Original Study

Effect of Body Mass Index– and Actual Weight–Based Neoadjuvant Chemotherapy Doses on Pathologic Complete Response in Operable Breast Cancer

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Abstract

The effect of body mass index (BMI) on pathologic complete response (pCR) accounting for neoadjuvant chemotherapy (NAC) dose reductions remains undefined. In 171 patients with operable breast cancer who received NAC, those with a BMI of ≥25 were less likely to tolerate uncapped taxane doses. Any chemotherapy dose reduction resulted in greater odds of not attaining a pCR in obese patients, independent of known predictors.

Introduction: The effect of body mass index (BMI) and chemotherapy dose reduction on pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) for locoregional breast cancer remains unclear. Contemporary studies have reported largely on trial populations and used dose-capping. **Patients and Methods:** Patient registries at the University of Iowa were queried to identify patients with operable breast cancer who received NAC. Dose reductions were calculated for taxanes (T), anthracyclines (A) and non–A-T chemotherapy. Clinical-pathologic characteristics, chemotherapy dose reductions, and adverse events were compared between normal (BMI <25) and overweight/obese patients (BMI ≥25). Additionally, the synergistic effect of BMI and chemotherapy dose reduction on pCR was assessed. **Results:** Of 171 eligible patients, 112 were overweight/obese. Chemotherapy dosing was capped in 2 patients; all others initiated full weight-based treatment. Overweight/obese patients required more frequent taxane (44.6% vs. 25.4%; $P = .01$) and any chemotherapy dose reductions (50.9% vs. 33.9%; $P = .03$). pCR was attained in 29.2% of patients. In a multivariable model, the interaction term for BMI as a continuous variable and any chemotherapy dose reduction was significant independent of the clinical stage and tumor receptor status ($P = .04$). For obese patients, any chemotherapy dose reduction was significantly associated with increased odds of not attaining pCR. **Conclusion:** During NAC, overweight/obese patients more often have chemotherapy dose reductions. Chemotherapy dose reduction in obese patients was a powerful predictor of not attaining pCR. This was not seen for normal or overweight patients. Opportunities might exist to improve pCR rates in this higher-risk group.

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Introduction

In the United States locoregional disease (stages I-III) constitutes 73% of all female breast cancers.[1] Neoadjuvant chemotherapy (NAC) might allow for breast conserving surgery in approximately 10% to 30%[2] of locally advanced tumors. In recent years the use of NAC has doubled, particularly in locally advanced disease.[3] In this context, pathologic complete response (pCR) after NAC has emerged as a surrogate for improved long-term breast cancer-specific outcomes, particularly in HER2-positive and triple negative breast cancer (TNBC).[4] This allows for assessment of tumor

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responsiveness to systemic therapy and is particularly attractive as a platform for drug development.[5]

Several clinical-pathologic characteristics have been reported to predict for pCR; these include (but are not limited to): younger age, smaller tumor, receptor expression status (pCR being superior in the absence of hormone receptor (HR) expression: TNBC and HER2-positive disease), and preoperative combination of taxanes with an anthracycline backbone.[2] Because obesity is associated with chemoresistance and poor breast cancer-specific outcomes,[6] the role of body mass index (BMI) as a predictor of pCR has been of interest. Several series have failed to show a consistent association of BMI with pCR.[7-12] The largest of these was a pooled analysis of 8 German neoadjuvant trials, which reported a negative association between higher BMI and pCR in their univariate analysis.[12] However, they did not find BMI to predict for pCR in their multivariable analysis which used data from only 2 of the pooled trials.[13-16] Of note, all obese patients in these 2 trials had received doses capped at a body surface area (BSA) of 2.0 m^2. The practice of capping chemotherapy doses in patients with a higher BMI might be even more common in the community, with a recent study suggesting that this rate might be as high as 20% in those with a BMI of $\geq$30.[17] Thus, any influence of the association between BMI and chemotherapy dose adjustments on pCR remains undefined.

In this study we investigated the effect of the interaction between BMI and chemotherapy doses on pCR after NAC while adjusting for other known predictors of pCR in patients seen at the University of Iowa between 2005 and 2015, while rigorously quantifying cycle-specific chemotherapy dose adjustments.

Patients and Methods

Patient Selection

Patients were identified using 2 data sources at the University of Iowa, the (1) Breast Molecular Epidemiologic Resource; and (2) Oncology Registry. Each registry database was queried to identify women at least 18 years of age with operable primary invasive mammary cancer treated with NAC followed by surgical treatment of the primary disease. Patients were excluded if cycle-specific chemotherapy dosing information or pathologic confirmation of pCR status after surgery was unavailable. The study was approved by the University of Iowa's institutional review board.

Clinical Staging and Pathology

Clinical breast cancer staging was determined for each patient by 3 separate investigators (R.R., J.M., and S.P.) in accordance with the American Joint Committee on Cancer seventh edition. Our institutional practice is to confirm lymph node involvement by biopsy of any radiographically or clinically suspected axillary lymph nodes.

Breast cancer was diagnosed by biopsy. Immunohistochemistry (IHC) was used to determine estrogen receptor (ER), progesterone receptor (PR), and HER2 status. HR positivity (HR-positive) was defined as $\geq$1% expression of ER or PR on the tumor. For equivocal HER2/*neu* results on IHC, in situ hybridization was performed. Tumors that were HR-negative and HER2-negative were considered TNBC. PCR was defined as absence of invasive disease in the nodes and breast (ypT0/is ypN0) and was determined by reviewing pathology reports.

Body Mass Index

Body mass index was calculated at or within 6 months of treatment initiation as weight (kg) divided by height (m^2) and categorized as underweight (BMI <18.5), normal (BMI = 18.5 to <25), and overweight/obese ($\geq$25) as per the National Institutes of Health and National Heart, Lung and Blood Institute.

Chemotherapy Dose Determination

Our institutional practice is to dose chemotherapy on the basis of actual body weight. BSA was calculated before each cycle as per the Mosteller method:

$$BSA\ (m^2) = \sqrt{\frac{height\ (cm) \times weight\ (kg)}{3600}}$$

Fewer than 10 patients were treated at a nonaffiliate practice. Of these, 5 had a BSA of >2.0 m^2 for whom dose-capping could not be ruled out. Dose reductions for these 5 patients were deduced from the review of outside medical records with cycle-specific information.

Dose reductions for each patient were calculated separately for taxanes (paclitaxel, nab-paclitaxel, and docetaxel); anthracyclines (doxorubicin or epirubicin), and other nontaxane/non-anthracycline chemotherapy (cyclophosphamide, carboplatin, 5-fluorouracil, capecitabine, and gemcitabine) by 3 separate investigators (R.R., J.E.M., and S.P.). Any aberrancy was reviewed by a separate investigator (A.T.). Doses for monoclonal antibodies and biologic agents (anti-HER2/*neu* and anti-vascular endothelial growth factor therapy) were not included in cumulative dose calculations. Determination of expected dose and number of cycles was on the basis of standard guidelines for commonly used regimens: for example, adriamycin with cyclophosphamide (AC) followed by taxane is commonly given as 4 cycles of AC (with 60 mg/m^2 of adriamycin per cycle) and a variable number of cycles of taxanes (Table 1).

Actual dose delivered (ADD) and expected dose (ED) on the basis of BSA were calculated for taxanes, anthracyclines, and other chemotherapy (nontaxane/nonanthracycline) for each patient. Any BSA capping was counted as a dose reduction. Dose reductions were determined by using the following formula:

Table 1 Example of Various Taxane Dosing Schedules Combined With Adriamycin and Cytoxan in the Current Study

Regimen	Expected Dose of Taxanes Per Cycle	Expected Number of Taxane Cycles	Expected Cumulative Dose of Taxane
AC-T (Paclitaxel Weekly)	80 mg/m^2	12	12 × 80 × BSA
AC-T (Dose-Dense: Paclitaxel Every 2 Weeks)	175 mg/m^2	4	175 × 4 × BSA
AC-T (Abraxane)	100 mg/m^2	12	100 × 12 × BSA

Abbreviations: A = adriamycin; BSA = body surface area; C = cyclophosphamide; T = taxanes.