

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## BSA-based Dosing and Alternative Approaches

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### **H&O** Why is body surface area–based dosing the dominant approach in cancer therapies?

**AS** Cancer patients have a highly variable capacity to metabolize and eliminate commonly administered drugs. This variability originates from a combination of physiologic variables and intrinsic characteristics, such as genetic components, as well as environmental factors, which together determine a patient's phenotype. Many anticancer agents are characterized by unique pharmacokinetic profiles and narrow therapeutic windows. This narrow window means that a small variation in dose can lead to severe and potentially life-threatening side effects in some individuals, while other patients may experience poor antitumor effects when the dose is lowered to avoid toxicity.

Obtaining therapeutic benefit is, of course, of primary importance to oncologists, particularly when the disease is curable. Likewise, avoiding unacceptable toxicity is also a primary concern, particularly for patients with impaired renal or hepatic functions. In order to eliminate variability between patients due to physiologic, genetic, and environmental factors, drug dose has been adjusted on the basis of body surface area (BSA). This strategy is very common across the spectrum of chemotherapeutic agents, and has been applied for a variety of reasons, as follows.

First, it has been established for several decades now that there are correlations between BSA and several specific patient characteristics including glomerular filtration rates, blood volume, and basal metabolic rate. These correlations have been assumed to provide a sufficient foundation for individualizing doses of chemotherapeutic agents.

Also, the starting doses of many cancer drugs currently in use are based on information derived from studies in animal models in which the dose was calculated relative to BSA or body weight. In animal studies, doses are generally tested until the “LD-10”—the dose at which 10% of animals die from the agent—is reached. In human studies, the first dose employed is usually derived from information obtained in animals (for example, one tenth of the LD-10).

Finally, as early as the 1950s, studies attempting to define more accurate methods for the administration of cytotoxic drugs in children have suggested a role for BSA in drug dose calculation. In one particularly well known study, published in 1958, Dr. Pinkel applied a BSA-based formula for dosing cancer drugs in pediatric patients in order to determine the optimal doses for this patient subgroup. Calculating drug doses per unit of BSA, the investigator found similar figures across a range of agents tested for adults and children, leading him to recommend the use of BSA to normalize the dose of cytotoxic agents in pediatric oncology. Since the publication of his report, the use of BSA for dose calculation has become standard practice for virtually all cytotoxic drugs in adults, without further investigation into the relationship—or lack thereof—between drug effect and BSA.

### **H&O** What problems are associated with BSA-based dosing, and what advantages do alternative strategies offer?

**AS** It has been demonstrated that the interindividual pharmacokinetic variability for some anticancer drugs is actually higher when the parameter of interest is expressed relative to BSA (for example, clearance expressed in L/h/m<sup>2</sup> rather than in L/h). This suggests that BSA further increases variability of the effects induced by such agents, and may thus even be harmful. Most importantly, drug preparation and administration errors are very common, especially for intravenous drugs, with an incidence of almost 50%, and are usually the result of systematic error (inaccuracy of the calculation algorithms used for BSA) and inevitable convergence error, including use of inaccurate height and weight for BSA calculation. BSA-based dosing can be particularly problematic with some of the standard oral cytotoxic agents (eg, capecitabine).

It can be anticipated that implementation of alternative dosing strategies such as the flat-fixed dosing concept in routine clinical practice would have significant economic implications. The ability to manufacture a unit dose has obvious benefits for the pharmaceutical company involved. Similarly, reconstituting a fixed dose without subsequent individualization for different patients is more efficient and cost-effective than preparing individualized doses. This approach is particularly useful with newer oral agents.

### **H&O** In what situations would BSA-based dosing be most appropriate?

**AS** It has been argued by several investigators that the use of BSA-based dosing should be restricted to those agents for which a relationship between BSA and clearance or with other pharmacokinetic parameters is established. This correlation has been described for agents mostly confined to the blood compartment, for drugs eliminated by processes taking place in the central compartment, and those eliminated mainly through urinary excretion.

### **H&O** What other strategies for dose calculation are being considered?

**AS** In the search for alternatives to BSA in drug dosing strategies, it would probably be inappropriate to try to identify a single variable to be applied to all anticancer agents. Knowledge of the pharmacokinetics of an agent is possibly the most accurate method to establish its effects and to fix a parameter that could be used to reduce the interpatient variability on drug exposure. This has of course been done for carboplatin, still the only cytotoxic agent for which dose is individualized according to pharmacokinetic parameters and not according to BSA.

Many investigators have suggested that with agents for which it has already been shown that the interindividual variability is not correlated with BSA, flat-fixed doses should be used in the absence of a better alternative, and doses adjusted for subsequent cycles on the basis of toxicity induced in each patient.

Several additional methods can be used in determining optimal dosing for anticancer agents, such as estimating the total activity of enzymes involved in the metabolic pathway of drugs transformed primarily in the liver. Investigators have attempted this through administration of a probe drug (ie, phenotyping) or through a careful assessment of a patient's genetic constitution (ie, genotyping). The metabolic pathways of most drugs that are routinely administered are reasonably well established; for example, 5-fluorouracil is extensively metabolized in the liver by the polymorphic enzyme dihydropyrimidine dehydrogenase (DPD). Hence, DPD phenotype may prove to be of value in prospective modeling of 5-fluoro-

uracil pharmacokinetics and drug dosing. By contrast, the cytotoxic activity of mercaptopurine, is regulated by the enzyme thiopurine methyltransferase (TPMT), and a lack of functional TPMT activity can produce life-threatening mercaptopurine-induced myelotoxicity. Therefore, the implementation of enzyme activity measurements might contribute to reducing variability of drug effects and to find the correct dose on the basis of an individual's capacity to metabolize the drug.

Finally, a potential candidate to supplant BSA is "therapeutic drug monitoring," which is already employed to reduce the toxicity of certain high-dose chemotherapy protocols that include methotrexate.

### **H&O** Is there resistance to changing from BSA-based dosing to another strategy and, if so, why?

**AS** Yes, and there are 2 likely reasons. First, the majority of drugs currently in clinical development are still being dosed on the basis of BSA. Thus, when such an agent reaches the market, it will be registered as one for which the dose is calculated on the basis of BSA. Transitioning to an alternative dosing strategy, such as one based on phenotype of any other aspect unrelated to BSA, would require additional investigation—which is likely to be very costly—to show improved efficacy (or better controlled toxicity) as compared to BSA-based dosing. Second, although many studies have now convincingly questioned the routine use of BSA, the message appears not to have been heard and many clinicians, regulators, and industrial drug developers remain skeptical. This skepticism is based on the intuitive belief that patients with a larger BSA require more drug to induce the same drug effects. Unfortunately, the selection of a dosing strategy for anticancer drugs is still most commonly based on tradition rather than physiologic relevance.

### **H&O** What are the inherent difficulties of calculating BSA?

**AS** Although the original BSA dosing formula, published in 1916, was quite complicated, it has been simplified in the years since then and now involves no complex mathematics. The most challenging aspect of calculating BSA is accurately assessing height and weight. Although these are the only 2 variables in the calculation, their measurement is prone to miscalculation.

### **H&O** How does BSA-based dosing work in frail and morbidly obese patients?

**AS** Drug dosing recommendations are usually based on results from clinical trials that included patients who are considered typical of those likely to receive the drug in clinical practice. In many cases, however, the morbidly

obese patient may not be well represented and therefore extrapolation of dosing recommendations to this group must be performed arbitrarily when the dose is required to be standardized to a particular patient demographic like BSA.

In clinical practice, this results in a diverse range of dosing regimens, including using the patient's actual body weight, using the patient's actual body weight up to an arbitrary cut-off ("dose capping"), or using some alternative estimate of the patient's weight, such as lean body weight. None of these practices are ideal and in many cases may result in significant under- or overdosing of the drug in question.

It is also clear that the usefulness of formulas used to calculate BSA has not been appropriately evaluated in cancer patients who are severely obese or frail. Furthermore, the original formulas for calculating BSA-based drug dosages were likely developed in a population with an average BSA. The majority of studies of alternative dosing strategies have also not taken into account patients at the upper or lower ends of BSA. Much remains to be understood about appropriate dosing strategies for severely obese patients, not only for the purpose of evaluating alternative dosing strategies but also for drugs that are already dosed according to BSA.

### **H&O** Does a BSA-based dose need to be adjusted for elderly patients?

**AS** Many of the currently approved regimens for cytotoxic chemotherapy are essentially unaltered when administered to elderly patients, and any adjustments are at the physician's discretion. However, with the growing elderly population across the world, more attention to this question is needed in order to define optimal dosing strategies for elderly patients.

### **H&O** Is BSA-based dosing being abandoned with the development of targeted agents?

**AS** Since many of the newer, target-based drugs are not necessarily cytotoxic, there is a trend of abandoning BSA-

based dosing. Already, many targeted agents, such as the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib (Tarceva, OSI), are being or have been developed with a dosing strategy that does not involve BSA.

### **H&O** Is this change in dosing strategies possible because of the mild toxicity profiles of the targeted agents?

**AS** Yes. The interest in individualizing treatment and therefore using BSA essentially started with highly cytotoxic drugs for which pharmacokinetic variability among patients is a crucial issue and of clinical importance. One of the underlying reasons for developing newer agents differently is the assumption that a change in strategies for dose calculation is unlikely to lead to a huge difference in variability in unmanageable toxicity. However, regardless of whether alternative strategies lead to differences in outcome, it will be important to demonstrate the feasibility of administering a cancer drug with a dose that is not based on BSA.

### **Suggested Reading**

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