Prospective Evaluation of Body Surface Area as a Determinant of Paclitaxel Pharmacokinetics and Pharmacodynamics in Women with Solid Tumors: Cancer and Leukemia Group B Study 9763

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ABSTRACT

Purpose: **To study a fixed dose (360 mg) of paclitaxel given i.v. over 3 hours to female patients, and to evaluate prospectively the relationships between the following: body surface area and toxicity; body surface area and pharmacokinetics; and pharmacokinetics and toxicity.**

Experimental Design: **The eligibility criteria included the following: female sex; solid tumors; no more than one prior chemotherapy regimen; no prior paclitaxel; performance status of 0 to 2; and normal organ function. Paclitaxel plasma concentrations were quantified by high-performance liquid chromatography. The area under the curve, total body clearance, and hours above 0.05 μmol/L ($T > 0.05$) were calculated.**

Results: **Thirty-two patients were enrolled, and 29 patients received the correct dose and regimen. For statistical analyses, 26 patients had complete follow-up blood counts, 23 patients had complete data to correlate blood counts and area under the curve, and 25 patients had data to correlate blood counts and $T > 0.05$. The main toxicity was neutropenia of grade 3 and 4 severity in 21% and 25% of patients, respectively, in cycle 1. The worst grade of any toxicity, nadir WBC and absolute neutrophil count, and survival fractions were assessed; no significant relationship was found between body surface area and any measure of toxicity. Body surface area correlated inversely with area under the curve ($r = -0.67$; $P < 0.001$) and correlated with total body clearance ($r = 0.69$; $P < 0.001$), but body surface area did not correlate with $T > 0.05$. Neither area under the curve nor total body clearance were correlated with nadir absolute neutrophil count or survival fractions, but a significant correlation was found between $T > 0.05$ and log(nadir absolute neutrophil count; $r = -0.41$; $P = 0.04$).**

Conclusions: **These results suggest that fixed dosing of paclitaxel is feasible in women, which would simplify the administration of this drug.**

INTRODUCTION

The dose of chemotherapy is important in producing a desirable outcome in the treatment of cancer. The clinically relevant drug effects are tumor response and toxicity. It is conventional oncology practice to normalize dose in an attempt to reduce the variability of drug effect among patients. The traditional method of individualizing cytotoxic drug dose is by using body surface area, which is equivalent to the two-dimensional surface area of the skin of an individual. Estimation of body surface area is most commonly done with a formula that was derived in 1916 by Du Bois and Du Bois but remains the most popular way to estimate body surface area in nomograms or computer programs (1). These authors examined nine individuals of various age, shape, and size and measured their body surface area directly with molds. By trial and error they derived a formula to estimate body surface area using height and weight. This formula was found to be useful because it was shown that body surface area correlated with the basal metabolic rate. The Du Bois formula was challenged in 1970 by Gehan and George (2) who directly measured the skin surface area of 401 individuals. They found that the Du Bois formula over-estimated body surface area by 15% in ~15% of cases, but otherwise the original formula was surprisingly accurate considering the small sample size used in its derivation.

An increasing number of authors have criticized the routine practice of dosing anticancer agents based on body surface area, because body surface area does not correlate with pharmacokinetic or pharmacodynamic parameters for the majority of anticancer drugs tested (3–10). Body surface area is proportional to blood volume. Body surface area is not correlated with the ability of an individual to metabolize or excrete cytotoxic drugs because it is not related to liver function (4) and is poorly correlated with glomerular filtration rate (11). Body surface area has a rational use for interspecies scaling and for calculating an

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initial starting dose for a human Phase I trial, based on prior experience in laboratory animals (12). However, the variability in body surface area from a mouse to a human is far greater than it is among humans, and the rationale for using body surface area-based dosing throughout Phase II and III studies of anticancer agents has never been shown. This has resulted in a paradoxical mix of scientific dose computation with the formula for body surface area estimation by Du Bois, followed by various empiric and poorly standardized dose manipulations (5).

Paclitaxel is a commonly used antineoplastic drug that produces cytotoxicity by stabilizing microtubules and inhibiting the dynamic reorganization of the network necessary for cell division (13). This study was designed to explore whether it is feasible to use a fixed dose of paclitaxel instead of the usual body surface area-normalized dose. The appropriate fixed dose of paclitaxel was determined by reviewing the experience in a Phase III study [Cancer and Leukemia Group B (CALGB) Study 9342] of paclitaxel used at three dose levels in the treatment of patients with metastatic breast cancer (14). Women in this three-arm trial were randomized to receive paclitaxel over 3 hours at doses of 175 or 210 mg/m^2 without filgrastim or 250 mg/m^2 with filgrastim. At the intermediate dose level of 210 mg/m^2 without filgrastim, the mean as well as median total doses of paclitaxel administered were 360 mg. Therefore, a fixed total dose of 360 mg of paclitaxel, regardless of body surface area, was chosen for all of the patients in the first cycle of the current trial. As in CALGB 9342, only women were eligible for this study. Our measure of the risk of clinically relevant toxicity concerned the degree of myelosuppression experienced by patients at the two extremes of the body surface area range observed in CALGB 9342. We based our study on this measure, because it provided a quantitative pharmacodynamic measure on which to base sample size calculations and from which to infer a relationship between body surface area and a clinically relevant endpoint. A retrospective study of patients who received body surface area-based doses of paclitaxel would not have allowed us to address this question because dose and body surface area would be confounded in the data. An appropriate comparison of toxicity experienced by patients could only be achieved in a setting where all were treated with the same dose, and body surface area was the only difference.

PATIENTS AND METHODS

Patient Eligibility. Women with any histologically documented cancer for whom single-agent paclitaxel was appropriate therapy were eligible. They had to be at least 18 years of age and have an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients with measurable or evaluable disease were eligible. Patients with known bone marrow metastasis were not eligible. The following eligibility criteria were applied regarding prior treatment: no prior paclitaxel; no more than one prior chemotherapy regimen for metastatic disease; no prior whole pelvic radiation therapy; at least 4 weeks because major surgery; and at least 4 weeks since prior radiation or chemotherapy (6 weeks for nitrosoureas, melphalan, or mitomycin). Required initial laboratory data were as follows: neutrophils $\geq$1,500/μL; platelets $\geq$100,000/μL; creatinine $\leq$1.5 $\times$ upper limit of normal; bilirubin $<$1.5 mg/dl; and aspartate aminotransferase (AST) $<$2.0 $\times$ upper limit of normal. The patient had to be aware of the neoplastic nature of her disease and willingly provide written informed consent before entering the study. Institutional review board or ethics board review and approval of the protocol at all of the institutions were required.

Treatment. Single-agent paclitaxel was infused over 3 hours at a fixed total dose of 360 mg in the first cycle to all of the patients. Paclitaxel treatment was repeated every 3 weeks at the discretion of the treating physician who was free to adjust the dosage in subsequent cycles. The following premedications were given: dexamethasone 20 mg p.o. 12 and 6 hours before paclitaxel infusion; and diphenhydramine 50 mg i.v. and cimetidine 300 mg i.v. (or ranitidine 50 mg or famotidine 20 mg) 30 minutes before paclitaxel infusion. Filgrastim (granulocyte colony-stimulating factor) and sargramostim (granulocyte macrophage colony-stimulating factor) treatment was not allowed in the first course.

Evaluations. Before registration and on day 1 of cycles 1 and 2, a complete history and physical examination were done, and the following laboratory tests were obtained: complete blood counts (including differential and platelets); serum creatinine; blood urea nitrogen; electrolytes; AST; alkaline phosphatase; bilirubin; total protein; and albumin. Complete blood counts were also obtained twice weekly in the first two cycles. Toxicities were graded according to the Common Toxicity Criteria of the National Cancer Institute. Absolute counts at the nadir for WBCs and neutrophils (absolute neutrophil count), surviving fractions (nadir count divided by baseline count), and $\log_{10}$ of the absolute counts at the nadir were assessed. After cycle 2 of single-agent paclitaxel, patients were evaluated for tumor response according to the contemporary National Cancer Institute criteria, which involved measuring lesions in two perpendicular dimensions. All of the additional follow-up and treatment were at the discretion of the physician and patient.

Pharmacokinetics. Paclitaxel pharmacokinetics were assessed in the first cycle of treatment only. Four blood samples were obtained as follows: before the paclitaxel infusion; and at 1, 6, and 24 hours from the start of the 3-hour infusion. The total (not free) paclitaxel concentrations were measured by high-performance liquid chromatography (15). Estimation of area under the concentration *versus* time curve (area under the curve) used a limited sampling strategy by which area under the curve (μmol/L $\times$ hour) was calculated from the following equation (16, 17): area under the curve = 4.7 (concentration at 1 hour) + 10 (concentration at 6 hours) + 0.63.

Total body clearance was calculated from the relationship as follows: clearance = dose $\div$ area under the curve.

The time (hours) above the threshold concentration of 0.05 μmol/L was calculated with the following equation (16, 17): T $>$ 0.05 μmol/L = 282 (concentration at 24 hours) + 9.8.

The limited sampling strategy used for area under the curve had a mean error (reflecting bias) of 2.9% and root mean squared error (representing precision) of 9.8%. The limited sampling strategy used for T $>$ 0.05 μmol/L had a mean error of 1.6% and root mean squared error of 5.6%.

Statistics. We examined data from patients with breast cancer enrolled in a study of single-agent paclitaxel, CALGB 9342 (14), when we planned the current study. At the time, data were available for 74 patients who had received 210 mg/m^2 of

paclitaxel. Body surface area seemed normally distributed. The mean body surface area and SD were 1.75 m^2 and 0.17 m^2, respectively; and the 5th and 95th percentiles were 1.47 m^2 and 2.04 m^2, respectively. We considered the logarithm of the nadir neutrophil count as the toxicity outcome of interest and characterized its relationship with body surface area as linear. For statistical hypothesis testing, we took the null hypothesis to be that the slope of the regression of the logarithm of the nadir count as a function of body surface area was at least 0.528 [= $\log_{10}(2)/(2.04-1.47)$]. This slope corresponds to the nadir absolute neutrophil count being two times larger for a woman with a body surface area in the 95th percentile relative to a woman with a body surface area in the 5th percentile, basing the body surface area percentiles on CALGB 9342. The alternative hypothesis was that the slope was smaller than this, with greatest interest being at zero, which would indicate no relationship between body surface area and nadir count. The statistical hypothesis test was stated as one-sided; the slope could have been negative, meaning that smaller patients were at lower risk of toxicity than were larger patients receiving the same total dose of paclitaxel, but this did not seem likely.

We determined by computer simulation that treating 50 patients with a fixed dose of paclitaxel would give 80% power to detect a slope of zero. For the simulations, we assumed the residual SD (about the regression line) to be ~0.25, as in the CALGB 9342 data, and the SD of body surface area to be 0.17 m^2. One thousand simulated studies served to determine the type I and type II errors (*i.e.*, size and one minus power) for a one-sided test of the null hypothesis "slope ≥0.528" *versus* the alternative of a smaller slope. In the simulations, the predicted nadir absolute neutrophil count for a patient with average body surface area was ~1,000/μL.

RESULTS

Thirty-two patients were enrolled on this study between January 1998 and September 2001. One patient received only 180 mg of paclitaxel, 1 patient had an infusion time of 5 hours instead of 3 hours, and 1 patient withdrew consent during the infusion. The characteristics of the remaining 29 patients are shown in Table 1. Of these, 26 patients had follow-up with blood counts to assess toxicity, 23 had blood and correctly drawn pharmacokinetic samples to correlate blood counts and area under the curve, and 25 had blood and pharmacokinetic samples to correlate blood counts and T > 0.05 μmol/L. The dose normalized for body surface area ranged from 162 to 300 mg/m^2.

Toxicity. The main toxicity was neutropenia. Grade 3 and 4 neutropenia occurred in 21% and 25% of patients, respectively, in cycle 1. Grade 3 and 4 lymphopenia was observed in 8% and 8%, respectively, in cycle 1. Grade 3 (no grade 4) sensory neuropathy and hyperglycemia were noted in 7% and 8%, respectively, in cycle 1. No other kind of toxicity exceeded 5% in incidence. One patient was admitted to the hospital on day 6 of cycle 1 with pharyngitis, fever, lethargy, and an absolute neutrophil count of 80/μL. She was a 69-year-old woman with a body surface area of 1.4 m^2 and a performance status of 2 who was treated for an adenocarcinoma of unknown primary site metastatic to liver and lung. She had not received any prior chemotherapy or radiation therapy. She was found to have *Streptococcus bovis* sepsis and treated with antibiotics. She recovered her neutrophil count to as high as 18,840/μL but died of multisystem organ failure on day 11 of cycle 1. No other patient had a fatal complication from protocol therapy in the first or second cycle.

Table 1 Patient characteristics

Age (y)	
Median	53
Range	35–72
Race	
White	18
Black	7
Other	4
Performance status (ECOG)	
0	13
1	13
2	3
Cancer (primary site)	
Breast	15
Lung	6
Other	8
Prior chemotherapy	19
No prior chemotherapy	10
BSA (m^2)	
Minimum	1.20
Maximum	2.22
Median	1.74
25th percentile	1.47
75th percentile	1.84

Abbreviations: ECOG, Eastern Cooperative Oncology Group; BSA, body surface area.

Body Surface Area and Toxicity. There were no significant relationships between body surface area and paclitaxel-induced leukopenia or neutropenia (Fig. 1). The estimated slope from the regression of the logarithm of the nadir absolute neutrophil count on body surface area was 0.096 (SEM = 0.287; $P = 0.74$; $R^2 = 0.00$). One can relate this slope to the ratio of absolute neutrophil count nadirs for a woman with body surface area 1.47 m^2 *versus* a woman whose body surface area is 2.04 m^2, as discussed in Patients and Methods. The 95% confidence interval for the ratio of absolute neutrophil count nadirs predicted for these women is 0.52 to 2.47. This interval includes 2, which is the smallest ratio we considered medically significant when we designed the study. Fig. 2 shows the relationships between body surface area and the grade of nadir neutropenia and between body surface area and the worst grade of any kind of toxicity in the first cycle. If body surface area were an important determinant of toxicity, one would expect that the patients with smaller body surface area would experience more grade 3, or worse, toxicity because they received a higher dose per square meter of body surface area. As Fig. 2 shows, this was not the case (Wilcoxon two-sided, $P = 0.69$).

CALGB 9342, which formed the basis for estimating an appropriate fixed dose of paclitaxel, was still accruing patients when we designed this study (CALGB 9763) but has now been completed. The data for the two studies are compared in Table 2. For the purpose of comparison, the calculated doses in mg/m^2 are shown for this fixed dose study, and the actual total doses administered are shown for the arm of CALGB 9342 that used

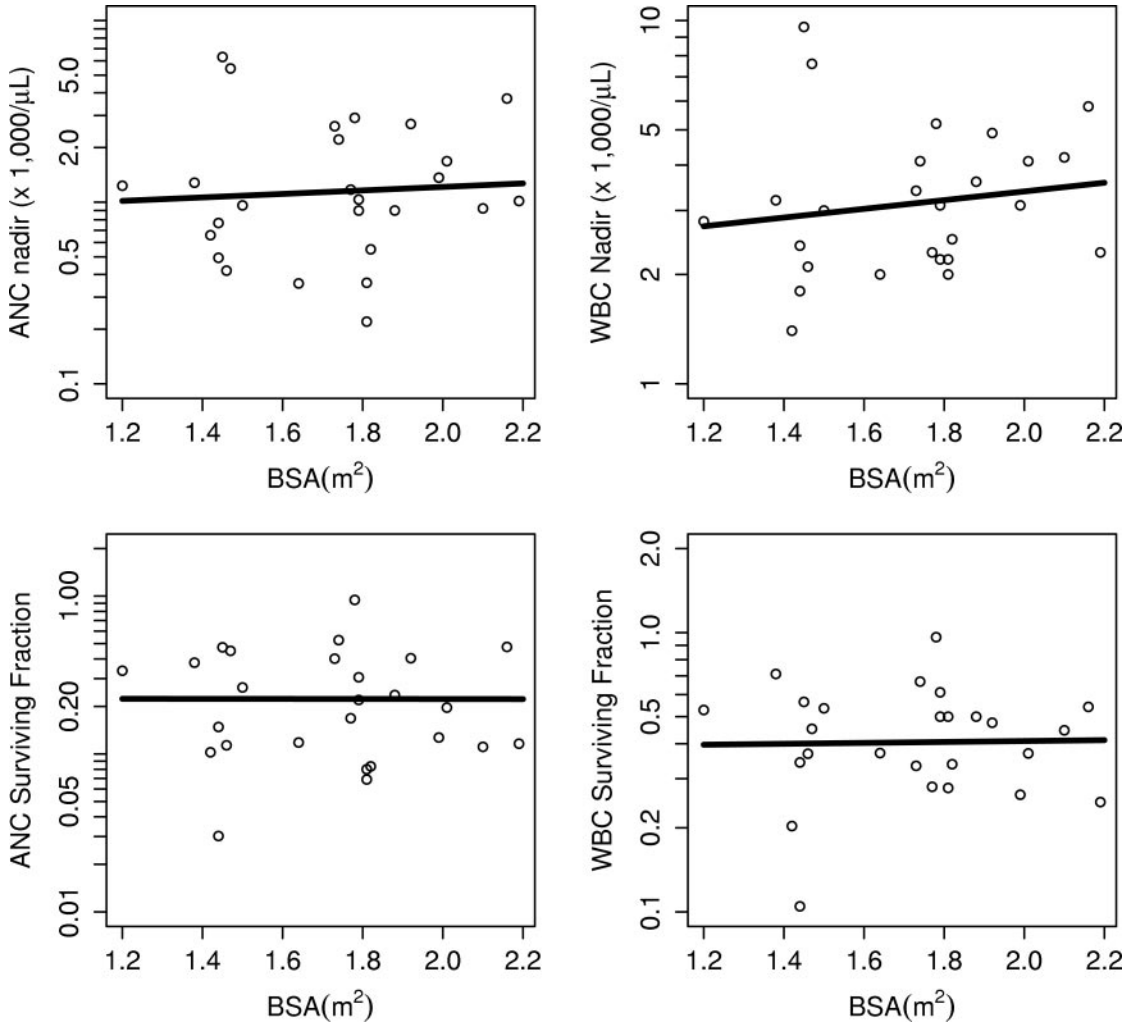

Fig. 1 Relationships between the body surface area and the WBC and absolute neutrophil count at the nadir and the WBC and absolute neutrophil count surviving fractions (nadir divided by baseline). The linear regression is shown as a *straight line*. (*BSA*, body surface area; *ANC*, absolute neutrophil count)

210 mg/m^2. The median body surface area for both studies was approximately the same. The actual doses given to patients in CALGB 9342 varied widely around the median of 370 mg (Table 2). The median calculated dose of 203 mg/m^2 on CALGB 9763 was only slightly less than the dose of 210 mg/m^2 used on CALGB 9342. The toxicity profiles for the two studies were similar.

Body Surface Area and Pharmacokinetics. Body surface area was inversely correlated with area under the curve ($r = -0.67$; $P < 0.001$) and correlated with total body clearance ($r = 0.69$; $P < 0.001$) as shown in Fig. 3, but body surface area was not correlated with T $>$ 0.05 μmol/L ($r = -0.038$; $P = 0.85$).

Pharmacokinetics and Toxicity. We examined the relationships between pharmacokinetic parameters and the most severe toxicity from therapy (lowering of the absolute neutrophil count). Neither area under the curve nor total body clearance was significantly correlated with absolute neutrophil count surviving fraction or nadir absolute neutrophil count. T $>$ 0.05 μmol/L was correlated with log(nadir absolute neutrophil count; $r = -0.41$; $P = 0.04$; Fig. 4) but was not correlated with log(absolute neutrophil count surviving fraction) [$r = -0.29$; $P = 0.16$].

Tumor Response. Response was not a major end point in this study, but we observed the following therapeutic outcomes: 4 patients had partial responses; 1 patient had regression; 12 patients had stable disease; 8 patients had progressive disease; and 4 patients were unevaluable for response. These numbers were too small to correlate response with pharmacokinetics.

DISCUSSION

As individual authors (6, 9, 10), we have pointed out that the dosing of anticancer agents based on body surface area is not founded on scientific data (3–5, 7, 8). Individual patient characteristics used for drug selection or dosing (*i.e.*, body surface

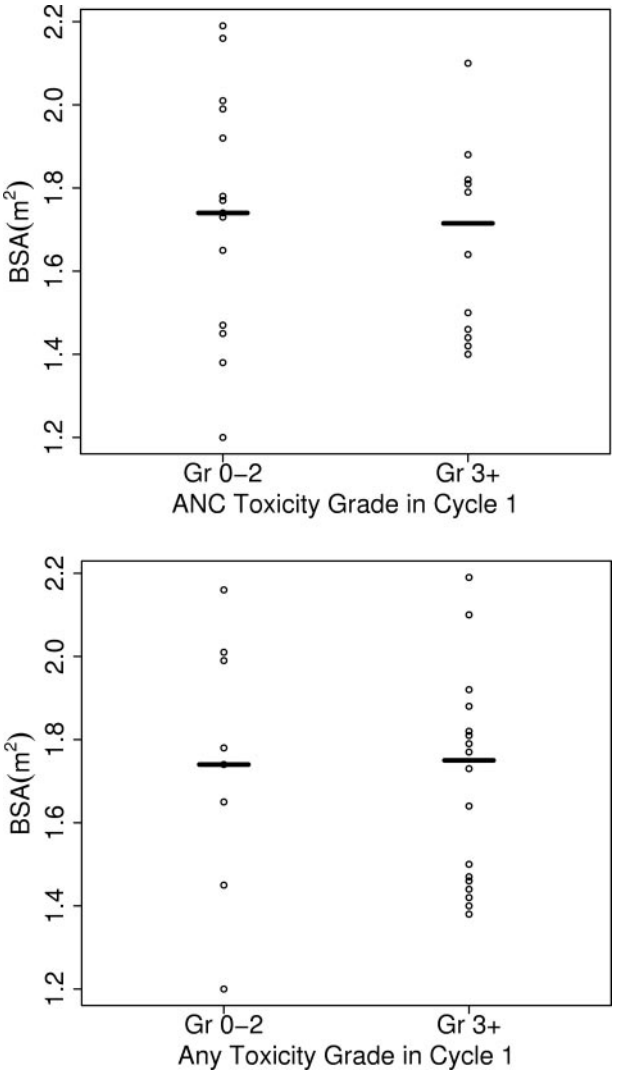

Fig. 2 *Scatter plots* of the body surface area and the grade of toxicity for the absolute neutrophil count at the nadir and the grade of any kind of toxicity in cycle 1 of paclitaxel therapy. The *horizontal bars* are medians. (*BSA*, body surface area; *ANC*, absolute neutrophil count)

area, race/ethnicity, and genetic polymorphism) should correlate with therapeutic results in patients (contrary to scaling between laboratory animals and humans) before being ingrained in standard practice. If we were to abandon the use of body surface area, we should consider using a fixed dose, as in other areas of internal medicine. For this pilot study, we therefore looked for a drug that was commonly used as a single agent when this study was initiated in 1997. Even in the cooperative group setting the accrual was slow, the target accrual of 50 patients was not reached, and the study was closed with 26 patients evaluable for toxicity. No significant relationship was identified between body surface area and absolute neutrophil count or WBC nadir. However, as stated under results for body surface area and toxicity, the 95% confidence interval for the ratio of absolute neutrophil count nadirs between large and small women was 0.52 to 2.47. This range included 2.0, which we deemed in planning the study to be medically significant. Therefore, we cannot rule out the possibility that body surface area is associated with toxicity to the extent we initially considered to be clinically relevant.

Despite the limitations of study size, we believe that there are three main conclusions. The first is that no significant relationship was found between body surface area and toxicity. The second is that although body surface area correlated inversely with paclitaxel area under the curve and correlated with total body clearance, it did not correlate with $T > 0.05$ μmol/L. Finally, neither area under the curve nor total body clearance was significantly related to absolute neutrophil count nadir or surviving fraction, but $T > 0.05$ μmol/L and log(nadir absolute neutrophil count) were correlated. The important observation is that body surface area is related to the pharmacokinetic parameters (area under the curve and clearance) but not to the one that has been related to toxicity ($T > 0.05$ μmol/L) by three separate groups of investigators (18–21). Thus, body surface area does not seem to be a determinant of toxicity. We caution that these conclusions apply only to women with cancer receiving treatment with single-agent paclitaxel as a 3-hour infusion regimen (*i.e.*, not other regimens of shorter or longer infusion durations). This study is also too small to address the utility of body surface area at the extremes of height and weight.

Reviews of the literature showed no significant correlations between body surface area and area under the curve or clearance for the majority of anticancer agents, but pharmacokinetic parameters such as area under the curve have been shown to correlate with toxicity (5, 7). In the case of paclitaxel, a review of the available data suggested that body surface area was correlated with the clearance of this drug (3, 8). The role of body surface area in the disposition of paclitaxel was recently tested by Smorenburg *et al.* (22) in a randomized study of body surface area-based dosing *versus* fixed dosing. The pharmacokinetics of total and unbound paclitaxel were assessed in 12 patients who were treated with paclitaxel at 175 mg/m^2 in cycle 1 and a flat fixed dose of 300 mg in cycle 2 (both 3-hour infusions) or *vice versa*. As in our study, body surface area was significantly correlated with area under the curve and clearance. Smorenburg *et al.* (22) concluded that this provided a pharmacokinetic rationale for body surface area-based dosing of this drug, but they did not investigate whether area under the curve or clearance was related to parameters of toxicity, and they also did not measure $T > 0.05$ μmol/L.

The advantages of using a fixed dose of a given drug for all of the patients are obvious (6, 9, 10). A standard vial size could be produced by pharmaceutical companies. The storage and dispensing by pharmacies would be more efficient. Most importantly, simplifying prescribing of antineoplastic agents could lead to a significant reduction in dosing errors. Physicians would also no longer have to wonder whether they should use actual body weight or lean body weight. The administration of anticancer drugs in hospitals and clinics would be streamlined. Because of the simplicity of fixed dosing, cost may be reduced.

Theoretically, the optimal dose is one that lies in the therapeutic window that exists above the level that gives an antitumor effect but below the level that results in unacceptable toxicity. For practical purposes, it is often feasible to use the presence of toxicity to indicate that the dose is near the effective

Table 2 Comparison of this fixed dose study (CALGB 9763) to the arm of the randomized Phase III study (CALGB 9342) that used paclitaxel 210 mg per square meter of BSA: Data are for cycle 1 of single-agent therapy

	Number of patients evaluable (enrolled)	Mean (SD)	Minimum	Median	Maximum
CALGB 9763 Paclitaxel 360 mg					
Paclitaxel (mg/m^2)	26 (32)	214 (34)	164	203	300
BSA (m^2)	26 (32)	1.72 (0.26)	1.20	1.77	2.19
Nadir WBC (per μL)	26 (32)	3,500 (1,880)	1,400	3,050	9,600
Nadir ANC (per μL)	26 (32)	1,620 (1,540)	20	1,020	6,300
CALGB 9342 Paclitaxel 210 mg/m^2					
Paclitaxel (mg)	155 (156)	369 (37)	289	370	546
BSA (m^2)	155 (156)	1.76 (0.18)	1.09	1.76	2.60
Nadir WBC (per μL)	143 (156)	2,780 (1,640)	400	2,400	7,600
Nadir ANC (per μL)	141 (156)	1,170 (1,190)	20	730	5,930

Abbreviations: BSA, body surface area; ANC, absolute neutrophil count.

anticancer dose. In fact, toxicity-based dosing has been the standard technique to select the conventional dose of cytotoxic chemotherapy because of the design features of Phase I clinical studies. If body surface area is not a determinant of paclitaxel toxicity, it seems preferable to observe the toxicity in an individual patient after a fixed dose and then make dose adjustments to avoid excess toxicity in subsequent cycles. As discussed by Smorenburg *et al.* (22), paclitaxel is eliminated mainly by hepatic metabolism through CYP2C8 and CYP3A4 activity (23) as well as by P-glycoprotein (24). Metabolic capacity of the liver is not associated with body surface area (4). The genetic polymorphisms in the population resulting in large variability of CYP2C8 (25), CYP3A4 (26), and P-glycoprotein (27) activities may have a greater impact on paclitaxel pharmacokinetics and pharmacodynamics than does body surface area.

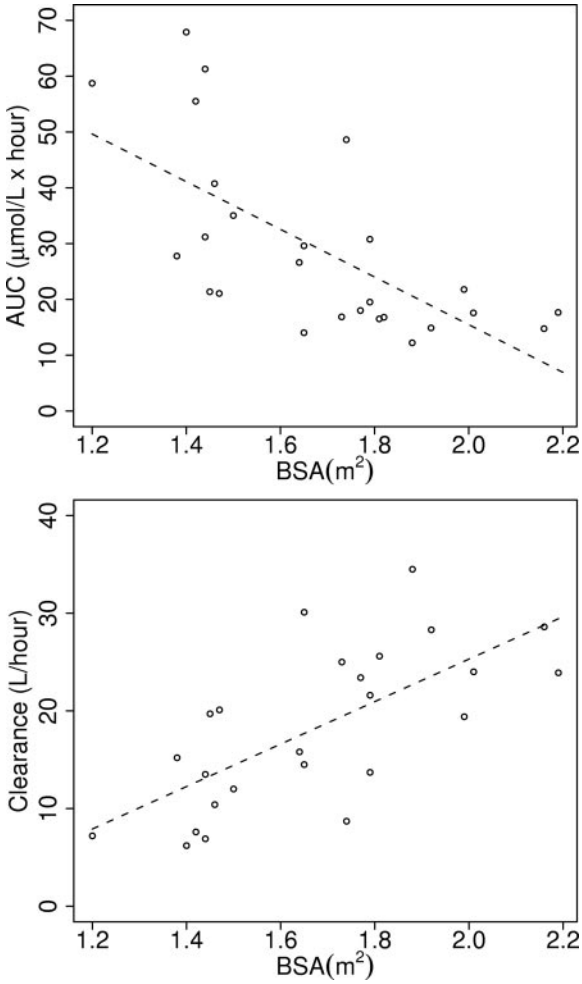

Fig. 3 Relationships between the body surface area and the paclitaxel area under the concentration *versus* time curve (area under the curve) and paclitaxel total body clearance. (*AUC*, area under the curve; *BSA*, body surface area)

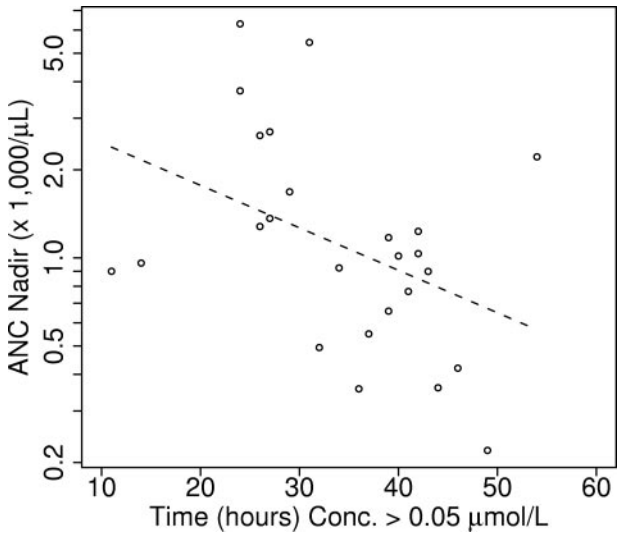

Fig. 4 Relationship between the absolute neutrophil count at the nadir and the time above the paclitaxel threshold concentration of 0.05 μmol/L. (*ANC*, absolute neutrophil count)

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