Should Anticancer Drug Doses Be Adjusted in the Obese Patient?

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Selecting drug doses can be a challenging decision for the clinician when treating a patient with cancer who is significantly overweight. If total body weight is used to determine body surface area, calculated doses can be as much as 25%-30% higher than if ideal body weight is used, with the potential for severe toxicity (1,2). In the absence of dosing guidelines, some oncologists calculate doses based on ideal body weight, others use an average of ideal body weight and total body weight, and some use total body weight. Despite the potential importance of this decision, few studies (3-5) have investigated the effects of obesity on anticancer drug disposition, providing a remarkably scant database to use as a basis for individualized dosing.

Traditionally, anticancer drug doses have been standardized to body surface area or body weight. This practice is based on relationships that exist between body size (e.g., total body weight and body surface area) and physiologic functions (e.g., cardiac output, liver or renal blood flow, and glomerular filtration rate) (6,7). The body surface area is particularly useful for scaling between species or between infants and adults. The goal of dose standardization is to produce consistent systemic drug exposure (e.g., area under the curve for drug concentration x time). In obese patients, however, it is difficult to obtain an accurate estimate of body surface area for drug dose normalization. As previously addressed (8), the nomogram most commonly used in clinical practice to estimate body surface area was devised from only nine non-obese individuals whose weights ranged from 25 kg to 90 kg. The usefulness of normalizing anticancer drug doses to body surface area in adults has been questioned by Grochow et al. (9). A retrospective analysis of more than 300 patients and nine anticancer agents showed that normalization of doses to body surface area, weight, or height was of minimal clinical value in achieving consistent drug exposure.

The physiologic changes that occur in obese individuals and their effects on drug disposition have been reviewed by several authors (10-12). Physiologic changes that may alter drug distribution and elimination in the obese include increased blood volume, cardiac output, lean body mass, organ size, and adipose tissue mass. An increase in the volume of distribution (Vd) of lipid-soluble drugs is the primary observation seen clinically in the obese. Changes in plasma protein concentrations in obese individuals may affect free drug concentrations: albumin and total protein appear unchanged, but α1-acid glycoprotein, the major protein to which basic drugs bind, is increased in the obese. Consequently, a smaller free fraction may result in reduced drug effect.

The effects of obesity on hepatic metabolism have not been fully characterized. Various drugs that undergo phase I metabolism (i.e., oxidation, reduction, and hydrolysis) have demonstrated either increased or unchanged drug clearance in obese subjects. Drugs that undergo the phase II metabolic reactions of glucuronidation and sulfation consistently show enhanced drug elimination. Studies investigating the influence of obesity on hepatic metabolism have not, however, included patients who have other underlying reasons for altered hepatic function, such as those that may be imposed by malignancy. Glomerular filtration and tubular secretion are increased in obese individuals compared with those in non-obese patients, resulting in higher clearances for drugs that are primarily renally eliminated. For many drugs, it appears clearance is actually increased in obese patients. Taken together, these observations suggest strongly that a more detailed knowledge of the effects of obesity on the pharmacologic behavior of anticancer agents is necessary to ensure appropriate drug therapy. The narrow therapeutic window that exists for many of these agents makes the establishment of dosing guidelines based on sound pharmacologic and toxicologic information a necessary step to assume effective drug exposure is achieved and toxicity is minimized.

Few studies (3-5) have investigated the effects of obesity on the disposition of anticancer agents. Powis et al. (3) studied the effects of body weight on the pharmacokinetics of cyclophosphamide in 16 breast cancer patients. Of these patients, seven were obese (20%-30% over ideal body weight), and five were severely obese (≥30% over ideal body weight). Obese patients had lower drug clearance normalized to ideal body weight and body surface area, but there was no significant correlation between body weight and either total clearance or clearance normalized to total body weight. Unfortunately, although this study attempted to address an important question, dosing guidelines for cyclophosphamide in the obese patient cannot be inferred because of the small numbers of patients and the fact that only the inactive pro-drug was measured. Lind et al. (4) studied the pharmacokinetics of ifosfamide in 16 patients, including four obese patients (29%-50% over ideal body weight). They found no difference in clearance (total or normalized to total body weight and ideal body weight) between obese and normal patients. They did, however, find a significant increase in Vd (total and normalized for ideal body weight). Rodvold et al. (5) investigated the effects of obesity on the pharmacokinetics of doxorubicin and its metabolite, doxorubicinol, in 21 patients.
Seven of the patients were obese (15%-30% over ideal body weight), and seven were severely obese (≥30% over ideal body weight). They observed a decrease in doxorubicin clearance (normalized to total body weight and body surface area) only between severely obese and normal patients. These data suggest that, for some drugs, the influence of obesity on drug clearance may not become a clinically important factor unless the patient is severely obese. The authors did not find a difference in doxorubicin clearance between obese and normal patients. These studies collectively suggest that differences in the pharmacokinetics of anticancer agents between normal and obese patients do exist, but these differences may be difficult to identify and characterize adequately in small studies, given that fivefold to 10-fold ranges in anticancer drug clearance are commonly reported in the absence of obesity (13).

In this issue of the Journal, Georgiadis et al. (14) retrospectively evaluated the effects of obesity on therapy-related toxicity in 262 patients with small-cell lung cancer (SCLC) receiving a regimen based on either cyclophosphamide alone or etoposide plus cisplatin. All patients received doses of chemotherapy based on body surface area calculated with total body weight. Of these patients, 27.1% were obese (approximately 20% over ideal body weight), and 10.7% were severely obese (approximately 40% over ideal body weight). Patients were divided into six cohorts, according to disease-specific patient characteristics and treatment received. In each cohort, the investigators found no consistent significant associations between obesity and toxicity measured primarily as white blood cell count nadir. Although the authors did not report absolute neutrophil count, there is no reason to suspect that the total white blood cell count did not accurately reflect drug effect in all groups. Since the etoposide- and cisplatin-based regimens consistently result in severe neutropenia, comparing the absolute neutrophil count nadir may have shown no difference in toxicity because all patients received treatment resulting in a near 100% reduction of absolute neutrophil count nadir; i.e., all the data would have been obtained at the flat upper end of a sigmoidal E_{max} (maximum effect) drug-effect curve. The same is true for comparisons between patients receiving the cyclophosphamide-based regimens in which leukocyte counts of 300-700 cells/mm³ reflect severe neutropenia. Although not reported in detail, nonhematologic toxic effects were also not different among the groups. These data do not support chemotherapy dose reductions based on ideal body weight. The authors did not find an association between obesity and decreased survival in patients with SCLC, contrary to the observation in breast cancer patients (15-17). However, the small numbers in each cohort make a firm conclusion regarding influence on survival premature.

Empiric decreases in the doses of anticancer agents given to obese patients based on ideal body weight are not supported by the available data. In this issue of the Journal, Georgiadis et al. (14) have demonstrated that doses based on total body weight can be given without an apparent increase in serious toxicity or decrease in survival in patients with SCLC. Clinicians facing this decision must bear in mind that inappropriate dose reduction may compromise efficacy, particularly when they are treating patients with curative intent. Our understanding of the influence of obesity on the pharmacology of anticancer drugs on clinical outcome can best be described as rudimentary. Clearly, additional studies will be required to clarify how this important demographic characteristic can influence treatment outcome. The most unambiguous approach to this question lies in the examination of pharmacokinetic data obtained from patients with varying anthropomorphic characteristics. However, Georgiadis et al. (14) have demonstrated that valuable information can be obtained at the practical clinical level from the retrospective analysis of homogeneous populations of patients treated with a consistent approach. We hope this encourages investigators to examine existing databases in addition to considering prospective studies to expand the information regarding drug dosing in obese patients to other drugs and clinical scenarios.

References


Note
Manuscript received January 23, 1995; accepted January 25, 1995.
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