

Body Surface Area in Dosing Anticancer Agents: Scratch the Surface!

Antonius A. Miller

Grochow et al. (1) questioned the use of body surface area in dose normalization more than a decade ago in this Journal. In this issue, Baker et al. (2) retrospectively assessed the pharmacokinetics of 33 investigational agents tested in phase I trials during the past decade as a function of body surface area in 1650 adult cancer patients. Based on their findings, they recommend that the practice of calculating starting doses on the basis of body surface area in phase I trials should be abandoned. Historically, we have initiated phase I dosing based on body surface area and then retained the practice, carrying it forward through phase II and III studies and ultimately to Food and Drug Administration labeling. Should we accept the recommendation by Baker et al. and abandon the use of body surface area for dose determination? To answer this question it may be useful to put body surface area-based dosing of anticancer agents into perspective.

What is body surface area and how did it enter our practice? Body surface area is equivalent to the two-dimensional surface area of the skin. It is difficult to measure and therefore commonly estimated on the basis of formulas that use body weight and height in the calculation. The most commonly used formula was published by Du Bois and Du Bois in 1916 (3). Obviously, the objective at that time was not to develop a formula to dose anticancer agents. Du Bois and Du Bois were working on "clinical colorimetry" (now known as basal metabolic rate). The body surface area of mammals correlates with basal metabolic rate. As may be expected in warm-blooded animals, body surface area is also proportional to blood volume. But, as Baker et al. point out (2), body surface area is not well correlated with glomerular filtration rate (4). Body surface area is also not associated with liver function (5). The practice of using body surface area in scaling drug doses began with Freireich et al. (6), who quantitatively compared toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and humans. Thus began the use of body surface area in scaling a dose from a mouse or other laboratory animal to an initial starting dose for a phase I study in humans.

The estimation of body surface area is based on nomograms or computer programs that contain the Du Bois and Du Bois formula or similar formulas. This practice has been handed down through generations of clinical oncologists.

Why do we still use body surface area? Hippocrates is credited with instructing us to do no harm. It is one of our deepest desires to benefit our patients when we prescribe drugs and not to cause harm. This is exceedingly difficult with a group of drugs that have a very narrow therapeutic index, such as anticancer drugs. In our quest to reduce variability in drug response among patients, we seek to reduce the variation in drug exposure. Drug doses that are "calculated" on the basis of body surface area give us a sense of accuracy and safety. However, in the experience of any practicing oncologist, pharmacokinetic and pharmacodynamic variability among patients remains great.

Is the continued use of body surface area based on scientific data and, therefore, rational? The work by Baker et al. (2) in this issue of the Journal suggests no on both counts. For the 33 investigational agents, body surface area-based dosing statistically significantly reduced the interpatient variability in drug clearance for only five drugs, namely docosahexaenoic acid-paclitaxel, 5-fluorouracil/eniluracil, paclitaxel, temozolomide, and troxacitabine. The authors point out that for the handful of drugs for which clearance was associated with body surface area, the relative reduction in variability of clearance was between 15% and 35%; thus, only up to one-third of the total variability could be explained by body surface area. For the agents for which body surface area was associated with clearance, the authors suggest a potential relationship with blood volume or glomerular filtration rate. Furthermore, in the case of paclitaxel, they point to the vehicle (Cremophor EL) that is used in the formulation of the drug as having an impact on the phar-

Correspondence to: Antonius A. Miller, M.D., Comprehensive Cancer Center of Wake Forest University, Medical Center Blvd., Winston-Salem, NC 27157 (e-mail: aamiller@wfubmc.edu).

macokinetics. This vehicle has a distribution volume that approximates the blood volume, and body surface area is a covariate for Cremophor EL clearance. In addition, it should be pointed out that even if clearance is related to body surface area, this relationship is clinically meaningless if clearance does not explain variability in drug response. Indeed, no convincing scientific data exist to link the clearance of paclitaxel to its toxic effects.

Are the results of Baker et al. consistent with the literature? Reviews by Reilly and Workman (7) and Gurney (5) suggest that the routine use of body surface area for dose calculation should be re-evaluated and that other methods of dose calculation should be investigated. In an editorial on the topic of body surface area-based dosing of anticancer agents, Ratain (8) posed the question "science, myth, or habit?" and concluded that myth and habit have gotten in the way of science.

How urgently should we reconsider our practice of using body surface area? Recently, the safety of drug dosing has become a concern, even for drugs that produce therapeutic effects at doses far lower than those that cause toxicity. Errors in dose calculation of anticancer agents are even a greater concern because of the high incidence of serious or even life-threatening toxicity associated with many of them. There are many steps involved in giving anticancer drugs, including the calculation of body surface area using height and weight, the calculation of the total dose based on body surface area, the preparation of the agent in the pharmacy, and the administration of the agent by the chemotherapy nurses. Therefore, the advantages of using a fixed or standard dose as opposed to a body surface area-based dose for anticancer drugs become obvious. Errors in calculations and transcriptions could be reduced. Pharmacies would have to store, handle, and deliver fewer unit sizes of anticancer drugs, which would result in greater efficiency. It is also perceivable that this practice would result in cost savings. For oral anticancer drugs, the adherence by patients could be improved (for instance, patients would not have to count out one 50 mg plus two 10 mg tablets for a total daily dose of 70 mg).

Where should we go from here? Even if we do not abandon the use of body surface area when we scale a dose from mouse to humans for phase I studies, we should discontinue the use of body surface area to determine drug doses for patients. The variability in body surface area from mouse to humans is far greater than it is among patients. We should also investigate the reduction of variability by using measurements of renal and hepatic function. The dosing of carboplatin based on estimated creatinine clearance is a good example. It is likely that we will find that genetically determined polymorphisms in drug-metabolizing enzymes in the liver are more important than body surface area in predicting clinical response. Pharmacologically based dosing or specific pharmacogenetically based dosing may be far more rewarding than body surface area-based dosing.

Baker et al. have provided scientific evidence that body surface area-based dosing has very limited utility. This should serve as a challenge to us to find alternative dosing strategies for anticancer agents.

REFERENCES

- (1) Grochow LB, Baraldi C, Noe D. Is dose normalization to weight or body surface area useful in adults? *J Natl Cancer Inst* 1990;82:323-5.
- (2) Baker SD, Verweij J, Rowinsky EK, Donehower RC, Schellens JH, Grochow LB, et al. Role of body-surface area in dosing of investigational anticancer agents in adults: 1991-2001. *J Natl Cancer Inst* 2002;94:1883-8.
- (3) Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 1916;17:863-71.
- (4) Dooley MJ, Poole SG. Poor correlation between body surface area and glomerular filtration rate. *Cancer Chemother Pharmacol* 2000;46:523-6.
- (5) Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. *J Clin Oncol* 1996;14:2590-611.
- (6) Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. *Cancer Chemother Rep* 1966;50:219-31.
- (7) Reilly JJ, Workman P. Normalisation of anti-cancer drug dosage using body weight and surface area: is it worthwhile? *Cancer Chemother Pharmacol* 1993;32:411-8.
- (8) Ratain MJ. Body-surface area as a basis for dosing of anticancer agents: science, myth, or habit? *J Clin Oncol* 1998;16:2297-8.