Evaluation of Chemotherapy-Induced Severe Myelosuppression Incidence in Obese Patients With Capped Dosing

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Abstract

Purpose: Clinicians typically cap an obese patient's chemotherapy regimen as a result of concern for excessive toxicity, without adequate clinical evidence. The purpose of this study was to evaluate the incidence of grade 3 or 4 myelosuppression in obese patients versus nonobese patients with capped dosing on the basis of body surface area (BSA).

Methods: A retrospective chart review was conducted comparing obese patients (body mass index [BMI] $\geq$ 30 kg/m^2) with capped dosing who received capped chemotherapy doses at a BSA of 2.2 m^2 with nonobese (BMI $<$ 25 kg/m^2) patients with lung, colorectal, or hormone-refractory prostate cancer.

Results: Forty-one obese patients with capped dosing and 244 nonobese patients were included. The obese patient group received on average significantly more cycles of chemotherapy (6 *v* 4 cycles) compared with the nonobese group. The overall incidence of any chemotherapy-related toxicity was 34% in the obese patient group, compared with 42% in the nonobese patient group (P = .356). The incidence of grade 3 or 4 myelosuppression was lower, but not statistically significant, in obese patients with capped dosing compared with the nonobese patient group (22% *v* 27%; P = .493).

Conclusions: Overall, obese patients with capped dosing experienced a lower incidence of severe myelosuppression and tolerated more cycles of chemotherapy compared with nonobese patients. The better tolerability of chemotherapy in obese patients with capped dosing suggests that there is room to increase the dose in obese patients above the nationally recognized BSA cap of 2.0 m^2, especially in early-stage lung or colon cancers in which the intention of treatment is curative.

Introduction

The prevalence of obesity, defined as body mass index (BMI) $\geq$ 30 kg/m^2, continues to increase in the United States. Data from the National Health and Nutrition Examination Survey show that in adults age 20 to 74 years, the prevalence of obesity has increased from 15.0% (in the 1976-1980 survey) to 32.9% (in the 2003-2004 survey).[1,2] Obesity is associated with an increased risk of developing several cancers including colorectal, breast, renal cell, and pancreatic.[3] There are several proposed mechanisms that account for the association between increased adipose tissue and the risk of developing cancer. One proposed mechanism is the effect of obesity on growth factor production. Obese patients can develop insulin resistance and chronic hyperinsulinemia as a result of the increased release of free fatty acids, tumor necrosis factor-α, and resistin and the decreased release of adiponectin. Increased insulin levels and increased insulin-like growth factor 1 (IGF-1) act as growth factors that promote cell proliferation and inhibit apoptosis in vitro.[4,5] In addition, increased serum levels of IGF-1 are linked to an increased risk of developing breast, prostate, and colorectal cancer.[6-11] Obese patients may also have a poorer prognosis than nonobese patients.[3,12,13] Multiple factors contribute to adverse survival in obese patients with cancer, including an increased number of comorbid conditions and unfavorable tumor characteristics.

Selecting drug doses can be challenging when treating an obese patient with cancer. The ultimate goal of chemotherapy is to produce consistent systemic drug exposure. This can be difficult in obese patients, given that there are many physiological changes that can affect drug distribution and elimination. There are only a few studies that have evaluated the effects of obesity on the pharmacokinetics of chemotherapeutic agents.[14-19] Additionally, limited literature is available and only a few chemotherapeutic agents have been studied—including cyclophosphamide, methotrexate, fluorouracil, and doxorubicin, to name a few. Therefore, the results cannot be extrapolated and applied to all patients who are obese and receiving chemotherapy.

Another plausible reason for poorer outcomes observed in obese patients is the reduced chemotherapy dose that is delivered.[20] Motivated by concerns that dosing on the basis of actual body weight puts patients at increased risk for toxicity, clinicians tend to empirically decrease chemotherapy dosage for obese patients. Clinicians use multiple methods for dose reductions including adjustments in the body surface area (BSA), which are used to determine the chemotherapy dose. BSA can be modified by using adjusted body weight or ideal body weight or by setting an arbitrary cutoff—known as capping the dose—for obese patients. These methods have not been studied in regard to safety and/or efficacy in this group of patients compared with nonobese patients. Given that one of every three Americans is obese, establishing optimal dosing for these patients is important to oncology practitioners.

The purpose of this study is to evaluate the incidence of grade 3 or 4 myelosuppression in obese patients with capped dosing versus nonobese patients. The incidence of other nonhematologic toxicities was also evaluated.

Methods

This retrospective cohort chart review included patient data from January 1, 2000, to September 30, 2008. Patients were eligible to be included in the review if they had a BMI of ≥ 30 kg/m^2 (obese group) or less than 25 kg/m^2 (nonobese group). Patients were required to have a diagnosis of lung, colorectal, or prostate cancer. Patients receiving their first cycle of chemotherapy were eligible for inclusion in the study. Exclusion criteria included any previous chemotherapy exposure, initial dosage adjustment (except when resulting from BSA capping), and concurrent or recent (defined as within the previous 8 weeks) radiation to the pelvis. Patients with baseline BMI of 25 to 29.9 kg/m^2 were excluded to keep the study sample distinct. Chemotherapy doses for obese patients were capped at 2.2 m^2; this group was defined as the obese patients with capped dosing cohort. BSA cap of 2.2 m^2 was chosen for the study in compliance with our institutional policy. Obese patients were excluded from analysis if their chemotherapy doses were capped at any other BSA. The nonobese group had received chemotherapy on the basis of their actual body weight. All patients' carboplatin doses were capped at the creatinine clearance of 150 mL/min on the basis of actual body weight.

International Classification of Diseases (9th revision; ICD-9) codes were used to identify all patients with lung (162.00), colorectal (153.00), or prostate cancer (185.00). Patients were then screened based on BMI and included in further analyses if obese ($\geq$ 30 kg/m^2) or nonobese ($<$ 25 kg/m^2). Demographic information collected included age, gender, BSA, BMI, and baseline performance status. In addition, cancer diagnosis (including stage and date of diagnosis), chemotherapy regimen (dose and date), total number of chemotherapy cycles planned and received, incidence of grade 3 or 4 hematologic toxicities, incidence of grade 3 or 4 nonhematologic toxicities, and date of disease progression were recorded for each patient. Chemotherapy toxicities were graded using the National Cancer Institute Common Toxicity Criteria version 2.0 recommendations. Computerized progress notes, pharmacy records, pathology reports, and radiologic scans were reviewed to collect data. The study was conducted in compliance with the institutional review board and the research and development committee of Veterans Affairs North Texas Heath Care System and Texas Tech University Health Sciences Center.

The primary objective of the study was to evaluate the incidence of grade 3 or 4 myelosuppression during any cycle of first-line chemotherapy in obese patients with BSA-capped doses versus nonobese patients. The secondary objectives were to compare the incidence of all other toxicities. Group comparisons for continuous variables were performed using t test. χ^2 and Fisher's exact tests were used to evaluate the significance between categorical variables. A multivariate regression model was used to test the relationship between the incidence of grade 3 or 4 myelosuppression and potential confounding factors. All statistical tests used were two-sided and considered significant at $P \leq .05$.

Results

Initially, 1,746 patients were identified with ICD-9 codes for lung, colorectal, or prostate cancer. Of these patients, 1,461 were excluded from the study for having a BMI between 25 and 29.9 kg/m^2, dosage adjustments for purposes other than dose capping, receiving any previous chemotherapy, and radiation therapy to the pelvis within the past 8 weeks. Nine obese patients were excluded because their chemotherapy doses were not capped at 2.2 m^2. For the remaining 285 patients, 41 patients were identified as obese patients with capped dosing and 244 as nonobese patients. Baseline characteristics are reported in Table 1. The mean BMI and BSA of the obese patients with capped dosing were significantly higher than those of the nonobese group ($P < .05$), as expected. The obese group included significantly fewer patients with lung cancer and had received, on average, significantly more cycles of chemotherapy versus the nonobese group ($P < .05$). Additionally, the obese group included fewer patients with metastatic disease compared with the nonobese group (36.6% *v* 49.6%).

Obese patients with capped dosing had a mean BSA of 2.36 m^2. Therefore, on average, the obese patients who were capped at 2.2 m^2 had their doses reduced by 7%. The overall incidence of any grade 3 or 4 chemotherapy-related toxicity (hematologic and/or nonhematologic) was 34% in the obese group compared with 42% in the nonobese group ($P = .356$). The incidence of grade 3 or 4 myelosuppression was lower but not statistically significant in the obese group compared with the nonobese group (22% *v* 27%; $P = .493$). Of the patients who developed myelosuppression, three (33%) of nine patients in the obese group and 13 (20%) of 66 in the nonobese group experienced myelosuppression on the first cycle of chemotherapy. The majority of myelosuppression occurred later in the chemotherapy cycles rather than in the first cycle of chemotherapy for both groups. The incidence of grade 3 or 4 nonhematologic toxicities was lower in the obese group compared with the nonobese group (17% *v* 21%; $P = .613$). The most common nonhematologic toxicities were nausea, diarrhea, and neuropathy. The subanalyses of the nonobese group according to BMI of 18.5 to 24.9 kg/m^2 and lower than 18.5 kg/m^2 were conducted. These subgroups were compared with the obese group, and the key comparisons of toxicities are provided in Table 2.

In the patients with lung cancer, the incidence of grade 3 or 4 myelosuppression was higher than for the rest of the cancer types in the study, but the incidence was similar across study groups (28% in the obese group and 32% in the nonobese group). Univariate regression analysis failed to show a significant impact in the subgroups of age greater than 63 years, of greater than four cycles of chemotherapy, or of stage IV cancer on the incidence of grade 3 or 4 myelosuppression (Table 3). Patients who received carboplatin and those with lung cancer or colorectal cancer showed significantly less myelosuppression on univariate analysis, but this impact failed to extend through multivariate analysis. Only a performance status of 0 to 1 showed a trend toward significantly lower risk of grade 3 or 4 myelosuppression (odds ratio, 0.58; 95% CI, 0.32 to 1.04; Table 3).

Table 1. Baseline Characteristics

Characteristic	Obese With Capped Dosing (n = 41) No. of Patients	%	Nonobese (n = 244) No. of Patients	%
Age, years				
Mean	63.2		63.2	
Median	63		63	
Range	51-78		29-83	
Male	41	100	239	98
BMI, kg/m^2*				
Mean	35.7		21.54	
Range	30.4-45.1		15.6-24.96	
BSA, m^2*				
Mean	2.36		1.83	
Range	2.21-2.82		1.46-2.15	
Diagnosis				
Lung*	25	61.0	186	76.2
NSCLC	20	48.8	143	58.6
SCLC	5	12.2	43	17.6
Colorectal	13	31.7	54	22.1
Prostate	3	7.3	4	1.7
Stage IV cancer	15	36.6	121	49.6
Performance status of 0 or 1	33	80.5	169	69.3
Chemotherapy regimens				
Carboplatin-based	21	51.2	161	66.4
Fluoropyrimidine-based	11	26.8	42	17.2
Cisplatin-based	3	7.3	22	9.0
Docetaxel	4	9.8	9	3.7
Mean No. of chemotherapy cycles	6		4.6	

NOTE. Obese is defined as a BMI ≥ 30 kg/m^2, and dosing was capped at BSA 2.2 m^2; nonobese is defined as a BMI < 25 kg/m^2.
Abbreviations: BMI, body mass index; BSA, body surface area; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer.
* $P < .05$.

Incidence of chemotherapy-related toxicity was reviewed for nine obese patients who were excluded from the original analysis because their chemotherapy doses were not capped at 2.2 m^2. These obese patients received full doses of chemotherapy at an average BSA of 2.4 (range, 2.3 to 2.8). Overall, 67% (six of nine) of these patients experienced any grade 3 or 4 toxicity. Grade 3 or 4 myelosuppression was experienced by 44% (four of nine) of the patients.

Table 3. Regression Analyses for Incidence of Grade 3 or 4 Myelosuppression

Confounder	Univariate Analysis Odds Ratio	95% CI	Multivariate Odds Ratio	95% CI
Age > 63 years	1.19	0.7 to 2.02	1.21	0.69 to 2.12
Carboplatin	2.15	1.18 to 3.91	0.97	0.41 to 2.30
Performance status of 0 or 1	0.55	0.31 to 0.96	0.58	0.32 to 1.04
Chemotherapy cycles > 4	0.94	0.54 to 1.63	1.28	0.7 to 2.34
Lung cancer	3.29	1.54 to 7.0	2.87	0.29 to 28.90
Colorectal cancer	0.31	0.14 to 0.68	0.82	0.08 to 7.98
Stage IV cancer	0.88	0.52 to 1.49	0.84	0.48 to 1.47

Discussion

Dosing chemotherapy on the basis of BSA has been widely accepted into oncology practice with the goal of providing consistent chemotherapy doses in regard to body size while minimizing toxicity. Empirical decreases in the chemotherapy dose for obese patients are commonly performed despite the lack of evidence to support this practice, which can ultimately affect the efficacy of the chemotherapy regimen. At the same time, results of published studies have varied widely in their determination of the relationship between BSA and drug clearance.[14,19]

In this study, obese patients with capped dosing experienced a nonstatistically significant decreased incidence of chemotherapy-related toxicity compared with nonobese patients. Obese patients with capped dosing experienced less grade 3 or 4 myelosuppression and grade 3 or 4 nonhematologic toxicity compared with nonobese patients. Incidence of toxicities failed to reach statistical significance, possibly as a result of lack of power given the small sample size. The majority of myelosuppression occurred later in the chemotherapy cycles rather than in the first cycle of chemotherapy for both groups. Although toxicities were not statistically significant between the two groups, it is

Table 2. Chemotherapy Toxicity and Tolerability of Nonobese Patients According to Subgroup

Toxicity and Tolerability	Obese With Capped Dosing (n = 41) No. of Patients	%	BMI 18.5-24.9 kg/m^2 (n = 212) No. of Patients	%	BMI < 18.5 kg/m^2 (n = 32) No. of Patients	%
Grade 3 or 4 toxicity						
Any	14	34	90	42	12	38
Hematologic	9	22	56	26	10	31
Mean No. of cycles	6		4.63*		4.13†	

NOTE. Obese is defined as a BMI ≥ 30 kg/m^2 and dosing was capped at BSA 2.2 m^2.
Abbreviation: BMI, body mass index; BSA, body surface area.
* Result is statistically significant ($P < .05$) compared with the obese with capped dosing group.
† $P = .012$.

likely that the obese patients with capped dosing were actually tolerating therapy better, as they received a significantly higher number of chemotherapy cycles than the nonobese patients ($P = .021$). The significance in the number of chemotherapy cycles received was also present when the nonobese group was broken down according to BMI of 18.5 to 24.9 kg/m^2 or less than 18.5 kg/m^2; and then both subgroups were compared with the obese group.

The majority of the studies to date have evaluated toxicity in obese patients receiving chemotherapy on the basis of actual body weight compared with nonobese patients.[21-25] Most of these safety studies used febrile neutropenia or platelet counts of less than 50,000/μL as a primary end point. Two studies used grade 3 or 4 hematologic or other toxicity as a primary end point. A study by Rosner et al[20] of patients with stage II breast cancer did not find a statistically significant relationship between dosing according to actual body weight and grade 3 or 4 toxicity during the first cycle of chemotherapy. The study did show a negative trend in overall efficacy outcome in patients who received reduced doses (less than 95% of actual body weight).

Meyerhardt et al examined the impact of BMI on treatment-related toxicity and survival in patients with early-stage colon cancer.[23,26] Patients were divided into five groups on the basis of BMI. In this study,[23,26] the investigators found statistically significant differences in safety between the groups. Obese patients (BMI $\geq$ 30 kg/m^2) experienced lower rates of grade 3 or 4 leukopenia or any grade 3 or 4 toxicity compared with patients with BMI between 21 and 24.9 kg/m^2. However, this was a large, prospective randomized trial in which a multivariate analysis found no statistically significant association between initial BMI or weight change on survival.

Several potential limitations of our study should be considered when interpreting the results. Retrospective study design has inherent challenges that can weaken the cause and effect relationship found in the study. National data suggests that capping BSA at 2.0 m^2 is more common than capping BSA at 2.2 m^2 as in this study.[27] The primary patients evaluated in this study are predominantly elderly males, as the study was conducted at the Veterans Affairs Heath Care System. There are baseline statistical and nonstatistical differences identified in clinical characteristics of patients between the two groups, but the impact of these differences on the primary end point has been provided through regression analysis. Another limitation of the study is that the grading of nonhematologic toxicities—such as nausea, vomiting, mucositis, or neuropathy—was subjective and based on the discretion of the provider at the time of the patient visit.

In conclusion, obese patients with capped dosing had a lower incidence of severe myelosuppression compared with nonobese patients. In addition, obese patients with capped dosing tolerated a significantly higher number of chemotherapy cycles. The majority of the severe myelosuppression occurred after the second and subsequent cycles of chemotherapy. Overall, obese patients with capped dosing tolerated chemotherapy better than nonobese patients. This suggests that there is room to increase the dose in obese patients above the nationally recognized BSA cap of 2.0 m^2, especially in early-stage lung or colon cancers for which the intention of treatment is curative.

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References

1. Flegal KM, Carroll MD, Ogden CL, et al: Prevalence and trends in obesity among US adults, 1999-2000. JAMA 288:1723-1727, 2002

2. Ogden CL, Carroll MD, Curtin LR, et al: Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 295:1549-1555, 2006

3. Calle EE, Kaaks R: Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nat Rev Cancer 4:579-591, 2004

4. Khandwala HM, McCutcheon IE, Flyvbjerg A, et al: The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 21:215-244, 2000

5. Prisco M, Romano G, Peruzzi F, et al: Insulin and IGF-I receptors signaling in protection from apoptosis. Horm Metab Res 31:80-89, 1999

6. Chan JM, Stampfer MJ, Giovannucci E, et al: Plasma insulin-like growth factor-I and prostate cancer risk: A prospective study. Science 279:563-566, 1998

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

By Gary H. Lyman, MD, MPH, FRCP(Edin)

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-Serrao et al[13] 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 m^2 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 m^2 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