BRIEF COMMUNICATIONS

Role of Body Surface Area in Dosing of Investigational Anticancer Agents in Adults, 1991–2001

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The prescribed dose of anticancer agents is most commonly calculated using body surface area as the only independent variable, and it has been shown that this approach still results in large interpatient variability in drug exposure. Here, we retrospectively assessed the pharmacokinetics of 33 investigational agents tested in phase I trials from 1991 through 2001, as a function of body surface area in 1650 adult cancer patients. Twelve of the drugs were administered orally, 19 were administered intravenously, and two were administered by both routes. Body surface area-based dosing was statistically significantly associated with a reduction in interpatient variability in drug clearance for only five of the 33 agents: docosahexaenoic acid (DHA)–paclitaxel, 5-fluorouracil/eniluracil, paclitaxel, temozolomide, and troxacitabine. These results do not support the use of body surface area in dose calculations and suggest that alternate dosing strategies should be evaluated. We conclude that body surface area should not be used to determine starting doses of investigational agents in future phase I studies. [J Natl Cancer Inst 2002;94: 1883–8]

In clinical oncology, the traditional method by which individualized anticancer drug doses are determined uses body surface area, because use of this measurement is thought to reduce the interpatient variability of drug exposure and, hence, drug effects *(1).* The use of body surface area measurements arose from the extrapolation of drug doses used in experimental animals to those considered safe as starting doses for human cancer patients in phase I clinical trials *(1).* However, a rigorous scientific rationale for body surface area-based dosing of anticancer drugs in adults is lacking, especially when one considers that the difference in size between mice and humans is far greater than the difference in size between individual patients. Although the primary objective of phase I trials is to evaluate drug toxicity, antitumor activity is usually a secondary objective. Other measures, such as drug clearance, have also been used as surrogate markers of drug effects. However, it has been widely recognized that large interpatient variability in drug clearance exists despite the use of body surface area in drug-dose calculations *(2).* Indeed, for most drugs that are used in clinical practice today, clearance cannot be reliably predicted by body surface area, because other factors involved in drug disposition may be more important for clearance *(1,3–5).* For example, several recent studies *(6–9)* have highlighted the importance of genetic polymorphisms in drug-metabolizing enzymes and drug transporter proteins in explaining interindividual pharmacokinetic variability. As a follow-up to a preliminary report by Grochow et al. *(10),* we assessed the pharmacokinetics of 33 investigational agents in adult cancer patients as a function of body surface area to provide a pharmacokinetic rationale for selecting the appropriate starting doses for phase I evaluation.

Data were obtained from 1650 patients who were treated with 33 anticancer drugs (involving 21 classes of agents) that were developed in phase I trials over a 10-year period at three institutions. Twelve of the drugs were administered orally, 19 were administered intravenously, and two were administered by both routes. Detailed clinical and pharmacokinetic profiles for these agents have been described elsewhere *(5,11–68).* All patients were at least 18 years old and had normal organ function, except for those enrolled in two studies that involved patients with varying degrees of renal and hepatic impairment *(65,66).* Drug clearance was calculated by using either noncompartmental or compartmental analysis *(69)* and was expressed either as liters per hour (L/h) or as L/h normalized to body surface area in meters squared (L/h/m^2). Interpatient variation in drug clearance was calculated by dividing the standard deviation by the mean and was expressed as a percentage (i.e., the coefficient of variation [CV]). We used the following arbitrarily defined criteria to determine whether body surface area-based dosing was statistically significantly associated with a reduction in interpatient variation in clearance: 1) a linear regression coefficient (R) $\geq$ .50; 2) $P<.01$; and 3) a relative reduction in the variability of clearance $\geq$15%, which was calculated by using the formula {[CV for clearance (L/h) – CV for clearance (L/h/m^2)] / [CV for clearance (L/h)]} × 100. All three of these criteria had to be met for the reduction to be considered statistically significant.

The median body surface area for the entire patient population was 1.86 m^2 (interquartile range = 1.68–2.00 m^2) and the mean body surface area was 1.86 m^2 (range = 1.25–3.06 m^2). The CV for clearance, the correlation between body surface area and clearance, and the relative reduction in variability for clearance for each of the agents are listed in Tables 1 and 2. For all but five agents (i.e., docosahexaenoic acid [DHA]–paclitaxel, 5-fluorouracil/eniluracil, paclitaxel, temozolomide, and troxacitabine), body surface area-based dosing was not associated with a statistically significant reduction in the interpatient variability in drug clearance.

In the case of drugs for which renal function plays a principal role in drug elimination, BSA-based dosing may decrease variability in drug clearance among patients. For example, troxa-

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See "Notes" following "References."

Table 1. Variability in drug clearance of orally administered agents*

Agent	CV for drug clearance/f, %		No. of patients	R†	P‡	RIV, %	Drug class	Reference
	L/h	L/h/m^2						
9-AC§	53.7	55.0	41	.04	.81	0	Topoisomerase I inhibitor	*(11,12)*
BN80915	151	148	17	.05	.85	2.0	Topoisomerase I inhibitor	*(13)*
Capecitabine	31.3	36.5	30	.07	.71	0	Oral fluoropyrimidine	*(14)*
CS-682‖	59.3	54.1	42	.32	.04	8.8	Cytidine analogue	*(15)*
DMDC§	67.1	63.9	140	.16	.06	4.8	Cytidine analogue	*(16)*
Eniluracil/5-FU	30.9	26.3	36	.57	<.001	15	Oral fluoropyrimidine	*(17)*
MMI270B	68.1	62.8	46	.44	.002	7.8	MMP inhibitor	*(18,19)*
Phenylbutyrate	36.5	39.6	19	.13	.60	0	HDAC inhibitor	*(20)*
PKI166	82.8	86.0	24	.03	.89	0	TK inhibitor	*(21)*
R115777	61.4	60.8	29	.17	.37	0.98	FT inhibitor	*(22)*
SCH66336	95.6	96.6	26	.12	.55	0	FT inhibitor	*(23)*
Temozolomide	20.0	13.0	24	.88	<.001	35	Alkylating agent	*(24)*
Topotecan§	47.0	44.5	54	.34	.01	5.3	Topoisomerase I inhibitor	*(25–32)*
ZD9331	66.7	71.2	42	.09	.60	0	TS inhibitor	*(33)*

*CV = coefficient of variation; drug clearance/f = apparent oral clearance; L/h = liters per hour; L/h/m^2 = L/h normalized to body-surface area in meters squared; RIV = relative reduction in variability for clearance; 9-AC = 9-amino-camptothecin; DMDC = 2′-deoxy-2′-methylidenecytidine; 5-FU = 5-fluorouracil; MMP = matrix metalloproteinase; HDAC = histone deacetylase; TK = tyrosine kinase; FT = farnesyltransferase; TS = thymidylate synthase.

†Regression coefficient from the relationship drug clearance/f (L/h) = [slope of line • body-surface area (m^2)] + [y-intercept].

‡P value was obtained from the regression analysis.

§Compartmental analysis.

‖Dose-normalized area under the curve of the active metabolite 2′-cyano-2′-deoxy-1-β-D-arabino-pentofuranosyl cytosine.

citabine, an L-nucleoside analogue, and 5-fluorouracil coadministered orally with the dihydropyrimidine-dehydrogenase inactivator eniluracil, are primarily excreted in the urine as unchanged drugs (≈60% and 75% unchanged, respectively). Normalization of drug dose to body surface area was associated with a 22% reduction in the interpatient variation in troxacitabine clearance and a 15% reduction in the interpatient variation in 5-fluorouracil/eniluracil clearance *(17,67)*. Body surface area-based dosing of pemetrexed, a novel multitargeted antifolate that is also mainly excreted in urine as unchanged drug (>70% unchanged) was also associated with a 16% reduction in interpatient variation in drug clearance *(70)*. The known association between body surface area and glomerular filtration rate *(71)* may explain the observed relationship between body surface area and clearance of these renally excreted agents. However, the finding that differences in body surface area among patients account for only a small percentage (i.e., ⩽22%) of the total variability in drug clearance is consistent with results from a recent study *(72)* that reported that body surface area was poorly correlated with glomerular filtration rate (R<.22). Therefore, for agents that are excreted principally by the kidneys, dosing strategies that are based on the accurate assessment of glomerular filtration rate and not on body surface area should be associated with decreased interpatient variability in clearance *(73)*.

Body surface area-based dosing may also be a preferred dosing strategy for drugs that are confined to blood volume because of the known relationship between body size and blood volume *(74,75)*. For example, we found that body surface area was highly correlated with temozolomide clearance (R = .88, P<.001) and was associated with 35% of the variation in temozolomide clearance among patients. Temozolomide is an alkylating agent that undergoes pH-dependent breakdown to the active moiety 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide immediately following drug administration and is virtually isolated to the central compartment. Interpatient variability in DHA–paclitaxel clearance was reduced by 26% when the dose of that agent was normalized to body surface area. DHA–paclitaxel has a low clearance (~0.11 L/h), has a small volume of distribution (~4 L), and is extensively (>99.6%) but nonspecifically bound to alpha$_1$-acid glycoprotein and albumin *(76)*. These characteristics indicate that DHA–paclitaxel is principally confined to blood volume, and that systemic exposure to total drug may be dictated by its capacity to bind plasma proteins. By contrast, drugs that bind a single protein with high affinity but low capacity [e.g., as 7-hydroxystaurosporine (UCN-01) binds alpha$_1$-acid glycoprotein *(77)*] are more likely than DHA–paclitaxel to show wide variations in unbound (i.e., pharmacologically active) drug concentrations among patients. For agents with disposition characteristics like UCN-01, measurement of total drug concentrations in plasma is a poor surrogate for that of unbound drug *(78)*, and accurate assessment of the relationship between body surface area and clearance requires measurement of unbound drug concentrations. Thus, the protein-binding characteristics of investigational agents across species should be characterized before those agents are evaluated in phase I trials.

Normalizing doses to body surface area may also provide an advantage for drugs, such as paclitaxel, that are formulated in vehicles that are known to affect drug disposition. For example, previous work *(51,79)* has shown that the distribution of paclitaxel in the blood depends on the duration of drug infusion and the dose of its formulation vehicle (Cremophor EL-dehydrated ethanol USP; Bristol-Myers Squibb, Wallingford, CT), which is likely due to the preferential affinity of paclitaxel for Cremophor EL in the circulation. It has been demonstrated that this vehicle has a distribution volume that approximates the blood

Table 2. Variability in drug clearance of intravenously administered agents*

Agent	CV for drug clearance, % L/h	CV for drug clearance, % L/h/m^2	No. of patients	R†	P‡	RIV, %	Drug class	Reference
9-AC§	29.9	27.6	12	.31	.32	7.7	Topoisomerase I inhibitor	*(34)*
BMS181174	33.2	27.2	15	.55	.04	18	Antitumor antibiotic	*(35)*
Carzelesin	84.5	92.8	27	.14	.50	0	DNA minor groove binder	*(36)*
CI-958	40.5	38.3	38	.33	.04	5.4	DNA intercalator	*(37)*
DHA-paclitaxel§	29.1	21.9	11	.66	.03	24	Antimicrotubule agent	*(60)*
DHA-paclitaxel§#	43.7	32.5	22	.61	.003	26	Antimicrotubule agent	*(60)*
Docetaxel§	36.0	34.7	168	.33	<.001	3.5	Antimicrotubule agent	*(14,38–42)*
EMD121974	25.7	28.0	36	.03	.87	0	Antiangiogenic agent	*(43)*
EO9§								
Phase I	54.5	54.4	31	.01	.94	0.2	Bioreductive alkylating agent	*(44)*
Phase II	170	162	72	.17	.16	4.7	Bioreductive alkylating agent	*(45)*
Irinotecan§	31.8	33.9	85	.16	.14	0	Topoisomerase I inhibitor	*(5,46,47)*
GI147211§	32.8	34.2	85	.06	.60	0	Topoisomerase I inhibitor	*(48)*
NX 211§	98.9	95.4	29	.35	.07	3.5	Topoisomerase I inhibitor	*(50)*
Paclitaxel§‖								
1-h inf	41.9	34.3	34	.57	<.001	18	Antimicrotubule agent	*(51,52)*
3-h inf	28.5	23.1	40	.45	.003	19	Antimicrotubule agent	*(51,53)*
Pemetrexed	39.0	32.8	34	.42	.01	16	TS inhibitor	*(49)*
PNU152243	59.2	62.4	13	.13	.66	0	Anthracycline	*(54)*
PNU159548	46.2	42.8	24	.36	.09	7.4	Alkycycline	*(55)*
PNU166196	30.8	28.5	23	.23	.30	7.5	DNA minor groove binder	*(56)*
SAM486A	57.6	55.2	60	.16	.21	4.2	Polyamine inhibitor	*(57,58)*
SN-38§¶	60.9	67.6	85	.22	.04	0	Topoisomerase I inhibitor	*(5,46,47)*
TAS-103	39.7	36.8	36	.36	.03	7.3	Topoisomerase I and II inhibitor	*(59)*
Topotecan§	97.3	94.5	82	.24	.03	2.9	Topoisomerase I inhibitor	*(61–64)*
Topotecan§**	82.5	80.6	55	.10	.46	2.3	Topoisomerase I inhibitor	*(65,66)*
Troxacitabine	31.4	24.4	39	.66	<.001	22	L-nucleoside analogue	*(67)*
UCN-01§	79.4	79.9	20	.003	.99	0	PKC inhibitor	*(68)*
UCN-01§#	51.8	51.6	20	.16	.50	0.4	PKC inhibitor	*(68)*

*CV = coefficient of variation; L/h = liters per hour; L/h/m^2 = L/h normalized to body-surface area in meters squared; RIV = relative reduction in variability for clearance; 9-AC = 9-amino-camptothecin; DHA = docosahexaenoic acid; TS = thymidylate synthase; inf = infusion; PKC = protein kinase C; UCN-01 = 7-hydroxystaurosporine.

†Regression coefficient from the relationship drug clearance (L/h) = [slope of line • body-surface area (m^2)] + [y-intercept].

‡P value was obtained from the regression analysis.

§Compartmental analysis.

‖Unbound drug levels.

¶Irinotecan metabolite, dose-normalized area under the concentration-time curve (×1000).

#Volume of distribution at steady state in L versus L/m^2.

**Patients with impaired renal or hepatic function.

volume and that body surface area is a statistically significant covariate for Cremophor EL clearance *(80).* Thus the impact of body surface area on the variability in paclitaxel pharmacokinetics is most likely associated with the affinity of paclitaxel for its vehicle in the circulation *(81),* the distribution of which is linked to total blood volume, and thus to body surface area *(75).*

For the majority of the anticancer agents we examined that underwent development in adult patients from 1991 through 2001, we found that body surface area-based dosing was not statistically significantly associated with a decrease in interpatient variability in clearance. For the few agents for which clearance was statistically significantly associated with body surface area, the relative reduction in variability in clearance was between 15% and 35%, which suggests that only up to one-third of the total variability can be explained by differences in body surface area. These results therefore do not support body surface area-based dosing for most anticancer agents but warrant the evaluation of alternate dosing strategies for phase I evaluation in adult humans. A non-body surface area-based dosing strategy (e.g., one based on a fixed dose) was successfully implemented in the development of five of the orally administered agents examined in our study [i.e., phenylbutyrate *(20),* PKI166 *(21),* R115777 *(22),* SCH66336 *(23),* and ZD9331 *(33)*], demonstrating that administration of a fixed total dose is feasible for the development of both cytotoxic and noncytotoxic targeted anticancer agents. We therefore recommend that the practice of calculating starting drug doses on the basis of body surface area in phase I trials should be abandoned and that future early clinical trials should instead evaluate the administration of fixed drug doses that are calculated on the basis of an average body surface area of 1.86 m^2. For novel targeted agents, dose refinement should be based on finding an exposure that produces a biologic or molecular effect on a drug target that is associated with a desired therapeutic outcome or avoidance of a toxicologic outcome. For cytotoxic agents that have a narrow therapeutic window, efforts should continue to focus on defining individual doses that are based on patient characteristics that are known to affect drug clearance (e.g., age, sex, renal function, and use of concomitant medications). A combination of these strategies should yield more rational dosing schemes that can be implemented in oncology practice.

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