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Dosing strategies for anticancer drugs: the good, the bad and body-surface area

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Abstract

Most anticancer drugs are characterised by a narrow therapeutic window; hence, a small change in dose can lead to poor antitumour effects or an unacceptable degree of toxicity. The rationale for using body surface area (BSA) to dose antineoplastic agents is to normalise the effects of drugs, and accordingly, it has been routinely employed as the only independent variable. In the last 10 years, however, several studies have shown a poor relationship of BSA for predicting drug exposure, and an irrelevant correlation between this variable and pharmacokinetic (PK) parameters. In this paper, the results of this relationship for various commonly used antineoplastic agents are reviewed, and the influence of BSA to decrease the total variability in clearance among patients is underlined. As reported, BSA failed to individualise the effects of the majority of the agents explored. The criteria that can predict a clinically meaningful relationship between BSA and drug clearance are discussed, and some alternative strategies to dose agents when BSA has proven to be useless are proposed. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Anticancer drugs; Body-surface area; Pharmacokinetics; Dosing strategies

1. Introduction

Individuals have a highly variable capacity to metabolise and eliminate drugs, which originates from a combination of physiological variables, intrinsic (genetic) characteristics and environmental factors that determine each patient's phenotype. In particular, many anticancer drugs are characterised by unique and peculiar pharmacokinetic (PK) and pharmacodynamic (PD) profiles, and also by a narrow therapeutic window. Thus, a small variation in the administered dose can lead to severe and life-threatening toxicity in some individuals, and poor antitumour effects in others. The achievement of therapeutic benefit is particularly important in patients with curable disease, such as Hodgkin's lymphoma or testicular carcinoma, and in the setting of adjuvant chemotherapy. Instead, the difficulty to reach this correct dose and to avoid an unacceptable degree of toxicity is one of the principal problems in current oncology practice, particularly in patients with impaired renal and/or hepatic functions, and in the elderly.

A high interindividual variability in clearance has been observed in adult cancer patients for most antineoplastic drugs, and this phenomenon can easily result in an over- or underdosage of agents (Fig. 1). In order to reduce the variability in PK and PD profiles, and thus to normalise the effects of antineoplastic drugs, it is customary to adjust the drug dose on the basis of the patient's body surface area (BSA). Different formulas can be applied to calculate BSA, but the most commonly used one is that derived by DuBois and DuBois [1]. In 1916, studying only 9 patients, these authors developed a formula using height and weight alone (BSA $(m^2) = \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184$), and this is still widely used. Subsequently, the formula was re-evaluated and challenged in several studies [2,3] and some alternative body-size measures have been proposed, such as lean body mass [4], ideal body weight [5], adjusted ideal body weight [5] and body mass index [5], but any proper scientific rationale for their use is lacking.

Why has BSA conventionally become the only variable to dose anticancer agents? Firstly, it is established that a correlation exists between BSA and some particular

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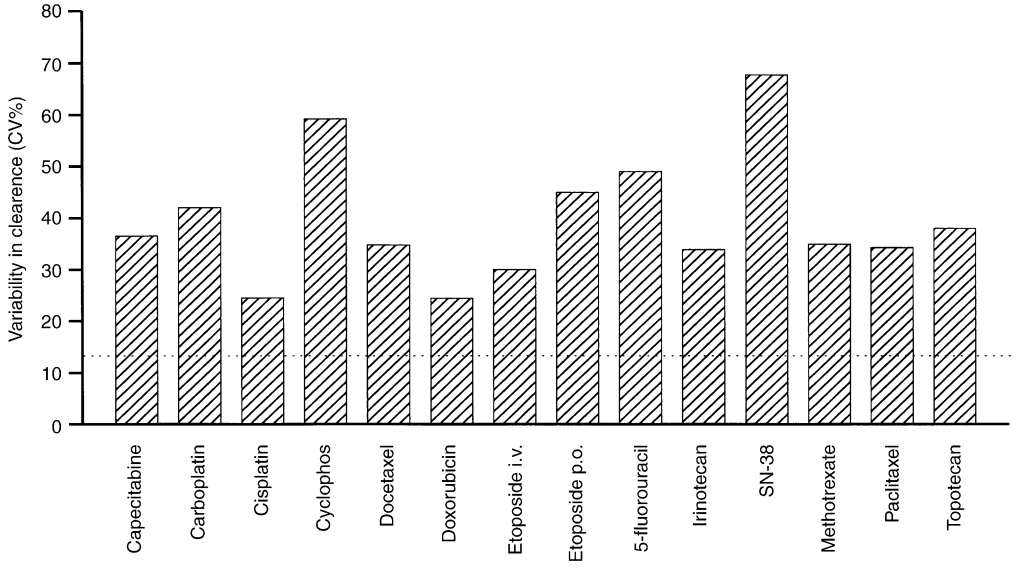

Fig. 1. Variability in the plasma clearance of commonly used anticancer drugs with data expressed as the coefficient of variation (%CV). The dotted line indicates the %CV in body surface area (BSA) in a group of 2355 patients treated at the Rotterdam Cancer Institute (mean (standard deviation (SD)), 1.855 (0.225) m^2). i.v., intravenous; cyclophos, cyclophosphamide; p.o., orally.

characteristics of each patient, such as the glomerular filtration rate (GFR) [6], blood volume [7] and basal metabolic rate [8] (Fig. 2), and certainly this provides a condition to individualise doses. A similar relationship with liver function has not been made, which is particularly noteworthy as the metabolic pathways of most drugs are strictly related to the activity of hepatic enzymes. Recently, however, these basic principles have been, in part, questioned by a study where a poor correlation between BSA and GFR was reported [9]. Secondly, the starting dose of agents calculated in phase I studies is based on data derived from animal models where drug dose is calculated relative to weight (mg/kg) or BSA (mg/m^2). In animals, doses are usually tested until the LD10 is reached (10% of the lethal dose), and in human phase I studies, the first dose employed is 1/10 of the LD10. Thirdly, some studies published in the 1950s suggested a role for BSA in the drug dose calculation,

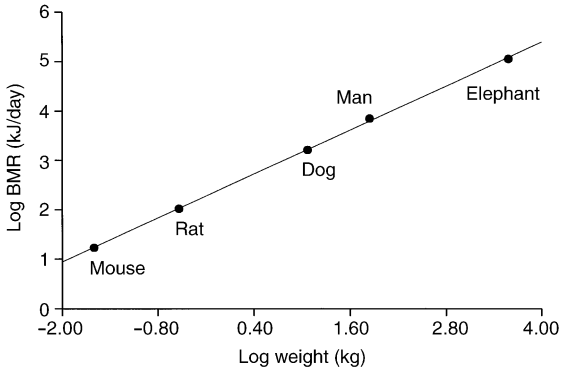

Fig. 2. Linear correlation between basal metabolic rate (BMR) (expressed in kJ/day) of several species and their weight (expressed in kg), known as the 'mouse–elephant curve'.

when attempts were made to define a more accurate method for the administration of cytotoxic drugs in children. Among these, Pinkel [10] reported in 1958 the results of a retrospective analysis applying a BSA-based formula in adults and in children, and Meeh's formula in animals, to determine the conventional paediatric and adult dose of five cytotoxic drugs (i.e. mercaptopurine, methotrexate, mechlorethamine, triethylene thiophosphoramide and actinomycin). This author calculated the doses per unit surface area, and found similar figures for all agents tested between children and adults, except for mercaptopurine, and recommended normalising the doses of cytotoxic agents using BSA.

Since the publication of this report, the use of BSA for dose calculation has become standard practice for dosing of all cytotoxic drugs, virtually without further investigation into the relationships between PK and BSA or other measures of body-size. Although a number of studies have appeared in the literature that clearly question the routine use of BSA (Table 1), the message appears not to have been heard and many clinicians, regulators and industrial drug developers are still concerned. This concern is based on the intuitive belief that patients with a larger BSA require more drug to induce the same drug effects. We now address this issue using a more systematic approach that will allow all those concerned to more fully understand the very limited cases when BSA may be important clinically.

2. BSA and anticancer drug clearance

Until 1990, when the first paper was published that criticised the routine use of BSA, this measure was

Table 1
Established relationships between body-surface area and anticancer drug pharmacokinetics

Drugs	Comments	Ref.
Busulfan i.v.	No correlation between BSA and CL	[11]
Busulfan p.o.	BSA is a significant determinant of CL	[5]
Capacitabine	No influence of BSA on PK parameters	[53]
Cisplatin	No correlation between CL(free) and BSA	[16]
Cyclophosphamide	Negative correlation between body weight and CL when normalised to BSA	[54]
Docetaxel	The only potential clinically relevant effect on the decrease of CL are altered levels of liver enzymes	[27]
Doxorubicin	CL is not correlated with BSA	[20]
Eniluracil/5-FU	CL is correlated with BSA	[14]
Epirubicin	Normalisation of epirubicin dosage according to BSA appears not to reduce either PK and PD variability	[19]
Epirubicin	No correlation between BSA and any PK parameters or with the degree of neutropenia	[18]
Etoposide	CL is not correlated with BSA	[20]
Etoposide	Only serum creatinine correlated to CL (no BSA)	[55]
5-Fluorouracil	BSA has no significant influence on CL	[24]
Gemcitabine	Its PK are influenced by gender, BSA and duration of infusion	[13]
Irinotecan	BSA is not a predictor of CL or SN-38 PK	[15]
Ifosfamide	CL is not correlated with BSA	[20]
Methotrexate	Normalisation for weight or BSA does not affect interpatient variability	[21]
Paclitaxel	Significant relationship between clearance and height	[11]
Paclitaxel	Paclitaxel disposition is significantly related to BSA.	[12]
Temozolomide	CL increased with BSA in both gender	[56]
Temozolomide	Temozolomide should be individualised according to BSA	[33]
Topotecan	High inter and intrapatient variability when the dose is administered using BSA	[17]
ZD 9331	BSA does not correlate with drug clearance	[29]

BSA, body surface area; CL, clearance; 5-FU, 5-fluorouracil; PK, pharmacokinetic; PD, pharmacodynamic; i.v., intravenous;. p.o. orally.

commonly used also for drugs not previously tested at fixed doses. Since then, however, several studies have been conducted looking for a correlation between anticancer drug clearance and BSA. In Table 1, the results of this correlation for several commonly used antineoplastic agents are summarised. Grochow and colleagues [11] conducted a study to find a relationship between morphometric measures (height, weight and BSA) of 287 patients receiving nine different antineoplastic agents, and pharmacokinetic parameters, including clearance and volume of distribution. They found that only the clearance, a parameter closely related to effects of cytotoxic agents, of paclitaxel (Taxol), was highly correlated with one of the measures considered (i.e. height). These authors concluded that normalisation of dose to BSA, for the drugs studied, did not modify the variability in PK parameters. The data for paclitaxel were later independently confirmed in another study [12], where it was shown that the coefficient of variation (CV) in unbound paclitaxel clearance was significantly reduced after correction for BSA, providing a pharmacokinetic rationale for BSA-based dosing of this drug.

Other drugs show the same PK behaviour as paclitaxel. For gemcitabine [13], the combination of eniluracil and 5-fluorouracil [14] and oral busulfan [5], BSA-based dosing has proven to have a PK basis. The different PK profiles observed between oral and intravenous (i.v.) busulfan [11] could justify the different dependence of clearance by BSA, expressed by the same drug in two different formulations; in fact, Grochow and colleagues [11] had already demonstrated that i.v. busulfan clearance did not correlate with BSA.

On the contrary, the absence of a link between clearance and BSA has been published for several drugs, including irinotecan (CPT-11). Recently, Mathijssen and colleagues retrospectively examined 82 patients undergoing chemotherapy with CPT-11 for malignant solid tumours, and reported an interpatient variation for the absolute CPT-11 clearance of 32.1% (expressed in l/h) and a BSA-corrected clearance of 34.0% (expressed in $l/h/m^2$) [15] (Table 2). The metabolic clearance of SN-38, the pharmacologically active metabolite of CPT-11, also remains similar after normalisation to BSA (63% when calculated in l/h and approximately 65% when calculated in $l/h/m^2$). Mathijssen and colleagues concluded that BSA, as well as several other body-size measures tested, is unrelated to CPT-11 clearance and metabolism, and recommended that development of alternative dosing strategies to reduce the marked interindividual variability should be pursued. Interestingly, the variability in CPT-11 clearance is higher when expressed relative to BSA (expressed in $l/h/m^2$ rather than in l/h), suggesting that BSA further increases the variability of the effects induced by this agent, and thus may even be harmful. This last evaluation seems to provide a further reason to change current practice and apply flat doses instead of BSA-based doses.

Similar results were reported for a group of patients treated with cisplatin. De Jongh and colleagues [16] found that the CV for cisplatin clearance was in the

Table 2
Variability in absolute and BSA-corrected clearance of several anticancer drugs

Drugs	Absolute		BSA-corrected		Patients (*n*)	References
	CV%	Clearance[a] (l/h)	CV%	Clearance[a] (l/h/m^2)		
Cisplatin	25.6	57.1±14.7	23.6	30.7±7.25	268	[16]
Cisplatin	26.8	56.3±15.1	24.5	30.8±7.54	391	[b]
Cyclophosphamide	54.8	4.10±2.25	59.2	2.38±1.41	16	[b]
Doxorubicin	26.9	74.2±20.0	24.4	38.9±9.51	44	[b]
Etoposide	22.8	2.25±0.51	21.0	1.36±0.29	25	[b]
Irinotecan	32.1	33.6±10.8	34	17.9±6.1	82	[15]
Methotrexate	36.6	0.14±2.98	34.9	4.45±1.56	23	[b]
Topotecan	42	194±80.4	38	103±39.0	112	[17]

Interpatient variation in clearance was calculated as the standard deviation divided by the mean and expressed as a percentage (CV%). CV, coefficient of variation.

[a] All data are represented as means±standard deviation.

[b] Unpublished work by Sparreboom and colleagues.

same order when expressed in absolute measures or adjusted to BSA (25.6% versus 23.6%) (Table 2). The authors recommended, unless other predictors of cisplatin clearance are identified, to apply fixed doses in adult cancer patients. Likewise, the interpatient variability in oral topotecan clearance is approximately 38% when corrected for BSA, and 42% for the absolute clearance [17] (Table 2). These two last examples show a very small reduction in CV when the dose is normalised to BSA, indicating that other variables or clinical factors (e.g. age, obesity, existence of other disease, comedication) may be more important in explaining the high variability observed (Tables 3 and 4).

Other studies have been conducted to determine whether BSA could be the correct parameter to dose anticancer drugs, and for many of these agents such as anthracyclines (epirubicin [18,19] and doxorubicin [20]), etoposide [20], ifosfamide [20], methotrexate [21], and others, no convincing relationship between this measure and PK parameters has been found (Tables 1 and 2). In the literature, contradictory results have been reported for some agents, including 5-fluorouracil. Port and colleagues [22] emphasised the important role of BSA, dose, age and sex, as variants influencing 5-fluorouracil clearance. This correlation has been criticised by Gurney [23], who re-analysed clearance measures for each patient and concluded that it was inappropriate to model clearance using BSA as performed in the original report. In fact, the results published by Etienne and colleagues [24], as well as our own retrospective analysis

Table 3
Factors contributing to variability in drug response

Parameter	Source of variability
Dose selection	Physician's preference; patient's condition (performance status)
Dose administration	Non-compliance; medication error; pharmaceutical formulation
Systemic exposure	Age; concomitant drugs; food effects; gender; route of administration; altered organ function; enzyme polymorphisms (pharmacogenetics)
Active site drug levels	Cellular uptake; intracellular activation; tumour sensitivity
Pharmacological effect	Host sensitivity (e.g. previous treatments)

Table 4
Examples of patient characteristics affecting anticancer drug pharmacokinetics

Characteristic	Anticancer drug
Renal function	Bleomycin, carboplatin, cisplatin, cyclophosphamide, etoposide, methotrexate, topotecan
Hepatic function	Docetaxel, doxorubicin, epirubicin, vinblastine, vincristine
Serum proteins	Etoposide, paclitaxel[a]
Third spaces	Methotrexate
Obesity	Cyclophosphamide, doxorubicin, 6-mercaptopurine, methotrexate
Cancer cachexia	5-Fluorouracil, methotrexate

[a] Altered binding of paclitaxel in plasma due to the presence of high concentrations of Cremophor EL, the formulation vehicle used for intravenous drug administration.

(Table 2), support Gurney's conclusion. Etienne and colleagues evaluated some co-variables, including BSA, to find which one could influence interpatient variability of 5-fluorouracil clearance during a 5-day continuous infusion of the agent. The data show that only age, dihydropyrimidine dehydrogenase activity in peripheral mononuclear cells, serum alkaline phosphatase, and elapsed time during infusion influence the drug clearance, but not BSA.

It is still debatable whether the interpatient variability of docetaxel clearance has a clinically meaningful relationship with BSA. Although Bruno and colleagues reported in 1996 [25] and in 1997 [26] that BSA is a significant covariate on docetaxel clearance, the only clinically relevant variables that impact upon clearance of this drug are altered transaminases and alkaline phosphatase levels [27]. Thus, although docetaxel clearance may be weakly related to BSA, this measure does not contribute substantially to explaining the interindividual variability (less than 10%). This is immediately evident from the wide overlap in the area under the concentration-time curve (AUC) values in patients receiving different doses of docetaxel (i.e. 75 and 100 mg/m^2), in spite of drug administrations being given on the basis of BSA (Fig. 3).

The dose of some drugs is established by their toxicological profile, as for bleomycin. This agent does not induce any clinically relevant degree of myelosuppression, although it does induce significant chronic skin reactions. Clinically, the most serious adverse reaction is pulmonary fibrosis, which is the dose-limiting toxicity. Nonetheless, bleomycin is usually given at fixed doses, even if no study is reported in the literature comparing

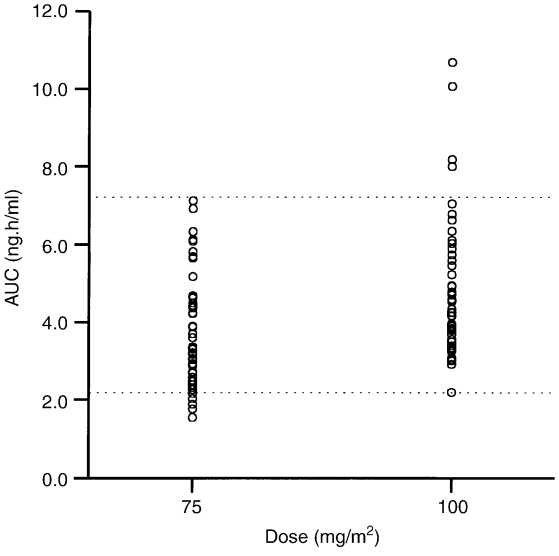

Fig. 3. AUC of docetaxel as a function of the drug dose in a group of 102 patients. The mean AUC values were 3.77±1.44 ng h/ml (75 mg/m^2; 51 patients) and 4.79±1.73 ng h/ml (100 mg/m^2; 51 patients). Unpublished data from patients treated at the Rotterdam Cancer Institute.

the effects and toxicity using flat doses or BSA normalised doses. Commonly, target-based drugs such as inhibitors of signal transduction pathways, angiogenesis, cyclin-dependent kinase and matrix metalloproteinase pathways are administered using either a flat-fixed dose or adjusted to the patient's body weight. For example, trastuzumab, a humanised monoclonal antibody that targets the human epidermal growth factor receptor (EGFR)-2, has been administered using flat doses in early clinical studies and using body weight-adjusted doses in phase II trials [28]. Non-cytotoxic agents are also usually tested and administered using non-BSA-based doses (generally giving as a total dose in mg). These include ZD9331, a non-polyglutamatable inhibitor of thymidylate synthase [29], R115777, a farnesyl protein transferase inhibitor [30], and PKI166, a EGFR and ErbB2 kinase inhibitor [31]. This clearly demonstrates that the administration of a fixed dose is feasible for the development of non-cytotoxic anticancer agents.

3. The correct use of BSA

Observing the results reported in Table 1, it becomes clear that the use of BSA should be restricted to those agents for which a relationship between BSA and clearance or with other PK parameters has been proven. This correlation has been described for agents mostly confined to the blood compartment, i.e. those characterised by a low volume of distribution [12]. This occurs when the drug shows a high binding affinity to serum proteins, or when it is linked to some formulation vehicle in the general circulation, as for paclitaxel, or also in case of liposomal formulations, as for liposomal doxorubicin [32]. This is largely due, as already mentioned, to the strong correlation demonstrated between BSA and the blood volume. This concept can also be applied to drugs eliminated by processes taking place in the central compartment, e.g. temozolomide [33], due to their clearance being restricted to an apparent volume, such as the total blood volume in the systemic circulation of the patient. In fact, temozolomide is an alkylating agent that is activated by a process occurring in the central compartment immediately following drug administration [34].

Concerning drugs primarily eliminated by kidneys, the use of BSA can reduce a small percentage of total variability in clearance among patients, in accordance with the poor correlation recently reported between GFR and BSA by Dooley and Poole [9]. For example, BSA-based dosing is recommended for oral 5-fluorouracil co-administered with the dihydropyrimidine-dehydrogenase inactivator eniluracil [14], which results in 75% of the drug being excreted unchanged in urine. It is noteworthy, however, that dosing strategies based on an accurate assessment of the GFR should result in a

further decrease of PK variability, as has been described for carboplatin [35].

4. Alternative proposals to BSA

In the search for alternatives to BSA in drug dosing strategies, it would probably be inappropriate to try and identify only a single variable to be applied to all anticancer agents; this is largely due to the wide complexity of metabolic and elimination pathways that characterise these drugs. Knowledge of the PK of each agent is 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 (Table 5). This has been done for carboplatin, the only cytotoxic agent for which dose is individualised according to PK parameters and not according to BSA. Carboplatin plasma clearance is linearly related to GFR and renal tubular excretion and absorption of the drug is minimal. Using creatinine clearance, Calvert found a formula that accurately describes its pharmacokinetics [36], and predicts the level of myelosuppression, the dose-limiting factor, of this agent.

Given the inappropriateness of BSA to normalise the effects of most anticancer agents, more adequate measures are urgently required. For agents such as CPT-11, cisplatin, and oral topotecan for which it has already been shown that the interindividual variability is not modified by employing BSA, we recommend using flat-fixed doses, in the absence of a better alternative, and adjusting the dose for subsequent cycles on the basis of the toxicity induced in each patient. Similarly, in early clinical trials, it can be safely advised to perform all studies using flat-fixed doses and to plan them in combination with a rigorous PK evaluation, with the aim of finding a correlation between patient variables (including BSA) and PK parameters (including clearance) of the drugs tested.

Table 5
Potential candidates to supplant BSA for anticancer drug dosing

Dosing type	Example
A. Based on patient characteristics	
1. Pathophysiological status (renal function)	Carboplatin
2. Based on enzyme phenotyping (CYP3A4)	Docetaxel
B. Based on pharmacokinetic–pharmacodynamic principles	
1. During repeated administration	5-Fluorouracil
2. Feedback-controlled dosing	Methotrexate
3. Circadian rhythm-based dosing	6-Mercaptopurine
4. Intentional biomodulation	
a. Pharmacokinetic modulation	5-Fluorouracil/eniluracil
b. Pharmacodynamic modulation	5-Fluorouracil/leucovorin
5. Drug scheduling	Etoposide
6. Drug administration sequence	Topotecan/cisplatin
C. Based on pharmacogenetic principles	5-Fluorouracil/DPD 6-Mercaptopurine/TPMT

DPD, dihydropyridine dehydrogenase; TPMT, thiopurine methyltransferase.

An alternative approach is the one taken by Goh and colleagues [29] in a phase I and pharmacokinetic trial of ZD9331. These investigators employed escalating doses normalised to BSA until mature results of the drug disposition were available. Following the demonstration of the lack of any correlation between this measure and clearance, fixed doses were used in the remainder patients enrolled, and this strategy was eventually recommended for future studies. Concerning registered drugs, when the relationship between clearance and BSA is not yet known, flat-fixed doses can probably be implemented without compromising safety and activity profiles. This procedure, besides reducing the variables influencing PK values, has significant economic implication. In fact, the ability to manufacture a unit dose of an agent has evident benefits for the pharmaceutical company involved, as reconstituting individualised doses is more expensive and less accurate than preparing fixed doses without modifications for different patients [37]. Accuracy can be compromised not only during the drug reconstruction, but also by the clinicians calculating the BSA, and the use of flat-fixed doses can eliminate a source of error that contributes to increased interindividual variability of PK parameters and outcome of treatment.

Several alternative methods can be applied to dose anticancer agents (Table 5), such as estimating the total activity of enzymes involved in the metabolic pathway of drugs transformed prevalently in the liver (i.e. phenotyping), as has been done recently for docetaxel. This drug is extensively metabolised by the CYP3A4, a member of the cytochrome P450 family responsible for the metabolism of various endogenous and xenobiotic substances that displays large interpatient differences in both content and catalytic activity in humans. Hirth and colleagues [38] proposed that the interindividual variability in CYP3A4 activity might explain, in part, the differences in toxicity and clearance observed with docetaxel chemotherapy. It was demonstrated that ERMBT (the [^{14}C-N-methyl] erythromycin breath test), used to measure the total activity of the isozyme, was the best predictor of docetaxel clearance compared with various other measures of hepatic function (i.e. serum alanine aminotranferase, albumin, alkaline phosphatase and serum α_1-acidic glycoprotein levels), and that the different activity of CYP3A4 accounts for 67% of the interpatient variation in docetaxel clearance. This test could be easily applied to all other drugs that are metabolised by CYP3A4, firstly by checking if their behaviour is the same as reported for docetaxel, and secondly, according to the results, by employing it as a dose measure. Moreover, other methods can be used to calculate the same activity, such as the urinary dapsone recovery test,

and measurement of the ratio of endogenous urinary 6-beta-hydroxycortisol to cortisol [39]. Yamamoto and colleagues have recently applied this latter method to confirm the role of this isozyme in interpatient variability of the docetaxel clearance [40].

The metabolic pathways of most drugs that are routinely administered is reasonably well established; for example, 5-fluorouracil is extensively metabolised in the liver by the polymorphic enzyme dihydropyrimidine dehydrogenase (DPD). Hence, the DPD phenotype may prove to be of value in prospective modelling of 5-fluorouracil PK and drug dosing [41], as reported in several studies [42–45]. The cytotoxic activity of mercaptopurine, instead, is regulated by the enzyme thiopurine methyltransferase (TPMT), and a lack of functional TPMT activity can produce life-threatening mercaptopurine-induced myelotoxicity [46]. Therefore, the implementation of enzyme activity measurements might contribute to reducing the variability of the drug effects and to find the correct dose on the basis of an individual's capacity to metabolise the drug.

Another potential candidate to supplant BSA is PK monitoring, which is already routinely employed to reduce the toxicity of high-dose chemotherapy protocols, which include methotrexate. The current standard of methotrexate monitoring requires the use of serum drug levels to determine the duration of leucovorin rescue [47]. Less conventional methods of monitoring PK parameters have also been explored for various other agents, including continuous infusion of etoposide [48,49] and 5-fluorouracil [50–52], but have not yet been widely applied.

5. Conclusions

Given the importance of improving the safety of antineoplastic agents and also of selecting a target population that might be able to tolerate dose intensification, there is a clear necessity to find the correct measure to dose cytotoxic drugs. During the last 40 years, BSA has certainly made a considerable contribution to dose adaptation, and it can still be correctly employed, albeit for a very limited number of anticancer agents. For most agents used in today's clinical practice, BSA is not a measure that can be used reliably to individualise treatment. Other measures that might be used in conjunction with or instead of BSA have already been explored for some agents, including PK monitoring for methotrexate and enzyme phenotyping strategies for agents like docetaxel. For the long list of anticancer agents where BSA-based dosing does not seem to be accurate, however, it is suggested that flat-fixed dosing strategies should be implemented and the routine use of normalising the dose to BSA should be abandoned.

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