The Effect of Chemotherapy in Patients with Node-Negative pT1c Breast Cancer

Lenf Nodu Negatif pT1c Meme Kanserli Hastalarda Kemoterapinin Etkisi

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ÖZET

GİRİŞ ve AMAÇ: PT1cN0M0 meme kanserili hastaların bazı alt grupları, yüksek bir relaps potansiyeli taşır ve bu nedenle adjuvan kemoterapi verilmesini gerektirebilir. Biz bu çalışmada, pT1cN0Mo meme kanserli hastalarda adjuvan kemoterapinin etkinliğini ve prognostik önemi olabilecek faktörleri tanımlamayı amaçladık.
YÖNTEM ve GEREÇLER: Çalışmamıza iki merkezden 1990-2013 tarihleri arasında opere edilmiş pT1cN0M0 meme kanserli kadın hastalar alındı. Adjuvan kemoterapi kısmen standardize edildi. (doksorubisin ve siklofosfamid kombinasyonuna ilabe taksan eklendi yada eklenmedi veya 5-florourasil, doksorubisin, siklofosfamid kombinasyonu uygulandı). Datanın analizinde Chi-Square ve Mann-Whitney U Testleri kullanıldı. İstatiksel anlamlılık $p<0.05$ olarak kabul edildi.
BULGULAR: Sadece T1cNoMo meme kanseri olan iki yüz on sekiz bayan hasta bu çalışma için alım kriterlerini karşıladı. Çalışmamızda düşük olay oranı olmasına rağmen tek değişkenli analizde adjuvan kemoterapinin etkili olduğu 2 grup belirledik. Bu gruplar Her2 negatif (p: 0.045) ve Grade 2 (p: 0.033) gruplarıydı. Çok değişkenli analizde, Her2 durumu ve progesteron durumu bağımsız prognoz faktörlör olarak saptandı.
TARTIŞMA ve SONUÇ: Bulgularımız, PR ve HER-2 durumlarının prognostik öneme sahip olduğunu ve adjuvan kemoterapinin bazı T1c tümör alt gruplarında hastalıksız sağkalım avantajı sağlayabileceğini göstermiştir. Tedaviyi daha iyi bireyselleştirmek ve sistemik tedaviyi sınırlamak için daha fazla yeni prognostik ve prediktif testlere ihtiyaç vardır.
Anahtar Kelimeler: adjuvan kemoterapi, meme kanseri, prognoz, pT1cN0M0

ABSTRACT

INTRODUCTION: A subgroup of pT1cN0M0 breast cancer carries a high potential of relapse, and thus may require adjuvant chemotherapy. In this study, we aimed to identify the efficacy of adjuvant chemotherapy in patients with pT1cN0Mo breast cancer and the factors that may be prognostic prognostic factors
METHODS: Retrospective analysis of all patients with pT1c breast cancer, who underwent surgery from 1990 to 2013 at two centers. AC was partially standardized (doxorubicin plus cyclophosphamide with or without taxan or 5-fluorouracil plus doxorubicin plus cyclophosphamide). Chi-square and Mann-Whitney U tests were used in the analysis of data. Statistical significance was accepted as $p<0.05$.
RESULTS: Two hundred and eighteen female patients only with T1cNoMo breast cancer met the eligibility criteria for this study. Despite the low incidence rate in our study, we identified 2 groups in which adjuvant chemotherapy was effective in univariate analysis. These groups were Her2 negative (p: 0.045) and Grade 2 (p: 0.033) groups. In multivariate analysis, HER-2 status and progesterone status were independent prognostic factors.
DISCUSSION and CONCLUSION: Our findings imply that PR and HER-2 statuses had prognostic significance and adjuvant chemotherapy may offer adisease free survival advantage in some subgroups of T1c

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tumors. New prognostic and predictive tests are needed to better individualize the therapy and confine the systemic treatment.
Keywords: adjuvant chemotherapy, breast cancer, prognosis, pT1cN0M0

INTRODUCTION

Over the past three decades, mammographic screening has led to an increased diagnosis of smaller, node-negative breast cancers (1). Those patients with breast cancer who are presented with T1c, node-negative tumors generally exhibit a good prognosis, and 10-year survival rates exceed 91% (2-4). Although the patients with T1c breast cancers present a long-term survival, recurrence and mortality are still the case. Nevertheless, disease outcomes for those patients may differ depending on biological sub-types (5-7). Generally, as the patients within the T1 group are excluded from adjuvant chemotherapy studies, the absolute benefit and risks of chemotherapy remain unclear. Not all breast cancer patients may benefit from the adjuvant chemotherapy and especially those with smaller primary tumors usually benefit less. Although the adjuvant systemic therapy reduces the risk of recurrence and improves survival for patients with node-negative breast cancer, the absolute benefit decreases as the risk of recurrence lessens (4). Existing prognostic and predictive factors must be established to better determine the absolute benefit of adjuvant therapy (8-10).

According to the 2016 National Comprehensive Cancer Network Guidelines, adjuvant systemic therapy is recommended for small breast tumors (>10 mm but ≥20 mm in diameter) (T1c) that do not involve the lymph nodes, under category 1. However, 2016 ESMO Guidelines recommend systemic treatment for early breast cancer subtypes for Luminal B, HER2 overexpression, 'Basal-like', and for luminal A-like, which has a high tumor burden (four or more positive LN or T3 or higher), or grade 3.

A series of studies by National Surgical Adjuvant Breast and Bowel Project (NSABP), namely B-13, B-19, and B-23, have consecutively evaluated adjuvant chemotherapy in node-negative and estrogen receptor–negative tumors and have shown that an adjuvant chemotherapy combined with methotrexate and 5-fluorouracil (MF) is more effective in reducing the risk of relapse than surgery alone (B-13). In NSABP B-19 study cyclophosphamide with MF is found to be more effective than MF and that CMF and doxorubicin with cyclophosphamide are equally efficacious (B-23) (11-13).

According to previous studies, premenopausal breast cancer women have an inferior disease-free survival (DFS) and breast cancer-specific survival when compared to the postmenopausal women. Nixon et al showed that being younger than 35 was a significant predictor for the time of recurrence, distant metastasis and overall mortality (14). More recent studies have demonstrated that certain biological subtypes, including HER2-positive and triple-receptor negative breast cancer (TNBC) tumors, exhibit a higher risk of relapse, despite their small size (15,16). Given all the aforementioned data about the early-stage disease, age at diagnosis, and receptor status, the question of whom to treat with adjuvant chemotherapy remains controversial for small tumors. In the present study, we sought to evaluate the benefit of chemotherapy with respect to outcome differences in T1cN0M0 breast tumors.

MATERIALS and METHODS

The study included 218 female patients who were exclusively diagnosed with T1cNoMo breast cancer at Izmir Katip Celebi University Ataturk Training and Research Hospital and Izmir Bozyaka Ataturk Training and Research Hospital Medical Oncology Clinic between 1990 and 2013. Male breast cancer patients were excluded from the analysis.

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We retrospectively analyzed the patient files to obtain data including age, histopathological characteristics of the tumor (ER status, PR status, cerb-B2 status, grade, lymphovascular invasion, size of tumor, nodal status, and stage) radiotherapy, chemotherapy or hormonotherapy status, menapausal status, and date of operation.

The disease-free survival was measured starting from the date of diagnosis to the date of first local or distant disease recurrence. Patients who died without a recurrence were considered censored at their date of death.

All statistical analyses were performed with the SPSS 20.0 (Chicago, Illinois) package software. We used Chi-Square and Mann-Whitney U Tests to analyze the data and $p<0.05$ value was taken to indicate statistical significance. The disease-free survival (DFS) ratio and survival curves were compared by using the Kaplan-Meier method and long-rank test, respectively. Cox-regression analysis was used in multivariate analysis.

RESULTS

Two hundred and eighteen female patients only with T1cNoMo breast cancer met the eligibility criteria for this study. The median age was 53 (range: 28 to 84). The majority of the patients exhibited invasive ductal carcinoma histology (66.5%), ER (73.9%) and PR (72.5%) positive, HER-2 negative receptor status (86.2%) and grade 2 differentiation (68.8%) and most of them received chemotherapy (75.7%) and endocrine therapy (85.3%). The HER2-positive patients were more likely to be grade 2, ER negative, and to have received chemotherapy. Relevant patient characteristics are presented in *Table 1*.

The overall median follow-up was 86.9±42.9 (min: 26, max: 293) months. Sixteen patients (7.3%) developed a relapse throughout the follow-up period. Ten patients experienced visceral metastasis, 3 had bone metastatis, and 10 had local recurrence. At the end of analysis period, 23 patients (10.6%) were found to be exitus. The 5-year and 10-year DFS estimates for the entire population were 95.1% and 87.4%, respectively. The 5-year and 10-year DFS estimates according to breast cancer subtype were 81.6% and 61.2 for HER-2-positive patients (n:30), 97.2% and 90.9% for HER2-negative (n:188) (p:0.001), 95.9% and 93% for PR-positive (n:158), 93% and 73.6% for PR-negative (n:60) (p:0.015) (*Figure 1a,b*).

Taking all the patients with T1c into account, the impact of adjuvant chemotherapy on disease-free survival was better in numerical terms but it did not indicate a statistical significance (P: 0.13). However, regarding the sub-groups, 5-year and 10-year DFS rates for the HER2-negative group treated with adjuvant chemotherapy were 98.5% and 93.3%, respectively while 5-year and 10-year DFS rates for the HER2-negative group treated without adjuvant chemotherapy were 93% and 83% for the HER2-negative group (p:0.045). The 5-year and 10-year DFS rates for the grade 2 group treated with adjuvant chemotherapy were 98% and 92%, respectively. However, the 5-year and 10-year DFS rates were 90% and 82% for the grade 2 group which did not receive adjuvant chemotherapy (p:0.033) *(Figure 2).* Lastly, the 5-year and 10-year DFS rates for the ER-positive, HER2-negative and Grade 2 group treated with adjuvant chemotherapy were 98% and 98%, respectively, while 5-year and 10-year DFS rates for the ER-positive, HER2-negative and Grade 2 group treated without adjuvant chemotherapy which were 89% and 89% respectively (p:0.05).

Prognostic risk factors with/without chemotherapy affecting 5/10-year disease-free survival are presented with an univariate analysis in *Table 2*. The multivariate analysis showed HER2-positivity and PR negativity as a poor prognostic factor (p:0.007 and p:0.043, respectively). Prognostic factors affecting survival were seen in *Table 3.*

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Table 1. Clinical characteristics of the patients with pT1c

Characteristics of the patients	***Number of patients (%)***
Age at diagnosis (years), Mean (range)	53 ± 11.8 (28-84)
ER status	
Positive	161 (73.9)
Negative	57 (26.1)
PR status	
Positive	158 (72.5)
Negative	60 (27.5)
HER2 status	
Positive	30 (13.8)
Negative	188 (86.2)
Grade	
Grade 1	33 (15.1)
Grade 2	150 (68.8)
Grade3	35 (16.1)
Menopausal status	
Premenopausal	101 (46.3)
Postmenopausal	117 (53.7)
Hormonotherapy	
Yes	186 (85.3)
No	32 (14.7)
Radiotherapy	
Yes	110 (50.5)
No	108 (49.5)
Chemotherapy	
Yes	165 (75.7)
No	53 (24.3)
Trastuzumab	
Yes	10 (4.6)
No	208 (95.4)

HER2, human epidermal growth factor receptor 2 gene; ER, estrogen receptor; PR, progesterone receptor; RT, radiotherapy

Table 2. Prognostic risk factors with/without chemotherapy affecting survival outcomes

Characteristics of the patients	***Chemotherapy yes 5 years/10 years survival (%)***	***Chemotherapy no 5 years/10 years survival (%)***	***n***	***p value***
All cases	96/89	91/82	165/53	0.13
Hormonotherapy: yes	96/88	91/91	137/49	0.448
HER2:neg	98.5/93.3	93/83	139/49	0.0001
Grade 2	98/92	90/82	114/36	0.033
ER:pos, HER2:neg,Grade 2	98/98	89/89	69/32	0.05

HER2, human epidermal growth factor receptor 2 gene; ER, estrogen receptor

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Table 3. Prognostic factors affecting survival (multivariate analysis)

Variable	*Relative risk*	*95 %CI*	*P value**
PR negative	4.09	0.13-0.96	0.043
HER2 positive	7.21	1.46-11.59	0.007

HER2, human epidermal growth factor receptor 2 gene; ER, estrogen receptor; PR, progesterone receptor; ***** Cox regression

DISCUSSION

With the present retrospective study conducted at two centers, we aimed to determine the effectiveness of adjuvant chemotherapy in patients with T1cNoMo breast cancer and the factors that may bear prognostic significance. We observed the breast cancer subtype to be significantly associated with patient outcomes among the patients with pT1cN0M0 tumors.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis has recently stated the relative benefit of chemotherapy which is similar in all the subgroups independent from age, histopathological grade, stage and ER status (17). However, this study largely included high-risk patients who were treated with a suboptimal endocrine therapy (ET) as per current standards. The absolute benefit to be obtained from adjuvant therapy may change to a great extent under such circumstances. It may depend on tumor burden or risk factors (grade, receptor status, HER-2, LVI, etc.). NSABP B13, B-19 and B-23 findings demonstrating the worth of adjuvant therapy for the treatment of patients with lymph-node-negative breast cancer have been amply confirmed by the findings presented in a meta-analysis by the EBCTCG in 1998 (18). The findings updated by the NSABP studies B-13, B-19, and B-23 showed 58% and 40% reductions in the recurrence risk and mortality, respectively, by chemotherapy throughout an 8-year follow-up period. No differences were noted in age groups regarding the outcome (19). These studies have demonstrated the benefit of adjuvant chemotherapy (AC and CMF in particular) even for early-stage node-negative breast cancers.

In the present study, despite a low event rate, on univariate analysis we found that the adjuvant chemotherapy had a positive impact on 2 subgroups; HER-2-negative and grade 2, which was statistically significant (p: 0.045, and p: 0.033, respectively). The general group did not exhibit a statistical significance although it displayed better numerical results (p: 0.13). Regarding the Grade 3 patient group, however, the analysis did not show a statistically significant difference because of a small sample size, despite better numerical results. In addition, although the triple-negative group presented significant results, the small sample size made it difficult to interpret the results. Some studies demonstrated the prognostic importance of the histological grade in patients with node-negative breast carcinomas (20-22) yet others did not report such a correlation (23,24). Another study reported no statistically significant difference in patients with node negative breast cancer when compared with HER-2 negative and with HER-2 positive groups which was numerically worse for overall survival while statistically significant difference for DFS and breast cancer-specific survival in favor HER2 overexpression (25).

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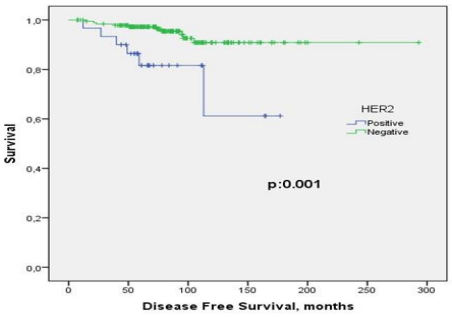

Figure 1a. Kaplan-Meier plot of disease-free survival for patients with T1cN0 breast tumors according to HER2 status: HER2-negative and HER2-positive

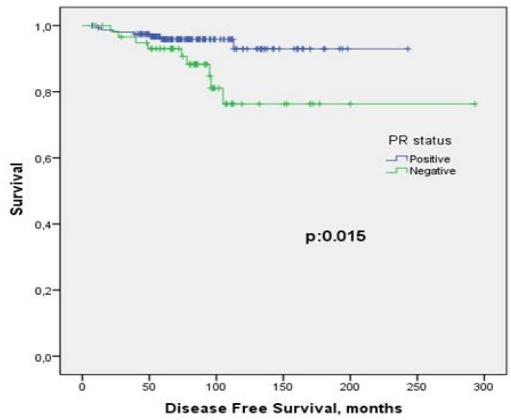

Figure 1b. Kaplan-Meier plot of disease-free survival for patients with T1cN0 breast tumors according to PR status: PR-negative and PR-positive

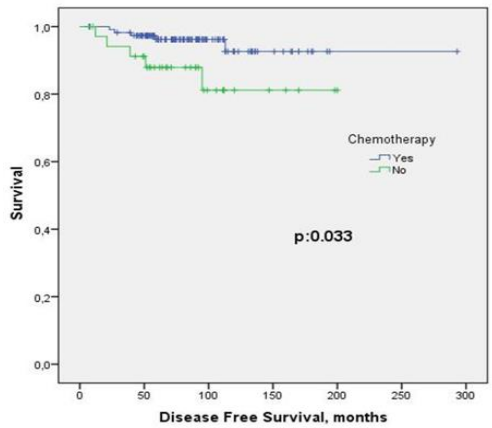

Figure 2. Kaplan-Meier plot of disease-free survival for patients with T1cN0 breast tumors according to grade 2 group treated with adjuvant chemotherapy

The multivariate analysis conducted as part of the present study found HER-2 and PR status as a prognostic factor (p:0.007 and p:0.043). The frequency of HER2 over-expression or amplification in our series was 13.8% which was similar to the HER-2 rates reported by other studies in T1 tumors (26). The majority of studies examining HER2 in the context of node-positive breast cancer have showed HER2 to be associated with poor prognosis (27-36). However, studies conducted on node-negative breast cancers have reported conflicting results (27-33, 35-40). The majority of those studies have limitations including a small sample size, non-homogeneous adjuvant systemic therapy and cut-offs for demonstrating HER2 overexpression. In one of the larger initial series of 453 node-negative breast cancers, analyzed by the Intergroup Study 0011, HER2 was not associated with a poor outcome (41). Other retrospective studies have shown that HER2-positivity is a powerful factor for poor prognosis in patients with pT1a/pT1bN0 tumors (15,16, 42-44). In a study including 852 patients with stage I breast cancer from Finland, of whom only 5% received adjuvant systemic therapy, HER2 amplification was associated with an inferior DFS (16). In the literature search, there was not any study in T1c tumors which was investigating the direct effect of PR. However, PR negativity may lead to hormonotherapy resistance in breast cancer which could decrease survival in this group of patients. In a study, lack of PR expression as well as HER-2 overexpression are both related with aggressive tumour features. But the prognostic importance of PR status on the risk of recurrence in breast cancer patients treated with hormonotherapy is stronger. In this study, lack of PR expression and HER-2 overexpression demonstrated a significant association with shorter DFS and as compared to HER-2, PR status showed a much stronger association with DFS (45). There were also similar results in another study which showed that both HER-2 overexpression and PR negativity is a marker of tamoxifen resistance in the first 3 years after primary treatment (46).

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For most of the early stage invasive breast cancer women, hormonal and/or cytotoxic chemotherapies are recommended as adjuvant treatment. The decision on the administration of adjuvant treatment should be based on the predicted sensitivity towards particular treatment types, the benefit from their use, and an individual's risk of relapse. The final decision should also take into account the axillary nodal status, age, tumor size, tumor grade, HER-2 status, hormone receptor status, proliferation index, histological tumor type and general health status, comorbidities, and preferences. (47). However, most patients with a node-negative disease who receive chemotherapy will not benefit from it because they would not continue to develop a recurrence even without such treatment, which also questions the necessity of performing the Oncotype Dx testing in T1N0 tumors.

Our study is a retrospective analysis with limited number of patients that may carry biases. Therefore, in some subgroup analysis we could not make a clear assessment because of small patient numbers with low statistical power. New prognostic and predictive tests are needed to better individualize the therapy and confine the systemic treatment, especially the cytotoxic chemotherapy, to those patients who are most likely to benefit (48,49). Nevertheless, our findings imply that PR and HER-2 statuses had prognostic significance and adjuvant chemotherapy may offer a DFS advantage in some subgroups of T1c tumors. This is particularly the case for ER-positive, Grade 2 and HER-2-negative tumors.

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We have not disclosure of potential conflicts of interest. Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

No financial disclosures were reported by the authors of this paper.

Author Contributions

U. Oflazoglu conceived paper, oversaw data collection, conducted data analysis, wrote manuscript and approved final version. H. Taskaynatan participated in study design, data analysis and interpretation, critically revised manuscript and approved final version. O. Unal participated in study design, data analysis, and interpretation of data and revision of manuscript and approved final version. U. Varol participated in study design, interpretation of data and revision of manuscript and approved final version. A. Alacacioglu participated in study design and interpretation of data; critically revised manuscript and approved final version. Y. Kucukzeybek participated in study design and interpretation of data; critically revised manuscript and approved final version. T Salman participated in study design and interpretation of data, critically revised manuscript and approved final version. M.O. Tarhan participated in data interpretation and revision of manuscript, and approved final version. The authors declare that they have no conflicts of interest.

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