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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

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Disclosure

All authors have stated that they have no conflicts of interest.

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.

Keywords

BMI; Chemotherapy dosing; Dose capping; Neoadjuvant therapy; pCR; Taxane; Weight-based dosing

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 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 m². 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 ≥ 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 ≥ 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 (m²) and categorized as underweight (BMI <18.5), normal (BMI = 18.5 to <25), and overweight/obese (≥ 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:

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

Fewer than 10 patients were treated at a nonaffiliate practice. Of these, 5 had a BSA of >2.0 m² 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/m² 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:

$$\text{Dose reduction (\%)} = \frac{|ADD - ED|}{ED} \times 100$$

Patients who were switched from paclitaxel to nab-paclitaxel because of allergic reactions were considered dose reduced if (1) they received <12 weeks of therapy with taxanes (paclitaxel or nab-paclitaxel); (2) the corresponding weekly dose for paclitaxel was <80 mg/m²; and/or (3) the corresponding weekly nab-paclitaxel dose was <100 mg/m².

We had rigorous cycle-specific dosing information for 97% (166 of 171) of the eligible patients. The primary reason for dose reduction of taxanes was abstracted.

Statistical Analysis

To investigate differences in demographic and clinical-pathologic variables along with rate of adverse events across BMI groups, χ^2 (Fisher exact where appropriate) and Wilcoxon rank sum tests were used. To examine whether BMI modified the effect of chemotherapy dose reduction on the odds of attaining a pCR, birth-penalized logistic regression models were used. More specifically, models under investigation included the interaction between BMI (continuous or categorical) and chemotherapy dose reductions (overall or drug-specific), along with pretreatment clinical stage and tumor receptor type. Estimated effects of predictors are reported as odds ratio (OR) with their associated 95% confidence interval (CI). All statistical testing was 2-sided and assessed for significance at the 5% level using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Results

In total, 171 unique women were included. Overall, 34.5% of patients (59 of 171) were normal weight and 65.5% were overweight/obese (112 of 171). None of the patients were underweight. Median age at diagnosis was 49 years (range, 25–81). Clinical-pathologic characteristics including chemotherapy delivered to patients in the BMI categories are shown in Table 2. The mean BSA for the normal and overweight/obese patients was 1.67 (SD = 0.10; range, 1.49–1.91) and 1.98 (SD = 0.21; range, 1.66–2.74), respectively.

Overweight/obese patients required significantly more taxane dose reductions (44.6% vs. 25.4%; $P = .01$) and any chemotherapy dose reduction during NAC (50.9% vs. 33.9%; $P = .03$) compared with the normal weight subjects. The difference noted in the BMI groups with respect to dose reductions for anthracyclines did not achieve significance (23% vs. 14%; $P = .23$). For other nontaxane/nonanthracycline chemotherapy, there was no difference between the groups (10.1% vs. 13.6%; $P = .50$). Chemotherapy dose reductions were confirmed as dose capping in 2 patients, whereas all other reductions were dictated either by adverse effects or anticipation of adverse events. The nature of indications for taxane dose reductions was not statistically different between the BMI groups and is reported in Figure 1.

pCR was attained in 29.2% of patients (50 of 171) at the time of definitive surgery. In univariable analysis, a significant association between BMI (continuously or categorically) and pCR was not evidenced. However, advanced stage (stage III-IV vs. I-II; OR, 2.35; 95% CI, 1.12–4.99), HR expression status: HR-positive/HER2-negative compared with TNBC (OR, 4.36; 95% CI, 1.88–10.10), taxane dose reduction (OR, 2.41; 95% CI, 1.15–5.02), and any chemotherapy dose reduction (OR, 2.13; 95% CI, 1.07–4.24) were each associated with greater odds of not attaining a pCR (Table 3).

After adjusting for pretreatment clinical stage and receptor expression status, the interaction between any chemotherapy dose reduction and BMI (continuously) was significant ($P = .04$; Figure 2). For obese patients, any chemotherapy dose reduction was significantly associated with greater odds of not attaining a pCR compared with patients at lower BMIs. Other combinations of BMI (continuous or categorical) and chemotherapy dose reductions (overall or drug-specific) did not result in a significant interaction. However, the interaction between continuous BMI and taxane dose reductions was trending toward significance in this cohort ($P = .13$).

Discussion

In this study we found that patients with a BMI of ≥ 25 before the initiation of NAC more frequently required chemotherapy dose reductions, particularly in taxanes, when doses delivered are based on actual body weight (ie, without capping at a BSA of 2.0 m^2). Most dose reductions were dictated by adverse effects. After adjusting for powerful known predictors of pCR, clinical stage, and tumor receptor status, the effect of any chemotherapy dose reduction varied according to BMI. At normal/overweight BMI chemotherapy dose reductions did not have a significant effect on the odds of attaining a pCR. However, when BMI was in the obese range, patients were at significantly increased odds of not attaining a pCR.

Previous studies showing a detrimental effect of a BMI of ≥ 25 on pCR were either unable to account for chemotherapy dose reductions¹¹ or were not representative of the treatment regimens and/or patient populations seen commonly in United States oncology practices.^{7,12,18} The largest of these¹² included a highly selective European trial population with an over-representation of HER2-positive tumors (72%), capped chemotherapy doses at a BSA of 2.0 m^2 and defined HR positivity as $\geq 10\%$ expression on IHC, all of which make

generalization of results challenging. Importantly, in the German analysis, the overweight/obese patients did require significantly more dose reductions in taxanes and in turn in multivariable analysis, dose reductions (but not BMI) negatively affected pCR. In the current study, when the interaction between BMI and any chemotherapy dose reduction (ie, dose reductions in taxane, anthracycline, or nontaxane/nonanthracyclines taken together) was accounted for, pCR outcomes did vary according to BMI.

The negative effect of chemotherapy dose reduction at higher BMIs on pCR might simply be a reflection of an over-representation of HR-positive tumors in these patients,¹⁸ which in turn are known to be less chemosensitive than TNBC and HER2-positive disease.^{19,20} In the current study, 36.7% of patients (63 of 171) were obese (BMI >30), had a mean BSA of 2.1 m² (SD = 0.19; range, 1.81–2.74) and did tend to have proportionally more HR-positive tumors. However, a negative association was shown independent of receptor expression status, suggesting additional mechanisms that might lead to increased chemoresistance of tumors in the presence of obesity. Possible examples include increases in procarcinogenic growth factors such as insulin like growth factors, adipose tissue secreted cytokine imbalances, and a state of chronic inflammation.^{21–23}

An important finding of this study is the significantly increased likelihood of any chemotherapy dose reduction in the overweight/obese patients when uncapped doses were delivered. These chemotherapy dose reductions were largely driven by taxane dose modifications. Similar findings emerged from the large German pooled analysis despite capping the chemotherapy doses. Together these findings might suggest a poor tolerance for full-dose taxanes in patients with a BMI of ≥25. Our results also suggest that physicians and patients were more likely to anticipate poor tolerance of chemotherapy in patients with a higher BMI leading to some preemptive dose reductions.

There is compelling evidence showing the detrimental effects of dose reductions in curative chemotherapy on long-term breast cancer-specific outcomes.^{24,25} The concern for increase in toxicities at higher BMIs is considered unfounded on the basis of several analyses that failed to show any significant increase in toxicities in the overweight/obese breast cancer patients at full weight-based doses.^{26–28} On this premise, the current guidelines from American Society of Clinical Oncology recommend actual weight-based dosing for chemotherapy in the adjuvant or neoadjuvant setting.²⁹ However, in patients with breast cancer, such evidence is largely derived from studies on patients who received nontaxane regimens.^{25–28} We now know that taxanes, when combined with other adjuvant chemotherapy, improve survival in localized breast cancer and form the backbone of contemporary curative regimens.^{30,31} In addition, neoadjuvant taxane improves the rate of pCR.³² Clinicians often struggle with appropriate dosing of taxanes at higher BMIs. Recent analysis using taxanes observed an increased propensity for nonhematologic¹² and hematologic toxicities¹⁷ in the overweight/obese, regardless of dose-capping. We did not find a significant difference in the rate of hematologic or nonhematologic adverse events in our patients who underwent taxane dose reductions on the basis of the BMI groups but noted a trend toward greater incidence of dose-limiting neuropathy (13.4% vs. 5.1%; $P = .12$) as well as of hematologic toxicities (6.3% vs. 0%; $P = .10$) in the overweight/obese patients.

Obesity might alter the pharmacokinetics of some anticancer drugs.³³ Alternatively, patients with a higher BMI might have coexisting conditions that predispose them to chemotherapy-induced toxicities.¹² How then, does one overcome the chemo-resistance of tumors in patients with a high BMI when our findings suggest that at uncapped chemotherapy doses (especially of taxanes), dose-limiting toxicities are more frequent for the overweight/obese patient? Our findings call for further inquiry into whether absolute amount of chemotherapy dose reductions rather than any reduction would make a difference in pCR outcomes. In addition, these results reiterate the importance of maintaining appropriate uncapped doses for all components of a chemotherapy regimen and minimizing dose reductions to the specific drug most likely to be implicated in causing a particular dose-limiting side effect.

The strengths of the current study include the rigorous accounting for cycle-specific chemotherapy doses and a closer representation of a typical North American oncology practice. However, treatment choices are reported for 1 geographic area, which is predominately rural and has less racial diversity than the United States population as a whole. In addition, 37% of this population was obese at diagnosis, which is slightly higher than the national average for women in North America.³⁴ Other limitations of this study include the relatively small number of cases and its retrospective nature, which did not allow controlling for several variables in our multivariable analysis. We were also not able to account for BMI changes during NAC or chemotherapy dose intensity.

Conclusion

In patients with a BMI above the normal range we saw significantly higher rates of chemotherapy dose reductions mostly because of adverse effects. This was particularly true for taxane therapy. For obese patients, independent of pretreatment clinical stage and tumor receptor status, any chemotherapy dose reduction significantly affected their ability to attain pCR and likely the outcome benefits associated with this. Further investigation into the complex interplay of chemotherapy and tumor milieu in obese patients could explain this dynamic and perhaps elucidate how we might attain better outcomes for this higher-risk patient group.

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Clinical Practice Points

- Being overweight/obese (BMI of ≥ 25) has been associated with poor outcomes in breast cancer. The effect of BMI on pCR after NAC for breast cancer is not well defined.
- Retrospective analyses have shown a negative and a positive correlation, although most studies are confounded by the inability to account for chemotherapy dose modifications or have used dose-capping.
- In this study we analyzed the association between pCR and BMI while accounting for the powerful known predictors of pCR: stage and tumor receptor status. In addition, individual chemotherapy dose modifications in taxanes, anthracyclines, and all other chemotherapy regimens were rigorously examined. Doses were not capped at a BSA of 2.0 m^2 in the overwhelming majority.
- Patients with a BMI of ≥ 25 were significantly more likely to undergo any chemotherapy dose reductions; largely driven by dose reductions in taxanes, because of adverse effects.
- In multivariable analysis, any chemotherapy dose reduction decreased the odds of attaining a pCR in those with a BMI in the obese range (≥ 30) independent of tumor receptor status or clinical stage.
- Our findings call for further inquiry into appropriate doses of taxanes in patients who have higher BMIs, specifically in the obese range. At the same time, we reiterate that dose reductions in any component of NAC should be minimized when possible to overcome the inherent chemoresistance of tumors in the presence of obesity.

Figure 1. Rate of Adverse Events Resulting in Taxane Dose Reduction According to Body Mass Index (BMI) Category^a

Abbreviation: GI = gastrointestinal.

^aNo significant difference between BMI groups were evidenced. Rates within the normal and overweight/obese were one the basis of 59 and 112 patients respectively.

Figure 2. Multivariable Regression Analyses of Clinical-Pathologic Factors and Odds Ratio (OR) of Not Attaining a Pathologic Complete Response (pCR)

Abbreviations: HR = hormone receptor; TNBC = triple negative breast cancer that did not express HR or HER2/*neu*.

Table 1

Example of Various Taxane Dosing Schedules Combined With Adriamycin and Cytosin in the Current Study

Regimen	Expected Dose of Cycle Taxanes Per	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.

Table 2

Clinical-Pathologic Characteristics of BMI Groups

Characteristic	Category	BMI		P
		Normal (n = 59)	Overweight-Obese (n = 112)	
Mean Age at Diagnosis, Years		47.7	50.6	.13
Clinical Stage, %	I-II	38 (64.4)	73 (65.2)	.92
	III-IV ^a	21 (35.6)	39 (34.8)	
Receptor Expression, %	HER2-positive (any HR)	20 (34.5)	27 (24.1)	.20
	HR-positive/HER2-negative	22 (37.9)	58 (51.8)	
	TNBC	16 (27.6)	27 (24.1)	
Taxanes, %	Full dose	44 (74.6)	62 (55.4)	.01
	Dose reduced	15 (25.4)	50 (44.6)	
Anthracyclines, %	Full dose	37 (86.0)	67 (77.0)	.23
	Dose reduced	6 (14.0)	20 (23.0)	
Other Chemotherapy, %	Full dose	51 (86.4)	98 (89.9)	.50
	Dose reduced	8 (13.6)	11 (10.1)	
Any Dose Reduction, %	No	39 (66.1)	55 (49.1)	.03
	Yes	20 (33.9)	57 (50.9)	

Abbreviations: BMI = body mass index; HR = hormone receptor; TNBC = triple negative breast cancer that did not express HR or HER2/*neu*.

^aTwo patients with stage IV disease, who had a solitary bone metastasis and underwent curative intent surgery for the breast tumor after stereotactic radiation to the metastasis, were included.

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