Undertreatment of Obese Women Receiving Breast Cancer Chemotherapy

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Background: Systematic undertreatment of breast cancer in overweight and obese women may contribute to the poorer prognosis in these women. The objective of this study was to investigate treatment patterns in overweight and obese women undergoing breast cancer adjuvant chemotherapy.

Methods: We performed a retrospective cohort study of 9672 women treated with doxorubicin hydrochloride and cyclophosphamide between 1990 and 2001. The main outcome measure was the quality of chemotherapy as measured by the use of reduced doses for the first treatment (compared with standard doses), the overall dose proportion (actual-expected dose ratio), and relative dose intensity.

Results: First-cycle dose reductions (defined as a dose proportion of <0.9 compared with standard published doses) were administered to 9% of the healthy weight, 11% of the overweight, 20% of the obese, and 37% of the severely obese women (P<.001). First-cycle reduction was independently associated with being overweight (P=.03), obese (P<.001), severely obese (P<.001), older than 60 years (P<.001), and having a serious comorbid condition (P=.03). Practices varied greatly in the use of dose reductions in overweight and obese patients. Severe obesity was independently associated with a lower likelihood of admission for febrile neutropenia, even among those subjects given full weight-based doses (odds ratio, 0.61; 95% confidence interval, 0.38-0.97).

Conclusions: Overweight and obese women with breast cancer often receive intentionally reduced doses of adjuvant chemotherapy. Administration of initial and overall full weight-based doses of adjuvant chemotherapy in overweight and obese women is likely to improve outcomes in this group of patients.

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Obesity is both a known risk factor for the development of breast cancer and a negative prognostic factor among women with breast cancer. The risk of recurrent breast cancer among women who are 20% to 25% over their ideal body weight is approximately 1.3-fold higher than in lean women. The association between obesity and breast cancer risk and prognosis is multifactorial. Biochemical explanations include the association between obesity and higher fasting insulin levels and between increasing body mass index (BMI) and estrogen levels.

Inadequate adjuvant chemotherapy dosing in overweight and obese woman may also contribute to the outcome disparity. Adjuvant chemotherapy is given to women who have no measurable metastases but who are at risk for a metastatic recurrence. The purpose of adjuvant therapy is to improve the likelihood of disease-free and overall survival. Large studies suggest that the beneficial impact of adjuvant chemotherapy is diminished when full doses of therapy are not given. Based on these studies, it is generally recommended that chemotherapy doses not be reduced below 85% of the standard doses over the entire course of treatment.

The optimal dosing of breast cancer adjuvant chemotherapy in obese women remains an area of clinical uncertainty. The doses of most chemotherapy drugs are based on body surface area (BSA), which is calculated using the patient’s height and weight and expressed in square meters. The narrow therapeutic index of most chemotherapy drugs raises the concern that obese women will experience excessive toxic effects when chemotherapy doses are based on actual body weight. Although small studies have shown that some chemotherapy drugs take longer to be cleared from the body in obese patients, there is little evidence to support the use of dose reductions in these patients. In overweight women, there is no evidence of altered handling of chemotherapy drugs. Nonetheless, some physicians use ideal

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body weight for dose calculations in their heavy patients, reduce the doses by some amount (eg, 15%), or use a maximum of 2.0 m² for dose calculations.

The purpose of this study was to examine the effect of obesity on patterns of breast cancer adjuvant chemotherapy dosing with a commonly used regimen, doxorubicin hydrochloride and cyclophosphamide. We were particularly interested in dose reductions below the standard doses for the first course of treatment. Reductions with the first treatment represent intentional physician behavior (rather than a response to the development of adverse effects). We were also interested in the likelihood of severe hematologic toxic effects in obese women who received chemotherapy dosed according to actual body weight. Febrile neutropenia is the most common short-term serious adverse effect of the doxorubicin-cyclophosphamide combination.

**METHODS**

**PATIENT SAMPLE**

Oncology practices were selected from all US practices and chosen to represent all geographical areas and the spectrum of practice size. Selected practices were instructed to submit data on consecutive patients with early-stage breast cancer recently treated with adjuvant chemotherapy including patients with localized or locoregional disease (stages I, II, and III). Oncology nurses at each of the practices collected data retrospectively from the treatment records. Investigational review board approval was obtained by the treatment sites. Each patient and treating physician was assigned a unique identifier.

**DATA COLLECTION**

Demographics and clinical characteristics at the start of treatment, including age at diagnosis, menopausal status, weight (kilograms or pounds), height (centimeters or inches), lymph node status, estrogen receptor status, chemotherapy regimen, serious comorbid conditions, and planned chemotherapy dose were collected. No information about race/ethnicity was collected. The comorbid conditions included in the data collection were angina, chronic heart failure, history of myocardial infarction, diabetes, hepatic disease, pulmonary disorders, and renal failure. The actual chemotherapy doses received, dates of treatment, and white blood cell and absolute neutrophil counts prior to treatment were collected for each cycle. The occurrence of febrile neutropenia requiring hospitalization was captured for each patient over the entire course of treatment. The use and duration of granulocyte colony-stimulating factor (G-CSF), a drug used to prevent and treat neutropenia, were collected for each cycle.

**DATA ANALYSIS**

Actual height and weight was used to calculated BSA, and BMI was calculated and categorized according to BMI category using the Quaetelet Index and the World Health Organization criteria. The expected dose for each drug was calculated using the Mosteller formula for BSA and the standard adjuvant chemotherapy doses for the doxorubicin and cyclophosphamide regimen (doxorubicin hydrochloride, 60 mg/m², and cyclophosphamide, 600 mg/m², every 3 weeks for 4 courses). The actual-expected dose ratio was less than 0.9 (or 90% of the expected dose) for the first cycle of chemotherapy. The relative dose intensity for the entire treatment course was calculated as previously described.

Descriptive analyses of subject characteristics were performed. Practice-based variation in the use of first-cycle dose reduction among overweight and obese women, including severely obese women, was examined in practices with at least 5 women with a BMI (calculated as weight in kilograms divided by the square of height in meters) of at least 25. Practice level correlation in first-cycle dose reduction between overweight and obese women was determined. All statistical tests for significance were 2-sided; \( P < 0.05 \) was considered statistically significant.

**MULTIVARIATE ANALYSES**

All multivariate analyses clustered on practice identifier, adjusting standard errors to account for the lack of independence between patients receiving treatment in the same practices (ie, the existence of a practice style) and using robust standard errors. Logistic regression was used to identify the relationship between BMI categories and the use of first-cycle dose reduction, controlling for age, menopausal status (premenopausal or perimenopausal vs postmenopausal), the presence of serious comorbid illnesses, white blood cell and absolute neutrophil counts at the start of treatment, lymph node status, and year of treatment. Analyses using linear regression examined the association of BMI category with dose proportion and relative dose intensity, controlling for age, menopausal status, the presence of serious comorbid illnesses, white blood cell and absolute neutrophil counts at the start of treatment, lymph node status, and year of treatment. A second set of models was estimated for dose proportion and relative dose intensity that included the use of first-cycle dose reduction. The first set of models provides the full effect of weight on dose proportion and relative dose intensity, while the second set provides the effect of weight independent of its effect through the use of first-cycle dose reduction.

We determined whether BMI category was associated with the likelihood of a febrile neutropenic episode (for the entire treatment course), controlling for age, white blood cell and absolute neutrophil counts at the start of treatment, use of G-CSFs in each of the 4 cycles, presence of severe comorbid illness, year of treatment, and the time ratio for the entire regimen. This model was restricted to the 8022 subjects who did not receive a first-cycle dose reduction.

There were 9672 women treated with doxorubicin and cyclophosphamide in 901 practices in our sample. Patients were treated between 1990 and 2001. Subject characteristics are given in Table 1. Most patients were healthy with few serious coexisting medical problems. Of the women, 62% had a BMI of at least 25, 31% were overweight, 17% were obese, and 14% were severely obese (BMI ≥ 35).

**FIRST-CYCLE DOSE REDUCTIONS.**

Among the severely obese women, 37% had a first-cycle dose reduction of 10% (0.10) or more compared with 20% of obese women, 11% of overweight women, and 9% of...
healthy women weight (P<.001) (Table 2). Among those women having a first-cycle dose reduction, the mean reduction was 0.20. The mean dose reduction did not vary significantly according to BMI category. The practice of “capping” dose calculations at a BSA of 2.0 m² was seen in 39% of the 1820 women whose BSA exceeded 2.0 m².

In multivariate logistic analyses, being overweight (P = .03), obese (P < .001), severely obese (P < .001), older than 60 years (P < .001), or having a serious comorbid condition (P = .03) were all associated with having a first-cycle dose reduction (Table 3). The likelihood of having a first-cycle dose reduction decreased over time, with patients treated in more recent years being less likely to have a first-cycle dose reduction.

Increases in doses for subsequent courses of chemotherapy were uncommon. Only 3% of the overweight, obese, and severely obese patients who had reduced doses for the first course had an increase in dose with the second. Among the underweight and healthy weight women, 4% had a dose escalation. Dose reductions for the second treatment cycle were less common among patients treated with first-cycle dose reduction compared with patients initially receiving full doses of chemotherapy (6% vs 8%; P < .05).

Women who were treated with a first-cycle dose reduction were more likely to receive more than the standard 4 cycles of doxorubicin and cyclophosphamide. Sixteen percent of women treated with first-cycle dose reduction.
reductions received a fifth course of treatment compared with only 6% of women not having first-cycle dose reductions (P<.001). A sixth cycle of chemotherapy was given to 13% of women who had a first-cycle dose reduction compared with 5% of those not having a first-cycle dose reduction (P<.001).

THE IMPACT OF WEIGHT ON DOSE PROPORTION AND RELATIVE DOSE INTENSITY

Average dose proportion and relative dose intensity decreased with increasing weight. Table 4 details the change in dose proportion associated with weight, age, clinical characteristics, and year of treatment from multivariate analyses. Being overweight (P<.001), obese (P<.001), severely obese (P<.001), or older than 60 years (P<.001) were associated with lower dose proportion (Table 4). When the use of first-cycle dose reductions was included in the model, the effect of the weight categories and age categories older than 60 years decreased substantially but remained statistically significant. This indicates that weight and age older than 60 years were independently associated with dose proportion and relative dose but that most of the effect was through the use of first-cycle dose reduction. In addition, the inclusion of first-cycle dose reductions in the model substantially increases the amount of variation explained by the models (adjusted R² increased from 0.11 to 0.54). The results of the analyses using relative dose intensity as the outcome variable were similar to those using dose proportion.

OCCURRENCE OF FEBRILE NEUTROPENIA

Over the course of their treatment, 462 (5%) of the women were hospitalized for treatment of febrile neutropenia. Women hospitalized with febrile neutropenia were more likely to be treated with G-CSF at each cycle of their chemotherapy compared with women not needing hospitalization (P<.001). The use of G-CSF increased throughout the first 3 cycles of chemotherapy from 16% in the first cycle to 25% in the third cycle.

While there were no significant differences in the mean dose proportion for the entire course of treatment between women who were and were not hospitalized for febrile neutropenia, the women requiring hospitalization had a statistically significantly (although not clinically significant) higher dose proportion for their first cycle of chemotherapy (0.970 vs 0.953, P<.001). Overweight, obese, and severely obese women were no more likely to require admission for febrile neutropenia compared with healthy weight and underweight women, regardless of whether a dose reduction was administered (Table 5). Severe obesity was associated with lower like-
The practices varied widely in their use of first-cycle dose reductions in their overweight and obese breast cancer patients, ranging from 0% to 100%. Among the 513 practices that had at least 5 patients in the database who were overweight, obese, or severely obese (57% of the practices that had at least 5 patients in the database who were overweight, obese, or severely obese), 33% of practices did not administer a first-cycle dose reduction in any of these patients. An additional 10% of practices reduced the dose in 10% or fewer of their patients. In 9% of practices, however, more than 50% of overweight and obese patients were administered first-cycle dose reductions. Among the 113 practices for which there were at least 5 overweight subjects and 5 obese subjects included in the study, the practice level correlation between the use of first-cycle dose reductions in overweight and obese patients was 0.44 ($P<.001$). The percentage of obese and overweight subjects having a first-cycle dose reduction overall was not correlated with the number of obese and overweight women subjects from the practice. There was, however, a significant negative correlation between the percentage of obese subjects administered first-cycle dose reductions and the number of obese women subjects from the practice ($r = -0.19$; $P<.05$).

**COMMENT**

In this community-based study of 9672 patients treated in 901 practices, we have shown substantial variation in the use of first-cycle dose reductions among overweight and obese women. We have also shown that such dose reductions have a significant impact on the overall dose proportion and relative dose intensity. Among the overweight and obese women receiving full weight-based doses, febrile neutropenia requiring hospitalization was no more common than among healthy and underweight women receiving weight-based doses. Moreover, the severely obese women who did receive full weight-based chemotherapy doses were significantly less likely to be hospitalized for febrile neutropenia.

Despite studies in small numbers of patients demonstrating reduced drug clearance in obese women, clinical studies do not support the practice of dose reductions. There is, in fact, accumulating evidence that obese patients do not experience increased toxic effects when dosed according to actual body weight. In addition, the use of actual body weight for calculating chemotherapy doses is associated with improved disease-free and overall survival in heavy patients.

The Cancer and Leukemia Group B performed an analysis of 1435 patients with breast cancer receiving treatment in study 8541, a 3-arm study randomizing patients to 1 of 3 dose levels of cyclophosphamide, doxorubicin hydrochloride, and fluorouracil. Of the 1435 patients, 40% were obese (BMI ≥27.3) and 17% were “very obese” (BMI ≥32.3). The expected doses of the drugs were calculated using the patients’ actual body weight in the BSA calculation. Patients were said to have received weight-based doses if the first-cycle chemotherapy doses were within 5% of the expected doses. In those patients who received weight-based dosing, there was no relationship between obesity and grades 3 or 4 toxicity (hematologic or nonhematologic). Obesity status was also not correlated with a decline in white blood cell count in patients treated with weight-based doses.
Obese patients who had a first-cycle dose reduction experienced worse disease-free survival. In contrast, those patients who received weight-based doses of chemotherapy had an outcome that was no different from non-obese patients in the same treatment arm.16

Additional support for use of actual body weight comes from a study of 340 patients undergoing adjuvant breast cancer chemotherapy with cyclophosphamide, methotrexate, and fluorouracil dosed according to actual body weight.24 In this study, higher BMI was associated with a higher proportion and relative dose intensity is substantial, large and obese patients (approximately 20%). The independence of the dose reduction was equivalent in the overweight and obese patients. Although our study is limited by the fact that we do not have information about nonhematologic toxicity, these 2 studies do not suggest a survival disadvantage or excess nonhematologic toxicity in women dosed according to actual body weight.25,26 This raises the possibility that even the use of actual body weight in dosing the severely obese may represent underdosing.28

Notable in our study is the fact that some practices have extended the use of first-cycle dose reduction to the treatment of overweight women despite the lack of data supporting alterations in drug disposition in overweight women. Our finding of reduced doses in overweight and obese women is consistent with 2 other published studies that examine patterns of care in adjuvant breast cancer chemotherapy.25,27 In addition, the extent of the dose reduction was equivalent in the overweight and obese patients (approximately 20%). The independent effect of first-cycle dose reduction on the overall dose proportion and relative dose intensity is substantial, large enough to reduce the dose proportion and relative dose intensity for the whole regimen below the 85% cutoff generally accepted as necessary to achieve the maximal benefit of adjuvant chemotherapy.9–11

Of the patients who received a first-cycle dose reduction, 16% received an additional cycle and 13% had a sixth cycle beyond the standard 4 cycles of doxorubicin and cyclophosphamide. The practice of reducing the doses of chemotherapy drugs and giving an additional cycle or two will increase the total dose of the chemotherapy given but will not achieve the dose intensity achieved with full doses for the entire treatment course. Early but compelling evidence supporting the use of full doses given more frequently (also called dose-dense chemotherapy) makes the strategy of giving more cycles of reduced chemotherapy even less appealing.29

The wide variation in the use of first-cycle dose reduction among practices is remarkable. Clearly, many physicians have accepted the use of full weight-based dosing. Although 60% of the practices reduced the doses in more than 10% of their overweight and obese patients, 33% of practices administered reduced doses in none of these patients. The practice of first-cycle dose reduction also decreased over time. The small number of patients in each of the practices and the lack of information about the practices and physicians do not allow for analysis of practice or physician characteristics associated with administration of first-cycle dose reductions. Nonetheless, the variation observed in the use of reduced doses of chemotherapy most likely reflects persistent clinical uncertainty regarding the optimal dosing of adjuvant chemotherapy in overweight and obese patients.30,31 It is also likely, as with other practice variations, that physicians tend to practice the way others do in their practice or local setting, giving rise to a practice style that is accepted among that community.31–33 However, given the evidence that maintaining dose intensity improves the likelihood of overall and disease-free survival and the lack of data supporting dose reductions in overweight and obese women, it is likely that the practice variations we have observed represent “unwarranted variation” in the adjuvant treatment of patients with breast cancer.30

The incidence of obesity, particularly severe obesity, is increasing in the United States.34,35 Eliminating unwarranted dose reductions will therefore become increasingly important in defining best practices for the care of overweight and obese women.

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