Volume 12, Number 8, August 2007

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The Oncologist®
Clinical Pharmacology

Flat-Fixed Dosing Versus Body Surface Area–Based Dosing of Anticancer Drugs in Adults: Does It Make a Difference?

RON H.J. MATHIJSSEN, FLORIS A. DE JONG, WALTER J. LOOS, JESSICA M. VAN DER BOL, JAAP VERWEIJ, ALEX SPARREBOOM

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Key Words. BSA • Flat-fixed dosing • Pharmacokinetics • Pharmacodynamics • Individualized dosing

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe how and why BSA-based dosing was implemented into oncology.
2. Discuss if flat-fixed dosing of adults has advantages over BSA-based dosing in terms of interpatient pharmacokinetic variation of anticancer drugs, efficiency, and costs.
3. Explain which alternative dosing strategies for BSA-based dosing may have potential, leading to a minimum of adverse events and superior therapeutic outcome.

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ABSTRACT

The current practice of using body-surface area (BSA) in dosing anticancer agents was implemented in clinical oncology half a century ago. By correcting for BSA, it was generally assumed that cancer patients would receive a dose of a particular cytotoxic drug associated with an acceptable degree of toxicities without reducing the agent's therapeutic effect. More recently, doubt has arisen to this hypothesis, and for many drugs, the effects of BSA on the pharmacokinetics of these agents have therefore been studied retrospectively. In (by far) most cases, use of BSA does not reduce the interindividual variation in the pharmacokinetics of adults, and thus, a logical rationale for further use of this tool in dosing adults is lacking. As a result, alternative dosing strategies have been proposed in order to replace BSA-based dosing. Flat-fixed dosing regimens have been suggested, thereby avoiding potential dose calculation mistakes. As flat-fixed dosing does not typically lead to greater pharmacokinetic variability, it does not seem worse than using BSA-based dosing. While it provides a simplification, it can, however, be questioned whether to call this an improvement or not. The implementation of so-called genotyping and phenotyping strategies, and therapeutic drug monitoring, may probably be of more clinical value. In the end, the nonscientifically based BSA-based dosing strategy should be replaced by alternative strategies. Despite the lack of basic fundamentals, BSA-based dosing still seems "untouchable" in clinical oncology. Even when alternatives will be shown to be indisputably better, many hurdles will probably have to be overcome before physicians will be willing to ban BSA-based dosing. *The Oncologist* 2007;12:913–923

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

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The Current Practice

Historic Development of Body Surface Area–Based Dosing

Classic cytotoxic agents are known for their relatively narrow therapeutic window. This means that "low" doses of these drugs may not be effective, while "high" doses may be (very) toxic for the patient. Therefore, the optimal dose should be somewhere in between, thereby leading to the best possible treatment, which means yielding maximal therapeutic effect given tolerable and manageable toxicities. Based on the theory that large patients have a larger volume of distribution and a higher metabolizing capacity, it is assumed that those patients need to be dosed higher than smaller patients to reach equal drug concentrations. For this reason, traditionally, the administered dose is typically adjusted to the body-surface area (BSA) of the individual patient. BSA was originally calculated using a formula based on length and weight developed by DuBois and DuBois in 1916 [1] from an investigation that involved only nine individuals (Table 1) [1–5]. Although validation of the derived formula was not performed initially [3, 4], the use of BSA was incorporated into animal studies for the purpose of allometric scaling, and in the 1950s, BSA-based dosing was introduced into pediatric oncology [6, 7]. Without further study, its use was also incorporated into drug dose calculation in adults (to get a safe starting dose in phase I trials). Currently it is still the standard for most agents used [8].

According to a study by Gehan and George in more than 400 individuals, the original formula was found to overestimate the real BSA by >15% in about 17% of people, while underestimating BSA in a much lower number (1%) of cases [3, 8]. This however, did surprisingly not lead to acceptance of the Gehan and George BSA formula as the medical standard. More recently, Mosteller changed the original formula to BSA (m^2) = $\sqrt{}$([length (cm) × weight (kg)]/3,600), which appeared to mimic the original formula quite closely and simplified its use (Table 1) [5]. Although today BSA can even be determined by a three-dimensionally derived formula [9], the correlation among all these formulas remains high ($r > 0.97$), suggesting only nonsubstantial differences among the formulas used [10]. An exception should be made, however, for overweight and obese patients, where values for BSA appear to differ significantly between the DuBois and DuBois formula and the other formulas [10]. In this specific group, BSA prediction according to the original formula underestimated BSA by 3% for male and 5% for female patients, compared with Mosteller's formula.

With the exception of carboplatin [11, 12], it was a long time before concerns were raised on the relevance of using BSA in oncology. Currently, many studies have been performed, which clearly show that (most frequently) BSA-based dosing does not yield the desired minimization in interindividual variation in exposure in adults. In this review article, the value of BSA-based dosing of adults for individual anticancer agents is questioned and potential alternatives are discussed. The dosing of children, however, is not comparable, and reaches beyond the scope of this manuscript.

Interindividual Variability

From daily experience, any physician knows that patients may respond differently to prescribed drugs. Many factors can influence systemic exposure to a given drug (Fig. 1), which include physiological factors (e.g., age, performance status score), intrinsic factors (e.g., genetic alterations), and environmental factors (e.g., comedication, use of herbal supplements) [13–15]. As a consequence, the pharmacokinetic parameters (exposure, i.e., area under the plasma concentration–time curve [AUC], and clearance, i.e., dose divided by exposure) of a particular agent may vary substantially among patients, which is expressed by the term interindividual variation. On the basis of the pharmacologic tenet that pharmacokinetic parameters can be used as a surrogate for pharmacodynamic outcome, this interindividual variation leads to an unpredictable variety in clinical response and adverse effects. For cytotoxic agents, interindividual variability, expressed as a coefficient of variation (which is the standard deviation divided by the mean times 100), of 25%–70% is very common (Fig. 2) [16–20], despite the use of BSA for dose calculation.

Back in 1990, relationships between pharmacokinetic parameters of several cytotoxic agents under development in phase II trials and body size measures (height, weight, and BSA) were described by Grochow et al. [21]. Of these drugs, paclitaxel clearance showed a relationship with height ($r = 0.70$; $p = .003$), while other relationships were surprisingly scant. At the same time, Ratain et al. studied etoposide [17] and found no correlation between clearance and BSA, and correction for BSA did not lead to a change in interindividual variability. Later, this lack of relationship was confirmed by others [22].

In addition, for epirubicin, no relationship between clearance and BSA was seen, although the small number of patients may have influenced outcome [23]. Also, Gurney

Table 1. Frequently used BSA formulas (in chronological order)

Study	Population size	Formula
DuBois and DuBois (1916) [1]	9	$BSA\ (m^2) = 0.20247 \times height\ (m)^{0.725} \times weight\ (kg)^{0.425}$ or $BSA\ (m^2) = 0.007184 \times height\ (cm)^{0.725} \times weight\ (kg)^{0.425}$
Boyd (1935) [2]	197	$BSA\ (m^2) = 0.0003207 \times height\ (cm)^{0.3} \times weight\ (g)^{(0.7285 - (0.0188 \times \log(g)))}$
Gehan and George (1970) [3]	401	$BSA\ (m^2) = 0.0235 \times height\ (cm)^{0.42246} \times weight\ (kg)^{0.51456}$
Haycock et al. (1978) [4]	81	$BSA\ (m^2) = 0.024265 \times height\ (cm)^{0.3964} \times weight\ (kg)^{0.5378}$
Mosteller (1987) [5]	na[a]	$BSA\ (m^2) = \sqrt{([height\ (cm) \times weight\ (kg)]/3{,}600)}$ or $BSA\ (m^2) = \sqrt{([height\ (in) \times weight\ (lbs)]/3{,}131)}$

[a] This formula is a modification of the Gehan and George [3] formula.
This information has partly been derived from http://www.halls.md/body-surface-area/refs.htm

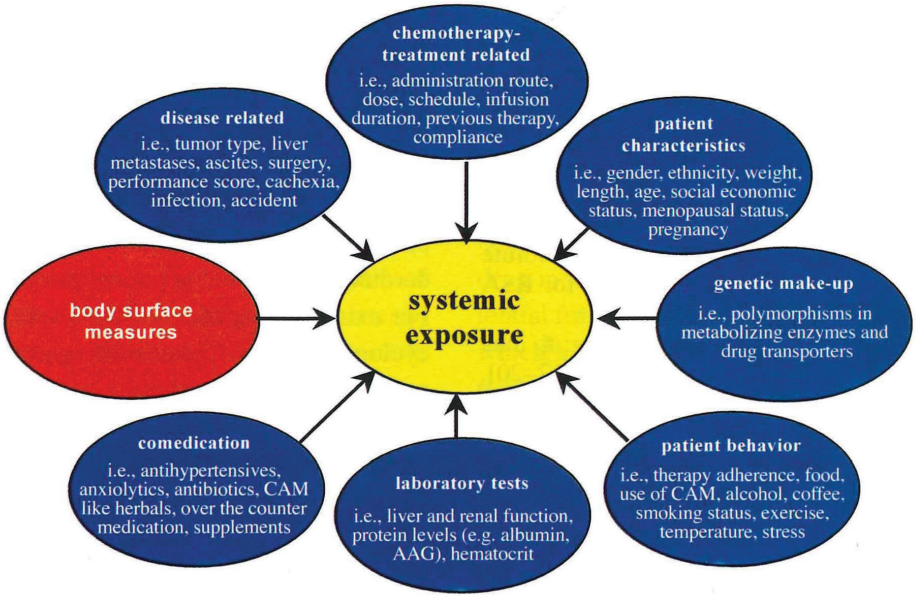


Figure 1. Factors affecting interindividual variability of drug therapy.
Abbreviations: AAG, alpha-1-acid glycoprotein; CAM, complementary and alternative medicine.

et al. wondered if parameters other than length and weight might be better predictors for epirubicin pharmacokinetics [24]. In an exploratory study, 20 patients received a "flat-fixed" dose of 150 mg of epirubicin, meaning that the given dose was independent of body size. In a multivariate analysis, only liver function tests predicted the pharmacokinetic behavior and hematological adverse effects of epirubicin, while BSA (and weight) did not. Retrospectively, Dobbs and Twelves [25] studied the same drug in patients who received a BSA-adjusted dose. By correcting epirubicin clearance for BSA, the coefficient of variation was determined in both the adjusted and unadjusted situations. This percentage appeared to be similar in both groups, suggesting that BSA does not lead to less variability. Both studies, although not comparable in study design, clearly demonstrated that BSA is an unimportant factor in epirubicin disposition. In addition, Ralph et al. performed a population pharmacokinetic analysis, including 109 cancer patients treated with this drug [26]. They found only a weak (negative) relationship between BSA and the clearance of epirubicin, clearly insignificant to base dose adjustments to this parameter. In contrast, aspartate aminotransferase reduced the interindividual variability from 49% to 39% [26].

In the years that followed, the strategy used by Dobbs and Twelves was also used to test the role of BSA in other cytotoxic compounds, including topotecan, cisplatin, and irinotecan [18, 27, 28]. It was noted that the variability in clearance of orally administered topotecan did not decrease as a result of BSA-based dosing [27], while just a small, and clinically unimportant, reduction in the coefficient of vari-

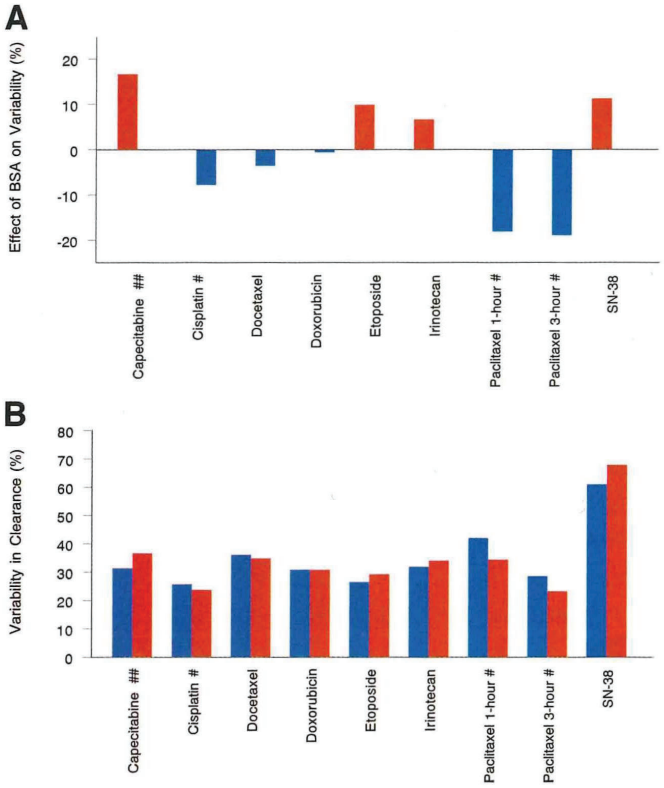


Figure 2. Effect of body-surface area (BSA) on the interindividual variability of anticancer agents. **(A):** Percentage difference without BSA dose adjustment. **(B):** Absolute variability in plasma clearance, without correction for BSA (blue bars) and after correction for BSA (red bars).

Symbols: ##, data from orally administered drug; #, data from unbound fraction of drug. Data are derived from [17–20].

ation of unbound cisplatin clearance was found after BSA correction [18]. For irinotecan, the absolute coefficient of variation for the unadjusted dose was even lower than for the BSA-adjusted dose (32.1% versus 34.0%), although this difference was not statistically significant [28]. Hence, for these three compounds it also should be concluded that the role of BSA in explaining interindividual variability is most likely insignificant. Next, Baker et al. [19] retrospectively studied the pharmacokinetics of 33 anticancer agents tested in phase I trials during the 1991–2001 period in 1,650 adult patients. For only five agents (including paclitaxel), BSA-based dosing *did* reduce the interindividual pharmacokinetic variability. In contrast, for the other 28, the variability was not statistically significantly reduced by BSA, and the rationale for using BSA in dosing these (and other) compounds could therefore be questioned [19].

The Role of Other Body-Size Measures

Other, less commonly used in clinical oncology, body-size measures have been investigated as well, because it was once suggested that they might be better predictors of drug clearance, and therefore of systemic exposure and the occurrence of adverse effects. Aside from BSA, the "direct" body-size measures weight and height have been tested as predictors of anticancer drug metabolism. Other "indirect" body-size measures involve lean body mass (LBM), ideal body weight (IBW), adjusted ideal body weight (AIBW), and body mass index (BMI).

As discussed before, Grochow et al. described a relationship between height and clearance of paclitaxel [21]. In a prospective evaluation by Smorenburg et al. [29], in addition to correlations with BSA, paclitaxel clearance correlated with weight, LBM, (A)IBW, and BMI, indicating that there is a relation with body size. LBM, (A)IBW, BMI, height, and weight have also been correlated with irinotecan pharmacokinetics, although all showed a higher extent of variability than BSA-adjusted clearance [28]. However, nonadjusted clearance in this group of 82 patients showed the lowest interindividual variability of all [28].

Drug dosing recommendations are usually based on results from clinical trials that have 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 can only be performed arbitrarily when the dose is required to be standardized to a particular patient demographic like BSA [30]. For extreme weights, the relationships with clearances of cyclophosphamide, doxorubicin, etoposide plus cisplatin, and ifosfamide were studied in obese cancer patients [31–34]. Correlations between extreme weights and clearances of these compounds appeared to be somewhat contradictory, possibly as a result of the small number of patients. In two studies of only 16 patients each, no effect of body weight on the total clearances of, respectively, cyclophosphamide and ifosfamide was noticed [31, 33]. Rodvold et al., studying 21 patients equally distributed over three classes of IBW, found a decrease in doxorubicin clearance, but only between the normal and the severely obese group [32]. In a much larger study ($n = 262$) by Georgiadis et al., it was shown that doses of cyclophosphamide alone or etoposide plus cisplatin based on total body weight can be given without increasing toxicity or decreasing survival in small-cell lung cancer patients [34, 35]. A recent study even showed a lower degree of febrile neutropenia in severely obese breast cancer patients treated with doxorubicin and cyclophosphamide [36]. As a result, in general practice, obese patients are often underdosed, with serious consequences for treatment outcome [36, 37]. This effect may even be enlarged as a result of "dose capping" (using the patient's actual weight or BSA, up to an arbitrary cutoff value), which is very common and may be the result of fear of overdosing the patient [30].

Similar to studies involving obese patients, it is clear that the usefulness of formulas used to calculate BSA has also not been appropriately evaluated in cancer patients who are very small and thin. Furthermore, the original formulas for calculating BSA-based drug dosages were typically 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. Hence, much remains to be understood about appropriate dosing strategies for severely obese or frail patients, not only for the purpose of evaluating alternative dosing strategies but also for drugs that are already dosed in daily clinical practice according to BSA.

Why Do Some Drugs Relate to BSA?

It has been suggested that, for drugs primarily eliminated by the kidneys and for drugs confined to the central compartment (blood volume), BSA-based dosing might reduce interindividual pharmacokinetic variability, because BSA is associated with both glomerular filtration rate (GFR) and blood volume [19]. However, the association between BSA and GFR is weak [38]. Therefore, in the case of carboplatin, a drug almost completely excreted by the kidneys, dosing based on BSA may result in serious patient under- and overdosing [12]. This urged the wish for better predictors of pharmacokinetic measures than BSA. As discussed later in this review, a dosing strategy based on GFR, using a simple formula, would become the first generally accepted alternative for BSA-based dosing in clinical oncology.

In the previously mentioned study by Baker et al. [19], for docosahexaenoic acid (DHA)-paclitaxel, paclitaxel, 5-fluorouracil/eniluracil, temozolomide, and troxacitabine, significantly less variability in drug clearance was seen after BSA-based dosing. For 5-fluorouracil and troxacitabine, renal elimination contributes to the positive relationship between BSA and drug clearance. A kinetic restriction to the central compartment may be the reason for the relationship found in case of temozolomide [19]. With respect to paclitaxel, which binds extensively to its pharmaceutical excipient Cremophor EL within the central compartment following i.v. administration, it should be pointed out that circulating concentrations of Cremophor EL have been shown to be related to total blood volume, and hence to BSA [29].

Should BSA Be Used if It Leads to a Reduction in Pharmacokinetic Variability?

The relationship between paclitaxel pharmacokinetics and BSA was further explored by Smorenburg et al. [29]. In a randomized crossover design, a BSA-based dose was compared with a flat-fixed dose in the same patients, resulting in a >50% lower coefficient of variation in the exposure of unbound paclitaxel in the BSA-based courses. Also, in a recently published U.S. study, a similar relationship between systemic paclitaxel exposure (AUC) and clearance versus BSA was seen [39]. So, is there a rationale for using an adjustment to BSA in this case? Insights differ, so this question is apparently not easy to answer. Smorenburg et al. [29] are generally positive about BSA-based dosing, because a flat-fixed dose of 300 mg (3-weekly, 3-hour infusion), compared with an identical regimen with a dose of 175 mg/m^2, led to a significant difference in variability in favor of the BSA-based dosing strategy. In contrast, Miller et al. reported that, although BSA is related to paclitaxel pharmacokinetics, it is not related to adverse effects, and therefore has no clinical utility and should be replaced by other strategies (i.e., flat-fixed dosing) [39, 40]. In a population analysis, BSA, bilirubin, age, and gender all appeared to affect paclitaxel pharmacokinetics [41]. Unfortunately, in that retrospective study, toxicity was not studied, and therefore the statement by Miller et al. was not tested. Obviously, additional studies are required to further elucidate the complexity of this topic, and in order to obtain a definitive answer.

Another problem is introduced if BSA does not seem to be related in a clinically relevant extent to the clearance of a drug in the usual normal-weighted population, but has potential for patients with extremely high or low BSA values, which has been shown for cisplatin [42]. Patients with extremely low or high BSA values were randomly exposed to one course of cisplatin based on a fixed dose, followed by one course of cisplatin based on a BSA-based regimen, or vice versa [42]. The use of fixed doses led to a significantly lower exposure to the drug in large patients, while a significantly higher exposure to cisplatin in small patients was seen, compared with a BSA-adjusted dose. Clearance was significantly related to BSA in that study, but nonetheless, interindividual pharmacokinetic variability was only slightly lower after BSA adjustment (interindividual variability, 20.8% versus 17.1%). A retrospective analysis was performed in the same study. Here, the clearance of (unbound) cisplatin was, although weakly related to BSA, significantly lower in patients with a low BSA value ($\leq$1.65 m^2) and significantly higher in patients with a high BSA value ($\geq$2.05 m^2), compared with the clearance in the average BSA group (Fig. 3) [18, 42]. Taking into account the small reduction in interindividual pharmacokinetic variability after BSA correction and the huge differences in clearance between patients with extremely high and those with extremely low BSA values, the authors recommended fixed dosing regimens per BSA cluster ($\leq$1.65 m^2, 1.66–2.04 m^2, and $\geq$2.05 m^2) [42]. Obviously, BSA clusters such as those developed for cisplatin could also be developed for

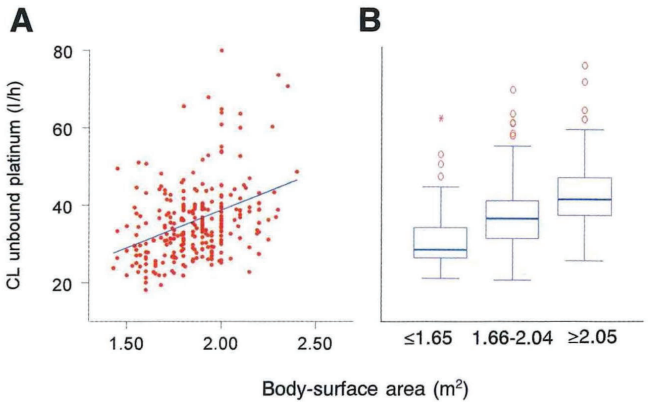


Figure 3. **(A):** Linear relationship ($r^2 = 0.12$) between body-surface area (BSA) and clearance of unbound cisplatin-derived platinum. **(B):** Same data clustered in three BSA clusters. Data are derived from [18, 42].

Abbreviation: CL, clearance.

other commonly used drugs [43]. However, it should be noted that such clustering and subsequent dose fixation based on the average BSA in each cluster may be dependent on the population (e.g., ethnicity) and region (e.g., prevalence of obesity).

Dosing Alternatives

From a pharmacological point of view, it is not surprising that body-surface measures based on height and weight alone do not explain all of the interindividual pharmacokinetic variability. Even for drugs with renal elimination or confinement to the central compartment (the intravascular volume), there is often no straightforward relationship between body-surface measures and clearance. As shown in Figure 1, systemic exposure is influenced by many factors. Although such influences may be represented in part by differences in body-surface measures, most of these factors may affect drug exposure independently (as well). For example, it is well known that polymorphisms in genes encoding metabolizing enzymes involved in the elimination of a particular drug can affect its clearance and exposure [44, 45]. Likewise, use of comedication, food substances, supplements, and herbals may result in (unexpected) serious effects [46]. Moreover, pharmacodynamic effects are not predicted by pharmacokinetic parameters alone, resulting in even more variability in toxicity and therapeutic outcome.

To find successful alternative dosing regimens, apart from body-surface measures, other and more relevant parameters should be included. Which parameters are most relevant depends on the specific kinetic characteristics (i.e., elimination pathways, hydrophilicity, distribution pattern) of the drug in question. In addition, therapeutic drug monitoring (see later) using pharmacokinetic and pharmacodynamic outcome parameters of earlier treatment cycles might be another useful dosing strategy for certain drugs.

Flat-Fixed Dosing

Flat-fixed dosing refers to dosing strategies without correction for body size or other (pharmacological) parameters. This is very common in the medical world, outside oncology. At first sight, this strategy does not look very elegant, but a "standard" dose may be a realistic alternative for BSA-based dosing as long as no tailored or individualized dosing strategy for a specific BSA-unrelated anticancer drug (characterized by a narrow therapeutic window and high interindividual variability in exposure) is introduced. For drugs characterized by a broad therapeutic window and/or small interindividual variability in exposure and/or limited toxicity (e.g., targeted drugs), flat-fixed dosing seems the best option. In addition, the use of this approach may have positive economic implications, because only a unit dose has to be produced and stored, while no time-consuming dosing method is involved. There are also safety implications, because fewer errors will be made in calculating, preparing, and administering the proper individual dose. Moreover, patient adherence to oral anticancer drugs could be improved if, for instance, only one standard tablet had to be taken instead of, for example, two large ones and a smaller one [47]. There is one other, more subtle, advantage: BSA dosing may give prescribers the false feeling of being precise.

Flat-fixed dosing regimens have been studied with and without comparison with BSA-based regimens (Table 2), and in most of these cases flat-fixed dosing did not lead to significantly different interindividual pharmacokinetic variability in drug exposure [24, 29, 39, 42, 48–54]. For instance, in the case of irinotecan, dosing based on BSA did not reduce clearance variability [28], compared with an unadjusted dose. Patients who received a flat-fixed irinotecan dose of 600 mg did not show greater interindividual pharmacokinetic variability than a control group who received the registered dose of 350 mg/m^2 [50]. As toxicity did not significantly differ either, it was concluded that flat-fixed dosing could safely be used to supplant the BSA dosing strategy of irinotecan.

For vinorelbine, a fixed dose was tested in a group of 41 cancer patients, leading to a 4.3-fold variation in clearance [53]. BSA was the only pretreatment predictor of fractional survival of neutrophils, independent of clearance. The authors concluded that a fixed dose of vinorelbine, guided by indicators of clearance and tissue reserve, is thought to be an appropriate option to dose this drug [53, 55]. However, in our opinion, additional data are required to exclude (or verify) the role of BSA in dosing vinorelbine. Moreover, re-

Table 2. Evaluation of flat-fixed dosing strategies for anticancer agents

	Fixed dosing strategy				
Drug	**Dose (mg) (schedule)**	**Tumor type**	**Evaluable patients**	**Conclusion**	**Reference**
Capecitabine	2,000 (days 1–14 orally)	Colorectal	55	Feasible	[48]
Cisplatin	90–180 (several i.v.)	Miscellaneous	25	Feasible	[42]
Docetaxel	180 (1 hour/q 3 wks i.v.)	Miscellaneous	12	Feasible	[49]
Irinotecan	600 (1.5 hours/q 3 wks i.v.)	Miscellaneous	26	Feasible	[50]
Paclitaxel	300 (3 hours/q 3 wks i.v.)	Miscellaneous	12	No advice	[29]
	360 (3 hours/q 3 wks i.v.)	Miscellaneous	29	Feasible	[39]
	175 (1 hour/q 1 wk i.v.)	Miscellaneous	12	Feasible	[51]
	175 (1 hour/q 1 wk i.v.)	Miscellaneous	13	Feasible	[52]
Vinorelbine	60 (10 minutes/ na i.v.)	Miscellaneous	41	Feasible	[53]
Vinorelbine and capecitabine	40 and 3,000 (days 1 and 8/q 3 wks i.v. and daily orally)	Breast	25	Feasible	[54]

Abbreviations: na, not applicable; q, every.

sults need to be confirmed in larger cohorts of patients. Until that time, there is no good reason for stop using BSA in dosing this anticancer drug.

GFR-Based Dosing

Carboplatin was the first anticancer drug for which an alternative dosing strategy was adopted on a worldwide scale. After early exploratory studies [10, 56], Childs et al. [57] compared a BSA-based dosing regimen with a GFR-based regimen (using ^{51}Cr-EDTA clearance, developed by Calvert et al.) [58], which appeared to be superior over the first one, as a result of a closer prediction of toxicity and efficacy. Development of this dosing strategy is described in more detail elsewhere [12]. In routine practice in many hospitals, the original Calvert formula for carboplatin dosing is adapted by measurement of the GFR in an alternative way, using cheaper, less invasive, and easier methods [59]. This, however, may have serious consequences for the validity of this method, as was recently found by Ekhart et al. [59]. In a population pharmacokinetic analysis, they found no relevant correlations between carboplatin pharmacokinetics and modifications of the Calvert formula. They, therefore, advise using the original formula for targeted carboplatin exposures. In patients with normal renal function, however, a flat dose based on the mean population carboplatin clearance seems justified [59].

Genotyping

In contrast to flat-fixed dosing, a dosing strategy based on a genetic variant involved in an agent's metabolic pathway may be a more patient-tailored strategy in cases in which this genetic variation has been shown to affect the pharmacokinetic and/or pharmacodynamic profile. Many polymorphisms have already been found to be related to anticancer drug metabolism, and probably many more will be found to be related in the (near) future. However, only a few of these have shown clinical relevance. Moreover, depending on the relationship, with the severity of its pharmacokinetic and/or pharmacodynamic consequences, the prevalence of the polymorphisms may be considered a factor for the value of this strategy.

For example, patients with functional variant alleles in genes coding for the enzymes dihydropyrimidine dehydrogenase (DPD), thiopurine-methyltransferase (TPMT), and uridine-diphosphate glucuronidase 1A1 (UGT1A1) are supposed to be at risk for unacceptable adverse effects when treated with 5-fluorouracil, 6-mercaptopurine, and irinotecan, respectively [45, 60, 61]. A priori genetic screening for polymorphisms in these genes subsequently followed by adequate action can identify patients at risk to optimize their anticancer treatment before harm is done.

A textbook example of a useful germline variant in predicting clinical outcome in anticancer drug therapy is TPMT. 6-Mercaptopurine is a prodrug that needs to be activated into thioguanine nucleotides, which inhibit DNA and RNA synthesis. TPMT inactivates 6-mercaptopurine, thus preventing formation of its active metabolites. Three different single nucleotide polymorphisms account for almost all dysfunctional *TPMT* alleles, resulting in higher formation of its active metabolites [62, 63]. Patients who carry one dysfunctional allele are at risk for nausea and myelosuppression, whereas those with two disfunctional alleles are highly at risk for severe, life-threatening myelosuppression. It has been clearly demonstrated that

TPMT genotyping can identify patients at risk before starting therapy with thiopurines, and that integration of this genetic screening strategy into the clinical management of 6-mercaptopurine therapy can optimize its outcome [64]. Therefore, in 2003, the U.S. Food and Drug Administration (FDA) met to consider the role of *TPMT* genotyping in the administration of this treatment to pediatric leukemia patients.

Likewise, a dinucleotide polymorphism (*UGT1A1*28*) in UGT1A1, which is involved in inactivation of the active irinotecan metabolite SN-38, has been shown to significantly influence the pharmacokinetics and pharmacodynamics (levels of diarrhea and neutropenia) of irinotecan therapy [44, 65–68]. As this *UGT1A1*28* allele has been related to greater hematological toxicity in particular, the FDA recently advised performing a genetic test for this polymorphism prior to irinotecan treatment as well [44]. Unfortunately, good dose advice in cases of patients who carry this mutation homozygously was not provided. Therefore, although relevance has been made clear, most clinicians still dose irinotecan based on BSA without a priori genetic testing [69].

Phenotyping

Helpful genotyping options are currently lacking for most anticancer agents, because polymorphic variants with functional consequences within the principal metabolizing enzymes have not been determined yet. Not only because of limited functional consequences of most polymorphisms, substrate overlap between metabolizing enzymes and drug transporters, and complicated metabolic pathways, but also because of the influence of other, nongenetic factors on drug exposure, genotyping may be insufficient in predicting interindividual pharmacokinetic variability. The development of an indirect enzyme activity measurement (inside the patient), using compounds metabolized the same way as the drug in question, may have additional value here [45]. Probe drugs, which are ideally cheap, safe, and easily available and determined agents, are given prior to the anticancer therapy. Because the metabolism, distribution, and elimination of the probe are related to the pharmacokinetic behavior of the anticancer drug in question, the subsequent given chemotherapy dose can be adjusted to probe-drug elimination. Such phenotyping strategies take the patient as a whole, including all factors affecting pharmacokinetic behavior of both the probe drug and the anticancer drug. Relationships have been studied for several cytochrome P450 probes (e.g., midazolam) and anticancer drugs [45]. Also, for other enzymes, like DPD, a phenotypic test is in development [70]. In addition, for drug transporting proteins (like ABCB1, P-glycoprotein), activity can be determined using drugs shown to be substrates for these proteins. For example, ^{99m}Tc-sestamibi is a substrate for ABCB1 excretion [71], and hepatic nuclear imaging using a ^{99m}Tc-sestamibi scan has been correlated with the pharmacokinetics of several agents, including vinorelbine [53] and irinotecan [72]. However, only very small numbers of patients have been studied yet, so more research is warranted to establish the findings and potentials of these exploratory studies.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) implies that, at regular intervals, systemic drug concentrations are determined to achieve and maintain a relatively constant circulating level. In general, administration of a standard dose is much easier than the dosing strategy of continuous systemic drug level determination and subsequent dose adjustment. Generally speaking, drugs that are monitored have a narrow therapeutic window and are supposed to be taken for a long time. Because factors affecting pharmacokinetic exposure may change during this time, exposure may change as well. Integrating TDM into clinical management helps to compensate for such influences to maintain optimal treatment, that is, the combination of stable levels, acceptable adverse effects, and therapeutic benefit. Through the years, in many drug therapies, such as antibiotics, immunosuppressive drugs, antipsychotics, and antiepileptics, TDM has earned a place in clinical practice. Likewise, in oncology, for drugs that are generally also prescribed based on pre-established dosing schedules, TDM can be an option. After determining the pharmacokinetic profile (exposure) of the first cycle, the dose to administer can be adjusted to these results to achieve optimal drug exposure and clinical results. This strategy may improve patient outcome and survival [73]. However, in daily clinical practice, this strategy has limitations, because drug levels need to be determined quickly, accurately, and precisely. In addition, pharmacokinetic sampling should be done at the right time points, and interacting drugs should be evaluated. Moreover, a clear relationship between toxicity/efficacy and drug exposure should exist, intrapatient variation should be limited, and it should be known how dose adjustments should be made. Costs, logistics, and patient inconvenience are frequently encountered potential problems as well.

Although many factors can be overcome, time will tell if TDM in routine clinical practice for chemotherapy administration in adults is feasible [74]. It has been suggested that TDM should be reserved for only a proportion of patients, depending on factors such as tumor type, anticancer drug, and patient characteristics [74]. However, despite its limitations, more and more research is being done on the use of TDM in oncology [73–75]. For example, Ratain et al. [17] introduced a (complex) formula to dose etoposide based on

pretreatment WBC, among others, whereas a population-based Bayesian methodology to routinely adjust etoposide therapy when given as a 5-day infusion, based on its pharmacokinetic profile as determined on the first day, was proposed by others [76]. In addition, de Jonge et al. [77] evaluated the performance and technical feasibility of pharmacokinetically guided dosing of paclitaxel. Twenty-five lung cancer patients, monitored for pharmacokinetics, were treated for a total of 92 courses. In 43% of the individualized courses, the dose was increased to achieve a predefined target value. Individualization of the dose led to a higher percentage of patients who attained the target value, compared with the control group. Currently, it is unclear if this dose individualization leads to better efficacy, and a randomized study should be performed first. In pediatric oncology as well, several good examples can be given for TDM-based therapy [78–80]. As this topic falls outside the scope of our review, we refer to other work for a detailed discussion [81].

In general, controlling systemic exposure based on TDM should maximize treatment efficacy, while at the same time prevent serious adverse effects, thus resulting in an optimal balance between efficacy and adverse effects.

Conclusions and Future Perspectives

A statistically significant correlation between a given demographic characteristic (i.e., BSA) and measures of a drug's pharmacokinetic profile does not necessarily guarantee that a meaningful relationship exists [82]. This is important to realize, because it largely explains why dosing based on BSA does not have to lead to significantly less variability in pharmacokinetic parameters for a given drug. The other way around, characteristics that do relate to a drug's clearance have a better chance to accurately predict the toxicities and activity of an agent, because a good correlation between pharmacokinetics and pharmacodynamics is likely for most anticancer drugs. Because most anticancer drugs have a narrow therapeutic index, it is clinically of utmost importance to control and even predict their exposure a priori. In the last decade, alternative strategies aimed at truly individualizing anticancer treatment and optimizing its efficacy have been considered, tested, and slowly brought into clinical practice. For some drugs, clear and unbiased relationships with genetic polymorphisms have been described, and a priori genotyping for one or a few mutations seems to improve treatment. In other cases, phenotyping is capable of predicting the pharmacokinetic behavior beforehand. For specific anticancer drugs, TDM may have potential, because it is possible to change the dose as a result of earlier experience in that patient. Unfortunately, except for some examples, such dose-individualization strategies have not yet been able to show their additive value in routine clinical practice, because they are mostly applied in experimental settings so far.

Probably for this reason, and despite the growing amount of scientific evidence regarding the (poor) utility of BSA-based dosing in oncology, clinical practice "anno 2007" has not changed that much [40, 43, 47, 55, 74, 82–84]. In addition to the lack of good alternatives, the lack of willingness of clinicians to change their policies may be part of the explanation for this phenomenon. Fortunately, for an increasing number of novel drugs, the use of BSA is already no longer included in dose calculation in the early phases of drug development, unless a significant role in reducing interpatient variability in exposure is assumed. In general, flat-dosing strategies are advised in the development of investigational drugs for the advantages mentioned earlier, and as long as no better alternatives exist. Flat-dosing has been shown to be feasible for many anticancer compounds and may, in due time, fluently be replaced by more individual (or tailored) drug-dosing strategies. Phase I and II trials with flat-fixed dosing strategies, including registered drugs, are performed at present to implement non–BSA-based dosing regimens [48, 54]. Ultimately, registration of anticancer drugs may take place without BSA-based dose adjustment. As a consequence, clinical practice would be unable to stick to one (irrational) dosing strategy, but would have to consider alternatives.

Acknowledgments

R.H.J.M. and F.A.de J. contributed equally to this manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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