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Population analysis of a 24-h paclitaxel infusion in advanced endometrial cancer: a gynaecological oncology group study

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Aims
To examine determinants of paclitaxel disposition and the association between paclitaxel exposure and toxicity or survival in patients with advanced stage or recurrent endometrial cancer treated with doxorubicin plus paclitaxel.

Methods
A limited sampling scheme was used to examine the population pharmacokinetics of paclitaxel in 160 patients from one arm of a randomized Phase III trial of doxorubicin plus paclitaxel or cisplatin. Four plasma samples per patient were collected at approximately 0, 3, 22 and 27 h after the first 24-h infusion of paclitaxel and submitted to the Gynecological Oncology Group (GOG) Pharmacology Core Laboratory. Total paclitaxel concentrations were quantified by LC/MS and paclitaxel disposition was examined using NONMEM. Paclitaxel exposure was evaluated for associations with toxicity or survival.

Results
Patient weight, age and serum glutamic-oxaloacetic transaminase level were determinants of paclitaxel clearance (clearance increased 0.437 l h^{-1} kg^{-1}; decreased 0.223 l h^{-1} $year^{-1}$ and 0.105 l h^{-1} IU^{-1}). Bayesian shrinkage was minimal for this parameter. In different measures of paclitaxel exposure, AUC was most predictive of toxicity, with higher AUC associated with granulocytopenia [probability of 1% at AUC = 1 to 22% at AUC = 4 μg l^{-1} h^{-1} for performance status (PS) = 0]. PS was more strongly associated with survival than disease stage and higher paclitaxel AUC was associated with worse survival irrespective of PS and stage.

Conclusions
Paclitaxel AUC is an independent predictor of granulocytopenia and survival in patients with advanced stage or recurrent endometrial cancer. Future studies are needed to validate the latter finding. This study confirms the appropriateness of evaluating pharmacokinetics and pharmacodynamics in multicentre oncology trials.

Introduction

Paclitaxel is active against a broad range of cancers [1]. As such, paclitaxel is routinely administered either as a single agent or as part of a multidrug chemotherapy regimen for the treatment of a variety of solid tumours. Paclitaxel has been shown to exhibit activity in endometrial cancer, but the population pharmacokinetics of this taxane are not well documented in this disease setting.

It is recognized that paclitaxel exists in both the bound and free states in plasma [2]. The drug may be bound to plasma proteins including albumin and α-glycoprotein [3] or red blood cells, or it may be trapped within micelles of Cremophor EL [4], which is used as a vehicle for paclitaxel. In general, it is the free or unbound concentrations that are pharmacologically active [5], although the ability to monitor free paclitaxel concentrations has only recently been made possible [6]. Consequently, most literature on the subject and the study reported here present the measurement of total paclitaxel, represented as the sum of free and bound concentrations. The pharmacokinetics of total paclitaxel has been described previously as being nonlinear [7], with the nonlinearity generally attributed to both saturable elimination [8] and saturable distribution via binding [9]. Some of the nonlinearity exhibited by total paclitaxel has also been attributed to Cremophor EL [4, 10, 11]. The nonlinearity of total paclitaxel pharmacokinetics is less apparent when the drug is administered over >6 h [12, 13], as was the case in the present study, which utilized a 24-h infusion. The pharmacokinetics of paclitaxel has been described using a three-compartment model [9, 14, 15] and a simpler, two-compartment model [8].

Granulocytopenia is the primary toxicity associated with paclitaxel [16], with the onset typically occurring 8–10 days following treatment and recovery by day 15–21. Attempts to correlate severity of granulocytopenia with steady-state paclitaxel concentrations have been unsuccessful [17]. In contrast, an association between the severity of granulocytopenia and the length of time that plasma concentrations exceed 0.05–0.1 μm l^{-1} has been documented [7, 18].

Consequently, the pharmacokinetic/pharmacodynamic relationship between paclitaxel exposure and granulocytopenia has often been described using a threshold model [7, 15, 19] relating the toxicity to the time above some critical plasma concentration. More elaborate relationships between the concentration–time profile of free paclitaxel and white blood cell or neutrophil count have also been reported [20].

In a randomized Phase III treatment trial in advanced stage or recurrent endometrial cancer known as Gynecological Oncology Group (GOG) Protocol 163 (GOG 163), the efficacy and toxicities associated with the chemotherapy combination of doxorubicin plus paclitaxel were compared with those of doxorubicin plus cisplatin [21]. This trial included an examination of the determinants of paclitaxel disposition and evaluation of the association between different measures of paclitaxel exposure and granulocytopenia or survival in GOG 163 patients randomly allocated to receive doxorubicin plus paclitaxel.

Methods

Study design and participants

GOG 163, a prospective, randomized Phase III first-line chemotherapy treatment trial, was undertaken to compare doxorubicin plus paclitaxel *vs.* doxorubicin plus cisplatin for advanced or recurrent endometrial cancer. The results of the treatment component of this trial have been previously published [21]. The objectives of the population pharmacokinetic study described herein were to examine the determinants of paclitaxel disposition (distribution and elimination) and to study the association between paclitaxel exposure and toxicity or survival in GOG 163 patients with advanced stage or recurrent endometrial cancer randomly allocated to the paclitaxel-based regimen.

Eligible patients who provided written informed consent (in accordance with federal, state and local laws) to participate in both the treatment and pharmacokinetic components of GOG 163 were enrolled between 1997 and 2000 at GOG member institutions having Institutional Review Board approval for this study in accordance with assurances filed with and approved by the US Department of Health and Human Services. Eligible patients had histologically confirmed primary stage III or IV or recurrent endometrial carcinoma with measurable disease and a GOG performance status (PS) of 0–2, as well as an absolute neutrophil count of ≥1500 μl^{-1}, serum creatinine ≤1.6 mg dl^{-1}, bilirubin within institutional normal limits and serum glutamic pyruvic transaminase (SGPT) ≤3 times the upper limits of institutional normal. Patients having a body surface area (BSA) >2.0 m^2 were dosed as if their BSA was 2.0 m^2. Of the 317 eligible patients enrolled on this protocol, 160 were randomly allocated to receive a rapid infusion of doxorubicin at a dose of 50 mg m^{-2} followed 4 h later by a 24-h infusion of paclitaxel at a dose of 150 mg m^{-2}. Cycles were to be repeated every 21 days. Patients who had received prior pelvic radiotherapy or who were >65 years old were to receive reduced starting doses (doxorubicin 40 mg m^{-2} and paclitaxel 120 mg m^{-2}). All patients on the paclitaxel-containing arm were to receive granulocyte-colony-stimulating factor (G-CSF) subcutaneously at a daily dose of 5 μg kg^{-1} on days 3–12 of each cycle, or until the postnadir white blood cell count was ≥10 000 μl^{-1}.

Specimen collection

A sparse pharmacokinetic sampling strategy was employed during the first cycle of treatment. Heparin-

ized blood (10 ml) was drawn from patients before and then 3, 22 and 27 h after initiating the first 24-h infusion of paclitaxel. The 22-h time point was envisioned to reflect the total paclitaxel concentration at steady state. Blood was placed on ice, centrifuged within 60 min of collection and the recovered plasma was aliquoted, frozen at 20 °C and shipped to the GOG Pharmacology Core Laboratory at Memorial Sloan Kettering Cancer Center (NY) for testing. Prior studies have shown that paclitaxel is relatively stable in plasma for at least 60 min since its clearance is dependent on hepatic p450 enzymes [22]. Of the 160 patients allocated to the doxorubicin and paclitaxel treatment arm, 31 cases were not included in the pharmacokinetic analysis and modelling for one of the following reasons: specimens were not collected ($n = 21$); paclitaxel infusion was interrupted ($n = 2$); or concentration data were either not provided or >4000 ng ml^{-1} ($n = 8$).

Pharmacokinetic analysis and modelling

Total paclitaxel concentrations were quantified using a sensitive and selective liquid chromatography/mass spectrophotometry (LC/MS) assay as described previously [23]. The lower limit of detection for the assay was 20 nM. Standard curves were prepared fresh and were rejected if the correlation coefficient fell below 0.98. The day-to-day error rate for the assay was <10%. All data (drug concentrations, adverse effects and survival information) were modelled using the nonlinear mixed effects modelling program, NONMEM (Version V, Level 1.1; GloboMax, Hanover, MD, USA) [24–28]. A plot of the frequency of samples *vs.* relative time postdose is provided in Figure 1. Although only three pharmacokinetic sampling times were incorporated in this study during cycle 1, the samples covered a wide range of the plasma concentration–time profile, with samples having been drawn up to >72 h after the start of the paclitaxel infusion.

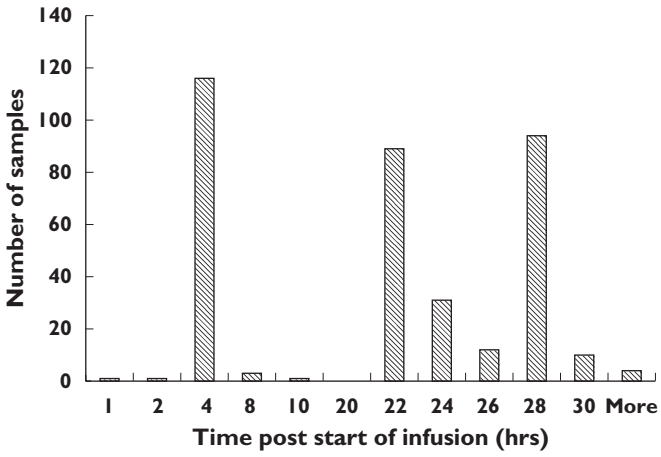

Figure 1

Frequency histogram for sample collection *vs.* relative time after the start of infusion

Creatinine clearance was estimated using the Cockroft and Gault formula [29]. Calculated creatinine clearance was capped at 150 ml min^{-1} as a reasonable upper estimate of this value [30]. BSA was estimated using the formula reported by DuBois and DuBois [31]. The effect of actual patient weight on clearance (CL) and volume of distribution of the central compartment (V_1) were predicted using a modified allometric scaling function [32, 33].

The analysis of the determinants of paclitaxel disposition employed standard model building and covariate identification techniques [34, 35]. The criteria for accepting a covariate into the model were strict ($P < 0.005$) and required the covariate to account for some portion of observed between-patient variability. After covariate addition was completed, the covariates were removed from the model serially to determine whether model performance degenerated ($P < 0.001$).

Model building and evaluation were conducted using the first order conditional estimation method (FOCE) with interaction [36, 37]. Model performance was evaluated using the likelihood ratio test, reduction in unexplained between-patient variability and by standard diagnostic plots and determination of the concordance criteria [38], which was used to measure the agreement between the predicted and the observed data. A modified correlation coefficient was calculated using the individual correlation coefficient and the overall mean used to account for the variable number of correlated repeated measurements in individual patients. In addition, a limited visual predictive check [39] was conducted on the final pharmacokinetic model to evaluate the agreement between the model's predictions and the actual observations. Simulations were also performed using the final pharmacokinetic model with 1000 replicates to generate 95% prediction intervals which were compared with the observed data.

Because the primary goal of the population pharmacokinetic analysis was to estimate individual patient paclitaxel exposure, the extent of Bayesian shrinkage was evaluated for each parameter in the final model using the following formula [40]:

$$\text{'Shrinkage'} = 1 - \frac{SD_{\eta\text{parameter}}}{\Omega_{\text{parameter}}}$$

In this formula, the $SD_{\eta\text{parameter}}$ is the standard deviation of the individual estimates of η for each parameter (e.g.

CL) and $\Omega_{parameter}$ is the estimate of the standard deviation of the estimated population variance. Large values of 'Shrinkage' (e.g. values close to 1) would be associated with generally poor individual estimates of that parameter. Lastly, the final parameter estimates were compared with published values.

More complex nonlinear pharmacokinetic models and other structural models were investigated early in the model development process and rejected based on poor performance or poorly estimated parameters, and a two-compartment model with linear elimination was determined to be the most appropriate to describe the paclitaxel concentration data obtained from the present study. The pharmacokinetic model was parameterized in terms of CL, V_1, volume of distribution of the peripheral compartment (V_2) and the intercompartmental clearance (Q). Between-patient variability in observed pharmacokinetic parameters was assumed to be log normally distributed and was described for CL, V_1 and V_2 using an exponential error model. The residual variability, which describes both assay error and model misspecification, was described using a combined additive and constant coefficient of variation (CCV) model.

The empirical Bayesian estimates of individual CL obtained from the final pharmacokinetic model developed in the first step of this analysis were used to approximate each patient's individual exposure to paclitaxel. Since pharmacokinetic data were available for only the first cycle of therapy, interoccasion variability could not be estimated and individual clearance was assumed to be constant for all subsequent cycles. This assumption was supported based on previous reports of low interoccasion variability of paclitaxel [15, 41] and random examination of serial changes in patients' weight and hepatic function in this study. These data revealed that 94% of patients experienced no more than 10% loss in weight and serious (grade 3) hepatic toxicity was reported in <1% of patients. Further, paclitaxel can induce cytochrome p450 enzymes, but the administration schedule in this study (21-day cycles) would not be expected to influence greatly its own clearance as might occur with more frequent dosing [42]. Taken together, these factors support the assumption that paclitaxel clearance did not vary much for any individual over successive cycles of treatment. Finally, while a pharmacokinetic interaction between doxorubicin and paclitaxel is possible, the literature suggests that while paclitaxel can alter doxorubicin pharmacokinetics, doxorubicin does not impact substantially on paclitaxel pharmacokinetics [43, 44].

Evaluating associations with toxicity and survival

Among patients who were followed for toxicity and survival but who were excluded from the initial pharmacokinetic modelling component of this study, CL was estimated based on individual covariate information using the clearance function which was defined during the pharmacokinetic model building. This approach was considered reasonable given the level of agreement observed between the individual predicted clearance and the estimated clearance in subjects with complete data (data not shown). Furthermore, CL was estimated in 12.8% or 16.2% of the patients included in the toxicity evaluation or the survival evaluation, respectively.

The AUC was calculated for each cycle using the typical predicted or the individual estimated value of clearance (as appropriate) and the administered dose for that cycle. AUC values were calculated as AUC = dose/CL, where dose was the actual amount of drug administered for each specific cycle and CL was the individual predicted clearance obtained from the pharmacokinetic model (or an estimated value if no pharmacokinetic data were available). AUC was treated as a continuous variable for all toxicity and as a continuous or categorized variable for survival evaluation. Analyses were performed to evaluate toxicity or survival in 148 or 154 patients, respectively. These subsets of the 160 patients (randomly allocated to the doxorubicin and paclitaxel treatment arm) were divided into equal-sized groups or 'bins' based on their calculated paclitaxel AUC.

Association with toxicity

Granulocytopenia was graded on a 0–4 scale in accordance with the GOG Common Toxicity Criteria during each cycle of chemotherapy. The severity of granulocytopenia in relation to paclitaxel exposure was evaluated by repeated measures using nonlinear logistic regression [45–47]. After defining a base model, which described the probability of each grade of effect occurring without the presence of drug, covariates including measures of drug exposure, PS, patient age and prior radiation therapy were evaluated to assess their likelihood of influencing toxicity. Paclitaxel exposure was evaluated as actual administered dose, BSA normalized dose or time above the threshold concentration of 0.1 $\mu m\ l^{-1}$, as well as total AUC. Several different structural functions including linear, nonlinear (which implies a maximum toxicity associated with a covariate) multiplicative and power functions, were tested. Once a logistic function describing the probability of adverse effects in this patient population was established, confidence intervals (CIs) of the probability curves were generated using nonparametric bootstrapping [48]. At each exposure

value for the constructed curve, the 95% CIs for the mean probability of a toxicity were determined.

Association with survival

Unadjusted and adjusted Cox proportional hazard analyses were performed for modelling time-to-death data in the presence of censored cases, i.e. for patients who were alive regardless of disease status [49, 50]. Survival time was calculated as the time in months from enrolment on the treatment protocol to death for noncensored events, or to the date of last contact for censored events. The likelihood ratio test was used to evaluate the overall model and the Wald test to assess the association between the individual covariates and outcome. Disease stage, GOG PS, age, weight, prior radiotherapy and doxorubicin dose were all evaluated as potential covariates based on their probability of impact on survival time; selected covariates were then incorporated into the final adjusted model using a stepwise method and inclusion criteria set at $P < 0.050$.

Results

Determinants of paclitaxel disposition

There were 362 evaluable specimens from 129 patients included in the pharmacokinetic analysis and modelling component of this study. Individual specimens were considered inevaluable for one of the following reasons: concentration = 0 (all predose values); nonlinear paclitaxel assay curve; no sample reported; invalid concentration data; high weighted residuals; and measurable predose paclitaxel levels. Specimens having a concentration = 0 were removed from the analysis because they provided no information about the pharmacokinetic behaviour of paclitaxel. Of these patients, 40 (31%) did not receive prior pelvic radiation and were ≤65 years old and were treated with 50 mg m^{-2} doxorubicin and 150 mg m^{-2} paclitaxel. Of the remaining 89 women who received prior pelvic radiotherapy and/or were >65 years old, 85 (95.5%) were administered the reduced starting doses as specified in the protocol (40 mg m^{-2} doxorubicin and 120 mg m^{-2} paclitaxel), whereas the required initial dose modification was not carried out in the other four (4.5%).

Table 1 lists the covariates that were examined as potential determinants of paclitaxel disposition and the distribution of characteristics among these 129 patients. The distributions of patient characteristics were similar between this group and the group randomized to paclitaxel as a whole. For this analysis, covariates were normalized based on median values and the reference patient was a 65-year-old White patient weighing 70 kg, with a BSA of 1.7 m^2, creatinine clearance of 70 ml min^{-1}, normal hepatic function [centred to a value of serum glutamic oxaloacetic transaminase (SGOT) of 50 IU l^{-1} and SGPT 50 IU l^{-1}] and no prior radiation therapy. Covariates were selected based on their potential to influence paclitaxel pharmacokinetics. Patient weight was the only covariate incorporated into the model to describe variability for V_1 and V_2. Inclusion of this covariate reduced the between-patient variability for V_1 from approximately 50% to 38%, and for V_2 weight reduced between-patient variability from 76% to 73%. Paclitaxel CL was shown to be dependent on patient weight, age and SGOT level. The addition of age reduced between-patient variability from approximately 36% to 34%. The addition of weight further reduced the between-patient variability to 33%, and when SGOT was added the variability was reduced further, to 31%. As a single covariate, between-patient variability in CL was best explained by SGOT, reducing the between-patient variability from approximately 36% to 31%. As individual covariates, age and weight resulted in smaller reductions in between-patient variability for CL and all covariates reduced the objective function. Table 2 indicates the population pharmacokinetic parameter estimates and the model-based equations that were determined for V_1 and CL in this study. As an example, a 50-year-old patient with an actual body weight of 70 kg and an SGOT of 50 would have a V_1 of 12.2 l and a CL of 36.9 l h^{-1}. The final pharmacokinetic parameters were well estimated with small standard errors. Estimates of the shrinkage for CL, V_1 and V_2 were 0.249, 0.179 and 0.405, respectively, suggesting that the individual estimates for CL and V_1 were reasonably robust and the individual estimates of V_2 were subjected to shrinkage and were therefore less reliable. Evaluation of the condition number (calculated as the square root of the ratio of the smallest to the largest eigenvalue) showed a value of 10.435, suggesting that the final model had no notable colinearity [51]. The constant coefficient of variation portion of the residual error function was somewhat high (35.4%). Residual variability can arise from many sources such as inaccuracy in the time, amount or duration of infusion, errors in pharmacokinetic sampling times, model misspecification and additional unidentified covariate influences. Any and all of these sources could have contributed to the residual variability in the present model and it is difficult to determine the actual cause of residual error in any specific analysis. However, the primary objective for this evaluation was to determine the individual measures of exposure (AUC). The estimated clearance was reasonable and did not appear to be influenced by the residual variability.

Table 1
Characteristics of patients included in the pharmacokinetic analysis and modelling (n = 129)

Variable (continuous)	Mean	Standard deviation	Minimum value	Maximum value
Age (years)	64.26	10.46	32	87
Weight (kg)	75.96	21.51	43	180
Height (cm)	161.5	6.92	142	179
Body surface area (m^2)	1.79	0.22	1.42	2.65
Doxorubicin dose (mg)	76.35	11.99	40	110
Paclitaxel dose (mg)	229.7	33.49	170	300
Creatinine clearance (ml min^{-1})*	82.81	32.30	32.20	150
SGOT (IU l^{-1})	26.46	20.84	3	191
SGPT (IU l^{-1})	26.60	11.27	4	110
ANC (μl^{-1})	6036	2976	1256	27324
Variable (categorical)		**No.**		**%**
GOG performance status				
0		62		48.1
1		57		44.2
2		10		7.8
Disease stage				
FIGO Stage III		19		14.7
FIGO Stage IV		29		22.5
Recurrent disease		81		62.8
Race				
White		108		83.7
Nonwhite		21		16.3
Prior radiotherapy				
No		64		49.6
Yes		65		50.4

**Calculated using Cockroft–Gault formula provided below and capped at 150 ml min^{-1} as a reasonable upper limit.* $CLCR\,(mL/min) = \frac{(140 - Age(y)) \cdot Body\ Weight\ (kg)}{72 \cdot Serum\ Creatinine\ (mg/dL)} \cdot 0.85$ *for Females SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; ANC, absolute neutrophil count; GOG, Gynecological Oncology Group.*

Table 3 illustrates the effect of weight, age and SGOT on total paclitaxel CL. The percent change in calculated CL is given relative to the calculated CL for the reference patient (70 kg, 50 years old, SGOT 50 IU). For example, a change in body weight from 40 kg to 150 kg, age from 30 to 80 years, or SGOT from 50 to 120 IU resulted in an expected change in CL of approximately 37% (increase), approximately 39% (decrease), or 16% (decrease), respectively.

Diagnostic plots for the final pharmacokinetic model are presented in Figure 2. Figure 2A shows the agreement between the typical predicted and observed concentrations. The data were reasonably uniformly distributed about the line of unity with adequate visual agreement between predicted and observed concentrations. The concordance coefficient generated for this final model was estimated to be 0.684, which was higher than estimated for the base model and suggests a reasonable agreement between the observed and predicted concentrations. Although not shown, a plot of the weighted residuals *vs.* the predicted total paclitaxel concentrations in the final model showed that the majority (96.7%) of observations were within the expected 3 SDs.

Figure 2B shows the results of the limited visual predictive check. The shaded area is the 95% prediction interval which contains the majority of the observed paclitaxel concentrations, with 14 (3.87% of the obser-

Table 2
Final population pharmacokinetics parameters for total paclitaxel

Parameter (units)	Parameter value	(% CV)	Between-patient variability (% CV)
CL (l h^{-1})	36.9	(11.0)	(31.2)
Effect of weight	0.750	(NE)	
Effect of age	–0.312	(66.7)	
Effect of SGOT	–0.214	(40.7)	
V_1 (l)	12.2	(16.9)	(37.8)
Effect of weight	1.0		
Q (l h^{-1})	51.9	(12.9)	(NE)
V_2 (l)	350.0	(38.6)	(73.5)
Constant coefficient of variation residual error (% CV)			(35.4)
Additive residual error (μg l^{-1})			(5.09)

NE, Not evaluated; % CV, constant coefficient of variation residual error; CL, clearance = 36.9 × (Weight / 70)$^{0.75}$ × (Age / 50)$^{-0.312}$ × (SGOT/50)$^{-0.214}$; V_1, central volume of distribution = 12.2 × (Weight / 70); V_2, peripheral volume of distribution = 350; Q, intercompartmental clearance = 51.9; SGOT, serum glutamic oxaloacetic transaminase.

vations) exceeding the predicted range of concentrations. The observations appear to be centred about the mean simulated concentration. Overall, the model performance was judged to be adequate.

Associations with toxicity

Data on the level of granulocytopenia were available for 148 patients. This adverse effect was graded using the GOG Common Toxicity Criteria version 2.0, as follows: grade 0 = within normal limits; grade 1 ≥1500 mm^{-3} but below normal limits; grade 2 ≥1000 mm^{-3} but <1500 mm^{-3}; grade 3 ≥500 mm^{-3} but <1000/mm^{-3}; grade 4 <500 mm^{-3}. The patients in this study were observed to experience multiple instances of granulocytopenia throughout as many as seven (the average number of treatment cycles was 4.6; the median number was six, with a minimum of one treatment cycle) (Table 4). Modelling was performed to determine the effect of different measures of paclitaxel exposure on the probability of a patient experiencing granulocytopenia. Relative to the model with no drug effect, all measures of paclitaxel exposure caused a statistically significant reduction in between-patient variability in granulocytopenic response (Table 5). Although paclitaxel exposure expressed as time above the threshold concentration of 0.1 μM l^{-1} was associated with the greatest reduction in between-patient variability, the lowest objective function and degrees of freedom (d.f.) were observed for total paclitaxel AUC using the linear model (d.f. = 1). The linear model describing paclitaxel AUC was therefore the best predictor of granulocytopenia compared with the other measures of paclitaxel exposure including actual dose, BSA normalized dose, time above threshold concentration and binned AUC. The effect of doxorubicin, evaluated using actual and BSA normalized dose, underwent only limited evaluation because the amount of drug administered was highly correlated with paclitaxel administration and the models using paclitaxel AUC together with either measure of doxorubicin exposure provided no additional improvements to either the between-patient variability or further reduction of the objective function. The high degree of correlation between the exposures for these two agents was expected given that they were administered sequentially, dosed based on patient BSA, excreted through the liver and dose reduced in the case of severe (grade 3) granulocytopenia. This colinearity interfered with the ability to determine the extent to which toxicity was attributable to any one agent.

PS but not patient age or prior radiation therapy was a significant predictor of granulocytopenia when added to the model alone or with a measure of paclitaxel exposure. Table 6 indicates the estimates of the model parameters for the optimal model for predicting granulocytopenia. To illustrate the impact of PS on the probability of a patient experiencing granulocytopenia, Figure 3 depicts the estimated probability curves for each grade of granulocytopenia with grade plotted *vs.*

Table 3
Effect of weight, age and liver function on clearance of total paclitaxel

Weight (kg)	Age (years)	SGOT (IU)	Predicted CL (l h^{-1})	Percent of reference patient
40	30	50	28.4	77.1
40	30	120	23.6	63.9
40	50	50	24.3	65.7
40	50	120	20.1	54.5
40	80	50	20.9	56.8
40	80	120	17.4	47.1
70	30	50	43.3	117.3
70	30	120	35.9	97.2
70*	50*	50*	36.9	100.0
70	50	120	30.6	82.9
70	80	50	31.9	86.4
70	80	120	26.4	71.6
120	30	50	64.8	175.7
120	30	120	53.8	145.7
120	50	50	55.3	149.8
120	50	120	45.8	124.2
120	80	50	47.7	129.4
120	80	120	39.6	107.3
150	30	50	76.6	207.7
150	30	120	63.6	172.2
150	50	50	65.4	177.1
150	50	120	54.2	146.9
150	80	50	56.4	153.0
150	80	120	46.8	126.8

*CL, Clearance: 36.9 × (Weight/70)$^{0.75}$ × (Age/50)$^{-0.312}$ × (SGOT/50)$^{-0.214}$; SGOT, serum glutamic oxaloacetic transaminase. *The reference patient in this analysis was 50 years old and had a body weight of 70 kg and an SGOT of 50 IU.*

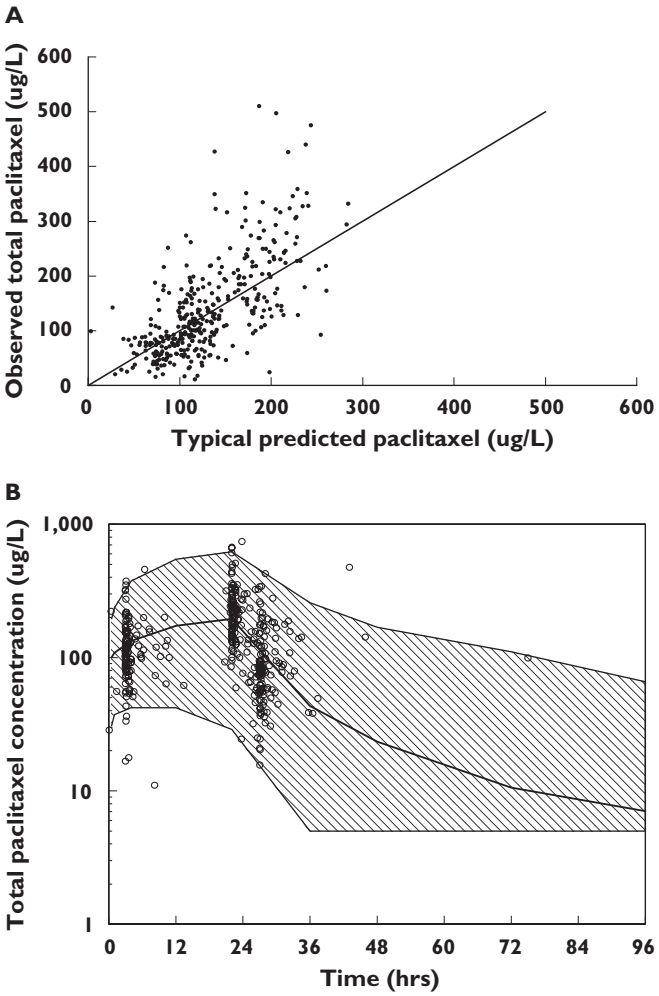

Figure 2
Diagnostic plots for pharmacokinetic models. (A) Observed *vs.* typical predicted total paclitaxel concentrations. Data (●), Line of Unity (—). (B) Ninety-five percent prediction interval (▨) with the mean predicted serum concentration (—). The observed paclitaxel concentrations (○) are overlaid on the interval

Table 4
Number of observations available for granulocytopenia analysis

	Grade				
	0	1	2	3	4
Granulocytopenia	304	67	85	86	124

paclitaxel AUC for patients with a PS of 0 (Figure 3A) or 2 (Figure 3B). The predicted probability curves for each grade of granulocytopenia are contained within the vertical bars, which represent the bootstrapped 95% CIs.

Association with survival

Survival analyses were performed to model the effect of covariates on overall survival (Table 7, Figure 4, and additional analysis not shown). Median survival for these patients was approximately 12 months. Although PS and disease stage were predictors of survival in this patient cohort, PS was more strongly associated with survival than disease stage. Patients with poor PS (PS = 2) and those who had recurrent disease had a shorter survival time than did patients with a better PS (PS = 0) and those who had previously untreated stage III or IV disease. After adjusting for PS and disease stage, paclitaxel exposure expressed as actual dose or BSA normalized dose was

Table 5
Effect of chemotherapy exposure on the granulocytopenia adverse effect model

Model	Objective function	Degrees of freedom	*P*-value	Between-patient variability
No drug effect	1811.293	–	–	1.75277
Paclitaxel exposure				
Linear actual dose	1802.754	1	0.003	1.61245
Nonlinear actual dose	1802.384	2	0.003	1.61245
Linear BSA normalized dose	1796.289	1	< 0.001	1.64012
Nonlinear BSA normalized dose	1796.514	2	0.001	1.64924
Linear time dose above 0.1 μM l^{-1}	1796.697	1	< 0.001	1.44568
Nonlinear time dose above 0.1 μM l^{-1}	1796.697	2	0.001	1.44222
Linear total AUC†	1784.276	1	< 0.001	1.56205
Nonlinear total AUC	1783.238	2	< 0.001	1.57797
Linear binned AUC*†	1788.815	1	< 0.001	1.54596
Nonlinear binned AUC*	1786.204	2	< 0.001	1.58745
Doxorubicin exposure				
Linear actual dose	1802.849	1	0.004	1.61864
Nonlinear actual dose	1801.938	2	0.009	1.62788
Linear BSA normalized dose	1790.163	1	< 0.001	1.63401
Nonlinear BSA normalized dose	1789.512	2	< 0.001	1.66433

AUC, Dose/CL; BSA, body surface area: estimated using the formula reported by DuBois and DuBois [27] BSA $(m^2) = 0.007184 \cdot \text{Body Weight (kg)}^{0.425} \cdot \text{Height (cm)}^{0.725}$. **Binned paclitaxel AUC was categorized into five equal sized groups or bins. †Optimal (final) model.*

Table 6
Final parameter estimates for granulocytopenia adverse effect model*

Relative probability	Population parameter value Log odds ratio	(% CV)
Of grade 0 to grade 1–4 granulocytopenia	$2.97 = \theta_1$	(25.4)
Of grade 1 to grade 2–4 granulocytopenia	$0.570 = \theta_2$	(11.9)
Of grade 2 to grade 3–4 granulocytopenia	$0.766 = \theta_3$	(10.8)
Of grade 3 to grade 4 granulocytopenia	$0.791 = \theta_4$	(9.6)

**Formula:* $\theta_1 + \theta_2 + \theta_3 + \theta_4 + (1.01 \times \text{paclitaxel AUC}) + (0.474 \times \text{performance status})$*; % CV, constant coefficient of variation residual error; AUC, dose/CL.*

not associated with a significant change in the estimated risk of death for patients with advanced stage or recurrent endometrial cancer randomly allocated to doxorubicin plus paclitaxel. In contrast, a trend towards an association with worse survival was observed when paclitaxel exposure was expressed as total paclitaxel AUC and evaluated as a continuous covariate [hazard ratio (HR) 1.77; $P = 0.055$]. In addition, when AUC was evaluated categorically, higher categorized paclitaxel AUC was associated with a significant increase in the estimated risk of death (HR 1.61; $P = 0.024$). There was no evidence to indicate that doxorubicin exposure expressed as actual dose or BSA normalized dose was associated with overall survival in this patient population, although the strong correlation between doxorubicin exposure and paclitaxel precluded any evaluation of the independent contributions of these agents.

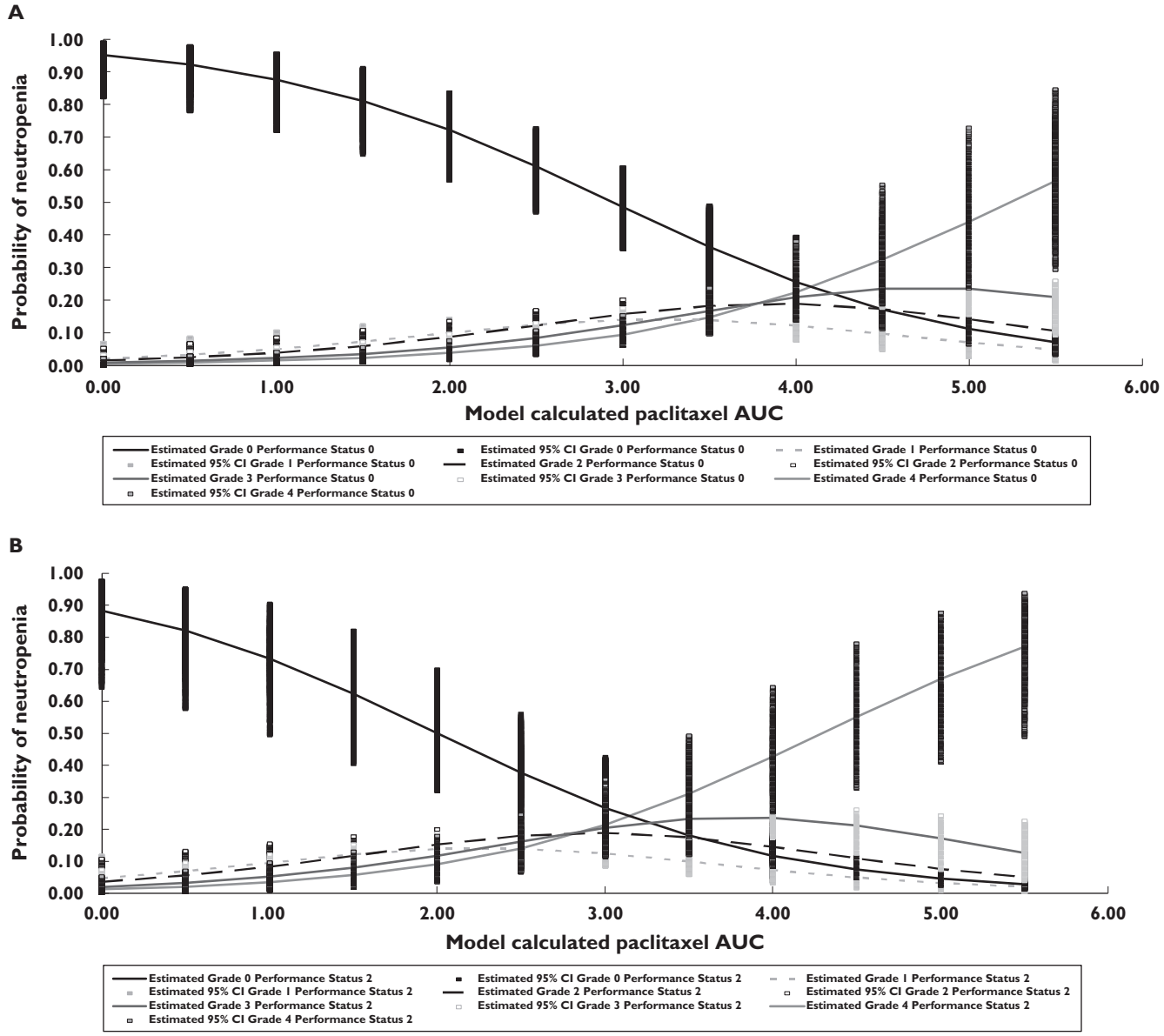

Figure 3

Estimated probability curves with 95% confidence intervals. (A) Probability curves for Gynecological Oncology Group (GOG) performance status 0. (B) Probability curves for performance status 2. Solid lines, Probability curves; horizontal lines, 95% confidence intervals for the probability curves

Discussion

The current study defines the determinants of paclitaxel disposition and describes the relationship between paclitaxel pharmacokinetics and granulocytopenia or survival among patients with advanced stage or recurrent endometrial carcinoma treated with doxorubicin plus paclitaxel. The pharmacokinetic data obtained in the present study were best described using a linear two-compartment model. Although total paclitaxel has been shown to follow nonlinear pharmacokinetic behaviour [7], it has also been reported that its nonlinearity is less apparent following a long (>6 h) infusion [12, 13]; therefore, the apparent linearity in the current study was reasonable given the 24-h infusion duration. The estimated CL, V_1, V_2 and Q for total paclitaxel determined from this population pharmacokinetic analysis in patients with advanced stage or recurrent endometrial cancer randomly allocated to receive treatment with doxorubicin plus paclitaxel were consistent with other published reports [8, 30, 31]. It should be noted, however, that although the covariates identified as important were consistent with other reports where paclitaxel was

Table 7
Relationship between drug exposure and survival

Analysis of overall survival	HR	95% CI	*P*-value
Individual unadjusted Cox models			
Covariates			
Disease stage	1.17	0.95, 1.45	0.140
Performance status	1.72	1.30, 2.27	0.0002
Paclitaxel exposure			
Actual dose	1.00	0.99, 1.00	0.270
BSA normalized dose	1.00	0.99, 1.01	0.950
Total AUC	1.59	0.82, 3.10	0.117
Categorized AUC*	1.54	0.65, 1.03	0.032
Doxorubicin exposure			
Actual dose	0.99	0.98, 1.0	0.210
BSA normalized dose	1.00	0.98, 1.02	0.720
Adjusted Cox models†			
Paclitaxel exposure			
Actual dose	1.00	0.995, 1.00	0.490
Total AUC	1.77	0.90, 3.46	0.055
Categorized AUC*	1.61	1.07, 2.44	0.024
Doxorubicin exposure			
Actual dose	0.996	0.99, 1.01	0.480

*HR, Hazard ratio (risk of death); 95% CI, 95% confidence interval; AUC, dose/CL. *Categorized paclitaxel AUC expressed as highest exposure (bins 2–5; 2.34–4.07) relative to lowest exposure (bin 1; 1.19–2.33). †Cox regression analysis adjusted for performance status and disease stage using a forward step-wise method.*

described using a nonlinear model, the applicability of the parameter estimates identified in the present analysis is limited to settings where paclitaxel is administered as an i.v. infusion over ≥6 h (which diminishes the apparent nonlinearity).

The covariates identified herein were also consistent with those identified in other population-based analyses of patients having other types of solid tumours and treated with various chemotherapeutic regimens, and are physiologically reasonable. The effect of weight is similar to the effect of BSA on CL and volume of distribution as identified by Henningsson *et al.* [19], although discussions concerning the relative advantages of dosing based on body size have been inconclusive [52–55]. The rationale to adjust doses for elderly patients is well established. Studies of the effect of age on hepatic drug-metabolizing capacity, especially the p450 microsomal system, have demonstrated up to 30% decreases in healthy elderly men and women compared with younger subjects [56]. This age-dependent reduction of enzymatic capacity may result in decreased metabolism and clearance of drugs that are highly extracted by the liver, such as paclitaxel [57, 58, 59]. Similarly, patients with hepatic dysfunction may also exhibit reduced paclitaxel clearance [52]. A Phase I pharmacokinetic study of paclitaxel administered as a 3-h and 24-h infusion was conducted in patients with liver dysfunction [59]. In that study patients with mild (bilirubin ≤1.5 mg dl^{-1}), moderate (bilirubin 1.6–3.0 mg dl^{-1}) and severe (bilirubin >3.0 mg dl^{-1}) liver dysfunction were evaluated and the recommendation was made that doses be reduced to <135 mg m^{-2}, 75 mg m^{-2} and 50 mg m^{-2}, respectively. Similarly, the clearance of docetaxel (a related compound) has been found to be influenced by measures of CYP3A4 activity [60].

The ability to individualize doses and to reduce between-patient variability in exposure is important when drug exposure is related to either adverse effects or to patient outcome and the present pharmacokinetic evaluation has shown that the variability in paclitaxel exposure is attributable to several covariates. In this study, patient exposure to paclitaxel was found to be predictive of granulocytopenia. The use of actual dose, BSA adjusted dose and time above a threshold concentration was tested, but did not prove to be a better predictor of toxicity than AUC. This finding did not agree with other published work [7, 15], in which toxicity was shown to be better correlated with time above a thresh-

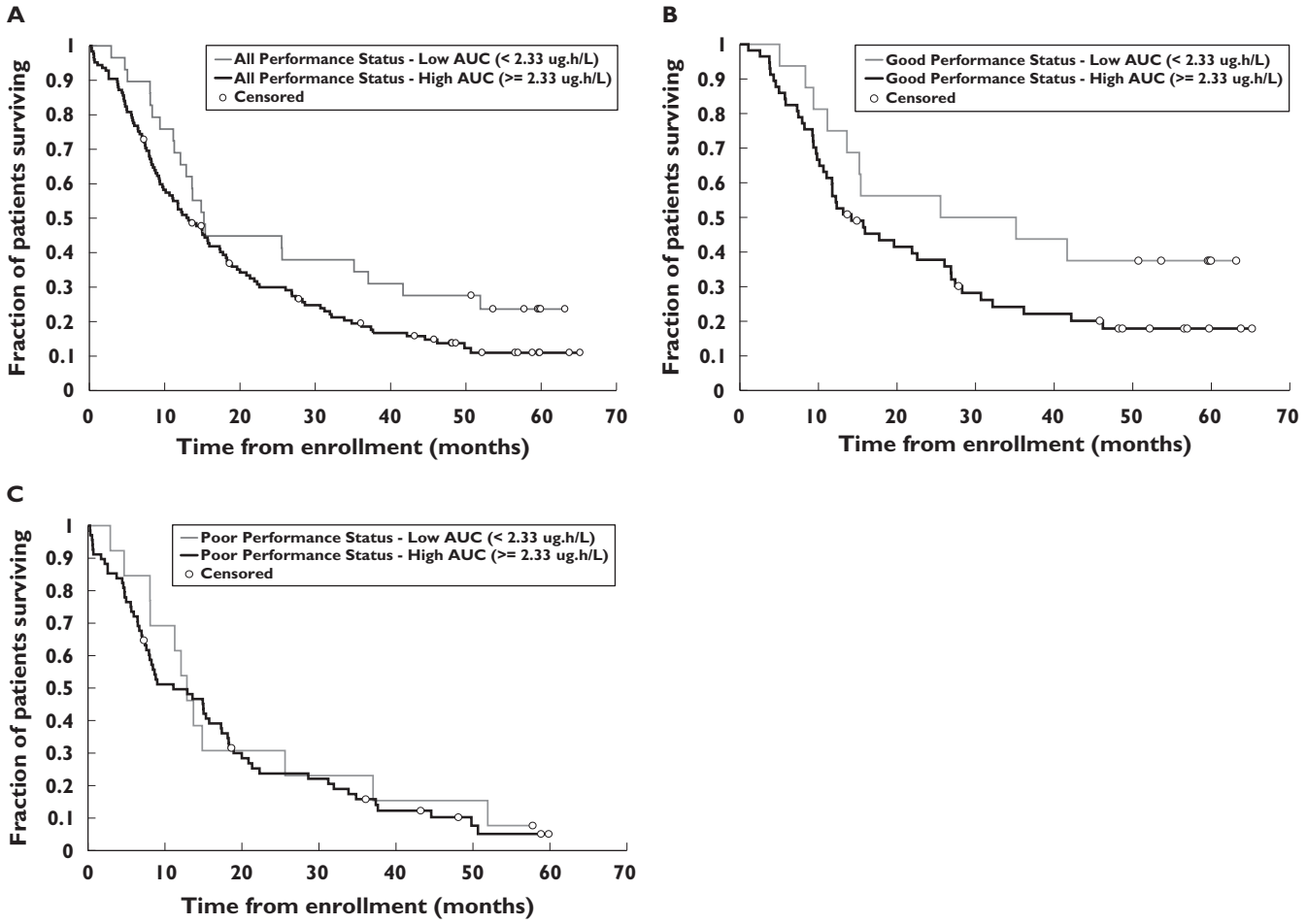

Figure 4

Effect of low *vs.* high paclitaxel AUC on survival (proportion surviving provided in months from enrolment) in patients with any performance status (A); with good performance status (PS = 0, B); or with poor performance status (PS = 1 or 2, C). Low AUC: <2.33 μg h^{-1} l^{-1} (bin 1); high AUC: ≥2.33 μg h^{-1} l^{-1} (bins 2–5)

old than with AUC. This inconsistency may be due to the fact that the nonlinearity of the pharmacokinetics of total paclitaxel is less apparent with longer infusions, making the distinction between AUC and time above a threshold less obvious. When the relationship between free paclitaxel (which exhibits linear pharmacokinetics) and adverse effects was evaluated, the use of time above a threshold was not distinguishable from AUC [15]. The identification of AUC instead of time above a threshold for total paclitaxel may also reflect toxicity that is attributable to doxorubicin or the active metabolite doxorubicinol, which was also administered to the patients randomly allocated to this treatment arm. Doxorubicin is well known to induce granulocytopenia, although the extent of toxicity attributable to doxorubicin could not be determined due to the colinearity between the doses administered for both agents in this study. For the finding that a more individualized estimate of exposure (AUC) was a better predictor than actual dose or BSA adjusted dose, the observations with normalized dose are consistent with other work [7].

There was a relationship observed between increased paclitaxel exposure and increased probability of severe adverse effects. For example, for a patient with a PS of 0, the probability of grade 4 granulocytopenia increases from 4% at an AUC of 2 (corresponding to a dose of 85–150 mg m^{-2}) to 22% at an AUC of 4 (corresponding to a dose of 120–150 mg m^{-2}). Given that there is considerable overlap in the AUC values for doses between 120 and 150 mg m^{-2} due to between-patient variability in the pharmacokinetics, the ability to estimate and control patient exposure *a priori* is an important tool for determining optimal treatment.

A relationship was also observed between disease

stage (stage 3 *vs.* 4 *vs.* recurrent disease), GOG PS (0 *vs.* 1 or 2) or paclitaxel AUC, and survival. Disease stage and PS are well recognized as being predictive of survival and were important covariates in the present study. In contrast, the observations that total paclitaxel AUC showed a somewhat weaker trend ($P < 0.05$) toward an association with worse survival, and high paclitaxel AUC appeared to be an independent predictor of increased risk of death, will require validation. Poor paclitaxel excretion (thus high AUC) may be a surrogate for diminished hepatic capacity (which is poorly measured by classic serum markers of bilirubin, SGOT, SGPT, etc.), poor nutritional status, concomitant medications and other less defined measures of overall 'sickness'. Additional studies are required to validate the finding in the trial reported here that higher paclitaxel AUC was associated with worse survival.

The majority of oncology studies that have been evaluated for pharmacokinetics are Phase I with limited numbers of densely sampled subjects, or are retrospective pooled analyses. In this evaluation of the pharmacokinetics and pharmacodynamics of paclitaxel, the data were collected during a multisite trial and were therefore available from a large number of patients, making the evaluation of covariate influences for paclitaxel exposure and its relationship to toxicity and survival more robust. The observed agreement between the estimated pharmacokinetic parameters and covariate factors in our study with those previously reported substantiate the approach.

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