7. Kaaks R, Toniolo P, Akhmedkhanov A, et al: Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst* 92:1592-1600, 2000
8. Keinan-Boker L, Bueno De Mesquita HB, Kaaks R, et al: Circulating levels of insulin-like growth factor I, its binding proteins-1,-2,-3, C-peptide and risk of postmenopausal breast cancer. *Int J Cancer* 106:90-95, 2003
9. Palmqvist R, Hallmans G, Rinaldi S, et al: Plasma insulin-like growth factor 1, insulin-like growth factor binding protein 3, and risk of colorectal cancer: A prospective study in northern Sweden. *Gut* 50:642-646, 2002
10. Schairer C, Hill D, Sturgeon SR, et al: Serum concentrations of IGF-I, IGFBP-3 and c-peptide and risk of hyperplasia and cancer of the breast in postmenopausal women. *Int J Cancer* 108:773-779, 2004
11. Stattin P, Bylund A, Rinaldi S, et al: Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: A prospective study. *J Natl Cancer Inst* 92:1910-1917, 2000
12. Berclaz G, Li S, Price KN, et al: Body mass index as a prognostic feature in operable breast cancer: The International Breast Cancer Study Group experience. *Ann Oncol* 15:875-884, 2004
13. Fleming ST, Pursley HG, Newman B, et al: Comorbidity as a predictor of stage of illness for patients with breast cancer. *Med Care* 43:132-140, 2005
14. De Jonge ME, Mathôt RA, Van Dam SM, et al: Extremely high exposures in an obese patient receiving high-dose cyclophosphamide, thiotepa and carboplatin. *Cancer Chemother Pharmacol* 50:251-255, 2002
15. Lind MJ, Margison JM, Cerny T, et al: Prolongation of ifosfamide elimination half-life in obese patients due to altered drug distribution. *Cancer Chemother Pharmacol* 25:139-142, 1989
16. Navarro WH: Impact of obesity in the setting of high-dose chemotherapy. *Bone Marrow Transplant* 31:961-966, 2003
17. Powis G, Reece P, Ahmann DL, et al: Effect of body weight on the pharmacokinetics of cyclophosphamide in breast cancer patients. *Cancer Chemother Pharmacol* 20:219-222, 1987
18. Rodvold KA, Rushing DA, Tewksbury DA: Doxorubicin clearance in the obese. *J Clin Oncol* 6:1321-1327, 1988
19. Sparreboom A, Wolff AC, Mathijssen RH, et al: Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. *J Clin Oncol* 25:4707-4713, 2007
20. Rosner GL, Hargis JB, Hollis DR, et al: Relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer: Results from Cancer and Leukemia Group B study 8541. *J Clin Oncol* 14:3000-3008, 1996
21. Georgiadis MS, Steinberg SM, Hankins LA, et al: Obesity and therapy-related toxicity in patients treated for small-cell lung cancer. *J Natl Cancer Inst* 87:361-366, 1995
22. Litton JK, Gonzalez-Angulo AM, Warneke CL, et al: Relationship between obesity and pathologic response to neoadjuvant chemotherapy among women with operable breast cancer. *J Clin Oncol* 26:4072-4077, 2008
23. Meyerhardt JA, Catalano PJ, Haller DG, et al: Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. *Cancer* 98:484-495, 2003
24. Poikonen P, Blomqvist C, Joensuu H: Effect of obesity on the leukocyte nadir in women treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil dosed according to body surface area. *Acta Oncol* 40(1):67-71, 2001
25. Poikonen P, Saarto T, Lundin J, et al: Leucocyte nadir as a marker for chemotherapy efficacy in node-positive breast cancer treated with adjuvant CMF. *Br J Cancer* 80:1763-1766, 1999
26. Meyerhardt JA, Catalano PJ, Haller DG, et al: Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. *Cancer* 98:484-495, 2003
27. Dooley MJ, Singh S, Poole SG, et al: Distribution and discordance of body surface area (BSA) and body mass index (BMI) in 4514 patients with malignancy: The utility of BMI to identify obese patients and its implications in BSA adjusted dosing of cytotoxics. *Proc Am Soc Clin Oncol* 21:90a, 2002 (abstr 356)

Commentary: Chemotherapy Dosing in Obese Patients With Cancer—The Need for Evidence-Based Clinical Practice Guidelines

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Chemotherapy dosing in adult cancer patients has been based, largely by convention, on a patient's estimated body-surface area, despite very few supporting data. At the same time, substantial preclinical and clinical evidence suggests that reductions in standard dose–intensity chemotherapy may compromise disease-free and overall survival in the curative setting.¹⁻⁴ In practice, however, the delivery of full standard dose–intensity chemotherapy is often not achieved for fear of excessive toxicity, particularly in overweight and obese patients.^{5,6} Concerns about overdosing the obese cancer patient on the basis of actual body weight appear to be unfounded, with obese patients often experiencing less, rather than more, hematologic toxicity.^{5,7-9} Pharmacokinetic studies have demonstrated that chemotherapy dose calculations should generally be based on actual rather than ideal body weight.¹⁰ It has been suggested, in fact, that chemotherapy-associated neutropenia may be considered a surrogate pharmacokinetic marker for drug exposure, as multiple studies have shown that neutropenic events during a course of chemotherapy may result in improved disease-free or overall survival years later.^{11,12}

The retrospective study reported by Lopes-Serraio et al¹³ in this issue of *JOP* highlights the common practice of chemotherapy dose capping in obese patients who receive cancer chemotherapy. Treatment duration and hematologic toxicity were compared between obese patients receiving cancer chemotherapy based on capping at a body-surface area of 2.2 m² and healthy weight patients. Despite receiving more cycles of treatment, there was a nonsignificant lower risk of hematologic toxicity in the obese patients, suggesting that there was room to increase the dose above the commonly used 2.0 m² cap. Because this was a relatively small, nonrandomized clinical trial and a number of factors may influence the decision to cap systemic chemotherapy, some differences in the two patient groups are apparent. The multivariate regression model is not especially helpful because of the small number of patients and relatively large number of covariates included. However, the results do illustrate the varying practice in oncology when it comes to dosing chemotherapy in obese patients.⁵ The results are also consistent with several previous studies demonstrating that the risk of hematologic toxicities in obese cancer patients receiving full- or near full-dose chemotherapy is no greater

than that in healthy weight patients receiving full weight-based dosing.^{9,11,14-16}

Continuing confusion concerning optimal dosing in obese patients with cancer, along with increasing rates of obesity in the United States and the consistently poorer life expectancy in the severely obese patient with cancer has prompted ASCO to develop evidence-based clinical practice guidelines on appropriate chemotherapy dosing for obese adult patients with cancer. After a systematic review of the medical literature on this topic, a panel of experts from a broad range of related disciplines was assembled to address several common questions faced by oncologists in everyday practice when treating an obese patient with chemotherapy. These questions will include, among several others: Is there evidence that full weight-based dosing increases toxicity among obese patients with cancer? Is there evidence that less than full weight-based dosing compromises efficacy among obese cancer patients? Should chemotherapy dose modification for severe toxicity be any different in obese patients than in healthy weight patients? Are the answers to these questions dependent on the particular chemotherapeutic agent, age, major comorbidities, and treatment intent? While providing practical evidence-based recommendations related to these and other relevant questions, the panel is also likely to highlight the need for more research, both retrospective and prospective, to address a range of additional issues for which data are sparse or completely lacking.

Although excitement around emerging and expanding indications for novel targeted therapies continues to grow, it is

apparent that the optimal use of many of these new agents is in combination with, rather than instead of, conventional myelosuppressive cytotoxic agents. Improving the delivery and dosing of conventional chemotherapeutic agents both alone or as adjuncts to novel biologic and molecular therapies in obese patients with cancer represents an extremely important strategy for the optimal care and treatment of patients with cancer. The forthcoming evidence-based clinical practice guidelines for chemotherapy dosing in the increasing population of obese patients with cancer should reduce persistent confusion and uncertainty around this topic, which have resulted in widespread practice and individual variation, and lead to more consistent dosing and improved clinical outcomes in this setting.

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Author's Disclosures of Potential Conflicts of Interest

The author has indicated no potential conflicts of interest.

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References

1. Lyman GH: Chemotherapy dose intensity and quality cancer care. *Oncology (Williston Park)* 14:16-25, 2006 (suppl 9)
2. Bonnetterre J, Roché H, Kerbrat P, et al: Epirubicin increases long-term survival in adjuvant chemotherapy of patients with poor-prognosis, node-positive, early breast cancer: 10-year follow-up results of the French Adjuvant Study Group 05 randomized trial. *J Clin Oncol* 23:2686-2693, 2005
3. Budman DR, Berry DA, Cirincione CT, et al: Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *J Natl Cancer Inst* 90:1205-1211, 1998
4. Lepage E, Gisselbrecht C, Haioun C, et al: Prognostic significance of received relative dose intensity in non-Hodgkin's lymphoma patients: Application to LNH-87 protocol. The GELA. (Groupe d'Etude des Lymphomes de l'Adulte). *Ann Oncol* 4:651-656, 1993
5. Lyman GH, Dale DC, Crawford J: Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: A nationwide study of community practices. *J Clin Oncol* 21:4524-4531, 2003
6. Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI: Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: A nationwide study. *J Clin Oncol* 22:4302-4311, 2004
7. Rosner GL, Hargis JB, Hollis DR, et al: Relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer: Results from Cancer and Leukemia Group B study 8541. *J Clin Oncol* 14:3000-3008, 1996
8. Griggs JJ, Culakova E, Sorbero ME, et al: Effect of patient socioeconomic

status and body mass index on the quality of breast cancer adjuvant chemotherapy. *J Clin Oncol* 25:277-284, 2007

9. Griggs JJ, Sorbero ME, Lyman GH: Undertreatment of obese women receiving breast cancer chemotherapy. *Arch Intern Med* 165:1267-1273, 2005

10. Sparreboom A, Wolff AC, Mathijssen RH, et al: Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. *J Clin Oncol* 25:4707-4713, 2007

11. Lyman GH: Impact of chemotherapy dose intensity on cancer patient outcomes. *J Natl Compr Canc Netw* 7:99-108, 2009

12. Mayers C, Panzarella T, Tannock IF: Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. *Cancer* 91:2246-2257, 2001

13. Lopes-Serrao MD, Gressert Ussery SM, Hall RG II, et al: Evaluation of chemotherapy-induced severe myelosuppression incidence in obese patients with capped dosing. *J Clin Oncol* 7:13-17, 2011

14. Field KM, Kosmider S, Jefford M, et al: Chemotherapy dosing strategies in the obese, elderly and thin patients: Results of a nationwide survey. *J Oncol Pract* 4:108-113, 2008

15. Shayne M, Culakova E, Wolff D, et al: Dose intensity and hematologic toxicity in older breast cancer patients receiving systemic chemotherapy. *Cancer* 115:5319-5328, 2009

16. Griggs JJ, Culakova E, Sorbero ME, et al: Social and racial differences in selection of breast cancer adjuvant chemotherapy regimens. *J Clin Oncol* 25:2522-2527, 2007