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Randomized crossover pharmacokinetic study of solvent-based paclitaxel and *nab*-paclitaxel

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Abstract

Purpose: Abraxane (ABI-007) is a 130 nm albumin-bound (*nab*™) particle formulation of paclitaxel, devoid of any additional excipients. We hypothesized that this change in formulation alters the systemic disposition of paclitaxel compared with conventional solvent-based formulations (sb-paclitaxel, Taxol®), and leads to improved tolerability of the drug.

Patients and Methods: Patients with malignant solid tumors were randomized to receive the recommended single agent dose of *nab*-paclitaxel (260 mg/m^2 as a 30 minute infusion) or sb-paclitaxel (175 mg/m^2 as a 3 hour infusion). Following cycle 1, patients crossed over to the alternate treatment. Pharmacokinetic studies were carried out for the first cycle of sb-paclitaxel and the first two cycles of *nab*-paclitaxel.

Results: Seventeen patients were treated, with 14 receiving at least one cycle each of *nab*-paclitaxel and sb-paclitaxel. No change in *nab*-paclitaxel pharmacokinetics was found between the first and second cycles (P =0.95), suggesting limited intrasubject variability. Total drug exposure was comparable between the two formulations (P= 0.55) despite the dose difference. However, exposure to unbound paclitaxel was significantly higher following *nab*-paclitaxel administration, due to the increased free fraction (0.063 ± 0.021 vs 0.024 ± 0.009, P <0.001).

Conclusion: This study demonstrates that paclitaxel disposition is subject to considerable variability depending on the formulation used. Since systemic exposure to unbound paclitaxel is likely a driving force behind tumoral uptake, these findings explain, at least in part, previous observations that the administration of *nab*-paclitaxel is associated with augmented antitumor efficacy as compared with solvent-based paclitaxel.

INTRODUCTION

nab-paclitaxel (ABI-007, Abraxane) is an albumin-bound particle formulation of paclitaxel, devoid of any solvent excipients. Paclitaxel, a semi-synthetic anti-microtubule chemotherapeutic agent currently used alone or in combination with other anticancer drugs in the treatment of a wide range of solid tumor malignancies, is highly lipophilic and insoluble in water (1,2). As such, it has traditionally been formulated as Taxol (sb-paclitaxel), in a mixture

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of Cremophor EL (polyoxyethylated castor oil) and ethanol, to allow for intravenous infusion (3). Due to the incidence of severe hypersensitivity reactions to Cremophor EL, patients are routinely pre-treated with histamine blockers and steroids (4). In addition to the need for pre-medication, the presence of Cremophor EL has been shown to affect the pharmacokinetics of paclitaxel, due to micellar encapsulation of the drug (3). This leads to a decreased fraction of unbound drug, which limits drug distribution and clearance, and eventually results in non-linear pharmacokinetics by decreasing the uptake of paclitaxel in red blood cells and tissues, thereby interfering with metabolism and biliary secretion.

Conversely, *nab*-paclitaxel can be simply dissolved in saline for infusion. An initial Phase I clinical trial has shown that this drug is tolerated up to a maximum tolerated dose (MTD) of 300 mg/m^2, administered as a 30 minute infusion, without any premedication (5). A subsequent Phase II study utilized this dosing regimen; however, dose reductions were required in 25% of patients due to toxicity, primarily neutropenia and neuropathy (6). Therefore, the Phase III study that led to FDA approval of *nab*-paclitaxel for treatment of metastatic breast cancer compared a 30 minute infusion of 260 mg/m^2 with the standard paclitaxel regimen of 175 mg/m^2 as a 3-hour infusion (7). This study demonstrated significantly higher response rates and longer time to tumor progression in the group receiving *nab*-paclitaxel.

Paclitaxel has been previously shown to be highly protein bound in plasma, with Cremophor EL further decreasing the free fraction of drug (8,9). Since the unbound fraction of paclitaxel is the pharmacologically active form, understanding factors influencing unbound paclitaxel concentrations might be important in predicting toxicity and antitumor activity. It has been hypothesized that the exclusion of this excipient will increase the unbound fraction of drug. To test this hypothesis, we evaluated the comparative pharmacokinetics of total and unbound paclitaxel following administration of *nab*-paclitaxel and sb-paclitaxel using a randomized, crossover design.

PATIENTS AND METHODS

The protocol and consent form were approved by the National Cancer Institute Institutional Review Board. The study was conducted in compliance with Good Clinical Practice, guidelines of the International Conference on Harmonization, and the Declaration of Helsinki. Consent was obtained from all patients prior to participation.

Patient Eligibility

Patients enrolled were required to have (a) histologically confirmed, locally advanced or metastatic, solid tumors that were likely to be responsive to taxanes, (b) an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, (c) life expectancy of >3 months, (d) adequate bone marrow and organ function as defined by a granulocyte count ≥ 1500/μL, platelet count of ≥ 100,000/ μL, total bilirubin within normal institutional limits, ALT and AST ≤ 1.5x upper limit of normal, and creatinine within normal limits or measured creatinine clearance ≥ 60 ml/min, and (e) left ventricular ejection fraction of ≥40% without clinical signs or symptoms of heart failure. Patients who were refractory to paclitaxel or had previously untreated locally advanced breast cancer were ineligible. Patients who had a seizure disorder requiring anticonvulsant therapy, untreated or symptomatic brain metastases, history of allergic reactions attributed to paclitaxel or Cremophor EL-containing compounds, and concomitant use of drugs or supplements known to influence the expression and function of CYP3A4 and/or CYP2C8, were excluded from the study. Other forms of concurrent antitumor therapy were prohibited.

Study Design

The randomized, crossover design was selected to provide the most direct comparison of the two paclitaxel formulations, partially eliminating the effect of interindividual variability. Statistical determination of the study size was calculated using data from previous studies. The mean clearance for (unbound) paclitaxel used in the calculation is 429 L/h, estimated from a group of cancer patients treated with paclitaxel that had sampling on at least 2 occasions (10). In this group of patients, the standard deviation (SD) of the differences of the two measurements, was estimated to be 121.3. The trial was designed to detect an effect size of 107.3/121.3, where 107.3 is 25% of the mean of the value of the clearance from unbound paclitaxel. Based on a pair-wise (two-sided) analysis, this results in a sample size of (at least) 14 for the prospective evaluation, with a significance level of 0.05 (5%) and power of 0.86 (86%).

Up to 20 patients were allowed to be enrolled on this trial and randomized according to the order of administration of the agent, to ensure enrollment of 14 individuals who completed at least the first two cycles of treatment. Randomization of the patients was done by the Orkand Corp. (Bethesda, MD). Patients were considered evaluable for pharmacokinetics if they completed at least two treatment cycles, including a single cycle of each agent. Patients who were unable to complete a second cycle of treatment were replaced. Pharmacokinetic analyses concluded after the 3rd cycle of therapy, but treatment with *nab*-paclitaxel was continued for patients until disease progression or toxicity was encountered.

Treatment Plan

Patients were randomized to receive either *nab*-paclitaxel (Abraxane (ABI-007), Abraxis Bioscience Inc., Los Angeles, CA) 260 mg/m^2 as a 30 minute infusion on cycle 1 day 1, followed 3 weeks later in cycle 2 day 1 by sb-paclitaxel (Taxol, Bristol-Myers Squibb, Princeton, NJ) 175 mg/ m^2 as a 3-hour infusion, or vice versa, followed every three weeks thereafter by repeated treatments with *nab*-paclitaxel 260 mg/m^2. Patients were premedicated with antihistamines (diphenhydramine 25 – 50 mg IV and ranitidine 150 mg PO or IV) one hour prior to infusion, regardless of treatment group. Though not specified in the Abraxane package insert, these were administered in all cycles to remove a possible cause of pharmacokinetic variability. In addition, during sb-paclitaxel treatment cycles, patients also received corticosteroids (dexamethasone 20 mg orally 12 hours and 6 hours prior to the planned infusion or a single 20 mg IV dose 30 – 60 minutes prior to infusion). Though only administered in the sb-paclitaxel cycle, dexamethasone is unlikely to affect the pharmacokinetics of paclitaxel (11,12). Standard blood chemistries and hematologic tests were obtained on approximately days 1, 8, 15 of cycles 1 – 3, but only hematologic tests were obtained for cycle 4 onwards on days 8 and 15. Radiographic studies (computed tomography scans of the chest, abdomen, and pelvis and technetium-99m bone scintigraphy for patients with known bone metastases) were performed at baseline and repeated every 12 weeks (following 4 cycles of treatment) to assess for response per RECIST.

Toxicity and Dose Modification

Toxicities were reported using the Common Toxicity Criteria for Adverse Events version 3. Dose reductions or interruptions were permitted at any time during the study following the occurrence of any dose-limiting toxicity that was not controlled by optimal supportive care or not tolerated due to symptomatology or interference with daily activities. Grade 3 or 4 events required the reduction of the subsequent dose of paclitaxel by 25% with no further dose reductions allowed beyond this level.

Sample collection and analysis

Blood samples were collected for pharmacokinetic analysis in each of the first three treatment cycles for each patient, allowing for comparison of *nab*- and sb- pharmacokinetics, in addition to evaluation of any changes in *nab*-paclitaxel pharmacokinetics with subsequent cycles. In *nab*-paclitaxel treatment cycles, approximately 7 mL of venous blood was obtained in a sodium heparin tube prior to the start of the infusion, 15 minutes after the start of the infusion, 2-5 minutes prior to the end of the infusion and at 30 minutes and 1, 1.5, 2, 4, 6, 8, 12, 24, 48 and 72 hours after the end of the infusion. In the sb-paclitaxel treatment cycle, approximately 7 mL of venous blood was obtained in a sodium heparin tube prior to the start of the infusion, 1.5 h after the start of the infusion, 2-5 minutes prior to the end of the infusion and at 1, 1.5, 2, 4, 6, 8, 12, 24, 48 and 72 hours after the end of the infusion. All samples were immediately centrifuged, the plasma transferred to cryovials and stored at −80 °C until the time of analysis.

All samples were analyzed using an analytical assay validated for measurement of both sb-paclitaxel and *nab*-paclitaxel (13). Briefly, 100 μL of plasma was transferred to a microcentrifuge tube and 500 μL of acetonitrile containing the internal standard, d_5-paclitaxel, was added. Following vortex mixing, samples, along with calibrators and quality control samples prepared from blank plasma and precipitated in the same way, were transferred to a 96-well filtration plate and the precipitate filtered out under vacuum. The collection tray was transferred to an Acquity UPLC (Waters Corp, Milford, MA) and 10 μL of the solution was injected. Chromatography was carried out using a Zorbax SB RP8 column (50 × 2.1 mm) and mass detection was achieved on a Micromass Quattro Premier Triple Quadrupole Mass Spectrometer (Waters Corp). This method has been validated for quantitation of paclitaxel (formulated as either Taxol or Abraxane) in plasma within the range of 10 – 2500 ng/mL, and each run included QC samples prepared from nab-paclitaxel. Within- and between-run imprecision was less than 9% at all QC concentrations. Accuracy error was less than 7%. Twenty-fold dilution analysis was also validated, allowing for measurement of sample concentrations up to 50,000 ng/mL.

For the measurement of unbound drug, 500 μL of each sample was transferred to a Millipore (Billerica, MA) Centrifree ultrafiltration device (30,000 NMWL) and centrifuged in a fixed-rotor for 30 minutes at 1500 × *g*, 20° C. Following centrifugation, 100 μL of the filtrate was treated as plasma and the standard sample preparation and analysis procedure detailed above was performed.

Pharmacokinetic and Statistical Analysis

Non-compartmental pharmacokinetic analysis of data for each individual, per cycle, was undertaken using the software package WinNonlin, version 5.0 (Pharsight Corp, Mountain View, CA). The peak plasma concentration (C_{max}) and the time to peak plasma concentration (T_{max}) are reported as observed values. The area under the plasma concentration versus time curve (AUC_{last}) was calculated using the linear trapezoidal method from time zero (at drug administration) to the time of the last sample with measurable drug concentration for each patient (C_{last}). The AUC_{inf} value was calculated by extrapolation by dividing C_{last} (the last measurable drug concentration) by the rate constant of the terminal phase. For samples with measured concentrations below the lower limit of quantitation (LLOQ), the measured value was used if within 20% of the LLOQ.

For unbound paclitaxel analyses, a partial AUC from the start of infusion until 4 hours after the end of infusion ($AUC_{0\text{-}4.5}$ for *nab*-paclitaxel and $AUC_{0\text{-}7}$ for sb-paclitaxel) was also calculated, to enable direct comparison of the two regimens, since many plasma samples had undetectable concentrations of paclitaxel more than 4 hours after the end of sb-paclitaxel infusion. The use of partial AUCs avoided the introduction of extrapolation errors.

All statistical analyses were carried out using NCSS 2004 (J. Hintze, Kaysville, UT). Outliers, defined as AUC_{inf} with greater than 2.5-fold deviation from the mean, were excluded as stated. A *P*-value of less than 0.05 was considered to be statistically significant in paired t-tests.

RESULTS

A total of 17 patients were accrued to the study from April 2005 to February 2006. The baseline clinical and biological characteristics are listed in Table 1. The median age was 65 years and the primary diagnosis consisted of 11 patients with metastatic prostate cancer, 3 patients with metastatic breast cancer, 2 patients with metastatic ovarian cancer and 1 with metastatic fallopian tube adenocarcinoma.

Eight patients were randomized to receive *nab*-paclitaxel and 9 patients to receive sb-paclitaxel, in the first cycle. All 17 patients had at least one cycle of treatment. Of the 17 patients, 14 proceeded to cycle 2. Two patients, one on each arm, died within 2 and 3 weeks of administration of cycle 1 of sb-paclitaxel and *nab*-paclitaxel, respectively. Both of these patients had a performance status of 2 at the time of enrollment. The patient who received sb-paclitaxel had a diagnosis of metastatic ovarian cancer and died of complications from small bowel obstruction, related to the primary diagnosis. The second patient, with a diagnosis of metastatic prostate cancer, had failure to thrive after the first cycle of *nab*-paclitaxel treatment, but already had debilitation secondary to bone pain upon study enrollment and died thereafter. The third patient who received only one cycle of treatment (sb-paclitaxel arm) discontinued treatment secondary to dyspnea and requested to come off study secondary to inability to travel. All other patients were treated and included in the assessment for toxicity and pharmacokinetic analyses.

nab-paclitaxel Pharmacokinetics

Thirteen patients completed multiple cycles of treatment with *nab*-paclitaxel, but one patient was deemed an outlier and excluded from the analysis. There was no statistically significant difference between the paired pharmacokinetic data, and the mean clearance remained unchanged between the first (either C1 or cross-over C2) and second (C3) cycles of *nab*-paclitaxel (13.15 versus 13.24 L/h/m^2, $P = 0.95$) (Table 2).

Comparison of *nab*-paclitaxel and sb-paclitaxel Pharmacokinetics

The observed peak plasma concentration of paclitaxel was 3.8-fold higher following administration of 260 mg/m^2 of *nab*-paclitaxel, as compared to 175 mg/m^2 of sb-paclitaxel (19556.42 ± 7070.93 versus 5127.96 ± 1678.65 ng/mL, $P < 0.001$) (Table 3). However, overall total drug exposure was comparable between the regimens (20324.49 ± 3965.89 hr*ng/mL following *nab*-paclitaxel versus 20821.07 ± 5391.37 hr*ng/mL following sb-paclitaxel, $P = 0.72$). As such, dose-normalized total drug exposure was higher following sb-paclitaxel, presumably due to considerably slower paclitaxel clearance following administration of the sb-paclitaxel formulation (8.94 ± 2.30 versus 13.21 ± 2.37 L/hr/m^2, respectively; $P = 0.00002$).

Unbound paclitaxel pharmacokinetics

As expected, the mean fraction unbound of paclitaxel was considerably higher with *nab*-paclitaxel as compared to sb-paclitaxel (0.063 ± 0.021 versus 0.024 ± 0.009, $P < 0.001$) (Table 4). In comparison, previous studies have demonstrated that paclitaxel spiked into blank plasma (without Cremophor EL) has a free fraction of approximately 0.08 or greater (14,15). This increase in free fraction, coupled with the higher dose and shorter infusion time led to a maximal concentration of unbound paclitaxel approximately 10-fold higher following *nab*-paclitaxel administration (1283.7 ± 532.17 versus 121.79 ± 39.62 ng/mL). In many individuals, plasma concentrations of unbound paclitaxel dropped below the limit of quantitation of the assay

within 10 hours after sb-paclitaxel infusion (Figure 1). As such, partial AUCs were calculated, from the start of infusion, until 4 hours after infusion for each drug, to allow direct comparison. The mean unbound paclitaxel exposure up to four hours post infusion was significantly higher (approximately 2.7-fold) after *nab*-paclitaxel ($AUC0\text{-}4.5_{nab\text{-}paclitaxel}$ 969.20 ± 318.82 versus $AUC0\text{-}7_{sb\text{-}paclitaxel}$ 361.08 ± 116.54 hr*ng/mL, $P = 0.00002$). Comparison of dose-normalized unbound drug exposure, up to 4 hours post infusion, was also approximately 80% higher with *nab*-paclitaxel ($P = 0.0007$).

Toxicity

All patients who received treatment were evaluated for toxicity. Hematologic toxicities were the main adverse events in both arms. Grade 3 neutropenia occurred in 2 patients while receiving *nab*-paclitaxel and 3 patients receiving sb-paclitaxel. However, Grade 4 neutropenia was experienced by two patients in the *nab*-paclitaxel arm only (Table 5). Febrile neutropenia occurred in 2 patients, one in cycle 1 of *nab*-paclitaxel and the other during cycle 3 of *nab*-paclitaxel. Non-hematologic toxicities occurred in no more than 38% of patients and included nausea, vomiting, alopecia, diarrhea, and increased PTT. In the first cycle of treatment grade 1 and 2 fatigue occurred only in the sb-paclitaxel arm (25% vs 0%); however, similar incidence of fatigue was noted in subsequent cycles of *nab*-paclitaxel. The incidence of sensory neuropathy did not differ between the two regimens during cycle 1 (13% vs 12.5%).

Response to therapy

Of the 14 remaining patients who received at least one cycle of sb-paclitaxel and at least one cycle of *nab*-paclitaxel, only 12 patients were evaluated for response due to withdrawal from study prior to the scheduled response assessment. Partial response was documented in one patient with metastatic prostate cancer. Stable disease was documented in 5 patients: 2 patients with a diagnosis of metastatic breast cancer and 3 patients with metastatic prostate cancer. The median duration of stable disease was 7.2 months (range 2.9 to 8.6), with these patients receiving a median of 10 treatment cycles (range 3 – 16). Overall, patients received a median of 4 cycles (range 1 – 16), including the first two crossover cycles. None had a complete response to treatment and the rest had progressive disease.

DISCUSSION

This trial was designed to assess the effects of a change in paclitaxel formulation, namely, the elimination of Cremophor EL as an excipient, on the resulting pharmacokinetics and toxicity, in patients with metastatic solid tumors.

Comparison of total drug exposure demonstrated that although higher initial concentrations of paclitaxel were observed following *nab*-paclitaxel (due to increased dose and shortened infusion time) as compared to sb-paclitaxel, the increased clearance results in similar systemic exposure. These pharmacokinetic parameters, including the similarity in terminal half-life, are in accord with previously published data (16). In this study, the use of a crossover design eliminated the possibility that clearance differences between the two formulations arose due to difference in the patient population in each arm. Furthermore, we did not observe an increase in interindividual pharmacokinetic variability with *nab*-paclitaxel as compared to sb-paclitaxel.

We have recently demonstrated augmented antitumor activity of paclitaxel with *nab*-paclitaxel in preclinical mouse xenograft models (17). which was supported by data showing increased intratumoral concentrations and increased binding to, and transport across, endothelial cells (18). This finding appears to be in part due to the ability of Cremophor EL to inhibit binding of paclitaxel to endothelial cells. However, it is highly possible that the 2.7-fold increase in unbound drug exposure we observed with the *nab*-paclitaxel formulation plays a role in the

increased response, simply by allowing for greater drug distribution, a possibility that is supported by the increased volume of distribution, as compared to sb-paclitaxel. What remains unclear is why this increase in free drug has not resulted in greater toxicity in other clinical studies, as unbound drug exposure or time above a threshold has been linked to hematologic toxicity (19).

In contrast to the larger Phase III study, which, despite the higher dose, demonstrated decreased grade 4 neutropenia after *nab*-paclitaxel as compared to sb-paclitaxel, we observed the opposite (13% vs 0% for the first cycle, with a 23% incidence rate in later cycles of *nab*-paclitaxel) (7). However, the current study was not statistically powered for comparison of toxicity between the two regimens.

Overall, this study demonstrates that paclitaxel disposition is subject to considerable variability depending on the formulation used. Since systemic exposure to unbound paclitaxel is likely a driving force behind tumoral uptake, these findings explain, at least in part, previous observations that the administration of *nab*-paclitaxel is associated with augmented antitumor efficacy as compared with sb-paclitaxel. The experimental design applied here may provide a template for future evaluation of pharmacokinetic comparisons of alternate paclitaxel formulations.

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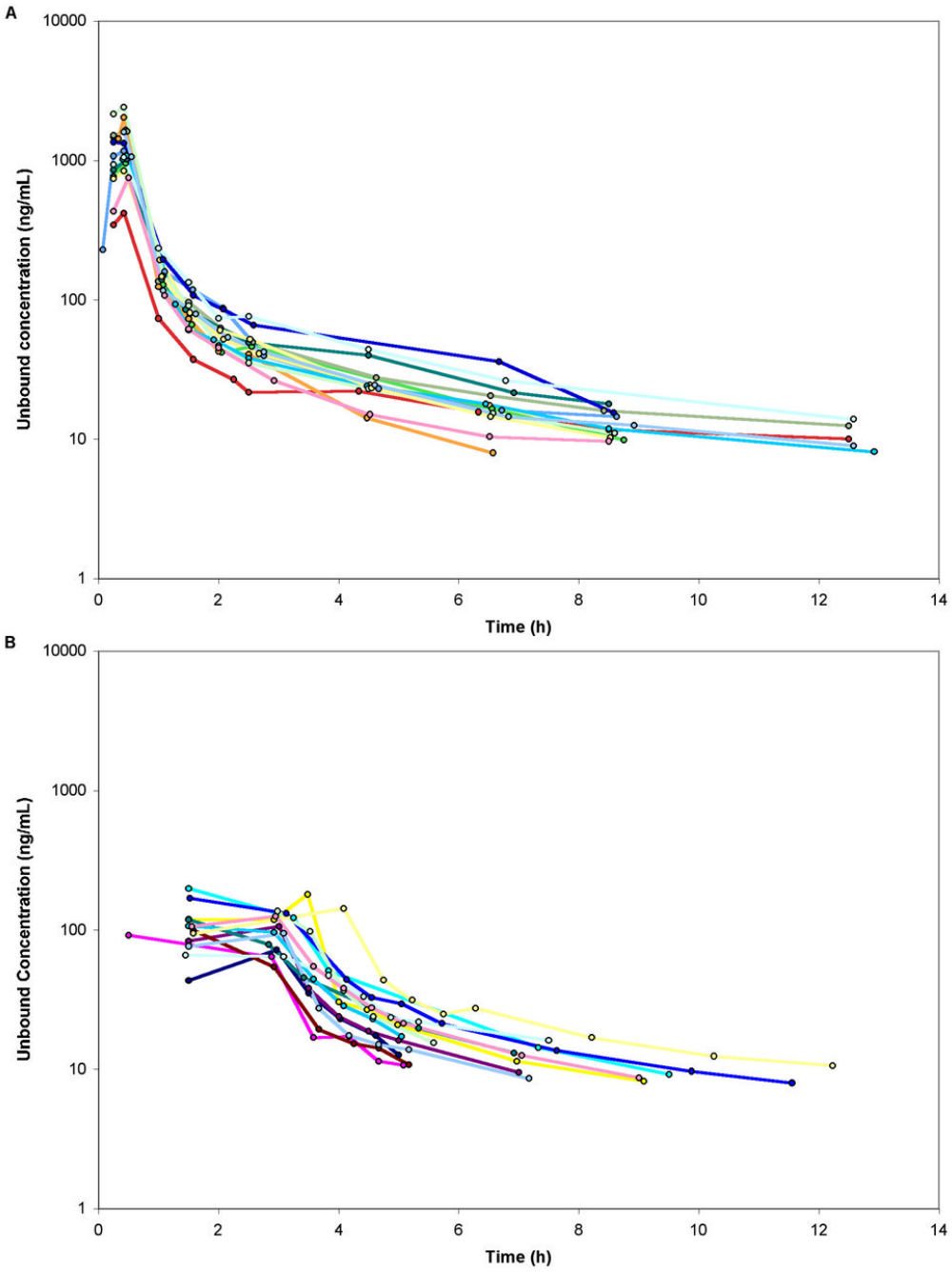

Figure 1.
Unbound paclitaxel concentration-time profiles following *nab*-paclitaxel (A) or sb-paclitaxel (B) administration, for all 14 individuals.

Table 1

Clinical Characteristics of Patients Enrolled (n = 17)

	No.
Primary Diagnosis	
Metastatic Prostate adenocarcinoma	11
Metastatic Ovarian Carcinoma	2
Metastatic Breast Carcinoma	3
Metastatic Carcinoma of the Fallopian Tube	1
Gender	
Males	11
Females	6
Median Age years (range)	65 (42 - 76)
Race	
White	14
Hispanic	2
Asian	1
ECOG Performance Status (median)	
0	2
1	10
2	5
Response	
Partial response	1
Progressive disease	6
Stable disease	5
Withdrawal prior to response assessment	3
Death on study	2

Table 2

Comparison of *nab* -paclitaxel cycles 1* and 2+ pharmacokinetics (n = 12)

	Mean Ratio (Cycle 2/Cycle 1)	95% Confidence Interval	P-value
T ½ (hr)	0.93	0.76 - 1.10	0.28
Cmax (ng/mL)	1.17	0.80 - 1.53	0.57
AUCINF (hr*ng/mL)	1.08	0.84 - 1.32	0.55
Vz_obs (L/m2)	0.96	0.68 - 1.25	0.70
Cl_obs (L/hr/m^2)	1.02	0.81 - 1.23	0.95

* Initial cycle of *nab* -paclitaxel – either C1 or cross-over C2

+ Third overall treatment cycle

Table 3

Comparison of total drug pharmacokinetic parameters for first cycles of *nab* -paclitaxel and sb-paclitaxel (n=14)

	nab -paclitaxel (260 mg/m^2)			sb-paclitaxel (175 mg/m^2)			
	Mean	Range	%CV	Mean	Range	%CV	P-value
T ½ (hr)	20.0	15.5 - 31.2	21.3%	20.9	15.7 - 34.0	21.4%	0.53
Cmax (ng/mL)	19,556.4	10,613.1 - 34,201.4	36.2%	5,128.0	3,136.0 - 8,832.3	32.7%	<0.00001
Cmax_Dose (ng/mL per mg/m2)	75.2	40.8 - 131.5	36.2%	29.3	17.9 - 50.5	32.7%	<0.00001
AUCINF (hr*ng/mL)	20,324.5	15,539.2 - 29,447.9	19.5%	20,821.1	12,973.4 - 30,622.2	25.9%	0.72
AUCINF_Dose (hr*ng/mL per mg/m^2)	78.2	59.8 - 175.0	19.5%	119.0	74.1 - 175.0	25.9%	0.0001
Vz_obs (L/m2)	375.4	269.6 - 571.1	21.9%	270.8	151.0 - 457.2	61.4%	0.003
Cl_obs (L/hr/m2)	13.2	8.8 - 16.7	17.9%	8.9	5.7 - 13.5	25.7%	0.00002

Table 4

Comparison of unbound paclitaxel pharmacokinetic parameters for first cycles of *nab* -paclitaxel and sb-paclitaxel (n = 14)

	nab -pacliataxel (260 mg/m^2)			sb-paclitaxel (175 mg/m^2)			
	Mean	Range	%CV	Mean	Range	%CV	P-value
Cmax (ng/mL)	1,283.7	419.3 - 2,401.9	41.5%	121.8	65.9 - 198.3	32.5%	−<0.000001
Cmax/Dose (ng/mL per mg/m2)	4.9	1.6 - 9.2	41.5%	0.7	0.4 - 1.1	32.5%	<0.000005
AUCINF (hr*ng/mL)	1,158.8	636.6 - 1,759.4	29.1%	409.9	207.3 - 649.3	35.0%	<0.000005
AUCINF_Dose (hr*ng/mL per mg/m^2)	4.5	2.5 - 6.9	27.4%	2.3	1.2 - 3.7	35.0%	0.0002
AUC 0-4.5 (hr*ng/mL)	969.2	355.0 - 1,661.9	32.9%				0.0002
AUC 0-7 (hr*ng/mL)				361.1	193.2 - 589.0	32.3%	

Table 5

Incidence of Treatment-related Adverse Events

	Cycle 1 and Cross-over Cycle 2 ABI-007 n = 15						Cycle 1 and Cross-over Cycle 2 Taxol n = 16						Cycle 3 ABI-007 and Beyond n = 13					
Toxicity	**Grade 1-2**		**Grade 3**		**Grade 4**		**Grade 1-2**		**Grade 3**		**Grade 4**		**Grade 1-2**		**Grade 3**		**Grade 4**	
Body as a whole	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Alopecia	5	33					6	37.5										
Anorexia/weight loss	1	7					2	12.5					1	8				
Arthralgia/Pain	2	13					2	12.5					3	23				
Fatigue							4	25					4	31				
Headache	2	13					1	6					1	8				
Hypersensitivity reaction															1	8		
Blood/Bone marrow changes																		
Anemia	1	7	1	7			1	6					2	15	2	15		
Thrombocytopenia															2	15		
Leukopenia	1	7	1	7	1	7	4	25	2	12.5					2	15	1	8
Neutropenia			2	13	2	13	1	6	3	19			1	8	2	15	3	23
Lymphopenia			3	20	1	7			2	12.5					1	8		
Febrile neutropenia			1	7											1	8		
Digestive system																		
Mucositis	2	13					1	6										
Nausea/vomiting	5	33					2	12.5					5	38				
Diarrhea	1	7					2	12.5	1	6			1	8				
Dyspepsia							2	12.5										
Dysgeusia	2	13					1	6					3	23				
Flatulence/Abdominal distention	1	7	1	7														
Pulmonary/Cardiovascular system																		
Dyspnea	1	7									1	6						
Nervous/Muscular system																		
Dizziness	1	7					2	12.5					2	15				
Neuropathy:sensory	2	13					2	12.5					2	15	1	8		
Muscle weakness							1	6	1	6								
Metabolic/Laboratory abnormalities																		

	Cycle 1 and Cross-over Cycle 2 ABI-007 n = 15			Cycle 1 and Cross-over Cycle 2 Taxol n = 16			Cycle 3 ABI-007 and Beyond n = 13		
Toxicity	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Increased PTT	1 7		2 12.5	1 6		1 8			
Hypermagnesemia							2 15		
Hypocalcemia						1 8	2 15		
Hypophosphatemia				1 6					
Hypokalemia							1 8		