumor type, grade, vascular or perineural invasion, hormonal status, c-erb-B2 expression and NAC type ($P > 0.05$). Factors which had a relation with DFS in the multivariate analysis are shown in Table 1.

## Discussion

NAC has been a viable option in the treatment of LABC [7, 9]. NAC increases the chances to do BCS [1, 4, 7, 10, 11].

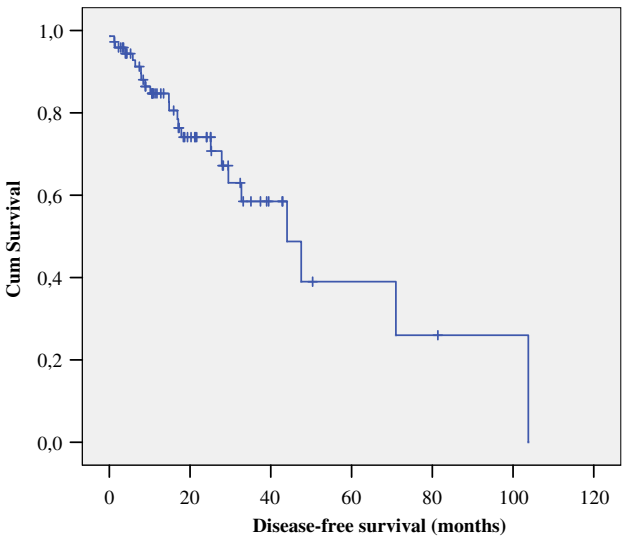


**Fig. 1** Disease-free survival after neoadjuvant chemotherapy in locally advanced breast cancer

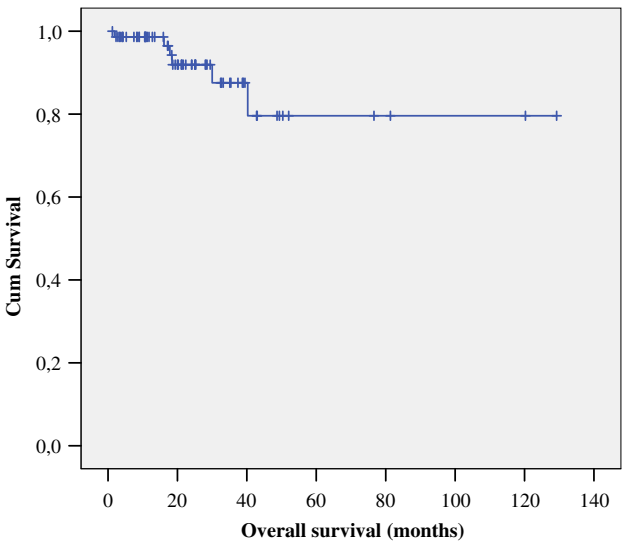


**Fig. 2** Overall survival after neoadjuvant chemotherapy in locally advanced breast cancer

In our series, 74% and 11% of patients underwent modified radical mastectomy and BCS, respectively. There was no difference in terms of survival between the two groups, consistent with the literature.

The patients who had pCR with NAC have improved survival [1, 7, 8, 12, 13]. In our study, the overall response rate was 94%. We did not report the clinical response rate due to its subjectivity. Even if a patient is complete responder clinically, there still might be residual tumor histologically. In our study 3 cases (4%) had pCR, 2 of them had T4, and the other one had T3 tumor initially. Although the majority of the tumors downstaged after

**Table 1** Relationship between prognostic factors and disease-free survival according to multivariate analyses

| Characteristics | No. of patients (%) | Median DFS (months) | *P* |
|---|---|---|---|
| Age (year) | | | 0.19 |
| <35 | 12 (16) | 28 | |
| >35 | 61 (84) | 44 | |
| Menopausal status | | | 0.70 |
| Premenopausal | 33 (45) | 48 | |
| Postmenopausal | 40 (55) | 44 | |
| Grade | | | 0.88 |
| 2 | 33 (66) | 47 | |
| 3 | 17 (34) | 45 | |
| Lenfovasculer invasion | | | 0.38 |
| Present | 13 (29) | 49 | |
| Absent | 32 (71) | 45 | |
| Perineural invasion | | | 0.34 |
| Present | 30 (67) | 48 | |
| Absent | 15 (33) | 44 | |
| Hormonal status | | | 0.92 |
| Positive | 50 (78) | 44 | |
| Negative | 14 (22) | 71 | |
| c-erbB2 | | | 0.73 |
| Positive | 10 (18) | NA | |
| Negative | 47 (82) | 33 | |
| Neoadjuvant chemotherapy response | | | 0.89 |
| CR | 3 (4) | | |
| PR | 63 (90) | | |
| SD | 1 (2) | | |
| PD | 3 (4) | | |

*NA* not available

NAC, it was not associated with improved survival ($P = 0.89$).

Heys et al. [14] reported that clinical or pathological response causes a significant increase in DFS at 3 years (90% vs. 77%) in patients with LABC ($P = 0.03$). We detected a DFS of 84% and 58% in 1 and 3 years, respectively. At the median follow-up of 20.2 months, OS could not be reached. We think that confirmatory studies with larger series and longer follow-up are needed.

In NSABP B-27 trial 8 years DFS was 70% for patients with negative nodes as compared to 40% in patients with four to nine positive nodes [12]. Abrial et al. [13.] reported that after NAC, 48% of patients were pathologically node negative at surgery and significant correlation between number of node involved and pathological response were observed ($P < 0.000001$). Node involvement was distributed as follows: 36% N1–3, 13% N4–9, and 3% N $\geq$ 10. In our study, after NAC, 15% of patients were pathologically node negative and 24% had N1, 37% had N2, and 7% had N3 involvement. In the NSABP B-18 trial, patients with operable breast cancer receiving NAC were 37% more likely to have negative nodes than patients without NAC [15]. Rouzier et al. [16] reported that in 152 LABC, pCR was seen in 23% in the axilla compared to 13% at the primary site, suggesting a higher response rate in the axilla than in the primary tumor. The conversion of lymph nodes from positive to negative was a strong predictor of survival ($P < 0.001$). In our trial, pCR were obtained in 8 patients for the axillary lymph nodes compared to 3 patients at the primary site (11% vs. 4%). All of the patients with a pCR of the primary tumor also had lymph node down staging. The pathological response rate in the primary site and axilla was consistent with earlier reports [16–19] but no prognostic relation between pCR and outcome noted in our study probably due to low pCR rate.

It has been reported that taxanes and anthracycline-based regimens achieved clinically complete responses ranging from 20% to 31% and pCR ranges from 7% to 18% [20, 21]. In NSABP B27 trial, the patients who received preoperative AC, clinical response rate was 86% compared with 91% in patients who received AC and taxanes. The pCR was increased from 13% to 26% with the addition of four cycles of taxanes ($P < 0.001$) [12]. Over 20% of patients were also treated with a taxane-based therapy but DFS was not statistically significant between the two groups.

Major toxicity of taxane-based regimen is myelotoxicity [22]. There was no severe toxicity in our patients who received NAC, non-hematological toxicities were grade 1–2, and no dose reduction was needed for myelotoxicity. Granulocyte colony stimulating factor was used in the TAC regimen; therefore febrile neutropenia occurred only in 1 of 13 patients who received it. Toxicity profile in our patients was compatible with the literature.

After NAC, the median DFS was longer in premenopausal than postmenopausal women, but this was not statistically significant ($P = 0.70$). The NSABP study has shown that ER negative patients had a better response to NAC than ER positive patients [2, 12, 23]. Similarly in GEPARTRIO study, pCR rates were noted in 41% of triple negative patients, 29% of hormone receptor (HR) negative, and 8% of others [24]. Although these studies indicate that negative HR status is strong predictor for the response to NAC, we could not confirm this in our patient population. Neither of HR status and c-erb-B2 expression were found to have statistically significant correlation with DFS ($P = 0.92$).

In conclusion, we did not find any pathological characteristics of LABC that is predicting the response to NAC and there was no relation between the survival and the tumor characteristic. However, the short median follow-up

time of 20.2 months and small sample size may cause this. Future studies in larger Turkish cohort and longer follow-up may be more convincing to all involved parties regarding the role of NAC in LABC.

## References


1. Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. Br J Surg. 2007;94:1189–200. doi:10.1002/bjs.5894.
2. Mayer EL, Carey LA, Burstein HJ. Clinical trial update: implications and management of residual disease after neoadjuvant therapy for breast cancer. Breast Cancer Res. 2007;9:110. doi:10.1186/bcr1755.
3. Mathew J, Asgeirsson KS, Agrawal A, Mukherjee A, Ellis IO, Cheung KL, et al. Neoadjuvant chemotherapy in locally advanced primary breast cancers: the Nottingham experience. Eur J Surg Oncol. 2007;33:972–6. doi:10.1016/j.ejso.2007.02.005.
4. Mathew J, Asgeirsson KS, Cheung KL, Chan S, Dahda A, Robertson JF. Neoadjuvant chemotherapy for locally advanced breast cancer: a review of the literature and future directions. Eur J Surg Oncol. 2009;35:113–22. doi:10.1016/j.ejso.2008.03.015.
5. Taucher S, Steger GG, Jakesz R, Tausch C, Wette V, Schippinger W, et al. The potential risk of neoadjuvant chemotherapy in breast cancer patients—results from a prospective randomized trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-07). Breast Cancer Res Treat. 2008;112:309–16.
6. Bélanger J, Soucy G, Sidéris L, Leblanc G, Drolet P, Mitchell A, et al. Neoadjuvant chemotherapy in invasive breast cancer results in a lower axillary lymph node count. J Am Coll Surg. 2008;206:704–8. doi:10.1016/j.jamcollsurg.2007.10.016.
7. Buzdar AU. Preoperative chemotherapy treatment of breast cancer—a review. Cancer. 2007;110:2394–407. doi:10.1002/cncr.23083.
8. von Minckwitz G. Breakthrough for neoadjuvant chemotherapy. Breast Cancer. 2008;15:27–30. doi:10.1007/s12282-007-0004-1.
9. Kai K, Arima N, Miyayama H, Yamamoto Y, Iwase H, Nishimura R. Pathological lymph node involvement at surgery is a significant predictive factor of recurrence in locally advanced breast cancer treated with concomitant epirubicin-docetaxel neoadjuvant chemotherapy: a cohort study. Breast Cancer. 2009;16:42–8. doi:10.1007/s12282-008-0055-y.
10. Heller W, Mazhar D, Ward R, Sinnett HD, Lowdell C, Phillips R, et al. Neoadjuvant 5-fluorouracil, epirubicin and cyclophosphamide chemotherapy followed by docetaxel in refractory patients with locally advanced breast cancer. Oncol Rep. 2007;17:253–9.
11. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. Br J Surg. 2006;93:1025–6.
12. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol. 2008;26:778–85. doi:10.1200/JCO.2007.15.0235.
13. Abrial SC, Penault-Llorca F, Delva R, Bougnoux P, Leduc B, Mouret-Reynier MA, et al. High prognostic significance of residual disease after neoadjuvant chemotherapy: a retrospective study in 710 patients with operable breast cancer. Breast Cancer Res Treat. 2005;94:255–63. doi:10.1007/s10549-005-9008-8.
14. Heys SD, Hutcheon AW, Sarkar TK, Ogston KN, Miller ID, Payne S, et al. Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial. Clin Breast Cancer. 2002;2(Supp):69–74. doi:10.3816/CBC.2002.s.015.
15. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997;15:2479–82.
16. 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;20:1304–10. doi:10.1200/JCO.20.5.1304.
17. Machiavelli MR, Romero AO, Pérez JE, Lacava JA, Domínguez ME, Rodríguez R, et al. Prognostic significance of pathological response of primary tumor and metastatic axillary lymph nodes after neoadjuvant chemotherapy for locally advanced breast carcinoma. Cancer J Sci Am. 1998;4:125–31.
18. Botti C, Vici P, Lopez M, Scinto AF, Cognetti F, Cavaliere R. Prognostic value of lymph node metastases after neoadjuvant chemotherapy for large-sized operable carcinoma of the breast. J Am Coll Surg. 1995;181:202–8.
19. 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;80:4–11. doi:10.1002/jso.10090.
20. de Matteis A, Nuzzo F, D'Aiuto G, Labonia V, Landi G, Rossi E, et al. Docetaxel plus epidoxorubicin as neoadjuvant treatment in patients with large operable or locally advanced carcinoma of the breast: a single-center, phase II study. Cancer. 2002;94:895–901. doi:10.1002/cncr.20335.
21. Lebowitz PF, Eng-Wong J, Swain SM, Berman A, Merino MJ, Chow CK, et al. A phase II trial of neoadjuvant docetaxel and capecitabine for locally advanced breast cancer. Clin Cancer Res. 2004;15:64–9.
22. Amat S, Bougnoux P, Penault-Llorca F, Fétissof F, Curé H, Kwiatkowski F, et al. Neoadjuvant docetaxel for operable breast cancer induces a high pathological response and breast-conservation rate. Br J Cancer. 2003;88:1339–45. doi:10.1038/sj.bjc.6600916.
23. 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. 2003;15(21):4165–74.
24. Von Minckwitz G, Blohmer J, Vogel P, Hanusch C, Eidtmann H, Hilfrich J, et al. Comparison of neoadjuvant 6 vs 8 cycles of dosetaxel/doxorubicin/cyclophosphamide (TAC) in patients early responding to TACx2-the GEPARTRIO Study. J Clin Oncol. 2006;24:576 (abstract).