RESEARCH ARTICLE

Retrospective Analysis of Neoadjuvant Chemotherapy for Breast Cancer in Turkish Patients

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Abstract

Background: Neoadjuvant systemic chemotherapy is the accepted approach for women with locally advanced breast cancer. Anthracycline- and taxane-based regimens have been extensively studied in clinical trials and consequently are widely used. In this study aimed to research the complete response (pCR) rates in different regimens for neoadjuvant setting and determine associated clinical and biological factors. Methods: This study included 63 patients diagnosed with breast carcinoma among 95 patients that had been treated with neoadjuvant chemotherapy between 2007 and 2010. TNM staging system was used for staging. The histologic response to neoadjuvant chemotherapy was characterized as a pCR when there was no evidence of residual invasive tumor in the breast or axillary lymph nodes. Biologic subclassification using estrogen receptor (ER), progesterone receptor (PR), HER2 were performed. Luminal A was defined as ER+, PR+, HER2-; Luminal B tumor was defined as ER+, PR-, HER2-; ER+, PR-, HER2+; ER-, PR+, HER2-; ER+, PR+, HER2+; HER2 like tumor ER-, PR+, HER2+; and triple negative tumor ER, PR, HER2 negative. Results: Patients median age was 54.14 (min-max: 30-75). Thirty-two patients (50.8%) were premenapousal and 31 (49.2%) were postmenapousal. Staging was performed postoperatively based on the pathology report and appropriated imaging modalities The TNM (tumor, lymph node, metastasis) system was used for clinical and pathological staging. Fifty-seven (90.5%) were invasive ductal carcinomas, 6 (9.5%) were other subtypes. Thirty nine (61.9%) were grade II and 24 (38.1%) were grade III. Seven (11.1%) patients were stage II and 56 (88.9) patients were stage III. The patients were classified for ER, PR receptor and HER2 positivity. Seventeen patients had complete response to chemotherapy. Forty patients (63.5%) were treated with dose dense regimen (cyclophosphamide 600 mg/m^2 and doxorubicine 60 mg/m every two weeks than paclitaxel 175 mg/m^2 every two weeks with filgrastim support) 40 patients (48%) were treated anthracycline and taxane containing regimens. Thirteen patients (76%) from 17 patients with pCR were treated with the dose dense regimen but without statistical significance (p=0.06). pCR was higher in HER2(-), ER(-), grade III, premenopausal patients. Conclusion: pCR rate was higher in the group that treated with dose dense regimen, which should thus be the selected regimen in neoadjuvant setting. Some other factors can predict pCR in Turkish patients, like grade, menopausal status, triple negativity, percentage of ER positivity, and HER2 expression.

Keywords: Breast cancer - neoadjuvant chemotherapy - ER - PR - HER2 - grade - Turkish patients

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Introduction

Neoadjuvant systemic therapy is the accepted approach for women with locally advanced breast cancer for whom immediate surgery is inappropriate and is an option for women with operable breast cancer, particularly when, based on tumor size, mastectomy rather than conservative surgery is indicated, and the patient desires an attempt at breast conservation (Shannon et al., 2003; Schwartz et al., 2004; Kaufmann et al., 2006; Gralow et al., 2008). The goal of chemotherapy given in the adjuvant or neoadjuvant setting is to eradicate occult distant metastases to ultimately improve disease-free survival. Theoretically, patients who have a pCR in both the primary breast tumor and axillary lymph nodes after neoadjuvant chemotherapy should have the highest disease-free survival rates, compared with lesser responses (Kuerer et al., 1999).

Neoadjuvant chemotherapy regimens continue to evolve as new agents and/or combinations are investigated. No one regimen has been shown to be superior. In the current study we analyzied the dose dense and the other regimens effect on pCR in neoadjuvant setting.The biological factors combined with clinical and pathologic information can be used to predict pCR.In the current study predictive factors for pCR in neoadjuvant setting were analyzed.

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Materials and Methods

This study include 63 patients diagnosed with breast carcinoma among 95 patients that had been treated with neoadjuvant chemotherapy between 2007 and 2010. Clinical and biological factors were assessed for predicting the pCR rate at surgery The overall pCR rate defined as no residual tumor in breast and axilla.

Results

Patients records were retrospectively reviewed and 63 patients were included to the study. Complete pathologic primary tumor and axillary lymph node response to neoadjuvant chemotherapy was analyzed. The impact of different factors were evaluated for the pCR.

Patients median age was 54.14 (min-max: 30-75). Thirty-two patients (50.8%) were premenapousal and 31 (49.2%) were postmenapousal. Staging was performed postoperatively based on the pathology report and appropriated imaging modalities The TNM (tumor, lymph node, metastasis) system was used for clinical and pathological staging. Histopathologic types were analyzied. Fifty-seven (90.5%) were invasive ductal carcinoma, 6 (9.5%) were the other subtypes. Thirty nine (61.9%) patients were grade II and 24 (38.1%) patients were grade III. Patients were staged for TNM staging system. Seven (11.1%) patients were stage II, 56 (88.9%) patients were stage III. The patients were classified for estrogen (ER), progesterone (PR) receptor and HER2 positivity. ER, PR, and HER2 were measured at the time of primary diagnosis before treatment: HER2 overexpression required either immunohistochemical (IHC) staining of 3+ or positivity by fluorescence in situ hybridization (FISH) technique. In case of 2+ score by IHC confirmatory FISH testing was required. ER and IHC were scored positive if at least 10% of tumor cell nuclei showed a staining signal. Biologic subclassification using ER, PR, HER2 were performed. Luminal A were defined as ER+, PR+, HER2-; Luminal B tumor was defined as ER+, PR-, HER2-; ER+, PR-, HER2+; ER-, PR+, HER2-; ER+, PR+, HER2+; HER2 like tumor was defined as ER-, PR+, HER2+; and triple negative tumors ER, PR, HER2 was negative (Huober et al., 2010).

Table 1. Characteristics of Patients

Characteristics		Complete Response n	(%)	İncomplete Response n	(%)
Stage	II	3	(5.0%)	4	(6.7%)
	III	14	(23.3%)	42	(65.0%)
Dose dense regimens		13	(32.5%)	27	(67.5%)
Grade	II	7	(11.1%)	42	(50.8%)
	III	10	(15.9%)	14	(22.2%)
Her2-neu	(-)	14	(33.3%)	25	(39.7%)
	(+)	3	(4.8%)	21	(22.2%)
Triple negative		8	(80.0%)	2	(20.0%)

Table 2. ER Positivity and pCR Correlation

ER percentage	Pathologic complete response			
(%)	(-) N	(%)	(+) N	(%)
0	4	(6.3%)	12	(19%)
1	1	(1.6%)	0	(0%)
5	1	(1.6%)	0	(0%)
10	2	(3.2%)	0	(0%)
15	1	(1.6%)	0	(0%)
20	4	(6.3%)	0	(0%)
25	0	(0%)	2	(3.2%)
30	4	(6.3%)	0	(0%)
50	1	(1.6%)	1	(1.6%)
60	3	(4.8%)	0	(0%)
70	1	(1.6%)	0	(0%)
80	0	(0%)	1	(1.6%)
90	11	(17.5%)	1	(1.6%)
95	2	(3.2%)	0	(0%)
100	11	(17.5%)	0	(0%)

Table 3. ER Positivity and pCR Correlation

Author/trial	No. of patients	Regimen 1	Regimen 2	pCR, %	p
Buzdar et al, 1999	174	FAC x 4	Paclitaxel x 4	23 v 14	0.17
Smith et al, 2002	162	CAVP	CAVP-D	15.4 v 30.8	0.06*
Burstein et al, 2003	40	Paclitaxel - trastuzumab	-	18	
Dieras et al, 2004	200	AC x 4	AT x 4	10 v 16	NA
Evans et al, 2005	363	AC x 6	AD x 6	16 v 12	0.61
von Minckwitz et al, 2005	913	AD	AC-D	16v12	<0.001
Buzdar et al, 2005	18	Paclitaxel - FEC + trastuzumab	-	67	
Bear et al, 2006	2411	AC	AC-D	13.7 v 26	<0.001
Hurley et al, 2006	94	Docetaxel - carboplatin + trastuzumab	-	100/17	
Coudert et al, 2006	33	Docetaxel - trastuzumab	-	47	
Moliterni et al, 2007	811	AT	EV	4 v 8	NA
Limentani et al, 2007	31	Docetaxel - vinorelbine - trastuzumab dose dense		-	45
Harris et al, 2007	48	Vinorelbine - trastuzumab	-	20	
von Minckwitz et al, 2008	2072	TAC x 6	TAC-NX	NR: 5.3 v 6	NA•
Sikov et al, 2009	18	Carboplatin - paclitaxel + trastuzumab	-	76	
Gianni et al, 2010 (NOAH)	117	Doxorubicin - paclitaxel - paclitaxel - CMF + trastuzumab	-	38	
Untch et al, 2010	445	Epirubicin - cyclophosphamide + capecitabine + trastuzumab	-	32	
Untch et al, 2011	217	Epirubicin - cyclophosphamide - paclitaxel + trastuzumab	-	39	
Untch et al, 2012	620	EC-T+trastuzumab	EC-T+Lapatinib	30.3v22.7	0.04

*NA: not available; NR: nonresponder; NSABP: National Surgical Adjuvant Breast and Bowel Project; pCR: pathological complete response; v: versus; AC: doxorubicin and cyclophosphamide; AC-D: AC and docetaxel; AD: doxorubicin and docetaxel; AT: doxorubicin and paclitaxel; CAVP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; CAVP-D: CAVP and docetaxel; EV: epirubicin and vincristine; FAC: fluorouracil, doxorubicin,and cyclophosphamide; NX: vinorelbine and capecitabine; TAC: paclitaxel, doxorubicin and cyclophosphamide. CMF: cyclophosphamide, methotrexate, and fluorouracil; cRR: clinical response rate; FEC: cyclophosphamide, epirubicin, and fluorouracil; EC-T=Epirubicine,cyclophosphamide and taxotere HER2: human epidermal growth factor receptor 2; pCR: pathologic complete response.

HER2 positive in 24 (38.1%) and negative in 39 (61.9%) patients. Trastuzumab was given to the HER positive patients. Statistically significant difference was not found the patients between trastuzumab containing and not containing regimens (p=0.582). The histologic response to neoadjuvant chemotherapy was characterized as pCR when there was no evidence of residual invasive tumor in the breast or axillary lymph nodes. Seventeen patients (26.6%) had complete response to chemotherapy. Fourty patients (48.5%) were treated with dose dense regimen (cyclophosphamide 600 mg/m^2 and doxorubicine 60 mg/m^2 every two weeks then paclitaxel 175 mg/m every two weeks with filgrastim support) 23 patients were treated anthracycline and taxane containing regimens (anthracycline cyclophosphamid (respectively 60 mg/m^2, 600 mg/m^2) combination followed by docetaxel 100 mg/m^2 every three weeks or weekly paclitaxel 80 mg/m^2). Thirteen patients (76%) from 17 patients with pCR treated with dose dense regimen. pCR were higher in group treated with dose dense regimen than other group but statistically significant difference was not found (p=0.06). HER2 expression negative 14 (23.3%) patients had pCR, and 3 (5%) had pCR in HER2 positive group; statistically significant difference was found (p=0.03) pCR rates were higher in the group of premenapousal group [13 (21.7%) versus 4 (6.7%) patients p=0.01] but when patients were divided into younger and older 40 years; there was not statistically significant difference (p=0.692). The rate of pCR was higher in the group of grade III tumor [7 (11.1%) patients in grade II group; 10 (16.9%) patients in grade III tumor p=0.03]. pCR rate was higher in triple negative group then other groups and the difference was statistically significant (p=0.0001). The percentage of ER positivity is the strong predictive for incomplete response (pCR was higher in the group of ER negative patients (12 patients 19%) but none of the patient had pCR in 100% ER positive group p=0.0001; (Table 2). The percentage of PR positivity was not correlated with pCR (p=0.5).

Statistics

Descriptive analyses were performed. Results were compared using chi-square and Fisher's exact test. All tests were two-sided with significance levels set at 0.05.

Discussion

Anthracycline- and taxane-based regimens have been extensively studied in clinical trials and consequently, are widely used. Neoadjuvant chemotherapy regimens continue to evolve as new agents and/or combinations are investigated. No one regimen has been shown to be superior. Most preoperative trials are powered based on a pCR endpoint, and are underpowered to compare differences in relapse and survival (Neoadjuvant regimens in Table 3).

Dose-dense treatment arms were investigated in several neoadjuvant trials but many additional differences also existed in drug delivery between study arms, no clear conclusion about the benefit of dose-dense therapy in the neoadjuvant setting can be made. In the adjuvant setting, dose-dense AC-paclitaxel (every two weeks) was clearly superior to standard dosing (every three weeks) of the same drugs (Citron et al., 2003; Therasse et al., 2003; von Minckwitz et al., 2005; Moliterni et al., 2007).

The GerparDuo trial randomly assigned 913 patients with T2-3N0-2 breast cancer to four cycles of doxorubicin and docetaxel every 14 days with growth factor support (concurrent dose-dense anthracycline, docetaxel (AD) to four cycles of AC every 21 days followed by four cycles of docetaxel every 21 days (sequential anthracycline, cyclophosphamide (AC) and docetaxel) (von Minckwitz et al., 2005) Sequential AC and docetaxel resulted in significantly higher pCR rates (22.4 versus 11 percent) and breast conservation rates (75 versus 66 percent) than concurrent dose-dense AD (von Minckwitz et al., 2005).

Similarly, a dose-intensified epirubicin and cyclophosphamide regimen compared to 28-day cyclophosphamide, epirubicin, and fluorouracil (FEC) failed to show a significant difference in the pCR rate (10 versus 14), median progression-free survival (33.7 versus 34 months), or five-year overall survival (51 versus 53 percent) (Therasse et al., 2003). In our study pCR rate was higher in the group that treated with dose dense regimen but statistically significant difference was not found (p=0,06).

GeparQuattro trial confirms that combining trastuzumab with anthracycline-taxane-based neoadjuvant chemotherapy results in a high pCR rate without clinically relevant early toxicity. Combination of chemotherapy with trastuzumab should be considered when neoadjuvant treatment is given to patients with HER2-positive breast cancer (Untch et al., 2010).

NSABP-B27 is a three arm randomised phase III trial in women with invasive breast cancer treated with preoperative doxorubicin and cyclophosphamide (AC) chemotherapy for four cycles followed by local therapy alone; preoperative AC followed by docetaxel for four cyles and AC followed by local therapy followed by four cycles docetaxel. Results from this study which involved 2411 patients documented higher pCR rate at the time of local therapy in patients treated with preoperatively four cycles AC followed by four cycles of docetaxel versus four cycles of preoperative AC. Disease free survival and overall survival have not been shown to superior with the adition of docetaxel treatment in B-27 (Bear et al., 2006).

In women with HER2 positive tumors treated with neoadjuvant chemotherapy the addition of neoadjuvant trastuzumab to paclitaxel followed by FEC chemotherapy was associated with an increase in pCR rate from 26% to 65.2% (p-0.016) (Buzdar et al., 1999).

The GEPARQUINTO and The Neoadjuvant Lapatinib and/or Trastuzumab Trial (NeoALLTO) confirm that in the preoperative treatment of HER2 positive primary breast cancer; HER2 targeted therapy is important (Baselga et al., 2012; Untch et al., 2012). NeoALLTO randomized 455 patients HER2 positive primary breast cancer to receive lapatinib plus paclitaxel or trastuzumab plus paclitaxel or combination of lapatinib and trastuzumab plus paclitaxel. The initial results showed the pCR rate was 51.3% in the lapatinib plus trastuzumab combination arm compared a rate of 24.7% for the lapatinib armand 29.5% for the trastuzumab arm. The difference in pCR rate between

the lapatinib plus trastuzumab arm compared to the trastuzumab arm was statistically significant (p=0.0001) (Baselga et al., 2012). In our study adding the trastuzumab to the neoadjuvant regimen did not differ the pCR rates (p=0.582).

Some biological predictive factors can effect the pCR except the chemotherapy regimen. Some predictive factors were analyzied in this current study. Huober et al. have reported the highest pCR rates in patients below 40 years of age, with triple negative or grade 3 tumors in GeparTrio study. Independent factors for midcourse response and pCR were: young age, nonT4 tumors, high grade, and hormone receptor status, the strongest single predictive factor. Within the biologic subtypes, grading was an independent factor to predict pCR for luminal tumors age for the triple ones. Grading gave independent information for midcourse response within the triple negative group in this study (Huober et al., 2010). In our study high grade, HER2 negativity, ER negativity and premenapousal status were predictive for pCR. The pCR and midcourse response were higher in the triple negative group (respectively p=0.0015, p<0.00001) in GeparTrio Trial (Huober et al., 2010). In our study pCR rate was higher in the triple negative group there was statistically significant difference (p=0.0001).

The biological factors combined with clinical and pathological information canbe used to predict pCR. Only the stage can't predict the neoadjuvant chemotherapy decision in the future. Some biological and pathological factors and gene arrays affect this decision. This study show this fact and chemosensitive triple negative group is the best group for neoadjuvant setting. The dose dense regimens have higher pCR in neoadjuvant setting for breast cancer.

Patients with high grade, premanopousal status, triple negative group were positive predictive factors for pCR and HER2 negativity and ER positivity percentage is important, PR negativity is important but its percentage of positivity is not important factor for pCR in Turkish breast cancer patients.

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