ASCO special articles

Appropriate Systemic Therapy Dosing for Obese Adult Patients With Cancer: ASCO Guideline Update

Jennifer J. Griggs, MD, MPH[1]; Kari Bohlke, ScD[2]; Edward P. Balaban, DO[3]; James J. Dignam, PhD[4]; Evan T. Hall, MD, MPhil[5]; R. Donald Harvey, PharmD[6]; Diane P. Hecht, PharmD, MEd[7]; Kelsey A. Klute, MD[8]; Vicki A. Morrison, MD[9]; T. May Pini, MD, MPH[10]; Gary L. Rosner, ScD[11]; Carolyn D. Runowicz, MD[12]; Michelle Shayne, MD[13]; Alex Sparreboom, PhD[14]; Sophia Turner, MSc[15]; Corrine Zarwan, MD[16]; and Gary H. Lyman, MD, MPH[5]

abstract

PURPOSE To provide recommendations for appropriate dosing of systemic antineoplastic agents in obese adults with cancer.

METHODS A systematic review of the literature collected evidence regarding dosing of chemotherapy, immunotherapy, and targeted therapies in obese adults with cancer. PubMed and the Cochrane Library were searched for randomized controlled trials, meta-analyses, or cohort studies published from November 1, 2010, through March 27, 2020. ASCO convened an Expert Panel to review the evidence and formulate recommendations.

RESULTS Sixty studies, primarily retrospective, were included in the review. Overall, the evidence supported previous findings that obese adult patients tolerate full, body-size–based dosing of chemotherapy as well as nonobese patients. Fewer studies have addressed the dosing of targeted therapies and immunotherapies in relation to safety and efficacy in obese patients.

RECOMMENDATIONS The Panel continues to recommend that full, weight-based cytotoxic chemotherapy doses be used to treat obese adults with cancer. New to this version of the guideline, the Panel also recommends that full, approved doses of immunotherapy and targeted therapies be offered to obese adults with cancer. In the event of toxicity, the consensus of the Panel is that dose modifications of systemic antineoplastic therapies should be handled similarly for obese and nonobese patients. Important areas for future research include the impact of sarcopenia and other measures of body composition on optimal antineoplastic dosing, and more customized dosing based on pharmacokinetic or pharmacogenetic factors.

Additional information is available at www.asco.org/supportive-care-guidelines.

J Clin Oncol 39:2037-2048. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 27, 2021 and published at ascopubs.org/journal/jco on May 3, 2021: DOI https://doi.org/10.1200/JCO.21.00471

Practice Guidelines Committee approval: February 10, 2021

Reprint Requests: 2318 Mill Road, Suite 800, Alexandria, VA 22314; guidelines@asco.org

INTRODUCTION

The purpose of this guideline is to provide recommendations on the appropriate dosing of systemic antineoplastic agents in obese adults with cancer. Obesity is commonly defined as a body mass index (BMI; kg/m^2) of ≥ 30, and the question of whether obese patients have unique dosing needs affects a large number of adults with cancer. Between 1999 and 2018, the age-adjusted prevalence of obesity in US adults increased from 30.5% to 42.4%.[1] The original ASCO guideline on this topic, published in 2012, focused on cytotoxic chemotherapy.[2] The relatively narrow therapeutic window for most cytotoxic agents underlies the conventional dosing of these agents based on body size descriptors such as body surface area (BSA) despite limited data supporting this practice and evidence that dose limits compromise outcome. Approaches that limit full calculated dosing in overweight and obese patients with cancer have gradually faded since the publication and adoption of the previous version of this guideline. However, with the introduction of multiple novel cancer therapies, the scope of this update has been expanded to include immunotherapy (specifically, checkpoint inhibitors) and targeted cancer therapies. Despite increasing pressure for the investigation and adoption of fixed dosing of cancer therapies, only selected agents have been approved for fixed or flat dosing at this time.

GUIDELINE QUESTIONS

This clinical practice guideline addresses six clinical questions: (1) What are the safety and efficacy of full, weight-based dosing of cytotoxic chemotherapy in obese adults with cancer? (2) Is the use of fixed-dose (dose prescribed independently of weight or BSA)

THE BOTTOM LINE

Appropriate Systemic Therapy Dosing for Obese Adult Patients with Cancer: ASCO Guideline Update

Guideline Question

How should antineoplastic doses be determined in obese adults?

Target Population

Obese adults who will receive systemic antineoplastic therapies (chemotherapy, immunotherapy, or targeted therapy).

Target Audience

Medical oncologists, oncology nurses, nurse practitioners, physician assistants, oncology pharmacists, and patients with cancer.

Methods

An Expert Panel was convened to develop updated clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Recommendation 1

Full weight-based dosing of cytotoxic chemotherapy should be offered regardless of obesity status (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Recommendation 2

The Panel recommends limiting fixed dosing of chemotherapy to select cytotoxic agents (eg, bleomycin). Although fixed dosing of other cytotoxic chemotherapeutic agents has been used in clinical trials, evidence remains limited that fixed-dosing strategies are equivalent to weight- or body surface area (BSA)-based dosing in terms of toxicity and efficacy (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Recommendation 3

US Food and Drug Administration–approved prescribing information for checkpoint inhibitors should be used in all patients, regardless of obesity status (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Recommendation 4

US Food and Drug Administration–approved prescribing information for targeted therapies should be used in all patients, regardless of obesity status (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Recommendation 5

If an obese patient experiences high-grade toxicity from systemic antineoplastic therapy, clinicians should follow the same guidelines for dose reduction for all patients, regardless of obesity status (type: informal consensus; evidence quality: insufficient; strength of recommendation: weak).

Recommendation 6

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 (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

cytotoxic chemotherapy ever justified? Are there unique dosing considerations for certain chemotherapeutic agents? (3) What are the safety and efficacy of approved doses of checkpoint inhibitors (fixed or weight-based) in obese adults with cancer? (4) What are the safety and efficacy of approved doses of targeted therapies (fixed or weight-based) in obese adults with cancer? (5) If an obese patient experiences high-grade toxicity, should systemic antineoplastic therapy doses or schedules be modified differently from modifications used for nonobese patients

with cancer? (6) How should BSA be calculated? Specifically, what is the best formula for use with an obese patient with cancer?

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel met via webinars and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were made available for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were considered while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. Ultimately, all ASCO guidelines are reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of the literature and clinical experience. PubMed and the Cochrane Library were searched for articles published from November 1, 2010, through March 27, 2020. Search terms are provided in the Data Supplement (online only). Articles were selected for inclusion in the systematic review based on the following criteria:

- Study designs: randomized controlled trials (RCTs), meta-analyses, and cohort studies.
- Population: overweight or obese patients with cancer. Patients with leukemia were excluded from the 2010 guideline but included in this update. Patients undergoing bone marrow or peripheral blood stem cell transplantation and pediatric patients were excluded.
- Interventions: systemic therapies for cancer, including chemotherapy, targeted therapy, and immunotherapy.
- Primary outcomes of interest: efficacy and toxicity of cancer therapy
- Sample size: $\geq$ 25 patients total

Articles were excluded from the systematic review if they were: (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; (3) published in a non-English language; or (4) addressed in an included systematic review.

The guideline recommendations were crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.[3] In addition, a guideline review regarding implementation was conducted. Based on the implementation review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Expert Panel and guidelines staff will work with cochairs to keep updated regarding new information related to this topic. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of March 27, 2020, the end date of the literature search for this Guideline.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

The literature review identified 532 potentially relevant citations. Of these, 101 were examined in detail, and 60 met eligibility criteria. These,[4-63] along with earlier evidence from the 2012 guideline,[2] comprised the evidence base for the guideline recommendations. The included studies consisted of retrospective and prospective cohort studies, post hoc analyses of RCTs, and meta-analyses of observational studies. Evidence tables and a summary of the search results are provided in the Data Supplement. Study quality was not formally assessed, but given the absence of RCTs, overall quality of evidence was considered to be low.

RECOMMENDATIONS

Clinical Question 1

What are the safety and efficacy of full, weight-based dosing of cytotoxic chemotherapy in obese adults with cancer?

Recommendation 1

Full weight-based dosing of cytotoxic chemotherapy should be offered regardless of obesity status (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Literature review and analysis. Ten retrospective studies[10-12,19,20,24,33,41,45,50] and one meta-analysis of observational studies[27] evaluated the toxicity of full, uncapped chemotherapy doses by body size in patients with solid tumors or lymphoma. The cancer types included were breast cancer,[10,19,41,45] gynecologic cancer,[24,33] non-Hodgkin lymphoma,[12,20] advanced colorectal cancer,[11] glioblastoma,[50] or any.[27] One of these studies focused specifically on older patients, evaluating 615 women of age 65 years or older with early breast cancer.[45] All but one study[19] reported that obese patients had toxicity rates that were similar to or lower than nonobese patients. The study that reported higher toxicity in obese patients given full, weight-based dosing involved 2,990 patients treated with dose-dense chemotherapy for high-risk, early breast cancer. Of the 555 obese patients, 173 were dosed according to their actual BSA, and 382 had their doses capped or adjusted to ideal weight. Obese patients who received full-dose chemotherapy had higher rates of several adverse events compared with obese patients who received adjusted-dose chemotherapy, with no significant improvement in overall survival (OS). Febrile neutropenia occurred in 8.4% of nonobese patients, 14.7% of obese patients who received full-dose chemotherapy, and 6.3% of obese patients who received adjusted-dose chemotherapy.

Additional studies did not compare full and reduced doses but did evaluate differences in toxicity by obesity status. A meta-analysis of 15 studies reported that overweight or obese women with breast cancer were more likely than normal-weight women to develop cardiotoxicity after treatment with anthracyclines or sequential anthracyclines and trastuzumab (odds ratio, 1.38; 95% CI, 1.06 to 1.80).[22] In the case of anthracyclines, risk of cardiotoxicity is associated with the cumulative dose over time, often limiting the total dose delivered.[64]

In leukemia, five retrospective studies evaluated chemotherapy toxicity by body size and dosing in patients with acute myeloid leukemia (AML).[38,39,43,47,61] Compared with normal-weight patients, toxicity from full-dose induction chemotherapy was not significantly increased in obese patients.

Efficacy of full versus reduced doses in the first cycle of chemotherapy was evaluated in five studies of patients with solid tumors,[4,11,19,55,62] and three reported that reduced doses result in worse outcomes in at least a subset of patients.[11,55,62] In a study of 4,781 patients with advanced colorectal cancer, obese patients who received reduced doses had shorter progression-free survival (PFS) than obese patients who received full doses (hazard ratio [HR], 1.21; 95% CI, 1.06 to 1.39).[11] The difference in OS was not statistically significant (HR, 1.12; 95% CI, 0.96 to 1.30). A second study of colorectal cancer evaluated 280 obese patients with stage III colon cancer and found a nonsignificant association between full versus reduced dosing of adjuvant chemotherapy and recurrence-free survival and OS.[55] However, in the subset of patients with both high BMI ($\geq$ 30 kg/m^2) and high BSA ($\geq$ 2 m^2), full dosing was associated with better recurrence-free survival (HR, 0.48; 95% CI, 0.27 to 0.85) and a borderline-significant improvement in OS (HR, 0.53; 95% CI, 0.28 to 1.01). In a study of 333 men with metastatic prostate cancer, patients who received dose reductions at the first dose had shorter OS than patients who received full-dose treatment (18.2 months *v* 22.4 months; $P = .001$).[62]

Two studies did not report significant associations between first-cycle dose reductions and treatment efficacy.[4,19] In a

study of 2,990 patients treated with dose-dense chemotherapy for early breast cancer, dose adjustments did not significantly affect OS. Five-year OS in obese patients given full doses, obese patients given adjusted doses, and nonobese patients was 86%, 88%, and 90%, respectively ($P = .14$)[19] Similarly, in a pooled analysis of five trials of first-line treatment for metastatic colorectal cancer, obese patients were more likely than normal-weight patients to receive first-cycle dose reductions, but these dose reductions were not significantly associated with OS or PFS in obese patients (OS: HR, 1.28; 95% CI, 0.88 to 1.87; PFS: HR, 1.03; 95% CI, 0.74 to 1.45).[4]

In AML, obese patients given full, body-size–based chemotherapy dosing had survival that was similar to[38,43,61] or better than[9] normal-weight patients. In AML studies in which chemotherapy dosing was capped or adjusted for patients with large body sizes, efficacy outcomes tended not to vary significantly by body size,[8,34,57] but these studies could not address whether outcomes would have been better if obese patients had been given full dosing. The results may also differ by patient subgroup, as one study that reported no overall difference in efficacy by weight with capped dosing did report worse OS in obese patients with favorable-risk AML.[57] Two studies compared full versus reduced dosing in obese patients with AML. A study in which seven of 21 obese patients received dose reductions reported no significant association between dose reduction and response rates,[39] whereas a larger study (132 patients overall received dose reductions) reported worse OS in overweight or obese patients given reduced doses.[14]

Clinical interpretation. Much attention has focused on total body drug distribution and the impact of obesity. Historically, cytotoxic chemotherapy dosing based on BSA was often capped or based on idealized weight in the severely obese patient with cancer over fear of excessive toxicity. There is little evidence to suggest that obese patients dosed on the basis of their actual body weight have increased toxicity, while there are data from retrospective studies that underdosing is associated with inferior outcomes.

Clinical Question 2

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 2

The Panel recommends limiting fixed dosing of chemotherapy to select cytotoxic agents (eg, bleomycin). Although fixed dosing of other cytotoxic chemotherapeutic agents has been used in clinical trials, evidence remains limited that fixed-dosing strategies are equivalent to weight- or BSA-based dosing in terms of toxicity and efficacy (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Literature review and analysis. In the updated systematic review, a single study compared fixed versus BSA-based capecitabine.[15] The study evaluated 2,319 patients (1,126 with fixed-dosing capecitabine and 1,193 with BSA-based dosing) with colorectal cancer, breast cancer, gastric cancer, or other cancers. Rates of capecitabine-related toxicity were generally similar with fixed or BSA-based dosing, and within the fixed-dose cohort, BSA was not significantly associated with efficacy.

Clinical interpretation. With the exception of bleomycin, there are no data to support the use of fixed dosing of cytotoxic chemotherapy agents. In the absence of data supporting the equivalence or superiority of fixed dosing, such a strategy should not be used. The practice of limiting vincristine doses to 2.0 mg in clinical trial protocols is not supported by existing data.[65] The US Food and Drug Administration (FDA)-approved prescribing information does not indicate that vincristine doses should be limited.[66]

Clinical Question 3

What are the safety and efficacy of approved doses of checkpoint inhibitors (fixed or weight-based) in obese adults with cancer?

Recommendation 3

FDA-approved prescribing information for checkpoint inhibitors should be used in all patients, regardless of obesity status (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Literature review and analysis. Obese patients treated with checkpoint inhibitors have been reported to experience greater toxicity[13,63] and improved survival[35,42,63] relative to nonobese patients. Whether and how these outcomes relate to dosing, however, remain uncertain.

Clinical interpretation. The dosing of checkpoint inhibitors currently varies by agent between fixed dosing and weight-based dosing depending on the dosing schedule used in pivotal trials. Although many checkpoint inhibitors were approved for weight-based dosing, pharmacokinetic (PK) data from clinical trials report that fixed dosing provides similar exposure with equivalent PK variability, leading to FDA labeling changes for nivolumab[67,68] and pembrolizumab.[69] Monoclonal antibodies generally have a wider therapeutic window and distribution in blood plasma and extracellular fluid, which correlates less with body size characteristics, making them potentially amenable to fixed dosing.[70]

The paradoxical association between obesity and improved outcomes in patients treated with programmed cell death-1 inhibitors appears to be independent of weight-based dosing of these agents. One proposed mechanism for this observation involves enhanced expression of programmed cell death-1 via elevated levels of leptin in the setting of obesity.[71]

Clinical Question 4

What are the safety and efficacy of approved doses of targeted therapies (fixed or weight-based) in obese adults with cancer?

Recommendation 4

FDA-approved prescribing information for targeted therapies should be used in all patients, regardless of obesity status (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Literature review and analysis. Several studies have evaluated the efficacy or toxicity of targeted therapies in relation to obesity, but whether and how different dosing strategies would modify these relationships remain uncertain. Studies of the small-molecule targeted therapies niraparib, gefitinib, and osimertinib reported that patients with higher BSA or body weight tolerated treatment as well as[29,46] or better than[7] patients with lower BSA or body weight. With regard to efficacy, a 2018 pooled analysis evaluated patients with metastatic melanoma who were treated with a checkpoint inhibitor, targeted therapy (either dabrafenib and trametinib or vemurafenib and cobimetinib), or chemotherapy (dacarbazine).[42] Obesity was associated with improved OS in patients treated with checkpoint inhibitors or targeted therapy but not in patients treated with chemotherapy. In four studies of patients treated with gefitinib for non–small-cell lung cancer, two studies reported that higher BSA was associated with shorter PFS, without having a significant effect on OS,[28,37] and two studies reported no significant association between BSA or BMI and survival.[29,30]

In patients treated with rituximab for aggressive B-cell lymphoma, several studies have reported that obese patients have survival that is similar to[12,26] or better than[54,60] nonobese patients. However, in a study of elderly patients with aggressive B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), obesity was associated with worse outcomes in female patients.[25] The authors postulated that this finding may have been because of a more rapid rituximab clearance in this subgroup. Two studies reported that toxicity of R-CHOP is not increased in obese patients.[12,20]

A 2011 pooled analysis of chemotherapy with or without bevacizumab for advanced colorectal cancer raised the possibility that bevacizumab may be less effective in obese patients.[52] Two subsequent studies, however, reported that the efficacy of bevacizumab[4] or any targeted therapy[49] did not vary significantly by BMI in patients with metastatic colorectal cancer. Findings in ovarian cancer were similar, with a 2014 study of 46 patients study indicating that bevacizumab was less effective in obese patients,[53] and a 2019 study of 1,538 patients reporting that the association of bevacizumab with survival did not vary significantly by adiposity.[58]

As noted previously, obese patients with breast cancer treated with anthracyclines and/or trastuzumab have been reported to have an increased risk of cardiotoxicity.[22]

Clinical interpretation. Among rituximab-treated patients, previous PK studies demonstrated a superior outcome in elderly females relative to elderly males, young males, and young females, on the basis of decreased clearance of rituximab leading to prolonged exposure time to the agent with resultant improved benefit.[72] This benefit may be diluted among older women who are obese, because of faster clearance of rituximab in obese patients. In a frontline R-CHOP-14 trial in older patients (age, 61-80 years), utility of a 500 mg/m^2 (*v* the traditional 375 mg/m^2) rituximab dose in males was examined, with this higher dose resulting in no increased toxicities, but a 32.5% improvement in PFS ($P = .039$) and 30% trend toward longer OS ($P = .076$).[73]

In the case of cardiotoxicity in patients with breast cancer treated with trastuzumab, studies are limited by previous or concomitant anthracycline use. Variables unrelated to dosing of human epidermal growth factor receptor 2 targeted therapy may influence cardiac toxicity in the setting of treatment for breast cancer, such as obesity-related imbalance in pro-inflammatory and anti-inflammatory adipokines contributing to an inflammatory state that promotes cardiovascular disease[74] or neurohormonal activation, elevated oxidative stress, and hemodynamic load and left ventricular remodeling associated with obesity.[75]

Clinical Question 5

If an obese patient experiences high-grade toxicity, should systemic antineoplastic therapy doses or schedules be modified differently from modifications used for nonobese patients with cancer?

Recommendation 5

If an obese patient experiences high-grade toxicity from systemic antineoplastic therapy, clinicians should follow the same guidelines for dose reduction for all patients, regardless of obesity status (type: informal consensus; evidence quality: insufficient; strength of recommendation: weak).

Literature review and analysis. None of the included studies specifically addressed this question.

Clinical interpretation. 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 nonobese 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 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, and significant improvement in performance status). Obesity status alone should not play a role in dose modifications in response to toxicity.

Clinical Question 6

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

Recommendation 6

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 (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Literature review and analysis. The one included study compared the DuBois and Mosteller equations for BSA, with a focus on doxorubicin dosing in the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine).[16] The results indicated that the Mosteller equation provided a greater chemotherapy dose, particularly for patients in the 50th-95th percentiles for height or weight, but that further study was necessary.

Clinical interpretation. Formulae for calculating BSA were not developed for use in the 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 the 21st century.

DISCUSSION

The proportion of people who are classified as obese is increasing globally.[76] Obesity is a risk factor for cancer[77] and, in many cases, for poorer cancer-specific outcomes.[78] Although treatment patterns do not fully explain the disparities in cancer-specific outcomes, avoiding systematic underdosing of this important population is one way to limit unwarranted variations in care. Moreover, avoiding the practice of limiting anticancer therapy doses in people with a large BSA applies not only to people who are classified as obese, but also to people who are taller than average. It should also be noted that the use of BMI is a useful screening tool for obesity, but that BMI is only moderately correlated with adiposity. BMI norms are based on those developed in people of European descent. Many people who are categorized as obese have no evidence of ill health and, conversely, people categorized as having normal body weight may have biomarkers that are typically associated with obesity.[79]

PATIENT AND CLINICIAN COMMUNICATION

Chemotherapy dose selection is not generally a shared decision between prescribers and patients. Obese patients do, however, experience stigma and weight-based implicit and explicit bias by many in the medical profession.[80] These biases affect the care experiences of people of larger body size. Multidisciplinary care team members, for example, physicians, pharmacists, and treatment nurses, must guard against reinforcing stereotypes faced by patients who are classified as obese.

For general recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.[81]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that not all patients have access to guideline-concordant care. Race, area-level socioeconomic status, and geography have all been associated with disparities in chemotherapy dose selection.[82,83] Patients with cancer who are members of marginalized groups, including racial and ethnic minorities, suffer disproportionately from comorbid illnesses, face more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[84-86] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers, health systems, and policy makers should implement strategies that deliver the highest level of cancer care to all of their patients. An updated ASCO policy statement on cancer disparities and health equity was published in August 2020.[87] The statement focuses on improving equitable access to care, improving clinical research, addressing structural barriers, and increasing awareness.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[88,89] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[90,91]

Discussion of cost can be an important part of shared decision making.[92] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[92]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[92]

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from November 20, 2020, through December 4, 2020. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation. Five of the seven respondents agreed with all recommendations as written, and two agreed with proposed modifications. The draft was also submitted to two external reviewers with content expertise. Review comments from all sources were reviewed by the Expert Panel and integrated into the final manuscript before final approval by the ASCO Clinical Practice Guidelines Committee.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the Panel. The additional role of this PGIN representative on the Panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the Journal of Clinical Oncology.

LIMITATIONS OF THE RESEARCH AND FUTURE RESEARCH

The role of sarcopenia in relation to toxicity and efficacy of systemic antineoplastic therapy has received increasing research attention in recent years. Sarcopenia refers to the loss of skeletal muscle mass and muscle function.[93] Although specific definitions and cutpoints have varied across studies, several studies have reported that that sarcopenia,[94-96] sarcopenic obesity,[97] lower skeletal muscle mass,[98,99] and higher chemotherapy dose per kg of lean body mass[100-102] were associated with increased chemotherapy toxicity. Awareness of a patient's body composition could allow identification of patients who may be at higher risk of treatment-related toxicities for intensified monitoring or supportive care. However, until the complex interaction between body composition, treatment toxicity, and dose modification with clinical outcome and quality of life is better characterized, it remains premature to make recommendations on empiric body composition–based dose modifications. Body composition analysis should be a consideration in the assessment of patients beginning cancer treatment, particularly in the context of clinical trials evaluating novel anticancer therapies. Prospective studies should explore the role of body composition in predicting dose-limiting toxicities and the relationship between dose modification and clinical outcome.

An additional area of interest involves the use of PK and pharmacogenetic information for guiding the dosing of IV and oral antineoplastic agents for obese adult patients with cancer. In the case of fluorouracil, for example, a 2016 meta-analysis compared standard BSA-based dosing with adjusted dosing based on PK monitoring.[103] PK-based dosing was associated with a higher overall response rate and a reduced rate of grade 3 or 4 mucositis. Therapeutic drug monitoring could also play a role in assessing

treatment adherence.[104] But although these findings are promising, there is a paucity of information on the influence of obesity on the PKs of most anticancer drugs from properly powered trials. Data presentation from PK and other trials is rarely categorized by BMI or other body size categories, making interpretation and hypothesis generation difficult for this population.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice[105] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[81] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

AFFILIATIONS

[1]University of Michigan, Ann Arbor, MI
[2]American Society of Clinical Oncology, Alexandria, VA
[3]Penn State Cancer Institute, Hershey, PA
[4]University of Chicago, Chicago, IL
[5]Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA
[6]Emory University, Atlanta, GA
[7]University of Texas MD Anderson Cancer Center, Houston, TX
[8]University of Nebraska Medical Center, Omaha, NE
[9]University of Minnesota Hennepin County Medical Center, Minneapolis, MN
[10]Flatiron Health, Inc, New York, NY
[11]Johns Hopkins University, Baltimore, MD
[12]Herbert Wertheim College of Medicine, Florida International University, Miami, FL
[13]University of Rochester Medical Center, Rochester, NY
[14]Ohio State University, Columbus, OH
[15]Independent Cancer Patient's Voice, London, UK
[16]Lahey Hospital and Medical Center, Burlington, MA

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

EQUAL CONTRIBUTION

J.J.G and G.H.L. were Expert Panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.00471.

AUTHOR CONTRIBUTIONS

Conception and design: Jennifer J. Griggs, Kari Bohlke, Edward P. Balaban, James J. Dignam, Vicki A. Morrison, Michelle Shayne, Corrine Zarwan, Gary H. Lyman
Collection and assembly of data: Kari Bohlke, Edward P. Balaban, R. Donald Harvey, Kelsey A. Klute, Vicki A. Morrison, T. May Pini, Michelle Shayne, Alex Sparreboom, Corrine Zarwan,
Data analysis and interpretation: Kari Bohlke, Edward P. Balaban, James J. Dignam, Evan T. Hall, R. Donald Harvey, Diane P. Hecht, Kelsey A. Klute, Vicki A. Morrison, T. May Pini, Gary L. Rosner, Carolyn D. Runowicz, Michelle Shayne, Alex Sparreboom, Sophia Turner, Corrine Zarwan, Gary H. Lyman
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The Expert Panel wishes to thank Drs Robin Zon, Jonathan Friedberg, Peter Van Veldhuizen, and Carey Anders, and the Clinical Practice Guidelines Committee for their thoughtful reviews and insightful comments on this guideline.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Appropriate Systemic Therapy Dosing for Obese Adult Patients With Cancer: ASCO Guideline Update

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Jennifer J. Griggs
Employment: Anglona Corporation
Stock and Other Ownership Interests: Anglona Corporation

James J. Dignam
Consulting or Advisory Role: Merck, Celgene, Northwest Biotherapeutics

Evan T. Hall
Travel, Accommodations, Expenses: Novartis
Other Relationship: Cancer Support Community
Uncompensated Relationships: Bristol Myers Squibb
Open Payments Link: https://openpaymentsdata.cms.gov/physician/1368769

R. Donald Harvey
Consulting or Advisory Role: GlaxoSmithKline
Research Funding: AstraZeneca, Calithera Biosciences, Pfizer, AbbVie, Boston Biomedical, Genmab, Nektar, Rgenix, Xencor, Meryx Pharmaceuticals, Abbisko, Actuate Therapeutics, Alkermes, Amgen, Bayer, Fujifilm, GlaxoSmithKline, Infinity Pharmaceuticals, InhibRx, Merck, Mersana, Puma Biotechnology, RAPT Therapeutics, Seattle Genetics, Sutro Biopharma, Takeda

Kelsey A. Klute
Consulting or Advisory Role: Cancer Expert Now

Vicki A. Morrison
Consulting or Advisory Role: Celgene, Merck
Speakers' Bureau: Celgene, Seattle Genetics
Patents, Royalties, Other Intellectual Property: UpToDate author (Pathogenesis of infection in CLL pts, prevention of infection in CLL pts)

T. May Pini
Employment: Flatiron Health, Premier Inc
Stock and Other Ownership Interests: Roche, Premier Inc

Gary L. Rosner
Stock and Other Ownership Interests: Johnson & Johnson, Walgreens
Honoraria: Novartis
Consulting or Advisory Role: Novartis, Medicago R&D Inc
Travel, Accommodations, Expenses: Novartis
Other Relationship: Novartis

Carolyn D. Runowicz
Honoraria: UpToDate
Patents, Royalties, Other Intellectual Property: Patent for High efficacy anticancer drug delivery, release and nanoscale heat treatment of cancerous cells

Michelle Shayne
Research Funding: BeyondSpring Pharmaceuticals

Sophia Turner
Employment: IQVIA

Corrine Zarwan
Consulting or Advisory Role: Perceptive Informatics, Revere Pharmaceuticals, Advance Medical
Research Funding: Tesaro, Novartis, Merrimack, EMD Serono

Gary H. Lyman
Consulting or Advisory Role: G1 Therapeutics, Sandoz-Novartis, Samsung Bioepis, BeyondSpring Pharmaceuticals, Teva
Research Funding: Amgen
Travel, Accommodations, Expenses: Bayer

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Appropriate Systemic Therapy Dosing for Obese Adult Patients With Cancer: ASCO Guideline Update Expert Panel Membership

Name	Affiliation or Institution	Role or Area of Expertise
Jennifer J. Griggs, MD, MPH, Cochair	University of Michigan, Ann Arbor, MI	Medical oncology, quality of cancer care, health disparities, cancer survivorship
Gary H. Lyman, MD, MPH, Cochair	Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA	Hematology and oncology, health economics, epidemiology, and biostatistics
Edward P. Balaban, DO	Penn State Cancer Institute, Hershey, PA	GI malignancies, health policy
James J. Dignam, PhD	University of Chicago, Chicago, IL	Biostatistics, clinical trials
Evan T. Hall, MD, MPhil	Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA	Medical oncology, specializing in skin cancers and kidney cancer
R. Donald Harvey, PharmD	Emory University, Atlanta, GA	Pharmacy, clinical pharmacology, phase I clinical trials
Diane P. Hecht, PharmD, MEd	University of Texas MD Anderson Cancer Center, Houston, TX	Pharmacy, clinical pharmacology
Kelsey A. Klute, MD	University of Nebraska Medical Center, Omaha, NE	Medical oncology, GI cancers, cancer cachexia
Vicki A. Morrison, MD	University of Minnesota Hennepin County Medical Center, Minneapolis, MN	Medical oncology, with a focus on lymphoproliferative disorders
T. May Pini, MD, MPH	Flatiron Health, Inc, New York, NY	Medical oncology, outcomes, and health services research
Gary L. Rosner, ScD	Johns Hopkins University, Baltimore, MD	Biostatistics
Carolyn D. Runowicz, MD	Herbert Wertheim College of Medicine Florida International University, Miami, FL	Gynecologic oncology
Michelle Shayne, MD	University of Rochester Medical Center, Rochester, NY	Medical oncology, breast cancer, cancer genetics, cancer survivorship
Alex Sparreboom, PhD	Ohio State University, Columbus, OH	Pharmacy, clinical pharmacology
Sophia Turner	Independent Cancer Patient's Voice, London, UK	Patient representative
Corinne Zarwan, MD, PGIN representative	Lahey Hospital and Medical Center, Burlington, MA	Breast and gynecologic cancer treatment and clinical research, PGIN representative
Kari Bohlke, ScD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

Abbreviation: PGIN, Practice Guidelines Implementation Network.