Evaluation of efficacy and toxicity of anthracycline plus cyclophosphamide every three weeks followed by weekly paclitaxel: The Izmır Oncology Group (IZOG) Study

Üç haftada bir antrasiklin ve siklofosfamidi takiben haftalık paklitaksel rejiminin etkinlik ve toksisitesinin değerlendirilmesi: Izmir Onkoloji Grubu (İZOG) Çalışması

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ÖZET

GİRİŞ ve AMAÇ: Doz yoğun kemoterapi (AC Q2 × 4 → P Q2 × 4), yüksek riskli meme kanserli hastaların adjuvan tedavisinde yaygın olarak kullanılmaktadır. Bununla birlikte, doz yoğun kemoterapi ile üç haftada bir antrasiklin ve siklofosfamidi takiben haftalık paklitaksel (AC Q3 × 4 → PW × 12) rejimini doğrudan karşılaştıran çalışma yoktur. Ayrıca, antrasiklin ve siklofosfamide haftalık paklitaksel ilave edildiğinde, doz yoğun AC' nin (AC Q2 x 4) konvansiyonel AC'den (AC Q3 x 4) daha üstün olup olmadığı bilinmemektedir. Bu çalışmada AC Q3 × 4 → P W × 12 rejiminin etkinliğinin ve toksisitesinin değerlendirmesi amaçlanmıştır.
YÖNTEM ve GEREÇLER: 2013 ve 2016 yıllarında meme kanseri tanısı konulan hastalar retrospektif olarak değerlendirildi. Çalışmaya lenf nodu pozitif (tümör evresi T1, T2 veya T3 ve nodal evre N1, N2 veya N3) ya da yüksek riskli lenf nodu negatif (T2 veya T3, N0) uzak metastazı olmayan hastalar dahil edilmiştir.
BULGULAR: Çalışmaya 150 hasta dahil edildi. Medyan 31 aylık takip süresinde 13 hastada uzak metastaz gelişti ve 6 hasta vefat etti. Beş yıllık hastalıksız sağkalım ve genel sağkalım oranları sırasıyla % 88.4 ve % 92 idi. Hastaların yüzde 38.6'sında ciddi nötropeni (grade 3,4) görülürken ciddi bir kardiyotoksisite gözlenmedi.
TARTIŞMA ve SONUÇ: AC Q3 × 4 → P W × 12, lenf nodu pozitif veya yüksek riskli lenf nodu negative erken evre meme kanserli hastalarda etkin ve iyi tolere edilebilir kemoterapi rejimidir.
Anahtar Kelimeler: Meme kanseri, adjuvan kemoterapi, doksorubisin, siklofosfamid, paklitaksel.

ABSTRACT

INTRODUCTION: Dose-dense chemotherapy (AC Q2×4→P Q2×4) is widely used in the adjuvant treatment of high-risk breast cancer patients. However, there is no direct comparison of dose-dense chemotherapy consisting of anthracycline plus cyclophosphamide every three weeks followed by weekly paclitaxel (AC Q3 × 4 → P W × 12) regimen. Moreover, when weekly paclitaxel is added to anthracycline plus cyclophosphamide, it is unknown whether or not dose-dense AC (AC Q2×4) is superior to conventional AC (AC Q3×4). The study aimed to evaluate the efficacy and toxicity of AC Q3 × 4 → P W × 12 regimen.
METHODS: Patients diagnosed with breast cancer from 2013 to 2016 were retrospectively evaluated. The study included women who had histologically-involved lymph nodes (tumor stage T1, T2, or T3 and nodal stage N1, N2, or N3) or high-risk, axillary node-negative disease (T2 or T3, N0) without distant metastases.
RESULTS: This study included 150 patients with breast cancer. After a median follow up period of 31 months, 13 patients had developed distant metastases and 6 patients had died. The estimated 5-year disease-free survival and overall survival rates were 88.4% and 92%, respectively. Severe neutropenia (grade 3, 4) occurred in 38.6%of the patients whereas no severe cardiotoxicity was observed.
DISCUSSION AND CONCLUSION: AC Q3 × 4 → P W × 12 regimen is well-tolerated and effective in patients with node-positive or high-risk node-negative early-stage breast cancer.
Keywords: Breast cancer, adjuvant chemotherapy, doxorubicin, cyclophosphamide, paclitaxel

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INTRODUCTION

In 2018, approximately 2.1 million new incidents of breast cancers were diagnosed worldwide, accounting for almost 1 in 4 cancer cases among women (1). Adjuvant chemotherapy significantly reduces the risk of recurrence and death among women with operable breast cancer (2). Compared to cyclophosphamide, methotrexate, and fluorouracil (CMF) alone, anthracycline-containing regimens have slightly greater effects on recurrence and mortality (3). The addition of a taxane (paclitaxel or docetaxel) to an anthracycline-containing regimen reduces the risk of recurrence either after anthracycline treatment or concurrently (4).

In the early 1990s, taxanes were clinically administered in metastatic breast cancer (MBC) and later in the adjuvant setting (5,6). Preclinical and indirect clinical evidence has shown that docetaxel is more effective than paclitaxel and that weekly paclitaxel is more effective than three-week paclitaxel (6). A randomized controlled trial (RCT) conducted by the Eastern Cooperative Oncology Group (ECOG) in the adjuvant setting demonstrated that weekly paclitaxel (80 mg/m2 every week x 12) is more effective than three weekly paclitaxel (175 mg/m2 every three weeks x 4). The comparison of paclitaxel every week versus docetaxel every three weeks did not suggest a difference in terms of disease-free survival (DFS) or overall survival (OS) (7).

Administration of dose-dense chemotherapy became possible by using granulocyte colony-stimulating factor, which allowed administration of chemotherapy without causing unacceptable toxicity. A dose-dense chemotherapy schedule using concurrent doxorubicin and cyclophosphamide followed by paclitaxel was evaluated in the pivotal Cancer and Leukemia Group B 9741 trial, a phase III prospective randomized trial of adjuvant treatment of women with node-positive early-stage breast cancer. This trial demonstrated a statistically significant improvement in terms of DFS and OS for the dose-dense chemotherapy arm (8). Dose-dense regimen has become the cornerstone for high-risk patients who are treated with adjuvant chemotherapy (9).

Results of a meta-analysis of dose-dense versus standard dosing, including data from 26 trials and over 37,000 women, demonstrate decrease in disease recurrence and improvement in 10-years breast cancer mortality for the dose-dense chemotherapy arm (10). However, there is no study comparing anthracycline plus cyclophosphamide every three weeks followed by weekly paclitaxel (AC Q3×4→P W×12) versus anthracycline plus cyclophosphamide every two weeks followed by weekly paclitaxel (AC Q2×4→P W×12) or two weekly paclitaxel (AC Q2×4→P Q2×4). Furthermore, when weekly paclitaxel is added to anthracycline plus cyclophosphamide, it is unknown whether or not the dose dense AC (AC Q2×4) is superior to conventional AC (AC Q3×4). In this retrospective study, we aimed to evaluate the efficacy and toxicity of AC Q3×4→P W×12 regimen.

MATERIALS and METHODS

Patients

Medical records of breast cancer patients with histologically confirmed adenocarcinoma who were admitted to the Medical Oncology Outpatient Clinic of Izmir Ataturk Training and Research Hospital between 2013 and 2016 were retrospectively evaluated. The study included women who had histologically-involved lymph nodes (tumor stage T1, T2, or T3 and nodal stage N1, N2, or N3) or high-risk, axillary node-negative disease (T2 or T3, N0) without distant metastases. Other inclusion criteria consisted of age between 18 and 80 years, Karnofsky performance status of ≥80%, and adequate organ and bone marrow function. Patients with history of invasive breast cancer or ductal carcinoma in situ (in either breast), who had received any prior radiation, chemotherapy or hormonal therapy for their present breast cancer or had a history of prior malignancy other than specified in situ cancers or other cancers from which they were disease-free for ≥ 5 years were excluded from the study.

Treatment

Patients received doxorubicin (60 mg per square meter of body-surface area,

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administered intravenously for 15 minutes) and cyclophosphamide (600 mg per square meter by intravenous infusion for 30 to 60 minutes) every 3 weeks for four cycles followed by 80 mg of paclitaxel per square meter by intravenous infusion for 1 hour weekly for 12 doses. In addition, patients with HER2-positive breast cancer received trastuzumab for one year. Treatment was discontinued if the patient experienced progressive disease or unacceptable toxicity.

End points, evaluation and toxicity assessment

The primary end point was disease-free survival, defined as the time of diagnosis to the date of disease recurrence, with histopathologic confirmation or radiologic evidence of tumor recurrence or death, whichever occurred first. Secondary end points included overall survival (i.e., the time from randomization until death from any cause) and toxic effects.

Blood counts and general biochemical and clinical assessments, including those for toxic effects, were performed in each cycle and then every three to six months for the first five years of follow-up, after which they were performed annually. Mammography was performed annually during follow-up. Echocardiography was evaluated in all patients before the start of treatment and was repeated every 3 months during treatment in patients receiving trastuzumab. Patients were evaluated for hematologic and non-hematologic toxicities using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

Data analysis was performed using the IBM SPSS Statistics (IBM Corp. Armonk, NY, USA) for Windows, version 20.0. Data were expressed as mean and standard deviation for continuous variables and as number and percentages for categorical variables. Probabilities of disease-free and overall survival were estimated using the Kaplan-Meier method. A p value of ≤0.05 was considered statistically significant.

RESULTS

The present study included a total of 150 patients with breast adenocarcinoma. The median age of the patients was 55 years (range, 28–80 years). The general characteristics of the patients are presented in Table 1. Approximately 13% of the patients had no positive lymph nodes, 33% had N1 disease, and 36% had N2 disease. The tumor was positive for estrogen receptor, progesterone receptor, or both in approximately 75% of patients and positive for HER2 in 34% (as determined in local institutional laboratories).

Adverse event of any grade developed in 90% of the patients. The incidence of grade 3 or 4 neutropenia was 38.6%and febrile neutropenia was observed in 1.3% of the patients. The incidence of grade 1 or 2 neuropathy was 18%, while grade 3-4 neuropathy occurred in only 2% of patients. Left ventricular ejection fraction decline was observed in 4% of patients. Adverse events related to treatment are presented in Table 2.

At the time of the analysis, after a median follow up of 31 months, 13 patients had developed distant metastases and 6 patients had died. All of these patients had died of disease progression. Figure 1 shows the Kaplan–Meier curves for disease-free survival. The estimated 5-year disease-free survival rate was 88.4%. Figure 2 shows the Kaplan–Meier curves for overall survival. The estimated 5-year overall survival rate was 92%.

Figure 1. Disease-free Survival.

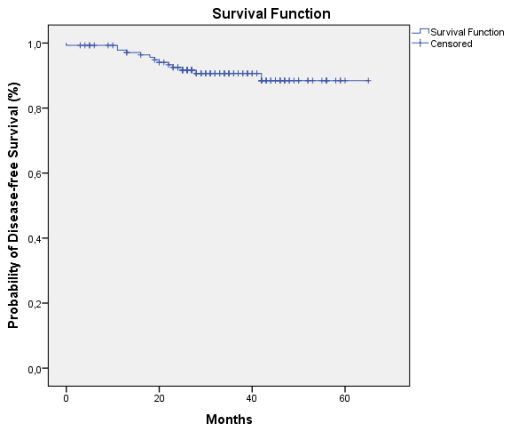

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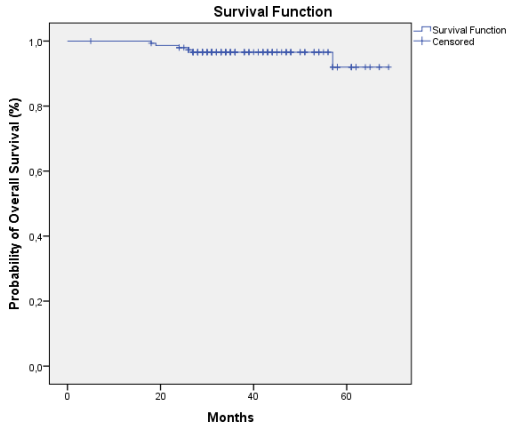
Figure 2. Overall Survival.



DISCUSSION

The use of anthracyclines and taxanes in the adjuvant treatment of high-risk breast cancer has become the standard**.** In the present study, we aimed to determine the efficacy and toxicity of AC Q3×4→P W×12 regimen. At a median of 31 months of follow-up, this trial revealed 5-year disease-free survival and overall survival rates as 88.4% and 92%, respectively. This result is similar to other studies in the literature on anthracycline and taxane (including dose-dense therapies) (7-9, 11).

The results of two randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillar lymph node-positive breast cancer suggest that addiction of paclitaxel improves disease-free survival rates (5, 11). The 5-year DFS for patients in the AC→PTX arm was 76%±2% (5). However, in this study, paclitaxel was administered every 3 weeks at a dose of 225 mg/m2 IV as a 3-hour infusion on day 1 of each cycle. The phase III E 1199 trial compared patients with axillary lymph node–positive or high-risk, lymph node–negative breast cancer who received 4 cycles of intravenous doxorubicin and cyclophosphamide at 3-week intervals who were then assigned to intravenous paclitaxel or docetaxel given at 3-week intervals for 4 cycles or at 1-week intervals for 12 cycles. The estimated 5-year survival rates were 76.9% for the group receiving paclitaxel every 3 weeks and 81.5% for the group receiving weekly paclitaxel. Compared to the group receiving paclitaxel every 3 weeks, there was significantly improved disease-free survival in the weekly paclitaxel group (7). The results of our study surpass the results of the study conducted by Mamounas et al. (5) and are similar to the results of E 1199 trial in terms of DFS. In our study, weekly administration of paclitaxel, as in the E 1199 study and unlike the study of Mamounas et al., may have caused this result. Weekly paclitaxel is known to have a survival benefit when compared with the regimen of paclitaxel every 3 weeks, however, it is unknown which of the common dose-dense strategies of every-two-weeks AC x 4 followed by every-two-weeks paclitaxel x 4 or every-two-weeks AC x 4 followed by weekly paclitaxel x 12 is superior.

Approximately 25% of women with early breast cancer have human epidermal growth factor receptor 2 (HER-2)-positive disease, and a more aggressive course is associated with early recurrence and poor prognosis (12, 13). Similar to the literature, in the phase III E 1199 trial, 20% of patients were HER-2 positive (7). In our study, 35% of patients were HER- 2 positive. The combination of anthracycline and taxane is preferred in early stage HER-2 positive breast cancer but this combination is not administered in early stage HER-2 negative breast cancer. Since our study included only patients receiving anthracycline and taxane treatment, the rate of HER- 2 positive patients is higher than in the literature and constitutes a more aggressive group.

The toxic effects associated with the AC Q3×4→P W×12 regimen we used were consistent with those reported in association with anthracycline and taxane treatment and were manageable with standard supportive measures. In the E1199 study, while the incidence of grade 2, 3, or 4 neuropathy was 27% in the weekly paclitaxel group (7), neuropathy incidence was 20% in our study. In the study conducted by Cancer and Leukemia Group B (CALGB), severe cardiac toxicity occurrence was less than 1% in both arm 3 (doxorubicin 60 mg/m2 plus cyclophosphamide 600 mg/m2 every 3 weeks for four cycles followed by paclitaxel 175 mg/m2 every 3 weeks for four cycles) and arm 4 (doxorubicin 60 mg/m2 plus cyclophosphamide 600 mg/m2 every 2 weeks for four cycles followed by paclitaxel 175 mg/m2 every 2 weeks for four cycles) (8). In our study, severe cardiac toxicity was not

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observed, whereas grade 1-2 cardiac toxicity occurrence was 4%.

The strength of the present retrospective study is its being the first study evaluating the efficacy and toxicity of AC Q3×4→P W×12 regimen in patients with node-positive or high-risk node-negative early-stage breast cancer; therefore, it contributes to the current knowledge in the literature. The present study also had a number of limitations. As this is a retrospective study, it is prone to common biases associated with similar studies. Toxicity may be overlooked by retrospective evaluation. In addition, the study included a small number of patients, which may limit its statistical power.

In conclusion, treatment with doxorubicin and cyclophosphamide every 3 weeks followed by weekly paclitaxel is well-tolerated and effective in patients with node-positive or high-risk node-negative early-stage breast cancer. In the current literature, dose-dense chemotherapy (AC Q2×4→P Q2×4) is widely accepted in the adjuvant treatment of high-risk breast cancer patients. However, there is no direct comparison of dose intensive chemotherapy with the AC Q3 × 4 → P W × 12 regimen, therefore the AC Q3 × 4 → P W × 12 regimen may be an alternative option.

Conflict of interest: None

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