Weight-Based Chemotherapy Dosing in Obese Patients With Cancer: Back to the Future

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Early in the history of modern cancer chemotherapy, preclinical and clinical studies demonstrated that both treatment efficacy and toxicity were associated with a clear dose-response relationship. In experimental tumor-bearing animals, the dose-response relationship is steep for most chemotherapeutic agents, with the steepness of the curve related to specific tumor sensitivity to a particular drug.¹ In fact, for highly sensitive tumors, the dose-response curve is very steep and generally linear.¹ Schabel² and Skipper³ demonstrated in animal tumor models that a reduction in chemotherapy dose of as little as 20% may virtually eliminate an otherwise high complete remission rate and reduce cure rates by as much as 50%.^{2,3} Goldie and Coldman^{4,5} demonstrated that higher chemotherapy doses reduce the likelihood of resistant malignant clones emerging in tumors. At the same time, Norton and Simon developed mathematical models suggesting that shortening the interval between chemotherapy doses would reduce the opportunity for tumor regrowth and the emergence of drug resistance.^{6,7} Prior to the study of new agents and regimens in definitive comparative clinical trials in humans, dose-finding and safety studies are designed to identify a maximum tolerable dose in an effort to move forward the most promising, effective, and tolerable doses and schedules for large-scale clinical studies. In addition, successful combination chemotherapy regimens have been introduced, designed to use a number of agents with different mechanisms of action and limited overlap in toxicities to enable each agent to be delivered at relatively full dose. Once demonstrated to be acceptably efficacious and safe, regimens associated with specific doses and schedules are considered standard options and are integrated into clinical care and practice guidelines. A positive relationship between chemotherapy dose intensity and complete and overall response rates has been demonstrated in many common human malignancies.^{1,8} Nowhere is the issue of optimal chemotherapy dosing and clinical outcomes more critical than in the adjuvant treatment of patients with early-stage disease. Frei and Canellos pointed out more than 30 years ago that “*in adjuvant chemotherapy situations, in which prolonged disease-free survival is improved, the dose-response curve would appear to be quite steep. Conservative dosing in this setting may compromise the cure rate, and the proposed approach is to maintain full dose therapy and consider reducing the total duration of treatment.*”^{9,10} Retrospective studies and prospective clinical trials have provided evidence for a significant association between dose intensity and both disease-free and overall survival.^{9,10} Given the association between chemotherapy dosing and both treatment effect and toxicity, several investigations have reported that patients who

experience myelosuppression while receiving chemotherapy may subsequently experience improved disease-free and overall survival.^{11,12} Although data from prospective randomized controlled trials are less abundant, deliberate randomization to different dose-intensity schedules in early-stage breast cancer has demonstrated a significant association with disease-free and overall survival.¹³⁻¹⁵ Although the shape or slope of the dose-response curve varies between cancer types, abundant evidence that patients who receive chemotherapy experience improved survival compared with untreated controls confirms a dose-response relationship between a dose intensity of 0 (untreated patients) and the dose intensity delivered in the trials.¹⁶⁻¹⁸ Extending the theoretical and experimental evidence in favor of shortened dosing intervals with standard doses (dose dense), several clinical trials have demonstrated improved disease-free and overall survival compared with standard dosing and schedule.¹⁹⁻²³

Therefore, considerable data support the importance of maintaining the chemotherapy dose and schedule used in the definitive clinical trials upon which a treatment indication is based, especially in responsive malignancies treated in the curative setting. Nevertheless, practice pattern surveys have demonstrated that frequent major reductions in chemotherapy dose intensity occur in clinical practice throughout the United States and in other countries.²⁴⁻²⁷ These studies have also demonstrated considerable variation and apparent uncertainty in the appropriate dosing of chemotherapy in obese cancer patients with cancer, resulting in dose modification, including the use of an idealized body weight or the capping of the total dose. Such arbitrary dose adjustments are major factors associated with reduced chemotherapy dose intensity received by obese patients with cancer.^{26,28} (Figure 1) Most of the reduction in dose intensity associated with obesity is evident from the start of therapy (planned), with no increase in dose reductions associated with toxicity that were planned at the start of treatment. At the same time, studies have demonstrated that obese patients being treated with curative intent have a significantly greater risk of mortality.²⁹ In a retrospective analysis of the Cancer and Leukemia Group B 8541 trial, Rosner et al found that obese women with early-stage breast cancer who received full-dose-intensity adjuvant chemotherapy experienced no excess toxicity or worse outcome than similarly dosed healthy-weight patients, whereas women who received reduced doses of chemotherapy had a worse failure-free survival.³⁰ In addition, pharmacokinetic studies have demonstrated that chemotherapy dose calculations should generally be based on actual rather than ideal body

Figure 1. Planned and unplanned reductions in dose intensity relative to published standard dose intensity (RDI) in women receiving chemotherapy for early-stage breast cancer stratified by World Health Organization body-mass index categories.²⁶

weight.³¹ Faced with a worsening national epidemic of obesity, ASCO has undertaken an exhaustive review of the medical literature on chemotherapy dosing in obese patients with cancer and has developed clinical practice guidelines consistent with the known evidence in an effort to reduce the variation observed in clinical practice and improve clinical outcomes for such patients.³² The questions addressed by the guideline panel include: Is there evidence that full weight–based dosing increases toxicity in obese patients with cancer? Is there evidence that less than full weight–based dosing compromises efficacy in obese patients with cancer? Should chemotherapy dose modification for severe toxicity in obese patients be any different than in healthy-weight patients? Finally, are the answers to these questions dependent on the particular chemotherapeutic agent, patient age, major comorbidities, and/or treatment intent?

The guideline panel recommends that full weight–based chemotherapy doses be used in the treatment of obese patients with cancer, especially when the goal of treatment is cure. Clinicians are encouraged to respond to treatment-related toxicities in obese patients in the same way they do for healthy-weight patients. The panel also recommends resumption of full weight–based doses that have been modified in response to toxicity when the cause of toxicity has resolved. The panel concludes that there is no evidence to support the need for greater dose reductions for obese patients than for healthy-weight patients. The use of fixed-dose cytotoxic chemotherapy is justified

only for a few select drugs. Finally, the panel emphasizes the need for more research to address a range of additional issues for which data are currently limited. Importantly, further research into the potential role of pharmacokinetic and pharmacogenetic information in tailoring drug doses and schedules in individual patients receiving cancer chemotherapy is needed.

Improving the delivery and dosing of conventional chemotherapeutic agents, both alone or as adjuncts to novel biologic and molecular therapies, in obese patients with cancer represents an important opportunity for further improving the treatment and clinical outcomes of patients with cancer. Despite the excitement around available and emerging novel targeted therapies, it is apparent that the optimal role of many of these agents will continue to be their use in combination with conventional myelosuppressive agents. ASCO clinical practice guidelines for chemotherapy dosing in the increasing number of obese patients with cancer will hopefully reduce the variation and uncertainty of chemotherapy dosing in clinical practice and result in more consistent evidence-based treatment and improved clinical outcomes in this population.

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