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Original article

Obesity is an independent prognostic factor of decreased pathological complete response to neoadjuvant chemotherapy in breast cancer patients

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ABSTRACT

Purpose: The relation between higher body mass index (BMI) and pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) in breast cancer (BC) is a controversial issue according to the data of Western and Asian patients. The aim of this study is to evaluate BMI and pCR to NAC and discuss the importance of pCR outcomes in Turkish BC patients as a bridging country between Europe and Asia.

Patients and methods: Of the 4423 BC patients diagnosed between the years 1994 and 2015 in Hacettepe University Cancer Institute, 295 female patients with stage II and III BC were enrolled in the study. Three different group divisions were done according to patients' BMI as normal or underweight (N/U) patients (BMI <25 kg/m^2), overweight (OW) patients (BMI = 25–29.9 kg/m^2) and obese (OB) patients (BMI ≥30 kg/m^2). BC subtypes were defined as luminal-like (ER/PR-positive and HER2-negative), HER2/luminal (ER/PR-positive and HER2-positive), HER2-type (ER/PR-negative and HER2-positive), and triple-negative (TNBC; ER/PR- and HER2-negative). The analysis of overall survival (OS) and recurrence-free survival (RFS) was performed according to Kaplan–Meier method. The Log-rank test was used to compare the subgroup analysis and logistic regression analysis to determine the independent prognostic factors.

Results: In this study, a total number of 93 (31.5%) patients were N/U, 107 (36.3%) patients were OW and 95 (32.2%) patients were OB. Among groups, except for the age, no baseline clinicopathological differences were found. In 70 (23.7%) patients, pCR was achieved. pCR rates in N/U, OW and OB were 31.2%, 22.4%, and 17.9% respectively, showing a considerable trend towards significance (P = 0.09 in chi-square test). In the multivariate logistic regression analysis, obesity was an independent adverse prognostic feature on pCR to NAC compared to N/U patients (OR, 0.34; 95% CI, 0.13 to 0.85, P = 0.02). The recurrence rates were slightly increased with the increase of BMI (N/U = 24.7%, OW = 29.0% and OB = 40%; P = 0.06 respectively). Median RFS was significantly higher in N/U group compared to OB patients (150 vs. 76 months respectively, P = 0.03) and was also higher in pCR group compared to non-pCR patients (151 vs. 77 months P = 0.004). Median OS was significantly higher in N/U patients compared to OB patients (N/U = not reached, OW = 211 and OB = 114 months; P = 0.01) and was also higher in pCR group compared to non-pCR patients (not reached vs. 211 months P = 0.04). In Cox regression analysis; pCR, histopathological grade and TNBC were found as independent prognostic factors on OS (HR, 0.29; 95% CI, 0.11 to 0.79, P = 0.015, HR, 2.09; 95% CI, 1.14 to 3.83, P = 0.017, HR, 1.95; 95% CI, 1.01 to 3.77, P = 0.046, respectively).

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Conclusion: It was observed that obesity was an important independent prognostic factor which has an adverse effect on pCR. Moreover it causes decreasing RFS and OS in BC patients who had received NAC. The probability of inefficient treatment in obese patients should be considered.

Introduction

Breast cancer (BC) is the most common cancer type in women worldwide. In 2015; about 234,190 new cases of BC patients in the USA were expected to be diagnosed, and an estimated number of 40,290 women and 440 men were supposed to die due to BC [1]. There are several treatment options available for patients with BC. In non-metastatic stages particularly, physicians and BC patients prefer breast conserving management. It has been well documented that neoadjuvant chemotherapy (NAC) increases the possibility of breast conserving surgery [2]. Moreover, this gives the advantage to monitor tumor response in-vivo indicating chemosensitivity, and tumor response helps to predict the prognosis of the disease [3,4]. Pathological complete response (pCR) is the desired outcome of NAC. The relation between pCR and BC was evaluated by many investigators. According to some retrospective and prospective studies, pCR to NAC is an independent prognostic and predictive factor for survival of BC [3–6]. The relations between the response to NAC and both pathological tumor properties and demographic features of patients were investigated in detail. It is supposed that the prediction of pCR to NAC helps clinicians to consider different treatment options. Triple negativity, Her-2 positivity without hormone receptor positivity and high histopathological grades are favorable NAC response predictors [4,7–10].

The relationships between body mass index (BMI) values and responses to NAC have provoked many interests in recent literature. BC patients with high BMI values (overweight 25–29.9 and obesity 30 or above) more commonly have adverse prognostic tumor features with higher hormone receptor negativity [11] and triple negativity rates [12]. Obesity is suggested to affect BC prognosis in a negative way [13]. This is secondary to the fact that obesity is associated with increasing serum leptin, insulin, estrogen hormones and other growth factors resulting in tumor size increase and metastatic cells stimulation which cause chemotherapy resistance [14]. It has been speculated that the chemotherapeutic agents may diffuse to lipid tissue at higher levels therefore reducing the amount of chemotherapeutics that need to circulate and diffuse into tumor tissue which may more commonly seen in obese patients. The dosage calculations of chemotherapeutic agents in BC treatments are done in regarding to the patients' body surface area (BSA) [15–17]. However, in most overweight and obese patients the BSA is rounded to 2.0-m square regardless to their exact measurement in order to prevent eventual overdoses of chemotherapeutics and to reduce increased toxicity. This on the other hand may result in an insufficient treatment dosage [16,18]. Hormone receptor negativity, triple negativity and Her-2 positivity comprise the best responded molecular subgroups to NAC and lower BMI patients frequently have hormone receptor positive (luminal-like) cancers which are related the more limited pathological responses [19–22]. Despite the fact that higher BMI patients have an increased incidence of neoadjuvant therapy favorable molecular subtypes (i.e. TNBC); yet many studies have stated the respond in these patients to be poorer indicating that BMI independently and negatively affect response rates including pCR [23,24,26].

Although, many studies support that increasing BMI values have a negative effect on the response to NAC; some other studies do not mention this relation [27–31]. Furthermore, the predictor effect of pCR on survival is a controversial issue; some studies and meta-analyses state that pCR generally increases the overall survival [6,32–34]. Some studies on the other hand claim that pCR has no effect on survival [35] while some other studies showed its favorable outcome in specific subgroups only [36].

In this retrospective single centered study, it is aimed to investigate the controversial results of the relation between BMI and pCR. We have explored this relationship in Turkish population to elucidate the fact if geographical location has any effect in our patient group in comparison to the literature.

Patients and methods

Of the 4423 BC patients diagnosed between 1994 and 2015 in Hacettepe University Cancer Institute, a total of 358 patients with stage II and III disease were given neoadjuvant chemotherapy. After excluding 63 patients due to missing data of BMI values, finally 295 patients were enrolled in the study. The clinical staging of the patients were performed according to the radiological and clinical findings in accordance with the criteria of The American Joint Committee on Cancer (AJCC 2010) 7th edition [37]. BMI (kg/m^2) was calculated as weight (kg) divided by square of height (m^2), and patients were divided into three groups as normal/underweight (N/U) (BMI <25 kg/m^2), overweight (OW) (BMI 25–29.9 kg/m^2), and obese (OB) (BMI ≥30 kg/m^2) in line with the description of the Institute of National Heart, Lung, and Blood [38]. BC subtypes were defined as luminal-like (ER/PR-positive and HER2-negative), HER2/luminal (ER/PR-positive and HER2-positive), HER2-type (ER/PR-negative and HER2-positive), and triple-negative (TNBC; ER/PR- and HER2-negative). In the N/U group, four patients had <18.5 BMI which by definition regarded as underweight. BC diagnosis was made by core biopsy or fine needle aspiration and the tissues were evaluated by a dedicated breast pathologist before the administration of NAC. Immunohistochemistry (IHC) was used to determine ER and PR status. **ER and PR nuclear staining with ≥1% were accepted as ER and/or PR-positive by IHC evaluation according to the ASCO/CAP- guidelines.** The histological types of all tumors were defined according to the World Health Organization Classification System [39] and nuclear grades were defined according to the Black's Nuclear Grading System [40]. HER-2/neu-positive tumors were defined as three positive (+++ or 3+) receptor overexpression on IHC staining and/or gene amplification found on FISH testing. Only 4 patients had the different pathological results in immunohistochemistry. Of the 4 cases, 1 has changed the HER2 status from HER2-positive to HER2-negative after neoadjuvant chemotherapy. Remaining 3 patients had insignificant changes in ER and PR staining, hence were disregarded. pCR was defined when no residual invasive carcinoma was found in pathological specimens of the breast and axillary tissue. Patients were still regarded as pCR if residual disease is ductal carcinoma in situ only [34,41,42].

Statistical methods

The computer program 'Statistical Package for The Social Sciences' version 18.0 for Windows (SPSS, Inc, Chicago, IL, USA) was

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