Flat-Fixed Dosing Versus Body Surface Area–Based Dosing of Anticancer Drugs: There Is a Difference

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Disclosure of potential conflicts of interest is found at the end of this article.

In a recent review, Mathijssen et al. [1] proposed using flat-fixed dosing regimens rather than body surface area (BSA)-based dosing for anticancer drugs because “it does not seem worse than using BSA-based dosing” with regard to pharmacokinetic variability. We feel that this statement, together with other recent publications arguing against BSA-based dosing, requires a counterpart.

Most cytotoxic drugs have a narrow therapeutic range and are often administered at a dose close to the maximum-tolerated dose (MTD) because of the fact that, for many solid tumors and leukemia, increasing systemic exposure often results in higher response rates. In contrast, molecularly targeted cytostatic drugs, like tyrosine kinase inhibitors, should have a greater therapeutic range and an optimal effective dose that can be much lower than the MTD [2].

For classic cytotoxic drugs, every patient should experience the same high systemic exposure close to, but clearly below, the MTD. Systemic exposure can be quantified as the area under the curve (AUC) of the plasma concentration versus time curve. The AUC is determined by the administered dose and the individual clearance of a drug according to the formula:

$$\text{Clearance} = \frac{\text{Dose}}{\text{AUC}}$$

Thus, to achieve a constant AUC in patients, clearance is the important pharmacokinetic parameter for dose adjustment. About 50 years ago, it was found that BSA shows a correlation with the MTD between species and it was therefore introduced into preclinical research [3]. At that time, BSA was also used in patients to adjust the dose of cytostatic drugs and BSA-based dosing also became the standard in pediatric oncology [4]. With the broader availability of methods to quantify drugs in biological fluids, pharmacokinetic investigations were conducted with the aim to provide a better insight into the disposition and elimination of the drugs to improve the therapeutic index.

It was found that BSA-based dosing did not necessarily result in a reduction in the variability of AUC. Therefore, the value of BSA-based dosing was questioned [5]. Alternative concepts, like therapeutic drug monitoring (TDM), were shown to be useful for certain drugs like busulfan; however, it is difficult to apply TDM for patients outside big treatment centers [6].

In 1996, the discussion of the appropriate way to adjust the dose of anticancer drugs started to heat up when Guerny [7] questioned the value of BSA-based dosing strategies. In the following years, several authors supported the arguments [8]. The latter authors concluded that BSA should not be automatically regarded as the dosing strategy in phase I studies. We also think that no automatism should be applied because with the availability of population pharmacokinetic methods, BSA and other covariates possibly useful to predict the clearance of drugs can be easily identified. In another retrospective investigation, BSA-based dosing was
statistically significantly associated with a reduction in interpatient variability (coefficient of correlation, \( r > 0.5; p < .01 \); reduction in variability of clearance >15%) for only five of 33 newer agents [9]. However, in the majority of the 33 drugs, a weak reduction in the variability was found with BSA-based dosing, while for 10 drugs variability increased with BSA-based dosing. The criterion “reduction in variability of clearance >15%” appears rather strict because for drugs with only a weak correlation between BSA and clearance, patients with extreme BSA values are more adequately dosed according to BSA. Interestingly, when prospectively evaluating BSA-based dosing for paclitaxel, it was found to be useful in order to reduce the variability of AUC [10].

It must be pointed out that the results of studies investigating the role of BSA and other covariates are highly dependent on the homogeneity or heterogeneity of the patient population. Heterogeneity in both the pharmacokinetic and the size parameters is very high in children [11]. In contrast, in an adult patient population with a BSA range of 1.6–2.2 m², it appears difficult to identify any correlation between BSA and pharmacokinetic parameters. In addition, extreme values of body mass indices also influence the clearance and distribution of drugs.

In pediatric oncology, the typical range of BSA is 0.4–2 m². In such a population, for almost any drug, there is a correlation between clearance and BSA. It is obvious that for children a scale parameter such as BSA or weight for dose calculation is absolutely necessary. In pediatric oncology, flat-fixed dosing regimens are not an option for cytotoxic drugs with a narrow therapeutic range. The question to be addressed in any patient population is: What is the best parameter to predict clearance for a certain drug?

This parameter can be BSA, weight, height, age, or any other parameter predictive of the elimination of xenobiotics from the body. Body mass index may also influence distribution and clearance. For drugs excreted through the kidneys, the glomerular filtration rate (GFR) often predicts the drug’s clearance sufficiently precisely. Dosing based on renal function was successfully applied for carboplatin and is now part of the clinical routine in many centers for both adults and children [12, 13].

The controversy over flat-fixed dosing concepts versus BSA-based dosing can be illustrated by recent investigations on cisplatin. In 2001, de Jongh et al. [14] published an investigation on the pharmacokinetics of cisplatin in 268 adults with BSA values of 1.86 m² ± 10.4%. The variability in BSA was relatively low and could not explain the variability in the clearance of unbound platinum (25.6%, versus 23.6% using BSA-based dosing). From these findings, the authors concluded that BSA-based dosing should not be used for dosing cisplatin and suggested a flat-fixed dosing regimen. Analyzing the same data using a more precise and sensitive population pharmacokinetic method, BSA was found to be the only covariate to be predictive of cisplatin clearance and volume of distribution [15]. In contrast to the former analysis, the population pharmacokinetic method applied could account for all kinds of variability, that is, interindividual, intranindividual, and residual variability. Therefore, it is not surprising that the interindividual variability in clearance was overestimated in the former study [14] using the standard two-stage approach. Therefore, the results presented in the former investigation do not allow drawing final conclusions. Consequently, the authors no longer recommend a flat-fixed dosing regimen and suggest three different dose groups depending on the patient’s BSA [16]. Another group investigating 43 cisplatin-treated patients with a BSA of 1.38–2.1 m² found BSA to be predictive of the volume of distribution and clearance [17]. From these findings, it appears that flat-fixed dosing for cisplatin can be applied only in well-defined, homogeneous populations.

Although cisplatin, besides irreversible tissue binding, is almost exclusively cleared through the kidneys, it was already shown earlier that GFR cannot be used to adjust the dose of cisplatin [18]. A recent approach to find other parameters predictive of cisplatin clearance in children failed to identify better covariates than BSA and suggested an approach using plasma concentrations and weight [19].

Neuroblastoma patients often receive 40 mg/m² cisplatin as a 96-hour infusion. The median BSA in a drug-monitoring program done in our lab was 0.57 m², with a range of 0.37–1.25 m². It is obvious that, in such a population with many infants and some older children, flat-fixed dosing regimens are not an option. Rather, children below the age of 1 year are dosed according to body weight, because BSA would result in relatively higher absolute doses than body weight. The reason for this dose reduction is a precaution, because infants may be more susceptible to side effects like ototoxicity and nephrotoxicity. However, the rationale for this is a matter of debate. Another problem with cisplatin is that the clearance of cisplatin decreases from cycle to cycle as a result of the nephrotoxic effect of the drug.

Arguments given for flat-fixed dosing regimens are economic advantages and a lower risk for calculating errors. However, hospital pharmacists responsible for the preparation of cytostatic drugs do not support the argument of economic advantages of flat-fixed dosing regimens. With central preparation units for cytostatic drugs, only very small amounts of the drug formulations have to be discarded as a result of the adjustment by BSA. From an industry point of view, flat-fixed dosing regimens might be advantageous but this does not necessarily result in a cost reduction for the hospitals.

From a pharmacist’s point of view, the safety arguments given for flat-fixed dosing are not very convincing. The risk...
for calculating errors may be justified in a setting where only the clinician calculates the dose and the cytostatic drug is prepared by nurses on the ward. However, to improve safety for both patients and hospital staff, nowadays the preparation of the cytostatic drugs and the recalculation of the dose should be done by experienced hospital pharmacists. With at least two health care professionals calculating the dose, the risk for dosing errors is relatively small compared with the possible over- or underdosing when flat-fixed dosing regimens are used.

Even if flat-fixed dosing regimens could be established in adults, in pediatric oncology, BSA-based dose adjustment is absolutely necessary and will remain the standard mode of dosing as long as there are no alternative validated parameters for dose adjustment such as GFR or serum creatinine for renally excreted drugs. Therefore, more population pharmacokinetic studies are required to identify covariates showing a higher predictability than BSA for the clearance of cytotoxic drugs. Hopefully, pharmacogenetic approaches will identify more parameters to predict the clearance of cytotoxic drugs. A good example is the genotyping on irinotecan uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which is now recommended in the U.S. Food and Drug Administration labeling of the drug [20]. Another interesting approach for dose individualization to reduce the variability in individual exposure is phenotyping of drug-metabolizing enzymes. The applicability of this approach was demonstrated recently by phenotyping of cytochrome P450 3A4 before administering docetaxel [21].

Using well-designed population pharmacokinetic studies with sufficient patient numbers representing the entire population, it should be possible to find parameters to precisely predict the clearance of cytostatic drugs. This should enable the oncologist to adjust the dose better than using flat-fixed dosing or BSA-based dosing regimens. A good example for this approach is the dosing of carboplatin in children using serum creatinine, gender, weight, and age [22]. For some drugs, especially the newer targeted drugs with a wider therapeutic range, flat-fixed dosing may be appropriate in not too heterogeneous populations, although dose individualization based on biomarkers appears to be most appropriate for such drugs. However, switching to flat-fixed dosing in general would be therapy deindividualization.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicate no potential conflicts of interest.

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**REFERENCES**


