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ORIGINAL ARTICLE

The efficacy and reliability of sequential adjuvant anthracycline-based chemotherapy and weekly paclitaxel regimen in human epidermal growth factor receptor 2 negative breast cancer: A retrospective analysis of a multicentre study

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Summary

Purpose: *To analyze the reliability and the effectiveness of chemotherapy and prognostic factors for survival in patients with HER2 (human epidermal growth receptor 2) negative early-stage breast cancer treated with adjuvant sequential anthracycline-based chemotherapy and paclitaxel.*

Methods: *This analysis retrospectively evaluated the medical records of 756 HER2 negative early-stage breast cancer patients who received adjuvant sequential anthracycline-based chemotherapy and weekly paclitaxel in 15 medical oncology centers in Turkey between 2008-2015. Estrogen receptor (ER), progesterone receptor (PR), HER2, age, tumor size and grade, nodal status, perineural and lymphatic invasion, disease-free survival (DFS) and overall survival (OS) were analyzed.*

Results: *The median patient age was 50 years (22-82). Median follow up period was 46 months (13-82).The rates of recurrence and death detected in this period were 14.8% and 7.4%, respectively.Median OS and PFS were not reached in this period. Five-year DFS and OS rates were 87% and 89%, respectively. Age (OR:0.35, 95%Cl 0.12-0.96, p=0.04), PR status (OR:0.44, 95%Cl 0.18-1, p=0.05), lymphatic invasion (OR:2.6, 95%Cl 0.97-7.4, p=0.05) were independent prognostic factors.Most common grade 3-4 toxicities were fatigue (6.7%), neutropenia (1.7%) and nausea (1.3%). Neutropenic fever developed in 1.8% of the patients and peripheral neuropathy in 16.9%. Dose reduction was necessary for 10%of the patients due to grade 3-4 toxicity, whereas postponement of chemotherapy was necessary for 7% of the patients.*

Conclusions: *This multicentric retrospective study confirmed that sequential adjuvant therapy with anthracycline-based chemotherapy and paclitaxel for HER2 negative breast cancer is an effective and reliable regimen.*

Key words: *paclitaxel, anthracycline, adjuvant, breast cancer*

Introduction

Adjuvant chemotherapy reduces the risk of recurrence and death among women with early-stage breast cancer [1,2]. In the adjuvant setting, the most commonly used chemotherapy regimens consist of anthracycline-based regimens (AC, FEC). In early 1990s, after attempts to optimize the AC regimen

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by intensifying and/or increasing the dose of cyclophosphamide or of doxorubicin did not result in improved outcome [3-5], while activity of taxanes was demostrated in the adjuvant setting [6].

After anthracycline-based regimens were considered as the standard adjuvant treatment for operable breast cancer, the addition of a taxane to these regimens further reduced the risk of relapse [2,6-9].CALGB 9344 trial with 69 months of median follow-up demonstrated that the addition of paclitaxel to AC significantly improved recurrence-free survival and OS [3].

Prognostic factors are very important in breast cancer treatment decision.The presence of lymph node involvement, higher T stage, high grade, ER negativity and/or HER 2 overexpression are the most important prognostic factors in breast cancer. Also, tumor characteristics predict which patients are likely to benefit from specific types of therapy in breast cancer.Several studies have suggested that the benefits of taxane-based therapy are much more pronounced in hormone receptor negative disease or HER2 positive disease [10,11].However, in subgroups analyses of GEICAM 9906 trial [12], no statistically significant interaction was found between HER2 status and paclitaxel treatment or between hormone receptor status and paclitaxel treatment.Sparano et al. [6] found no evidence that women with hormone receptor–positive, HER2-negative breast cancer derived less benefit than those with breast cancer negative for hormone receptors or positive for HER2.

In this study, we performed a retrospective analysis of the reliability and the effectiveness of a chemotherapy regimen and the prognostic factors for survival in patients with HER2 negative early-stage breast cancer treated with adjuvant sequential anthracycline-based chemotherapy and paclitaxel.

Methods

We retrospectively evaluated the medical records of HER2 negative early-stage breast cancer patients who received adjuvant sequential anthracycline and paclitaxel in 15 medical oncology centers in Turkey between 2008-2015.

In this study included were women who had operable, histologically confirmed adenocarcinoma of the breast without distant metastases. Estrogen receptor (ER), progesterone receptor (PR), HER2, age, tumor size and grade, nodal status, perineural and lymphatic invasion, DFS and OS were analyzed.

ER and PR status were detected by immunohistochemical staining (IHC). Positive ER or PR was defined as the positive staining of more than 1% cells and HER2 status was evaluated with IHC and fluorescence *in situ* hybridization (FISH). IHC scoring was based on a 0 to 3+ intensity point scale. Tumors with HER2 scores of 0 or 1+ were considered negative and those of 3+ were considered positive. For the borderline positive (2+) staining, HER2 amplification was confirmed by FISH. Patients who had HER2 positive tumors but no available data of ER, PR were excluded from the study. Patient age, sex, menopausal status, histopathological features, tumor size, lymph node involvement, hormone receptor, HER2 status, and treatment features were recorded.

All patients received 4 cycles of anthracycline-based chemotherapy and 12 cycles of paclitaxel (80/m^2, weekly). Anthracycline-based chemotherapy included doxorubicin (60 mg/m^2, day 1) and cyclophosphamide (600 mg/m^2, day 1, (AC). Chemotherapy cycles were repeated every 21 days for a total of 4 cycles.

Table 1. Baseline patient characteristics

Characteristics	*Patients, n (%)*
Age, years, mean (range)	50 (22-82)
Sex	
Female	756 (100)
Male	0 (0)
Menopausal status	
Pre	379 (50.1)
Post	377 (49.9)
Histological diagnosis	
Ductal	634 (83.9)
Lobular	56 (7.4)
Other	66 (8.7)
Primary tumor size	
T1	170 (22.5)
T2	487 (64.4)
T3	99 (13.1)
Nodal status	
N0	82 (10.8)
N1	352 (46.6)
N2	199 (26.4)
N3	123 (16.3)
Histologic grade	
1	60 (8)
2	402 (53.2)
3	294 (38.8)
Estrogen receptor	
Negative	208 (27.5)
Positive	548 (72.5)
Progesterone receptor	
Negative	227 (30)
Positive	529 (70)
Surgery	
BCS*	263 (34.8)
MRM**	493 (65.2)

*breast conserving surgery, **modified radical mastectomy

Statistics

DFS was the time from definitive surgery to local or distant relapse or death without relapse. OS was the time from the definitive surgery to the time of death or last follow up. SPSS 18.0 software was used for statistical analyses. Univariate analysis was performed with independent samples using t-test, chi-square test and Fisher's exact test. For survival analysis Kaplan-Meier method was used and log-rank test was performed to evaluate differences between groups. Multivariate analysis was performed using the Cox model. The parameters identified as prognostic factors for breast cancer in the univariate analysis were entered in the Cox model. P value <0.05 was considered as statistically significant.

Results

A total of 756 patients were included in this study. Median age was 50 years (22-82). All of the patients were female. Premenopausal at the time of diagnosis were 379/756 (50.1%). Invasive ductal carcinoma was the most common histologic subtype (83.9%, n=634/756). Grade 3 tumors were observed in 38.8% (n=294/756) of the patients. Node positive patient rate was 89.3% (n=674). ER and PR positivity was 72.5% (n=548) and 70% (n=529), respectively (Table 1).

Modified radical mastectomy was performed in 493 patients (65.2%) and breast-conserving surgery in 263 (34.8%). The median metastatic lymph nodes number was 3 (0-60) and the median tumor diameter was 3 cm (0-17). All of the patients received anthracycline-based regimens (regimens described in Methods section) followed by paclitaxel (80 mg/m^2, weekly) and all positive ER/PR patients were administered hormonal therapy with tamoxifen or aromatase inhibitors after completion of chemotherapy. Adjuvant radiotherapy was performed according to tumor's clinical, pathologic and treatment characteristics listed in Table 1.

Median follow-up time was 46 months (13-82). Of the patients 112 relapsed (14.8%) and 56 died (7.4%) during this period. Median OS and PFS were not reached during follow-up. Five-year DFS and OS rates were 87% and 89%, respectively. The prognostic factors including patient age, tumor size and grade, nodal status, hormone receptor status, lymphatic and perineural invasion were analyzed in univariate and multivariate analyses and the results are summarized in Table 2.

Factors that were determined to affect OS in univariate analysis were age (>50 vs ≤50 years, p=0.045), tumor size (T1-2 vs T3, p=0.024), tumor grade (grade 1-2 vs 3, p=0.004), whereas PR status was close to the level of statistical significance (p=0.076). Nodal status was found not to have statistical impact on OS. Lymphatic and perineural invasion and ER status were not found to affect OS rates. In multivariate analysis, age (OR:0.35, 95%Cl 0.12-0.96, p=0.04), PR status (OR:0.44, 95%Cl 0.18-1, p=0.05), lymphatic invasion (OR:2.6, 95%Cl, 0.97-7.4, p=0.05) were determined as independent prognostic factors (Table 2).

Table 2. Univariate and multivariate analysis

Prognostic factors	*Univariate analysis*			*Multivariate analysis*		
	OR	*95% Cl*	*p value*	*OR*	*95% Cl*	*p value*
Age	1.39	0.15-1.4	0.045	0.35	0.12-0.96	0.04
Tumor size	2.7	1.1-6.5	0.024	2.1	0.84-5.5	0.11
Nodal status	1.6	0.39-6.9	0.486	2.1	0.27-16.1	0.47
Grade	3.3	1.4-7.4	0.004	2.9	1.2-7.2	0.17
ER	0.65	0.33-1.3	0.233	0.89	0.3-2.6	0.83
Negative						
Positive						
PR	0.55	0.28-1	0.076	0.44	0.18-1	0.05
Negative						
Positive						
Lymphatic invasion	1.7	0.76-3.9	0.185	2.6	0.97-7.4	0.05
Negative						
Positive						
Perineural invasion	1.1	0.73-1.85	0.515	1.4	0.55-3.5	0.46
Negative						
Positive						

OR: odds ratio, CI: confidence interval

Most common grade 3-4 toxicities were fatigue (6.7%), neutropenia (1.7%) and nausea (1.3%). Toxic effects are shown in Table 3. Neutropenic fever developed in 1.8% of the patients and peripheral neuropathy in 16.9%. Dose reduction was necessary for 10% of the patients due to grade 3-4 hematological toxicity. Delay of chemotherapy course was necessary for 7% of the patients. No chemotherapy-related toxic deaths occurred.

Discussion

Doxorubicin and cylophosphamide followed by taxanes is the preferred regimen for adjuvant treatment of breast cancer . İn the adjuvant setting, the addition of a taxane to an anthracycline-containing regimen provides significant benefit, particularly in node positive cases [2,6]. Several adjuvant therapy trials comparing anthracycline-containing chemotherapy with taxanes (paclitaxel and docetaxel)-containing regimens showed an absolute improvement in 5-year DFS of 4-7% [7,12,13]. The GEICAM 9906 trial [12] showed that lymph node positive breast cancer patients treated with adjuvant therapy consisting of 4 cycles of FEC-P (fluorouracil, epirubicin and cyclophosphamide, followed by weekly paclitaxel) had statistically significantly better 5-year DFS than those treated with 6 cycles of FEC (78.5 vs 72.1%, p=0.006). A metaanalysis performed to determine the efficacy of taxanes (docetaxel, paclitaxel) included 17 trials and 30, 672 patients. This analysis proved that the addition of taxanes increased significantly DFS and OS (HR 0.82, 95% Cl 0.76-0.88 for DFS and HR 0.83 95% Cl 0.75-0.91 for OS) [14].

Table 3. Most common adverse events occurring during therapy

Event	*Grade*				
	1 *n (%)*	*2* *n (%)*	*3* *n (%)*	*4* *n (%)*	*Total* *n (%)*
Fatigue	124 (16.4)	86 (11.3)	51 (6.7)	11 (1.4)	272 (35.8)
Diarrhea	31 (4.1)	3 (0.3)	3 (0.3)	0	37 (4.7)
Neuropathy	78 (9.9)	32 (4.2)	21 (2.4)	4 (0.4)	135 (16.9)
Neutropenia	31 (4.1)	14 (1.8)	13 (1.7)	5 (0.5)	63 (8.1)
Febrile neutropenia	11 (1.4)	3 (0.3)	2 (0.2)	0	16 (1.9)
Allergic reaction	3 (0.3)	1 (0.1)	1 (0.1)	0	5 (0.5)
Elevated alanine aminotransferase	4 (0.4)	3 (0.3)	0	0	7 (0.7)
Anemia	68 (8.9)	7 (0.7)	3 (0.3)	0	78 (9.9)
Renal toxicity	1 (0.1)	1 (0.1)	0	0	2 (0.2)
Vomiting	53 (7)	13 (1.7)	4 (0.4)	1 (0.1)	71 (9.2)
Nausea	80 (10.5)	32 (4.2)	10 (1.3)	4 (0.4)	126 (16.6)
Myalgia	68 (8.9)	12 (1.5)	1 (0.1)	0	81 (10.5)
Thrombocytopenia	12 (1.5)	6 (0.6)	2 (0.2)	1 (0.1)	21 (2.4)

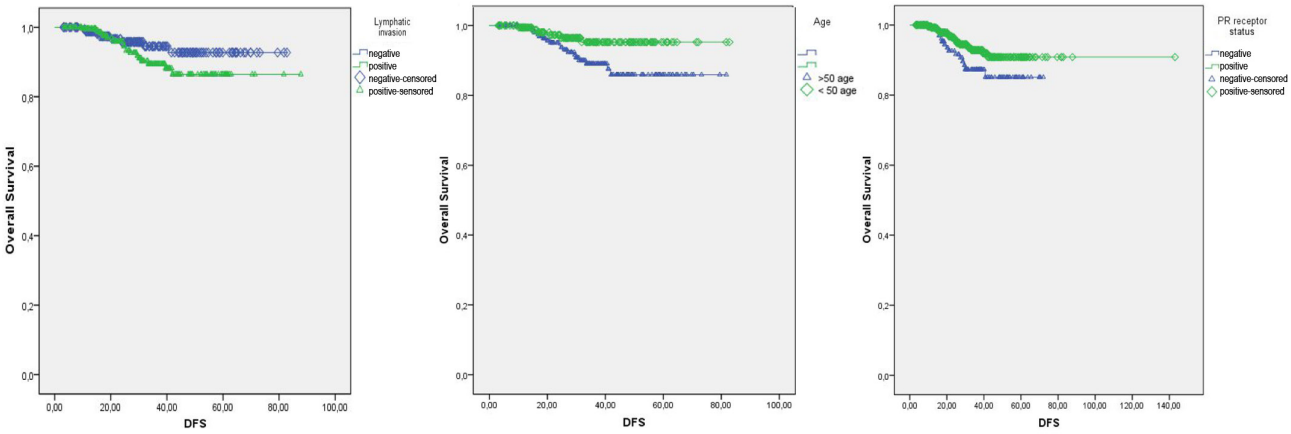

Figure 1. Age, lymphatic invasion, PR status and survival. P=0.04 for age, p=0.05 for lymphatic invasion and p=0.05 for PR status.

Weekly paclitaxel has become the standard administration with the ECOG 1199 study [6]. In this analysis it was concluded that treatment with doxorubicin and cyclophosphamide followed by weekly paclitaxel was associated with improved DFS and OS in comparison with paclitaxel given every 3 weeks [6].

In general, the choice of whether to give chemotherapy has been based on anatomic prognostic considerations more than tumor characteristics. Useful prognostic factors are size of the tumor, presence or absence axillary lymph node metastases and grade. ER and HER2 are modestly prognostic and predictive factors in breast cancer for endocrine therapies and anti-HER2 therapies [15]. This analysis included HER2-negative patients. ER and PR positivity was 72.5% (n=548) and 70% (n=529), respectively. Node positive patient rate was 89.3%. Grade 3 tumor rate was 38.8%. In our analysis, 5-year DFS and OS were 87% and 89%, respectively. The chemotherapy regimen (AC followed by weekly paclitaxel) had survival efficacy similar to other previous studies [6]. In univariate analysis, age, tumor size and grade at the time of diagnosis had significant impact on PFS and OS, whereas no effect of nodal status was found. The small number of node-negative patients may have contributed to this result. PR status was close to the level of statistical significance (p=0.076). Lymphatic and perineural invasion and ER status were also not found to affect patient survival rates. In multivariate analysis we demonstrated that age (p=0.04), PR status (p=0.05), and lymphatic invasion (p=0.05) were independent prognostic factors (Figure 1).

HER2 status and hormone receptor status are believed to predict resistance or sensitivity to different types of chemotherapeutic agents, including anthracyclines and taxanes [3]. A retrospective analysis of CALGB adjuvant trials has indicated that the benefit of paclitaxel is limited mainly to ER negative patients regardless of HER2 status and to HER2 positive patients regardless of ER status, while there was no evidence of benefit in the subgroup with ER positive/HER 2 negative. This finding, however, has not been confirmed in other taxane trials [6,11,16]. Neoadjuvant trials also confirm that patients with receptor-negative tumors achieve higher pathologic response rates compared with patients with receptor-positive tumors [12,17,18].

NSAPB 28 study [12] confirmed the benefits of incorporating a taxane (paclitaxel) in the adjuvant setting. Most common grade 3 or greater toxicity during paclitaxel therapy included neurosensory toxicity, neuromotor toxicity, arthralgia and/or myalgia, and febrile neutropenia in 15%, 7%, 12%, and 3% of patients, respectively. Saprano et al. [6] showed that weekly paclitaxel was associated with significantly more moderate-to-severe neuropathy than standard 3-week paclitaxel. Neurotoxicity is an important side effect in paclitaxel-associated treatment. In our study we found that a significant rate of patients (16.9%) had peripheral neuropathy during treatment. Also, in this analysis, febrile neutropenia (1.8%) and neutropenia (8.1%) were encountered.

The results of this study showed low risk of cancer recurrence (14.8%) and low rate of serious toxic effects with sequential adjuvant therapy with anthracycline and paclitaxel for HER2 negative early-stage breast cancer. This analysis is the the largest analysis evaluating retrospectively anthracycline-based chemotherapy and sequential adjuvant paclitaxel that had previously been shown to be effective for HER2 negative early-stage breast cancer in prospective studies.

The present study contains some limitations due to retrospective design and inadequate registration (no information about regional and distant recurrences and chemotherapy toxicity-related death). Also, we did not make luminal A, B group distinction of the tumor.

In conclusion, age, PR status, and lymphatic invasion were identified as important prognostic factors. This multicentric retrospective analysis confirmed that sequential adjuvant therapy with anthracycline-based chemotherapy and paclitaxel for HER2 negative breast cancer is an effective and reliable regime.

Conflict of interests

The authors declare no conflict of interests.

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