Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline

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More than 60% of adults in the United States have a body mass index (BMI) over 25 and are considered overweight or obese. Clinicians traditionally order chemotherapy doses based on a patient's estimated body-surface area (BSA) using formulas that were developed decades ago. Despite studies confirming the safety and importance of full weight–based chemotherapy dosing, many overweight and obese patients receive limited chemotherapy doses that are not based on actual weight. When chemotherapy doses are calculated according to actual body weight, and delivered to obese patients, they are less likely to experience toxicity and/or bone marrow suppression. Although poorer outcomes among obese patients are most likely multifactorial, systemic chemotherapy at less than full weight–based dosing and unnecessary dose reductions may partially explain the significantly higher cancer mortality rates observed in overweight and obese individuals. Underdosing of chemotherapy is of particular concern in patients with chemotherapy-responsive and potentially curable malignancies; reductions in standard chemotherapy dose intensity may increase the risk of disease recurrence and mortality.

With these issues in mind, ASCO recently published a new clinical practice guideline on appropriate chemotherapy dosing for obese adult patients with cancer, in *Journal of Clinical Oncology*.[1] The guideline is based on a systematic search and review of the literature. An expert panel considered literature identified by the systematic review. Details are provided in the full guideline and its Data Supplements. The primary efficacy outcomes of interest included overall, disease-specific, disease-free, relapse-free,

THE BOTTOM LINE

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Intervention

- Recommendations for appropriate chemotherapy dosing for obese adult patients with cancer

Target Audience

- Medical oncologists, pharmacists, oncology nurses

Key Recommendations

- Panel recommends that full weight–based chemotherapy doses be used in the treatment of the obese patient with cancer, particularly when the goal of treatment is cure.
- Clinicians should respond to all treatment-related toxicities in obese patients with cancer in the same ways they do for nonobese patients.
- If a dose reduction is used in response to toxicity, consideration should be given to the resumption of full weight–based doses for subsequent cycles, especially if a possible cause for the toxicity (eg, impaired renal, hepatic function) has been resolved. There is no evidence to support the need for greater dose reductions for obese patients compared with nonobese patients.
- The use of fixed-dose cytotoxic chemotherapy is rarely justified (except for a few select agents).

Methods

- Systematic review of medical literature and analysis of the medical literature by the update committee of an expert panel

Additional Information

- The recommendations, clinical questions, and a brief summary of the literature and discussion are in the *JCO* Guideline publication (http://jco.ascopubs.org/content/early/2012/03/27/JCO.2011.39.9436/suppl/DC1).
- The full guideline, with comprehensive discussions of the literature, methodology, full reference list, evidence tables, and clinical tools and resources, can be found at www.asco.org/guidelines/wbd.
- A commentary by Gary H. Lyman is available at http://jop.ascopubs.org/content/early/2012/04/03/JOP.2012.000606.full.pdf+html

Table 1. Clinical Questions and Recommendations

Clinical Question	Recommendation(s)
1. Is there evidence that full weight–based dosing increases toxicity in obese patients with cancer?	Recommendation 1.1: The Panel recommends that actual body weight be used when selecting cytotoxic chemotherapy doses, regardless of obesity status. There is no evidence that short- or long-term toxicity is increased among obese patients receiving full weight–based chemotherapy doses. Most data indicate that myelosuppression is the same or less pronounced among the obese than the nonobese administered full weight–based doses. Recommendation 1.2: The Panel recommends full weight–based chemotherapy dosing for morbidly obese patients with cancer, subject to appropriate consideration of other comorbid conditions. Data are extremely limited regarding optimal dose selection among the morbidly obese and other special subgroups. More studies are needed to evaluate optimal agents and agent combinations for obese and morbidly obese patients with cancer; however, based on available information, it seems likely that the same principles regarding dose selection for obese patients apply to the morbidly obese.
2. Is there evidence that less than full weight–based dosing compromises efficacy in obese patients with cancer?	Recommendation 2.1: The Panel recommends that full weight–based chemotherapy doses (IV and oral) be used in the treatment of the obese patient with cancer, particularly when the goal of treatment is cure. Selecting reduced doses in this setting may result in poorer disease-free and overall survival rates. There are compelling data in patients with breast cancer that reduced dose-intensity chemotherapy is associated with increased disease recurrence and mortality. Although data in other malignancies are more limited, based on improved survival observed with chemotherapy compared with controls, a dose-response relationship exists for many responsive malignancies. Therefore, although data are not available to address this question for all cancer types, in the absence of data demonstrating sustained efficacy for reduced dose chemotherapy, the Panel believes that the prudent approach is to provide full weight–based chemotherapy dosing to obese patients with cancer, especially those receiving treatment with curative intent. Most of the data in support of full weight–based dosing come from the treatment of early-stage disease. Data supporting the use of full weight–based doses in the advanced disease setting are limited.
3. If an obese patient experiences high-grade toxicity, should chemotherapy doses or schedules be modified differently from modifications used for nonobese patients with cancer?	Recommendation 3.1: Clinicians should follow the same guidelines for dose reduction, regardless of obesity status, for all patients, depending on the type and severity of toxicity, any comorbid conditions, and whether the treatment intention is cure or palliation. There is no evidence to support the need for greater dose reductions for obese patients compared with nonobese patients. If a dose reduction is employed in response to toxicity, consideration should be given to the resumption of full weight–based doses for subsequent cycles, especially if a possible cause of toxicity (eg, impaired renal, hepatic function) has been resolved. The Panel recognizes the need for clinicians to exercise judgment when providing care for patients who have experienced grade 3 or 4 chemotherapy toxicity. The presence of obesity alone should not alter such clinical judgment.
4. Is the use of fixed-dose (dose prescribed independently of weight or BSA) cytotoxic chemotherapy ever justified? Are there unique dosing considerations for certain chemotherapeutic agents?	Recommendation 4.1: The Panel recommends consideration of fixed dosing only with select cytotoxic agents (eg, carboplatin and bleomycin). On the basis primarily of neurotoxicity concerns, vincristine is capped at a maximum dose of 2.0 mg when used as part of the CHOP and CVP regimens. Several other cytotoxic chemotherapeutic agents have been used in clinical trials at a fixed dose independent of patient weight or BSA. However, it is not clear that fixed dosing is optimal for any of these other agents.
5. How should BSA be calculated? Specifically, what is the best formula for use with the obese patient with cancer?	Recommendation 5.1: The Panel recommends that BSA be calculated using any of the standard formulae. There is no evidence to support one formula for calculating BSA over another.
6. What is the role of pharmacokinetic and/or phamacogenetic factors when determining optimal chemotherapy dose and delivery (bolus, infusional, therapeutic drug monitoring) for obese patients with cancer?	Recommendation 6.1: The Panel recommends further research into the role of pharmacokinetic and pharmacogenetic information for guiding the dosing of IV and oral chemotherapeutic agents for adult patients with cancer who are obese. It should be emphasized that there is a paucity of information on the influence of obesity on the pharmacokinetics of most anticancer drugs from properly powered trials. This is the result, in part, of empiric eligibility restrictions from the outset in clinical trials and a lack of pharmacokinetic analyses performed and published for this subpopulation. Overall, there are insufficient pharmacokinetic data to reject the recommendation to use a full weight–based dosing strategy for chemotherapeutic agents in patients with cancer who are obese, regardless of route of administration and/or infusion time.

Abbreviations: BSA, body surface area; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; IV, intravenous.

Table 2. Toolkit Contents

Toolkit Contents
Online slide set and one-page summary
"5 Things To Remember" tips for clinicians on chemotherapy dosing for patients with cancer who are obese
Answers for clinicians to frequently asked questions
Dosing table
Podcasts

event-free, and progression-free survival. Treatment-related toxicities were also a primary outcome. In addition to abundant preclinical studies, clinical evidence in support of this guideline comes from several randomized controlled trials (RCTs) comparing delivered dose intensity, retrospective analyses of RCTs and cohort studies, as well as pharmacokinetic studies.

Recommendations

Table 1 is reprinted from the ASCO Clinical Practice Guideline[1] published in *JCO* and includes the recommendations.

The *JCO* publication is a brief overview of the guideline and provides a brief discussion of the relevant literature for each recommendation. The full guideline, including expanded discussions of the literature, a description of methodology, all cited references, and a data supplement with evidence tables; a patient guide; and a toolkit (Table 2), is available at www.asco.org/guidelines/wbd. A slide set is provided as a data supplement to this article.

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Reference

1. Griggs JJ, Mangu PB, Anderson H, et al: Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 30:1553-1561, 2012