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Original article

The effect of obesity on pathological complete response and survival in breast cancer patients receiving uncapped doses of neoadjuvant anthracycline-taxane-based chemotherapy

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ABSTRACT

Purpose: The effect of obesity in breast cancer patients undergoing neoadjuvant chemotherapy (NAC) remains controversial. The aim of this study was to determine the obesity-related effect on pathological complete response (pCR) and survival in women receiving full uncapped doses of NAC.
Methods: We retrospectively analyzed the data of all consecutive women who underwent anthracycline-taxane-based NAC for primary breast cancer between 2005 and 2015 at the Department of Obstetrics and Gynecology, Medical University of Vienna. Following the WHO criteria, women with a body mass index (BMI) $\geq$30 kg/m^2 at baseline were considered obese, whereas those with a BMI <30 kg/m^2 were considered non-obese. Those with dose reductions or dose capping were not eligible for study inclusion. Cox regression and logistic regression were performed. The Kaplan-Meier method was used to analyze disease-free, progression-free, and overall survival. The pCR served as the main outcome measure.
Results: Among 120 women who received neoadjuvant epirubicin plus cyclophosphamide and docetaxel, 28 (23.3%) were obese and 92 (76.7%) were non-obese. In the multivariate logistic regression model that adjusted for potentially confounding variables, obesity had an independent positive predictive effect on pCR (OR 4.29, 95% CI, 1.42–13.91; $p = 0.011$), which was significant in the postmenopausal subgroup (OR 4.72, 95% CI, 1.47–15.84; $p = 0.01$). When comparing non-obese with obese women, we found that obese women experienced longer progression-free survival (HR 0.10, 95% CI, 8.448 $\times$ 10^{-4}–0.81; $p = 0.025$).
Conclusions: Obese women receiving full uncapped doses of anthracycline-taxane-based NAC have increased pCR and favorable progression-free survival. This could result from increased dose intensity with increased efficacy and toxicity.

1. Introduction

During the past decade, the prevalence of obesity defined by a body mass index (BMI) $\geq$30 kg/m^2 experienced an increase in most industrialized countries [1]. Throughout the entire world, obesity has nearly doubled since the early 1980s, and almost 15% of all women worldwide are obese at present time [2]. Given the fact that breast cancer is still the most common cancer among women, it is important to understand the mechanisms by which obesity affects the prognosis and outcomes of women suffering from breast cancer [3].

The currently available data on the influence of obesity on adjuvant or neoadjuvant chemotherapy (NAC) outcomes are relatively sparse and inconsistent. Indeed, it is known that multi-agent regimens increase the risk of gaining weight during chemotherapy, and that this weight gain might reduce the treatment efficacy [4]. In 2008, Litton and colleagues investigated this topic by analyzing the data of 1169 women who underwent NAC [5]. The authors found

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that obese and overweight patients were less likely to achieve pCR. Studies from Asia reported similar results [6,7]. However, ethnicity is known to have a great impact on diet, physiognomy and body composition, which could be of value in this context. Recently, Warner et al. [8] reported no significant difference between the pCR rate of obese and non-obese women in a cohort of 1797 women from four clinical trials (CALGB 40601, 50603; ACOSOG Z1041, Z1071).

Apart from this inconsistency, applied doses and definitions used among the existing studies were very heterogeneous. In addition, changing practice led to an increased use of anthracycline-taxane-based regimen in the neoadjuvant setting. We therefore considered it of paramount importance to further evaluate this topic with special emphasis on the obesity-related effect on pathological complete response (pCR) and survival in a homogeneous cohort receiving anthracycline-taxane-based NAC, who were neither dose-capped nor dose-reduced.

2. Patients and methods

2.1. Setting and procedure

In the present study, the data of all women who consecutively presented with primary breast cancer at the Department of Obstetrics and Gynecology, Medical University of Vienna, between January 1, 2005 and December 31, 2015, were retrospectively analyzed. All study patients underwent pretreatment core needle biopsy. They were diagnosed with invasive breast carcinoma as a treatment indicator. Every treatment decision was provided by a multi-disciplinary tumor board, which strictly adhered to international and national guidelines. NAC was assigned to the patients according to their risk on the basis of clinical and histopathological parameters. In accordance with current recommendations on the primary therapy of early breast cancer, patients with HER2-positive, ER-/PR-negative or grade 3 tumors, and those who were at age 35 or younger, with nodal positive or nodal negative but high recurrence risk, were offered neoadjuvant chemotherapy [9]. Women with the risk for Hereditary Breast and Ovarian Cancer (HBOC) were offered genetic counseling and testing at our breast center. Male patients with breast cancer were considered ineligible for the study. Treatment consisted of four cycles of epirubicin (90 mg/m^2, q3w) plus cyclophosphamide (600 mg/m^2, q3w), followed by four cycles of docetaxel (100 mg/m^2, q3w), which was co-administered with trastuzumab in case of HER2-positive disease. Data of women with dose reductions or dose capping were not included in the analyses. Biopsy and surgical specimens were both assessed for the histologic subtype; hormone receptor (HR) and HER2 status as well as Ki67 proliferation index were examined by immunohistochemistry by expert pathologists specialized in breast cancer.

2.2. Data acquisition

Eligible patients were identified using the CATO software (Becton Dickinson Corp., Franklin Lakes, NJ, USA). Prior to the analyses, personal data were de-identified by using consecutive identification numbers. Subsequently, the first step was to enroll patient- and treatment-specific data using the AKIM software (SAP, Baden-Württemberg, Germany). Since all our patients are routinely weighed at every ward round, body weight data were available. Together with the patients' measured height, information about the BMI was provided. The individual chemotherapy dose was calculated on the basis of the patients' body surface area (BSA) using the CATO software. Missing data were extracted from patient charts and tumor board reports.

2.3. Study groups

The World Health Organization (WHO) has defined obesity by the individually calculated BMI for women. According to the WHO, obesity class I–III is defined by a BMI $\geq$30 kg/m^2 [10]. Since the BMI is an easy-to-use, simple, and reliable surrogate measure for studies, we also applied it for our study. The BMI of each patient was calculated at enrollment as the weight (kg) divided by the square of the height (m^2). Patients were assigned to one of the following groups: (i) non-obese women with a BMI <30 kg/m^2, or (ii) obese women with a BMI $\geq$30 kg/m^2. The BMI was calculated by [BMI = W/(H/100)^2], whereas the BSA (used by the dose calculation software) was calculated on the basis of the actual body weight by [BSA = (W$^{0.0425}$ × H$^{0.0725}$) × 0.007184] with “W” being the patient's weight and “H” being the patient's height.

2.4. Outcome measures

Since the neoadjuvant setting offers the opportunity to assess the direct response of the primary tumor, the post-NAC pCR served as the primary outcome measure. The pCR was defined as the complete absence of invasive residues in the breast and axillary lymph nodes (i.e., ypT0 and ypN0). Noninvasive breast residuals (DCIS) were allowed to achieve pCR. Secondary outcome parameters of our study were disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS). DFS was defined as the time period after curative treatment without any signs or symptoms of the disease; PFS was defined as the period that passed from the first day of the treatment until the date on which a progression of the invasive breast cancer was detected; OS was defined as the period that passed until death or last follow-up was recorded.

2.5. Statistical analysis

Demographic information is summarized and displayed using descriptive statistics. Continuous data are given as mean ± standard deviation (SD), whereas discrete data are presented as the number (percentage). In an explorative manner, Welch's *t*-test was used to compare continuous data, and Fisher's exact test was used to compare categorical data without adjustment for multiple testing. Logistic and linear regression models were adjusted for variables that were unequally distributed between the groups and were compared and considered to have an impact on the end-point. Adjustment for potentially confounding variables was performed using Welch's *t*-test for continuous variables and Fisher's exact test for dichotomous or categorical variables. A two-sided p-value < 0.05 indicated statistical significance in all tests. Analyses were performed using R-Project for Statistical Computing, version 3.1.3 (http://www.r-project.org/; R Development Core Team, Boston, MA, USA).

3. Results

Retrospective analysis identified a total of 120 women who had undergone NAC according to the eligibility criteria of our study. Out of this patient cohort, 46 (38.3%) women were premenopausal, and 74 (61.7%) women were postmenopausal. The mean (±SD) age of the women was 52.6 (±10.9) years at the time of diagnosis. Descriptive statistics showed a mean body weight of 71.6 (±14.1) kg, which corresponded to a mean BMI of 26.4 (±5.2) kg/m^2 and a mean BSA of 1.78 (±0.16) m^2 at baseline. Following the WHO criteria, this led to the assignment of 28 (23.3%) women to the obese group and 92 (76.6%) women to the non-obese group [10]. The analyses of age, menopausal status, tumor stage and nodal status, grading of differentiation, histologic subtype, hormone