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Body mass index mediates the prognostic significance of circulating tumor cells in inflammatory breast cancer

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ABSTRACT

Background: Obesity (BMI≥30) may be an etiologic and prognostic factor in inflammatory breast cancer (IBC). We examined the relationship between BMI, pathologic complete response (pCR), and circulating-tumor-cell (CTC) levels in IBC.

Methods: Cohort included IBC patients diagnosed 2005–2015 who had neoadjuvant chemotherapy during a prospective trial on CTCs and pathologic review describing pCR. Chi-square, logistic regression, and Cox proportional hazards models were used to identify clinicopathologic associations with event-free survival (EFS).

Results: Of 73 patients, 61 (84%) had CTC values, 22 (30%) achieved a pCR, and 39 (53%) were obese. There was no difference between obese and non-obese patients for pCR rates (31% vs. 29%, $p = 0.90$) or presence of CTCs (23% vs. 26%, $p = 0.80$). Among non-obese patients, CTCs were associated with worse EFS (HR 11.69, $p < 0.01$), but among obese patients, there was no difference in EFS between those with and without CTCs.

Conclusions: BMI mediates CTCs' prognostic significance in IBC.

1. Introduction

Breast cancer is increasingly recognized as a heterogeneous disease, the prognosis for which is shaped by numerous biochemical, molecular, and clinical characteristics. Breast cancer biomarkers – specifically, tumor expression of the estrogen receptor (ER) and the progesterone receptor (PR) as well as amplification of HER2/neu – not only serve as indicators of tumor differentiation and aggressiveness but have also been utilized as targets for numerous effective therapies. Furthermore, there is an established and expanding body of evidence that tumor biomarker status can have strong, reproducible associations with the clinical characteristics of patients in whom breast cancer develops. For example, breast cancers diagnosed in obese, postmenopausal women are more likely to be ER-positive (ER+), in keeping with the observed phenomenon of greater estrogen production in obese postmenopausal women when compared with their normal-weight counterparts.[1] Indeed, patient obesity – often defined using body mass index (BMI) – may play an important role in both the

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pathogenesis of breast cancer and in patient response to breast-cancer treatments, with proposed mechanisms of interaction including not only increased estrogen production but also insulin resistance and chronic, low-grade inflammation.[2]

As rates of obesity continue to increase both in the United States (US) and around the world, the impact of obesity on breast cancer prognosis is a topic of increasing relevance to both clinical practice and translational investigation. Elevated BMI is associated with elevated risk both for the development of breast cancer and for relapse following treatment.[3] A number of studies examining the impact of BMI on outcome following neoadjuvant chemotherapy (NACT) have demonstrated lower rates of pathologic complete response (pCR, i.e., absence of residual invasive disease in the breast and lymph nodes after NACT) in overweight (BMI $\geq$ 25) and obese (BMI $\geq$ 30) patients.[2,4] Both pCR and the presence of residual systemic microscopic disease in the form of circulating tumor cells (CTCs) after receipt of NACT are important positive and negative prognosticators, respectively, of breast cancer outcomes, but their relationship to each other remains unclear. Also unknown is whether BMI affects the likelihood of CTCs' being present after NACT and what relationship, if any, exists between BMI, pCR, and CTC levels. Here, we describe an analysis of the relationship between patient BMI at diagnosis, pCR, and CTC levels after NACT in a cohort of patients with inflammatory breast cancer (IBC), a rare but aggressive variant of breast cancer that is more commonly seen in obese women[5] and is often triple-negative.[6] We hypothesized that higher BMI would be associated with lower likelihood of attaining pCR and an increased likelihood of having CTCs after NACT. We also hypothesized that higher BMI would diminish the prognostic significance of pCR and CTCs, making them less reliable prognosticators in obese patients with breast cancer.

2. Materials and methods

We used the TNM staging system of the American Joint Commission on Cancer (AJCC) for pathologic stage and Black's nuclear grading system for histologic grade. We defined clinical stage as the TNM stage established at the time of the first diagnostic procedure confirming invasive breast cancer, which, at our institution, also involves sonographic and pathologic staging of all adjacent nodal basins including the axilla. BMI (weight in kilograms [kg] divided by height in square meters [m^2], i.e., kg/m^2) is calculated for all patients at our institution at their initial visit and is automatically updated at each subsequent visit by incorporating the most current patient weight. For this study, we utilized the BMI values from each participant's first visit at The University of Texas MD Anderson Cancer Center with a breast surgical oncologist (A.L, H.M.K., and S.M.D.) and considered this to be a patient's BMI at diagnosis.

This study included T4d breast cancer patients diagnosed between March 2005 and March 2015 who received NACT as part of a prospective trial at MD Anderson Cancer Center examining the relationship between CTC levels and patient outcomes. All participants either received NACT at MD Anderson or consulted an MD Anderson medical oncologist even if they chose to receive NACT closer to home. Following completion of NACT and prior to surgical resection, a peripherally drawn, venous blood sample (7.5 mL) was obtained from each participant. Within 72 hours of collection, CTCs were identified via the CellSearch® method using previously described techniques.[7]

Patients with bilateral breast cancer or another malignancy diagnosed within 5 years of the primary breast cancer were excluded from the trial. Furthermore, inclusion in this statistical analysis was limited to patients whose postoperative pathologic review definitively described whether pCR had or had not occurred in the breasts and axillary lymph nodes. The institutional review board at MD Anderson approved this prospective study (04–0698; PI: A.L.), and written informed consent was obtained from all patients prior to blood collection.

Chi-square tests and logistic regression were used to examine the relationships between pCR, CTCs, and clinical variables including BMI (categorically divided into non-obese [BMI<30] and obese [BMI$\geq$30] for regression analyses); age; race/ethnicity; tumor biomarkers stratified as (1) ER+ (includes all ER + tumors regardless of PR and HER/neu status), (2) HER2/neu-amplified (HER2+) only, (3) ER-negative (ER-) and HER2/neu-non-amplified (HER2-), and (4) triple-negative (TNBC) (see Appendix Table 1 for number of participants per receptor status); tumor grade (1 = well-differentiated/low grade, 2 = moderately differentiated/intermediate grade, and 3 = poorly differentiated/high grade); tumor histology (i.e., ductal, lobular, mixed, or other); menopausal status; type of neoadjuvant chemotherapy received (anthracycline [i.e., doxorubicin or epirubicin] only, taxane [i.e., docetaxel or paclitaxel] only, anthracycline and taxane, none; axillary nodal status (N0-N3); and the presence of lymphovascular invasion (LVI). These variables were also included in Cox proportional hazards models to calculate predicted event-free survival (EFS, i.e., no recurrence or death between date of diagnosis and date of last follow-up). We report proportions, adjusted odds ratios (OR), and adjusted hazards ratios (HR) with 95% confidence intervals (CI) significant at 2-tailed $p < 0.05$. For the EFS analysis, we also report Harrell's C indices in order to indicate the ordinal predictive power of the survival models, with values closer to 1 demonstrating greater predictive power than values closer to 0.5.[8] Statistical analysis was performed using STATA 13 (StataCorp, College Station, TX).

3. Results

From a cohort of 113 trial-enrolled patients, 73 (65%) patients with IBC were identified (Table 1). Median follow-up time was 40.4 months. Of the 73 IBC patients, 61 (84%) had CTC values and 22 (30%) achieved a pCR (Table 1). Only 16 (22%) patients had a normal BMI (25 > BMI$\geq$18.5) or were underweight (BMI<18.5), while 18 (25%) were overweight (30 > BMI$\geq$25) and 39 (53%) were obese (BMI$\geq$30). Twenty-six patients (37%) had TNBC, which was the most common biomarker subtype in our cohort and has been more frequently observed among IBC patients as compared to non-IBC patients.[6,9,10]

There was no difference between obese and non-obese patients with regards to pCR rates (31% [12/39] vs. 29% [10/34], $p = 0.90$) or the presence of CTCs (23% [9/39] vs. 26% [9/34], $p = 0.80$). In univariate regression, the presence of LVI (OR 0.07, CI 0.01–0.35, $p < 0.01$) was associated with lower likelihood of pCR. HER2/neu amplification (OR 4.4, CI 1.17–16.57, $p = 0.03$) and receiving either epirubicin (vs. doxorubicin; OR 4.65, CI 1.39–15.52, $p = 0.01$) or no anthracycline (vs. doxorubicin; OR 7.75, CI 1.53–39.12, $p = 0.01$) were associated with an increased likelihood of achieving pCR. In bivariate regression in which BMI and another covariate served as independent variables, anthracycline regimen (epirubicin: OR 4.73, CI 1.39–16.05, $p = 0.01$; none: OR 7.74, CI 1.53–39.07, $p = 0.01$) and the presence of LVI (OR 0.07, CI 0.01–0.35, $p < 0.01$) continued to be associated with likelihood of achieving pCR, but HER2/neu amplification was not. There were no covariates associated with increased likelihood of CTCs' being present in either univariate or bivariate analyses. Additionally, there was no association between BMI and pCR, BMI and CTCs, or pCR and CTCs in univariate or