

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

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A B S T R A C T

Purpose

To provide recommendations for appropriate cytotoxic chemotherapy dosing for obese adult patients with cancer.

Methods

The American Society of Clinical Oncology convened a Panel of experts in medical and gynecologic oncology, clinical pharmacology, pharmacokinetics and pharmacogenetics, and biostatistics and a patient representative. MEDLINE searches identified studies published in English between 1996 and 2010, and a systematic review of the literature was conducted. A majority of studies involved breast, ovarian, colon, and lung cancers. This guideline does not address dosing for novel targeted agents.

Results

Practice pattern studies demonstrate that up to 40% of obese patients receive limited chemotherapy doses that are not based on actual body weight. Concerns about toxicity or overdosing in obese patients with cancer, based on the use of actual body weight, are unfounded.

Recommendations

The Panel recommends that full weight-based cytotoxic chemotherapy doses be used to treat obese patients with cancer, particularly when the goal of treatment is cure. There is no evidence that short- or long-term toxicity is increased among obese patients receiving full weight-based doses. Most data indicate that myelosuppression is the same or less pronounced among the obese than the non-obese who are administered full weight-based doses. Clinicians should respond to all treatment-related toxicities in obese patients in the same ways they do for non-obese patients. The use of fixed-dose chemotherapy is rarely justified, but the Panel does recommend fixed dosing for a few select agents. The Panel recommends further research into the role of pharmacokinetics and pharmacogenetics to guide appropriate dosing of obese patients with cancer.

INTRODUCTION

Optimal doses of chemotherapy drugs or drug combinations are generally established through randomized controlled clinical trials (RCTs). In adult patients with cancer, drug dosing has traditionally been based on a patient's estimated body surface area (BSA).¹ Despite continuing controversy concerning the value of dose escalation and intensification schedules, there exists compelling preclinical and clinical evidence that reductions from standard dose and dose-intensity may compromise disease-free (DFS) and overall survival (OS) in the curative setting.²⁻⁷ Furthermore, a number of authors have suggested that the optimal delivery of cancer chemotherapy should be considered an indicator of quality of care.^{3,8,9}

Despite studies confirming the safety and importance of full weight-based chemotherapy dosing (Data Supplement 1 at www.asco.org/guidelines/wbd), many overweight and obese patients continue to receive limited chemotherapy doses.¹⁰⁻¹³ Many oncologists continue to use either ideal body weight or adjusted ideal body weight or to cap the BSA at, for example, 2.0 m² rather than use actual body weight to calculate BSA. Practice pattern studies demonstrate that up to 40% of obese patients receive limited doses that are not based on actual body weight.^{10,12-17} Moreover, considerable variation in the dosing of chemotherapy in overweight and obese individuals with cancer has been documented,^{3,13,14,16,18-22} suggesting considerable uncertainty among physicians about optimal dose selection. Such uncertainty likely arises from the fact that many published

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Editor's note: This is the complete American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on Appropriate Chemotherapy for Obese Adult Patients with Cancer, and it provides the recommendations with comprehensive discussions of the relevant literature for each. The Executive Summary of the guideline and Data Supplements with evidence tables and other tables and figures are available at www.asco.org/guidelines/wbd.

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clinical trials present neither the planned chemotherapy dosing nor the delivered dose-intensity.²³ Because there are no available data, this guideline does not address adjusting chemotherapy doses because of ascites or anasarca for overweight or obese patients. Although nearly all cooperative groups specify that actual body weight be used in the calculation of BSA, the published reports from these trials rarely include the delivered dose-intensity specifically for obese patients.¹¹

The practice of limiting cytotoxic (intravenous [IV] and oral) chemotherapy doses in overweight and obese patients may negatively influence the quality of care and outcomes at a population level, given the rise in rates of obesity both in the United States^{24,25} and globally.²⁶ Rates of obesity have increased in recent years, reaching epidemic

proportions in the United States. The Centers for Disease Control and Prevention estimates that a majority (> 60%) of adult Americans have a body mass index (BMI) > 25 (overweight, obese, morbidly obese) and that this proportion is steadily increasing.^{24,25} Thus, appropriate chemotherapy dosing for obese patients with cancer is a significant issue for many oncology practices. Many cancers are more common in obese people, and cancer-specific outcomes tend to be worse among the obese.²⁷ Poorer outcomes among obese patients are most likely multifactorial. Systemic chemotherapy at less than full weight–based dosing and unnecessary dose reductions may explain, in part, the significantly higher cancer mortality rates observed in overweight and obese individuals. Underdosing of chemotherapy is of particular concern in patients with chemoresponsive and potentially curable malignancies, for whom reductions in standard chemotherapy dose-intensity may increase the risk of disease recurrence and mortality. Concerns about overdosing in the obese patient with cancer based on the use of actual body weight are unfounded.^{10,13,19,28-30} Even when chemotherapy doses are calculated according to actual body weight, obese patients are less likely to have bone marrow suppression, supporting the safety of full weight–based dosing. Unlike body size, it is well established that comorbid conditions such as hepatic and renal dysfunction are relevant predictors of toxicity.³¹

There are few RCTs directly addressing optimal methods of dose calculation and delivery.^{2,32-36} A compelling body of evidence exists, however, supporting the important relationship between selection of chemotherapy doses (IV and oral) in adult patients with cancer and treatment efficacy and toxicity as well as pharmacokinetic correlates of dose selection.^{2,5,6,28,32,37-96} Ironically, in lean patients, in whom outcomes are less sensitive to full weight–based dosing,^{28,51} physicians are more likely to administer doses based on actual body weight, whereas obese patients, in whom outcomes are worse with a dose reduction of even 5%, are the most likely to have their doses reduced. Recent pharmacokinetic studies have clearly demonstrated that actual rather than ideal body weight should be used in dose calculations.⁹⁷

THE BOTTOM LINE

ASCO GUIDELINE

ASCO Guideline on Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer

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 non-obese 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; there is no evidence to support the need for greater dose reductions for obese patients compared with non-obese patients.
- The use of fixed-dose cytotoxic chemotherapy is rarely justified (except for a few select agents).

Methods

- Systematic review of the medical literature and analysis of the medical literature by the Update Committee of an Expert Panel

Additional Information

Data Supplements, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/wbd.

GUIDELINE QUESTIONS

The overarching question for this clinical practice guideline is: How should cytotoxic chemotherapy doses be selected for people with cancer who are obese? Specific questions addressed by the Panel include:

1. Is there evidence that full weight–based dosing increases toxicity in obese patients with cancer?
2. Is there evidence that less than full weight–based dosing compromises efficacy in obese patients with cancer?
3. If obese patients experience high-grade toxicity, should chemotherapy doses or schedules be modified differently from modifications used for non-obese patients with cancer?
4. Is a fixed dose (dose prescribed independently of weight or BSA) of cytotoxic chemotherapy ever justified? Are there unique dosing considerations for certain chemotherapeutic agents?
5. How should BSA be calculated? Specifically, what is the best formula for use in the obese patient with cancer?
6. What is the role of pharmacokinetic and/or pharmacogenetic factors when determining optimal chemotherapy dose and delivery (bolus, infusional, therapeutic drug monitoring) for obese patients with cancer?

CLINICAL PRACTICE GUIDELINES

Practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, use of clinical guidelines may provide:

1. Improvements in outcomes
2. Improvements in medical practice
3. A means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas in which future research is needed

METHODS

Panel Composition

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee convened an Expert Panel consisting of experts in clinical medicine and research relevant to appropriate chemotherapy dosing for obese adults with cancer, including medical and gynecologic oncologists, clinical pharmacologists, pharmacokinetic and pharmacogenetic experts, health services researchers, and biostatisticians. Academic and community practitioners and a patient representative were also part of the Panel. The Panel members are listed in Appendix Table A1.

Literature Review and Analysis

Literature search strategy. The MEDLINE and the Cochrane Collaboration Library electronic databases were initially searched with the date parameters of 1966 through October 2009, and articles published after the initial literature search were monitored through PubMed updates until October 2010 and added to the systematic review literature. The National Cancer Institute Physician Data Query database of clinical trials and the National Library of Medicine ClinicalTrials.gov database were also searched for ongoing trials. Electronic search results were supplemented with hand searching of selected reviews, expert consensus meeting notes, and reference lists from excluded articles. The literature search was limited to articles in English with human participants. MeSH headings and keywords searched were neoplasm, drug therapy, chemotherapy, dose, schedule, dose-intensity, obese, and overweight. The search excluded pediatric patients and patients with hematologic malignancies undergoing bone marrow transplantation. Design or publication type included studies comparing different dosing approaches, and articles had to report one or more major toxicities or response criteria. MEDLINE search terms are included in Data Supplement 3 at www.asco.org/guidelines/wbd. A summary of the literature search results is provided in Data Supplement 4 at www.asco.org/guidelines/wbd.

Inclusion and exclusion criteria. Articles were selected for inclusion in the systematic review if they were published English language studies on cytotoxic IV or oral chemotherapy dosing approaches for overweight or obese patients with cancer, excluding leukemias. Data were extracted from prospective or retrospective cohort studies that addressed withholding, delaying, early cessation, or reduction of chemotherapy doses, including capping doses (eg, at a BSA of 2.0 m²). Data were also extracted about treatment toxicity, DFS and OS, and quality-of-life outcomes. Systematic reviews of RCTs, meta-analyses, and other clinical practice guidelines were also conducted. Because of the paucity of data, this guideline does not address dosing for novel targeted agents

such as tyrosine kinase inhibitors, immunotherapies (eg, interleukin-2, interferon), or monoclonal antibodies. Pharmacokinetic studies with pharmacodynamic or clinical outcomes with appropriate controls were also included. Meeting abstracts, letters, commentaries, editorials, case reports, nonsystematic (narrative) reviews, and studies limited to pediatric patients were excluded. Studies also were excluded if they addressed dose selection of noncytotoxic agents, such as tamoxifen or finasteride.

Data extraction. Primary outcome measures of interest included OS, disease-specific survival, DFS, relapse-free survival, event-free survival, progression-free survival (PFS), and treatment-related toxicities. Secondary outcomes and/or other data elements of interest included quality of life and costs of care. Abstracts were reviewed, and articles were deemed appropriate for full text review and data extraction by one reviewer and reviewed by the Co-Chairs as well. Screening and data extraction were completed using DistillerSR (Evidence Partners, Ottawa, Ontario, Canada) and data were exported into evidence tables (evidence tables provided in Data Supplements 1 and 2 at www.asco.org/guidelines/wbd). Data were extracted by one reviewer and subsequently checked for accuracy by a second reviewer. Disagreements were resolved by discussion and by consultation with Panel Co-Chairs, if necessary.

Study Quality and Limitations of the Literature

There are no prospective randomized studies comparing full weight-based chemotherapy dose selection and non-full weight-based dose selection. Retrospective analyses of randomized trials and comparative observational studies comprise the majority of the studies included in this guideline. This guideline is based on evidence derived primarily from subgroup analyses and registry data. Although the results are important, it should be clear to the reader that the evidence base for this guideline is necessarily different from those for other ASCO guidelines (eg, Antimetetics or Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer, which rely on large, prospective randomized trials).

Consensus Development Based on Evidence

The entire Panel met once in person, and additional work on the guideline was completed through teleconferences and electronic communications. The purpose of the Panel meeting was to refine the clinical questions, draft guideline recommendations, and distribute writing assignments. All members of the Panel participated in the preparation of the draft guideline document, which was then disseminated for review by the entire Panel. The guideline was submitted to *Journal of Clinical Oncology* (JCO) for peer review. Feedback from external reviewers was also solicited. The content of the guideline and the manuscript were reviewed and approved by the ASCO Clinical Practice Guideline Committee before publication.

Definition of Terms

A glossary of terms, including information on calculating BSA (eg, Mosteller, Dubois and Dubois, Haycock, Gehan and George, Boyd formulas) and toxicity grades, appears in Data Supplement 5 at www.asco.org/guidelines/wbd.

Guideline Policy

This clinical practice guideline is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This guideline does not recommend any particular product or course of medical treatment. Use of the practice guideline is voluntary.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with the ASCO Conflict of Interest Management Procedures for Clinical Practice Guidelines (summarized at <http://www.asco.org/guidelinescoi>). Members of the Panel completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the

guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Panel did not disclose any of these relationships.

Revision Dates

At annual intervals, the Panel Co-Chairs and two Panel members, designated by the Co-Chairs, will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire Panel or an Update Committee will reconvene to discuss potential changes. When appropriate, the Panel will recommend a revised guideline to the ASCO Clinical Practice Guideline Committee for review and approval.

Other Guidelines and Consensus Statements

There are no published guidelines that address appropriate chemotherapy dosing for obese patients with cancer.

GUIDELINE RECOMMENDATIONS

The overarching question for this clinical practice guideline is: Should actual body weight be used to select chemotherapy doses in obese individuals with cancer? Overweight and obesity are both labels for ranges of weight that are greater than what is generally considered healthy for a given height. The terms also identify ranges of weight that have been shown to increase the likelihood of certain diseases and other health problems. For adults, overweight and obesity ranges are determined by using weight and height to calculate BMI. Although for most individuals BMI correlates with amount of body fat, BMI is not a direct measure of body fat. As a result, some people, such as athletes, may have a BMI that identifies them as overweight even though they do not have excess body fat. For more information about BMI, visit the Centers for Disease Control and Prevention Web site.⁹⁸ An adult who has a BMI between 18.5 and 24.9 kg/m² is considered normal weight; an adult who has a BMI between 25 and 29.9 kg/m² is considered overweight; an adult who has a BMI of ≥ 30 kg/m² is considered obese; an adult who has a BMI > 40 kg/m² is considered morbidly obese (or > 35 kg/m² with comorbid conditions). More information about interpreting BMI for adults is provided in Data Supplement 6 at www.asco.org/guidelines/wbd. Table 1 provides a summary of the following guideline recommendations.

Clinical Question 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 non-obese when administered full weight–based doses.

Literature review and analysis. Observational studies and retrospective analyses of participants in clinical trials have not demonstrated increased hematologic or nonhematologic toxicity in obese patients receiving chemotherapy doses calculated using actual body weight. For example, no excess toxicity was observed among patients with small-cell lung cancer when actual weight was used to calculate chemotherapy doses.²⁹ In a retrospective analysis of CALGB (Cancer and Leukemia Group B) Protocol 8541, obese patients receiving full

weight–based dosing of adjuvant cyclophosphamide, doxorubicin, and fluorouracil had no excess grade 3 hematologic or nonhematologic toxicity at any of the three dose levels in the study compared with non-obese patients.²⁸ In obese patients receiving full weight–based doses of cyclophosphamide, methotrexate, and fluorouracil in the adjuvant treatment of breast cancer, patients with the highest BMIs had the highest leukocyte nadir values, or leukocyte nadirs were less pronounced among obese patients compared with non-obese patients.³⁰ A large study of 9,672 patients with breast cancer treated in practices across the United States with adjuvant doxorubicin and cyclophosphamide demonstrated that the likelihood of febrile neutropenia, if anything, decreased as BMI increased among those patients who received full weight–based dosing.¹³ Similar findings were reported in the treatment of 59 women with endometrial or ovarian cancer and BSA > 2.0 m² who received paclitaxel and carboplatin based on actual body weight.⁹⁹ On the basis of these studies and others included in the systematic review,¹⁰⁰⁻¹⁰³ the Panel concluded that there is no evidence indicating higher rates of hematologic or nonhematologic toxicity among obese patients who received full weight–based doses. The heavier a patient is, even fully dosed, the less likely he or she is to have febrile neutropenia, especially in the absence of additional comorbid illness.

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, on the basis of available information, it appears likely that the same principles regarding dose selection for obese patients apply to the morbidly obese.

Literature review and analysis. A search of MEDLINE and the Cochrane Collaboration Library was conducted to identify literature specifically addressing treatment of patients who are morbidly obese. Nine articles¹⁰⁴⁻¹¹² were found, a majority of which were small observational studies or case reports and primarily presented data on the pharmacokinetics of chemotherapy in this subgroup. For this reason, there are no separate recommendations for morbidly obese patients in this guideline. From the available evidence, it seems that morbidly obese patients being treated with curative intent and receiving full weight–based doses were no more likely to experience toxicity than lean patients.¹¹³ Clinicians need to calculate full weight–based dosing and use clinical judgment when monitoring toxicity, as they would for all patients.¹¹⁴ In this same early study, it was recommended that BSA be recalculated when body weight has changed by more than 5% to 10%.¹¹⁴ However, there are limited data on recalculating dose when body weight changes, and more research studies are needed. The Panel recognizes that there may be cases in which obese patients have other serious medical problems, and it encourages clinicians to use judgment when dosing, as they would if the patients were not obese (eg, heart, renal, pulmonary problems).

Clinical Question 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

Table 1. Clinical Questions and Recommendations

Clinical Question	Recommendation
1. Is there evidence that full weight-based dosing increases toxicity in obese patients with cancer?	<p>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 non-obese administered full weight-based doses.</p> <p>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.</p>
2. Is there evidence that less than full weight-based dosing compromises efficacy in obese patients with cancer?	<p>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.</p>
3. If an obese patient experiences high-grade toxicity, should chemotherapy doses or schedules be modified differently from modifications used for non-obese patients with cancer?	<p>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 non-obese 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.</p>
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?	<p>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.</p>
5. How should BSA be calculated? Specifically, what is the best formula for use with the obese patient with cancer?	<p>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.</p>
6. What is the role of pharmacokinetic and/or pharmacogenetic factors when determining optimal chemotherapy dose and delivery (bolus, infusional, therapeutic drug monitoring) for obese patients with cancer?	<p>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.</p>

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

is cure. Selecting reduced doses in this setting may result in poorer DFS and OS 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 cancer patients, 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.

Literature review and analysis. Retrospective analyses and observational studies suggest that dose limits in obese patients may com-

promise DFS and OS rates.¹¹⁵⁻¹¹⁸ An analysis of outcomes among obese patients treated in CALGB 8541 demonstrated that obese patients who received < 95% of the expected chemotherapy (based on full weight-based dosing) had worse failure-free survival rates.²⁸ Additional data supporting the use of full weight-based dosing came from a retrospective analysis of four adjuvant chemotherapy studies conducted by the International Breast Cancer Study Group (previously the Ludwig Study Group). In this analysis, obese patients with estrogen receptor-negative breast cancer who received < 85% of the dose experienced a higher relapse rate and had a lower survival rate.⁵¹

Clinical Question 3

If an obese patient experiences high-grade toxicity, should chemotherapy doses or schedules be modified differently from modifications used for non-obese 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 non-obese 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.

Literature review and analysis. There are no RCTs that specify differential management of moderate to severe toxicity (grades 3 to 4) according to obesity status (Glossary in Data Supplement 5 at www.asco.org/guidelines/wbd provides more information on toxicity grades). Similarly, no observational studies describe BMI-based management of toxicities from chemotherapy. Given the lack of evidence citing harms in differential treatment, the Panel recommends clinicians respond to treatment-related toxicities in obese patients with cancer in the same ways they do for non-obese patients with cancer. Excess toxicity usually results from the fact that the patient has reduced drug elimination in reference to the dose of one (or more) chemotherapeutic agents. A return to initial dosing after toxicity is resolved rarely occurs unless the reason for the toxicity is clearly established and fully resolved. Thus, the dose should only be increased to the initial dose if it is established that drug elimination has improved (eg, improvement in renal function, return of bilirubin to normal, significant improvement in performance status). Obesity status alone should not play a role in dose modifications in response to toxicity.

Clinical Question 4

Is a fixed dose (dose prescribed independently of weight or BSA) of 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 (cyclophosphamide, hydroxydoxorubicin [doxorubicin], vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone) 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.

Literature review and analysis. The Panel recommends consideration of fixed dosing only with a select group of agents. For example, carboplatin clearance depends on glomerular filtration rate (GFR), and doses are calculated best using the Calvert formula^{119,120} (total dose [mg] = [AUC (target area under the plasma concentration-time curve)] × [GFR + 25]) to achieve a targeted AUC. The GFR used in the Calvert formula to calculate the AUC dosing should not exceed 125 mL/min. The maximum carboplatin dose should not exceed AUC (mg × min/mL) × 150 mL/min. Because carboplatin clearance is dictated by renal filtration, and GFR correlates with BSA, dosing of carboplatin in the obese patient with cancer based on GFR may be most reasonable. Note that the US Department of Health and Human Services issued the “Follow-Up for Information Letter Regarding AUC-Based Dosing of Carboplatin” on October 22, 2010,¹²¹ about the

AUC-based dosing of carboplatin. The National Institute for Standards and Technology standardized the measurement of serum creatinine using isotope dilution mass spectrometry (IDMS), and reagents for older methodologies should no longer be available. All laboratories in the United States by 2010 should have switched to the IDMS measurement. Older and other^{122,123} methods were not standardized, and this led to variable creatinine values; the use of a single correction factor to convert IDMS creatinine values to non-IDMS creatinine values will not work across all laboratories. If the total carboplatin dose is calculated based on an estimated GFR using an IDMS-measured serum creatinine and the Calvert formula, carboplatin dosing could be higher than desired and could result in increased toxicity. There are several agents that are sometimes prescribed at a fixed dose or capped based on the dose that was used in clinical trials. The usual adult dose of bleomycin for testicular cancer is a fixed dose in a BEP (bleomycin, etoposide, cisplatin) regimen.¹²⁴ In the R-CHOP (rituximab plus CHOP), CHOP, and CVP regimens, the dose of vincristine is capped at a maximum of 2 mg.^{125,126}

Of note, the use of flat-fixed dosing of irinotecan has been previously examined but not in large clinical trials. In one trial, just 26 patients were treated with a fixed irinotecan dose of 600 mg over a 90-minute infusion, and pharmacokinetic and pharmacodynamic parameters were compared with those of 47 patients treated with irinotecan at a dose of 350 mg/m². No significant differences were observed, and hematologic adverse effects were also noted to be similar.⁴⁵ In another study of 82 patients receiving irinotecan as a 90-minute IV infusion from 175 to 350 mg/m², BSA was not a predictor of clearance or other drug pharmacokinetics.¹²⁷ In general oncologic practice, dosing for irinotecan remains based on BSA.

There are other agents that have been used in fixed doses in non-RCTs of the treatment of specific cancers in unique patient populations; these include agents such as metronomic cyclophosphamide¹²⁸⁻¹³³ and capecitabine.¹³⁴ Fixed dosing based on BMI or BSA categories is possible and has been proposed for some agents (eg, cisplatin), but such approaches have never been prospectively evaluated.¹⁰⁷

Clinical Question 5

How should BSA be calculated? Specifically, what is the best formula for use in the obese patient with cancer?

Recommendation 5.1. The Panel recommends that BSA be calculated using any of the standard formulas (eg, Mosteller, DuBois and Dubois, Haycock, Gehan and George, Boyd formulas). There is no evidence to support one formula for calculating BSA over another.

Literature review and analysis. It should be noted that the formulas for calculating BSA were not developed for use in the obese or morbidly obese and/or those with multiple comorbid conditions and do not take into account patient sex. In fact, there may be noticeable differences (> 10%) in calculated values of BSA, especially at the extremes of weight and/or height, resulting in noticeable differences in dosing. There are ongoing efforts to establish a new BSA equation suitable for a typical 21st century population, because > 60% of adult Americans have BMIs > 25 kg/m², and this proportion is steadily increasing.^{24,25} Data Supplement 5 at www.asco.org/guidelines/wbd includes BSA formulas currently used.

Clinical Question 6

What is the role of pharmacokinetic and/or pharmacogenetic 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.

Key measures of pharmacokinetics. Clearance is the most important pharmacokinetic parameter to consider when devising a dosing regimen for anticancer agents, because it is inversely related to the AUC. This parameter has clinical relevance because it correlates with clinical outcomes, although there are only a few examples in which the association is reproducible.¹³⁵ For the majority of anticancer drugs, the liver is the principal organ mediating clearance. The accumulation of fat in the liver of obese patients may alter hepatic blood flow, and this pathologic change might have an impact on clearance. There is limited evidence of an increase in cytochrome P450 (CYP) 2E1 activity with obesity.¹³⁶ Because few anticancer drugs are substrates for CYP2E1, the clinical significance of this finding is probably minimal. It has also been reported that the phenotypic activity of certain other isoforms of the CYP system, such as CYP3A, might be elevated in the obese,¹⁰⁹ but it is unclear to what extent the findings can be definitively linked with any particular enzyme. In regard to phase II conjugation pathways, the results of studies with various drugs have suggested that increases in glucuronidation and sulfation occurring in obese individuals are proportional to total body weight.¹³⁷ The other primary organs involved in the clearance of drugs are the kidneys. The processes involved in drug elimination through the kidneys include glomerular filtration, tubular secretion, and tubular reabsorption. The effect of obesity on these functions is not entirely clear.¹³⁷ Studies of creatinine clearance, used to estimate GFR, have found increased, decreased, or similar GFR measurements in obese versus non-obese individuals.¹³⁷ The variable results probably reflect the imprecision of creatinine as an index of the GFR.

The pharmacokinetics of some but not all drugs may be altered in obese patients, but there is no single valid method to relate drug clearance to degree of obesity, so changes in drug dosing are not currently recommended. Nevertheless, it was suggested that lean body weight may be the best descriptor in 35% of the studies in which it was considered (across the therapeutic areas).⁶⁸ From a physiologic standpoint, this seems plausible, because the major drug-clearing organs are constituents of lean body weight. Three observations regarding drug clearance and obesity were recently described¹³⁸: (1) obese individuals exhibit higher absolute drug clearance than do their non-obese counterparts; (2) clearance does not increase linearly with total body weight; and (3) clearance and lean body weight are linearly correlated. Although findings from

several studies are in agreement with observations (1) and (2), less evidence exists to support observation (3). In the context of anti-cancer drugs, the contention¹³⁸ that a semi-mechanistically derived lean body weight is an ideal size descriptor to ascertain the impact of body composition on the clearance of anticancer drugs has been challenged.¹³⁹

Pharmacokinetic changes in obese patients with cancer. There is a general paucity of information from sufficiently powered clinical studies on the influence of obesity on the pharmacokinetics of most anticancer drugs. 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. In particular, dosing recommendations in oncology are usually based on results from clinical trials that included patients who are considered to be the typical weight of those likely to receive the drug in clinical practice. In many studies, the obese patient may be under-represented. Therefore, extrapolation of dosing recommendations based on pharmacokinetic principles to this group must be performed arbitrarily when the dose is required to be standardized to a particular patient characteristic such as BSA.

In a retrospective analysis, absolute clearance of cisplatin, paclitaxel, and troxacitabine⁹⁷ was significantly higher in patients who were obese (BMI ≥ 30 kg/m²) compared with lean controls (BMI ≤ 25 kg/m²), but this was not observed for carboplatin, docetaxel, irinotecan, or topotecan.^{38,47,97} The data on the renally cleared drugs cisplatin and troxacitabine are consistent with the notion that tubular secretion, rather than glomerular filtration, is disproportionately increased in obese individuals.¹⁴⁰ It is possible that the impact of obesity on the clearance of the hepatically cleared drug paclitaxel originates from changes in activity of one or more CYP enzymes. Nonetheless, a similar effect of obesity on absolute clearance was not observed for the structurally related drug docetaxel. This discrepancy might be related to the finding that for docetaxel, the volume of distribution and the half-life of the terminal phase were statistically significantly increased in the obese. This has been described previously for other hydrophobic drugs that have a high affinity for adipose tissue.¹³⁷ In addition, it is possible that paclitaxel and docetaxel are differentially influenced by hepatic transporters, because the function is altered in the obese. Regardless of the exact explanation for this incongruence, this example of the two taxanes clearly weakens the ability to support broad recommendations for dose calculation in the obese for drugs on the basis of physicochemical characteristics alone.

Additional retrospective investigation has revealed that the absolute oral clearance of busulfan in obese and severely obese patients was significantly faster compared with that in normal-weight patients.¹⁴¹ When normalized to BSA, the oral clearance of busulfan was not significantly different between underweight, normal-weight, obese, or severely obese patients. Using the same classification scheme, there were also no significant differences in BSA-adjusted clearance among BMI classes in a study in which busulfan was administered intravenously.¹⁴² The potential usefulness of alternative weight descriptors in the equation for BSA to calculate drug dose in obese patients has been evaluated through a simulation analysis for various anticancer drugs.⁹⁷ This work demonstrated that dose calculation in the obese on the basis of BSA using actual body weight is an appropriate strategy for cisplatin, paclitaxel, and troxacitabine.

For carboplatin, consideration of either predicted normal weight or the mean of ideal and actual weight resulted in the best

prediction of systemic exposure in both men and women.⁹⁷ In line with this finding, a prior analysis of data obtained in obese patients receiving carboplatin demonstrated that neither actual body weight nor ideal body weight was a perfect size descriptor and that the average of actual body weight and ideal body weight, obtained from a nonlinear mixed-effect modeling analysis, was the best predictor of carboplatin clearance within the formula integrating body weight and GFR.¹⁴³ These findings for carboplatin, in conjunction with an assessment of cystatin C measurements as a marker of GFR, were confirmed in a large cohort of patients.^{122,144}

For docetaxel and doxorubicin, applying lean body weight as a dosing scalar seems to have particular merit in predicting pharmacokinetic end points.¹³⁷ Nonetheless, the weight of clinical and pharmacodynamic evidence suggests that full weight–based dosing of anthracyclines in patients with cancer who are obese is important in achieving optimal outcomes.^{13,28,97} Similarly, despite pharmacokinetic data suggesting that lean body weight predicts pharmacokinetic end points with docetaxel, Cooperative Group clinical trials have not limited doses of taxanes in obese patients with cancer.¹⁴⁵

Taking currently available pharmacokinetic data into consideration, it seems that: (1) the pharmacokinetics of some, but not all, cancer drugs are significantly altered in the obese; (2) the selection of alternative size descriptors for dose calculation in the obese is drug specific and sex dependent and seems unrelated to intrinsic physicochemical properties or route of elimination; (3) obesity may affect, possibly in a drug-specific manner, treatment outcome through currently unknown mechanisms that are unrelated to pharmacokinetics; and (4) empiric decreases in drug dose for obese patients (eg, dose capping) are not supported by pharmacokinetic findings for any agent. Overall, there are insufficient pharmacokinetic data to reject the Panel's 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. To date, there are no published pharmacogenetic articles meeting the inclusion and exclusion criteria for this guideline that could have been included in the discussion. Nevertheless, there may be a future role for applying pharmacokinetic and pharmacogenetic principles in cancer chemotherapy dosing to achieve a more personalized approach to treatment for the obese,¹⁴⁶ although large prospective studies are certainly required to support this practice.

PATIENT AND CLINICIAN COMMUNICATION

Chemotherapy dose selection generally lies within the purview of the treating physician. If obese patients or caregivers inquire about dosing, however, a discussion of the evidence contained within this guideline is appropriate. Physicians may have to explain to obese patients and caregivers that higher doses are needed to be effective. In fact, suboptimal treatment could result if dosing is not full weight based. It is important to reassure patients that toxicity from the appropriate dose of chemotherapy is not expected to be greater. Adverse effects will be monitored closely. Patients should be warned that costs, even insurance copays, may be higher.

Communication with other health care providers is also warranted, particularly if the use of full weight–based dosing has not been the practice in a given setting. Pharmacists and nursing professionals

who are accustomed to limiting chemotherapy doses for obese patients should be informed of the existing evidence.

IV and oral doses may be prepackaged for patients of normal weight, but appropriate dosing should be delivered regardless of doses contained within a given vial. Arbitrary capping based on drug procurement costs is unacceptable (eg, one vial v 1.5 vials). The use of full weight–based dosing may have cost implications for payers, particularly if full weight–based doses of chemotherapy lead to more frequent use of WBC growth factors as prophylaxis to reduce the incidence of febrile neutropenia.

If a suboptimal dose is administered initially, it should be increased to a full weight–based dose as tolerated. Patients need to be made aware of appropriate doses and be encouraged to monitor dose changes.

HEALTH DISPARITIES

Some racial and ethnic minorities and patients of lower socioeconomic status (SES) are at risk of suboptimal cancer care. Members of some racial and ethnic minority groups and patients with fewer financial resources tend to have a higher burden of comorbid illness, are more likely to be uninsured or underinsured, and face greater challenges in accessing high-quality health care.¹⁴⁷⁻¹⁴⁹ Awareness of disparities in quality of chemotherapy dose selection should be considered in context.

Black/African American patients and patients of lower SES are more likely to receive reduced doses of adjuvant chemotherapy in the treatment of breast cancer.^{19,150} The higher rates of obesity among blacks/African Americans, Hispanics/Latinos, and people of lower SES¹⁵¹⁻¹⁵³ only increase the likelihood of chemotherapy dose limits among these patients, who already experience higher case-fatality rates.¹⁵⁴ Up to 40% of obese patients with breast cancer receive substantially reduced chemotherapy doses (> 10% to 15% dose reduction), compared with doses that would be administered if actual body weight were used in dose calculations.^{13,51} Given the systematic differences in chemotherapy dose selection, it may be that black/African American women and women of lower SES will reap the greatest benefits from a change in the common practice of dose limitations in obese patients to full weight–based dosing. It is reassuring that there is no evidence that toxicity is more likely to occur when full weight–based doses are used.^{13,28,113,155,156}

LIMITATIONS OF THE RESEARCH AND FUTURE DIRECTIONS

The most obvious limitation of the evidence provided in support of these guidelines is the limited number of prospective RCTs directly addressing the issue of weight–based dosing. A prospective systematic review of obese patients enrolled onto a (specific) Cooperative Group trial of this issue would be helpful. Nonetheless, in addition to RCTs supporting the small but significant incremental benefit of dose-intensified therapy compared with standard dose-intensity, several trials have demonstrated a substantial reduction in treatment efficacy, with reductions in relative dose-intensity below standard doses and schedules. Although still representing the gold standard for demonstrating clinical efficacy, RCTs also have several well-recognized limitations. Relevant RCTs are only available for the

most common malignancies (eg, breast, lung, and gynecologic cancers). Studying the impact of relatively small reductions in dose-intensity would require a large sample size to have sufficient power to assess the impact on long-term outcomes such as OS. RCTs often use strict and limiting eligibility criteria, excluding patients with comorbidities commonly encountered in those with cancer, which may reduce the effectiveness or increase toxicity but which often disqualify the patients from the trial. Therefore, RCTs may not adequately address effectiveness in the broader, unselected cancer population with major medical comorbidities and treatment safety issues that may not emerge until years later.

Given the data that do exist, many consider deliberate random assignment of patients with responsive and potentially curable malignancies to lower and potentially less effective dose-intensity to be unethical. However, a rigorous systematic review of data from a series of patients enrolled onto Cooperative Group trials—examining data on all patients (with and without comorbid conditions) who are defined as obese—could shed light on the issue of outcomes for obese patients with cancer.

Therefore, for both economic and ethical reasons, it is unlikely that additional data from RCTs directly addressing this issue will become available. Fortunately, there are abundant and compelling supportive data from both prospective cohort studies and well-done retrospective analyses of RCTs, which have almost universally supported the clinical importance of maintaining relative dose-intensity in patients with cancer with responsive and potentially curable malignancies. Consistent pharmacokinetic and pharmacodynamic studies as well as data from preclinical models including human tumor xenografts and animal studies all provide a firm underlying basis for the recommendations provided in this guideline. Nevertheless, it is essential that the same rigorous attention to accepted measures of high-quality RCTs (ie, study design, conduct, analysis, and reporting) be applied in non-RCT studies as well. It is also essential that the study hypothesis, study population, controls, measurements, analytic methods, and any subgroup analyses be defined a priori. Well-designed

prospective studies with planned analysis of body composition and adverse events would be valuable. There is a real need for data on both toxicity and efficacy in special populations such as the obese. As new drugs are being developed, it is important for industry to at least provide pharmacokinetic and pharmacodynamic data in real-world subgroups that may have been excluded from the clinical trials.

The Panel acknowledges that there are limitations to study results based on data not specifically designed for prospective randomized comparisons. It is clear that clinician dosing decisions for obese patients and missing and/or inaccurately recorded clinical data affect prognosis and response to treatment. Given the numerous challenges to conducting well-designed RCTs on appropriate dosing for obese patients, other study designs will need to play a prominent role in future research. However, optimal care must be the ultimate goal of research on appropriate chemotherapy dosing for obese adult patients with cancer.

ADDITIONAL RESOURCES

An Executive Summary of this guideline has been published in *JCO*. Data Supplements, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/wbd. Patient information is available at www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Appendix

Table A1. Expert Panel Members

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