Breast Cancer Adjuvant Chemotherapy Dosing in Obese Patients
Dissemination of Information From Clinical Trials to Clinical Practice

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BACKGROUND. Substantial variation in adjuvant breast cancer chemotherapy dosing in obese women suggests that there is uncertainty about optimal practices. The purpose of this study was to investigate variations in dose determinations in clinical trial protocols and publications over the last 3 decades as potential sources of this uncertainty.

METHODS. The National Cancer Institute database was used to identify protocols of breast cancer adjuvant chemotherapy conducted by cooperative groups between 1970–2000, and these protocols were then obtained directly from the cooperative groups. Dose determinations were categorized in each protocol and in published reports from each clinical trial. Fisher exact tests were used to compare the proportions of protocols that used full weight-based doses over time.

RESULTS. Protocol-specified chemotherapy dosing was obtained for all of 44 eligible trials. A significant increase was identified in the use of full weight-based doses in the later time period compared with the earlier (P = .004; 2-sided Fisher exact test). A notable exception was 1 cooperative group that continues to require dose limitations for doxorubicin and cyclophosphamide in patients with a body surface area of more than 2.0 m². Regardless of publication date, published reports of clinical trials rarely provide information on use of full or limited weight-based doses.

CONCLUSIONS. Variations in dose determinations among clinical trial protocols and lack of information on use of full weight-based doses in most publications are 2 likely sources of variation in chemotherapy dosing in obese women. Developing consensus and disseminating information on optimal chemotherapy dosing will likely reduce such variation and may improve survival among obese patients with breast cancer. Cancer 2008;112:2159–65. © 2008 American Cancer Society.

KEYWORDS: breast cancer, obesity, clinical trials, practice variations, practice guidelines.

Chemotherapy doses in the adjuvant treatment of breast cancer are generally normalized to body by size using the patient’s body surface area (BSA). The BSA is, in turn, calculated by using height and weight according to one of several methods.1 Although the majority of overweight and obese women are treated with full weight-based chemotherapy doses, the practice of administering reduced doses (compared with those doses that would be expected if actual weight were used to calculate chemotherapy) to heavy women is common.2-5 For example, in a national study of patients treated in 901 practices with adjuvant chemotherapy for breast cancer between 2002 and 2005, 13.8% of overweight patients, 17.7% of
obese patients, and 26.6% of severely obese women received initial dose reductions of greater than 15% when compared with doses that would have been given had full weight-based dosing been used. Reduced doses were not explained by age, comorbidity, or other clinical factors. The use of reduced doses varies according to treating physician and even according to geographic region. Such practice variation suggests that there is uncertainty about the optimal dosing of chemotherapy, including perhaps the safety and necessity of using actual body weight when calculating chemotherapy doses. Uncertainty clearly persists despite compelling evidence that full weight-based doses are not only safe but also necessary if the full benefit of chemotherapy is to be achieved.

The purpose of the current study was to answer the following questions: 1) How have cooperative groups specified that chemotherapy doses be determined in obese patients? That is, do protocols specify the use of full weight-based doses or a dosing limit? 2) Is there variation among cooperative groups in how chemotherapy doses are determined? 3) How much information is available on chemotherapy dose determinations in published articles from cooperative group trials?

The premise of this study is that clinical trial protocols provide a standard of care for prescribing physicians with respect to such issues as dose determinations in studies of nonmyeloablative chemotherapy. A second premise is that physicians use published medical literature to inform their chemotherapy-prescribing decisions and that lack of information on dosing contributes to uncertainty about best chemotherapy dosing practices in the treatment of obese women.

MATERIALS AND METHODS

Dose determinations in cooperative group clinical trials are not compiled in a central source, and publications rarely provide information on dosing limits (see below). Primary data collection thus involved the retrieval of study protocols from cooperative groups in the United States and in Europe. We used the Physician Data Query (PDQ) of the National Cancer Institute (NCI) to identify all registered and completed cooperative group, nonmyeloablative, breast cancer, adjuvant chemotherapy clinical trials. The search, which was conducted in August 2005 and repeated in April 2007, was limited to closed protocols that enrolled female patients with stage I, II, or III breast cancer and that used chemotherapy. We did not limit by geographic location or trial activation date. Each trial in the generated set of trials was individually examined and required to meet the following criteria. We included only adjuvant, nonmyeloablative, chemotherapy trials that were authored by 1 or more cooperative groups. Myeloablative regimens that required stem-cell support or bone-marrow support were excluded because the doses of chemotherapy used in myeloablative regimens are generally several-fold higher than those used in standard adjuvant regimens, and there is little information on safety of full weight-based doses in this setting. The only remaining inclusion criterion for each trial was the publication of an article or articles that reported patient survival by using data from no more than 2 clinical trials. Written protocols were requested from each cooperative group.

Dosing instructions were categorized into 1 of 3 categories: 1) full weight-based dosing, 2) dose adjustment or maximum limit in heavy patients (ideal or corrected body weight used to calculate BSA or a maximum BSA “cap”), or 3) no specific instructions.

We searched PubMed, Ovid, the NCI database, the cooperative group websites, and the Dana Farber Cancer Institute database to identify for each trial a published article that focused on outcomes. In cases where more than 1 article reported on outcomes, 1 article was selected at random. For each article, dose determinations in obese patients were categorized into 1 of the 3 categories described above.

Fisher exact test was used to compare the proportion of trials that specified use of full weight-based dosing (no dose limits) during the study time period and the proportion of published studies that provided information on the use of full doses versus limited doses.

Permission was obtained from either the cooperative group chairperson or disease-site chairperson of the cooperative group to allow us to publish information on protocol-specified details of dose determinations and limits.

RESULTS

Clinical Trial Protocols

Search criteria generated 44 eligible clinical trials from the NCI database spanning the years 1970 through 2000. Dosing instructions were successfully obtained for all. The included protocols are listed in Table 1.

Eleven (25%) of the protocols used actual body weight in dose determinations. Nineteen (43%) specified some form of dose limits, whether through use of ideal body weight, the lesser of actual or ideal
body weight, adjusted ideal body weight, or a BSA limit of 2.0 m\(^2\). Dose determinations changed over time (Fig. 1) and were more likely to be specified in later protocols. Of the 22 protocols initiated through December 1984, 21 (95\%) either did not directly address dose determinations in heavy patients (n = 9) or specified dose reduction (n = 12) in heavy patients. One trial specified use of actual body weight in dose determinations. Of the 22 protocols initiated after 1984, 10 (45\%) specified full weight-based dosing, 7 (32\%) specified dose limits, and 5 (23\%) provided no specific information on chemotherapy dosing in heavy patients. The difference in the use of full weight-based doses in the 2 time periods was significant (P = .004; 2-sided Fisher exact test). All protocols that required dose limits were authored by 1 cooperative group and specified dose limits only for cyclophosphamide and doxorubicin; no dose limitations were specified for taxanes. The 4 remaining US cooperative groups required full weight-based doses in protocols initiated after 1984.

**Clinical Trial Publications**

Information on chemotherapy dose determinations in published clinical trial reports corresponding to cooperative group protocols is shown in Figure 2. Of the 43 published articles (1 article reported on findings from 2 trials; see Table 2), information on dose determination in heavy patients was included in only 10 (23\%). Dosing information was provided in 8 (42\%) of the 19 publications from studies that specified dose limits compared with only 2 (18\%) of the 11 that used actual weight-based doses, but this difference was not statistically significant (P = .25; 2-sided Fisher exact test).

**DISCUSSION**

Early cooperative group protocols included in the Physician Data Query of the National Cancer Institute used dose limits or did not address dosing practices in obese patients. Over the last 2 decades, all but 1 of the United States cooperative groups and 1 of the 2 European cooperative groups have specified use of actual body weight with no dose limitations in trial participants. Information on dosing practices is generally lacking in published reports of these clinical trials.

A substantial body of research supports the use of full weight-based doses in heavy patients who are receiving adjuvant chemotherapy for breast cancer.\(^7\)\(^{-14}\) There is no evidence that use of actual body weight to determine chemotherapy doses is associated with greater myeloid or nonmyeloid toxicity.\(^2\)\(^{-12}\) Moreover, receipt of full weight-based doses appears to be required for patients, particularly for those with estrogen receptor-negative tumors, to achieve the full benefit of chemotherapy.\(^7\)\(^,8\) For example, in 1 clinical trial of adjuvant chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil, obese patients who had a 5\% or greater reduction in chemotherapy doses below those expected if actual body weight were used had inferior failure-free survival.\(^7\) Likewise,
in a pooled analysis of 4 adjuvant chemotherapy trials, obese patients with hormone receptor-negative breast cancer who received less than 85% of full weight-based doses had inferior disease-free and overall survival. On the basis of available evidence, the Southwestern Oncology Group (SWOG) generated a written policy in 2001 (Siu-Fun Wong, PhD, personal communication) that actual body weight should always be used in calculating treatment doses in patients who are participating in clinical trials. The Cancer and Leukemia Group B (CALGB) considers failure to use actual body weight in the calculation of drug doses to be a major protocol deviation.

Despite evidence against dose limits in heavy patients who are receiving adjuvant breast cancer chemotherapy, many obese and overweight patients receive reduced chemotherapy doses as described above. The present-day practice of limiting adjuvant chemotherapy doses in heavy patients and the finding that use of reduced chemotherapy doses varies according to provider suggests that there is persistent uncertainty about best practices for this patient population. The finding that the protocols of 1 of the largest cooperative groups specify dose limits of cyclophosphamide and doxorubicin suggests that uncertainty may also exist among clinical trialists.
TABLE 2
Breast Cancer Adjuvant Chemotherapy Publications

Cancer and Leukemia Group B (CALGB)


Eastern Cooperative Oncology Group (ECOG)


 Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC)


International Breast Cancer Study Group (IBCSG)


North Central Cancer Treatment Group (NCCGT)

National Surgical Adjuvant Breast and Bowel Project (NSABP)


TABLE 2 (continued)


Southwest Oncology Group (SWOG)


Dose determinations specified within clinical trial protocols may serve as a form of guideline for chemotherapy dosing in heavy patients, even in patients being treated “off protocol.” The lack of information on chemotherapy dosing in most of the corresponding published articles further indicates that physicians may not have sufficient information on standard practices in the dosing of obese patients. Without specific information to the contrary, a physician may elect to fall back on older practices of limiting doses in the heavy patient.

Our study is restricted to published cooperative group trials registered in the Physician Data Query. The findings of this survey thus cannot be generalized to all published clinical trials of adjuvant breast cancer chemotherapy. Nonetheless, cooperative group trials are highly influential, and their publications are widely cited.

We contend that present-day variations in chemotherapy dosing in heavy patients represent unwarranted variation. Developing and disseminating standards for dose determinations in heavy patients is critical to decreasing variation in dosing practices and may improve outcomes among obese women. As the prevalence of obesity and severe obesity increases, we suggest that cooperative groups come to consensus on dose determinations in obese patients on the basis of existing evidence and further suggest that guideline-development groups and biomedical journals provide specific information on the
standard of care for dosing obese patients who are receiving adjuvant breast cancer chemotherapy.17

REFERENCES