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A phase II/pharmacokinetic trial of high-dose progesterone in combination with paclitaxel

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Abstract *Purpose*: The purpose of this study was to investigate the effect of high-dose progesterone, an inhibitor of P glycoprotein, on the pharmacokinetics and toxicity of paclitaxel. *Patients and methods*: A total of 29 patients with various tumors were treated with single-agent paclitaxel (125 mg/m^2 administered over 3 h once every 3 weeks) until progression of disease, at which point high-dose progesterone (3 g administered i.v. over 24 h) was added to the paclitaxel treatment program in 20 patients (13 women, 7 men). Pharmacokinetic studies of paclitaxel administered alone and with progesterone were performed in eight patients. *Results*: The pharmacokinetic parameters of paclitaxel were highly variable. High-dose progesterone increased the peak plasma levels (3.00 ± 0.94 vs. 4.15 ± 1.63 μM; $P = 0.029$; mean ± SD) and the area under the curve (AUC; 14.3 ± 4.75 vs. 17.3 ± 5.59 $\mu M \times$ h; $P = 0.006$) of paclitaxel. The absolute neutrophil and platelet nadir counts did not differ significantly between the paclitaxel and the combined treatment cycles. Three of the 20 patients documented to have progressive disease on paclitaxel alone had partial responses when high-dose progesterone was added to the paclitaxel regimen. *Conclusion*: Progesterone had a statistically significant impact on the pharmacokinetics of paclitaxel. The addition of high-dose progesterone to paclitaxel is feasible, but the small number of patients prevents conclusions being drawn about the clinical efficacy of combined progesterone and paclitaxel.

Key words Paclitaxel · Progesterone · NONMEM

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Introduction

Resistance to cytotoxic drugs presents a major obstacle to the cure of numerous tumors. Exposure of cells to certain drugs can result in cross-resistance to a variety of other drugs. A well-characterized mechanism of resistance is based on the increased expression of the *MDR1* gene. Its product, P-glycoprotein, is a transmembrane energy-dependent efflux pump which efficiently transports naturally occurring substances such as taxanes, anthracyclines, vinca alkaloids, and epipodophyllotoxins and their derivatives out of the cell (reviewed in [7]).

Paclitaxel, one of the most active cytotoxic agents, is a substrate for P-glycoprotein [28]. Tumor cells can develop resistance to paclitaxel through mutations [17] and differential expression of β-tubulin isoforms [12] and overexpression of P-glycoprotein [9]. Based on in vitro studies, overexpression of *MDR1* seems to be the predominant mechanism of resistance, and P-glycoprotein is amenable to pharmacological intervention.

Inhibitors of P-glycoprotein function such as dexverapamil, cyclosporin A, and tamoxifen have yielded

mixed results in clinical studies, with response rates of 6–59% in various solid tumors thought to be drug resistant when combined with cytotoxic agents for which P-glycoprotein mediates resistance (reviewed in [19]). In addition, the interpretation of these studies has been complicated by pharmacokinetic interactions between the modulators and the cytotoxic drugs [1, 3, 15]. P-glycoprotein is highly expressed in kidney tubules and biliary canaliculi [20], and inhibitors of P-glycoprotein interfere with the excretion of many drugs [23]. For instance, dexverapamil causes a twofold increase in the area under the time–concentration curve of paclitaxel [3], and PSC 833 decreases the clearance of etoposide by 45% [5]. Furthermore, inhibitors of P-glycoprotein have toxic effects of their own, such as arrhythmia and hypotension in dexverapamil [18] and cerebellar ataxia in the cyclosporine analogue PSC 833 [5].

Progesterone inhibits the function of P-glycoprotein in murine [29] and in human cells [11, 26] in vitro and in vivo [6]. Progesterone has a short plasma half-life of 27 min [6]; in order to investigate the ability of progesterone to reverse P-glycoprotein-mediated drug resistance, a formulation of the drug was developed that could be administered intravenously in very high doses [6]. This formulation was used in a trial of high-dose progesterone in combination with doxorubicin, and we demonstrated both the safety of administering very high doses of progesterone intravenously and the fact that, unlike most other P-glycoprotein modulators tested to date, progesterone did not alter the pharmacokinetics of doxorubicin [6]. In the study reported here, we have extended our investigation to paclitaxel and conducted a clinical and pharmacokinetic study in which patients were first treated with paclitaxel alone until their tumors were documented to be clinically resistant and were then treated with the same paclitaxel dose schedule with the addition of high-dose progesterone.

Patients and methods

Patient eligibility

Twenty-nine patients were entered in this study between January 1993 and July 1994. All patients were 18 years old or more, had histologically proven, evaluable (CA-125) or measurable metastatic cancer of a potentially paclitaxel-responsive type, and were unlikely to benefit from conventional treatment modalities. Their World Health Organization (WHO) performance score was 2 or less. The patients' hepatic and renal functions had to be adequate as evidenced by a serum bilirubin level of 2 mg/dl (34 μM/l) or less, serum transaminases less than twofold normal levels, and a serum creatinine level of less than 1.5 mg/dl (133 μM/l). A white blood cell count of more than 3000/μl and a platelet count of more than 100,000/μl were also required. Patients with a history or evidence of coronary heart disease or with any evidence of a cardiac conduction system abnormality were excluded. Medication known to affect the cardiac conduction system or to inhibit P-glycoprotein such as beta blockers, digoxin, other antiarrhythmics (including quinidine), and calcium channel blockers (including verapamil) was discontinued prior to study entry.

Pretreatment and safety evaluations

Before the initiation of chemotherapy, all patients underwent a complete history and physical examination. Laboratory studies included a complete blood count, blood chemistry profile, urinalysis, and an electrocardiogram (ECG). A chest X-ray, bone scan, or a computed tomography (CT) of the liver were obtained if clinically indicated or required for the measurement of a lesion. Complete blood counts were repeated weekly, and X-rays or scans needed for the measurement of lesions were repeated monthly. Laboratory values showing clinically significant changes were repeated until they returned to normal, returned to pretreatment values, or stabilized. Toxicities were graded using the Common Toxicity Scale of the National Cancer Institute.

Study design and treatment plan

The protocol was approved by the institutional review board for clinical investigation. Written informed consent was obtained from all patients before study entry in accordance with federal, state, and local guidelines. Single-agent paclitaxel was infused at a dose of 125 mg/m^2 over 3 h; this low dose was chosen because the patients were extensively pretreated with cytotoxic drugs. All patients received prophylactic treatment with dexamethasone (20 mg p.o. or i.v. at 12 and 6 h prior to paclitaxel), diphenhydramine (50 mg i.v. 30 min prior to paclitaxel), and cimetidine (300 mg i.v. 30 min prior to paclitaxel). The treatment was repeated at 3-week intervals if the white blood cell and platelet counts were above 3000/μl and 100,000/μl, respectively. Otherwise, the treatment was deferred until these values were reached. Patients who developed grade 4 neutropenia were treated on all following cycles with recombinant granulocyte colony-stimulating factor (G-CSF) (filgrastim) at a fixed dose of 5 μg/kg per day starting on day 3 after paclitaxel and continuing until the absolute neutrophil count was more than 1000/μl. The treatment with paclitaxel was repeated until there was evidence of progressive disease as documented by a more than 25% increase in the size of measurable lesions or an increase of the serum concentration of CA-125 in patients with ovarian cancer.

The patients whose tumors were progressive after single-agent paclitaxel were treated with the same dose schedule of paclitaxel, to which progesterone was added at a dose of 3 g administered by continuous i.v. infusion over 24 h. When the two drugs were given together, paclitaxel was infused at a dose of 125 mg/m^2 over 3 h, starting 2 h after the start of the infusion of progesterone. Based on a previous study, steady state plasma progesterone concentrations had already been reached by the time the paclitaxel infusion was started [6]. This moderate dose of paclitaxel was chosen to avoid the excessive bone marrow toxicity that was observed in an earlier study of combined treatment with progesterone and doxorubicin [6]. This treatment was repeated at 3-week intervals as described for single agent paclitaxel for a minimum of two cycles or until progressive disease was documented.

Evaluation of response and hematological toxicity

Clinical response was defined and evaluated according to standard criteria. Measurable lesions were always assessed for response using the same radiologic diagnostic modality or tumor marker (CA-125). A partial response was defined as a more than 50% decrease in the maximum diameter of the measurable lesions or a decrease in CA-125 of more than 50% in patients with ovarian cancer [22].

The leukocyte, absolute number of neutrophils, and platelet counts were performed at weekly intervals throughout the study as detailed above. Multivariate logistic regression analysis was used to model the probability of use of G-CSF with the following covariates: patient identifier, cycle number, and progesterone (coded as 0 or 1).

Drug formulation

Paclitaxel was provided by Bristol-Myers Squibb (Princeton, NJ). The dose of 125 mg/m^2 was diluted in 1 l 5% dextrose for injection USP or 1 l 0.9% sodium chloride for injection USP. Paclitaxel was administered over a 3-h period via an infusion pump through dedicated non-polyvinylchloride (PVC) tubing.

Progesterone was formulated as previously described [6]. It was first dissolved in ethanol at a concentration of 66.67 mg/ml and was stored in 50 ml glass vials. On the day of treatment, the progesterone–ethanol stock solution was diluted 1:11 in Intralipid 20% and administered as a 24-h continuous infusion.

Sampling schedules

Plasma samples were scheduled at the following times: before treatment and at 0.08, 0.33, 0.67, 1, 2, 3, 3.17, 3.25, 3.54, 7, 11, 15, 19, 23, and 27 h following the start of the infusion of paclitaxel. Blood samples were collected from an arm vein opposite the infusion of paclitaxel. The exact timing was recorded for each blood sample. The blood was collected in glass tubes (Vacutainer) containing ethylenediaminetetraacetic acid (EDTA) and was immediately placed on ice. The blood was centrifuged at $600 \times g$ for 10 min to remove formed elements, and the plasma was frozen at −70 °C until analysis.

Paclitaxel assay

Paclitaxel in plasma was measured by a previously described high performance liquid chromatography (HPLC) method [14] with minor modifications. A stock solution of paclitaxel was prepared in dimethylsulfoxide (DMSO) and kept frozen at −70 °C. Standards were prepared by adding appropriate amounts of paclitaxel to pooled normal human plasma. Similarly, the internal standard, β-estradiol-17-acetate, was dissolved in ethanol (150 μg/ml), and 25 μl was added to each specimen. 3 ml double distilled water and 4 ml of ethylacetate were added to each aliquot of patient plasma or standard. Paclitaxel and β-estradiol-17-acetate were extracted into the organic phase by vigorous shaking for 5 min. The organic phase was then evaporated under nitrogen at 37 °C. The residual material was solubilized in 200 μl acetonitrile. HPLC separation was performed on a Waters HPLC system using a waters C18 Radial-Pak cartridge column (10 μm Microbondapack) fitted to a Waters radial compression module. A C18 pre-column was present at all times. Elution was achieved at a flow rate of 2.5 ml/min using a gradient beginning with 50% (v/v) acetonitrile in water and increasing exponentially over 20 min to 100% acetonitrile. The column was then flushed for 7 min with 100% acetonitrile, and initial conditions were reestablished by equilibrating the column for 5 min. Paclitaxel and β-estadiol-17-acetate were detected by online ultraviolet (UV) absorption at 227 nm. The retention time for paclitaxel was 8.5 min and for the internal standard 17 min. Standard curves were constructed daily by plotting the ratio of the peak heights of the internal standard and paclitaxel standard. The curves were linear up to 5.8 μM. Repeated analysis of the same sample yielded a coefficient of variation of 5.7% ($n = 5$).

Pharmacokinetics: structural model

One linear and three different nonlinear three-compartment structural models were fitted to the plasma paclitaxel concentration versus time data. The first nonlinear model with eight parameters was the nonlinear three-compartment model described by Gianni et al. [8]. The second and the third model tested were derived from this model by reducing the number of parameters, i.e., by removing the nonlinear characteristic of the intercompartmental drug exchange and of the elimination, respectively. Population pharmacokinetic models without covariates were estimated with NONMEM using the "first-order conditional estimation" method and "η–ε" interaction [4]. The interindividual error on each of the model parameters was modeled using an exponential variance model:

$$P_i = \theta_{TV} e^{\eta_i}$$

where P_i is the value of the parameter in the individual, θ_{TV} is the typical value of the parameter in the population, and η is a random variable with mean zero and variance ω^2. When ω is small, it is approximately the coefficient of variation of P. A constant coefficient of variation model (constant c.v.) was used for the residual intraindividual error. The final structural model was selected according to the Akaike information criterion [4].

The effect of progesterone on the kinetics of paclitaxel was modeled by treating the use of progesterone as a covariate. Each of the parameters of the final structural model was expressed as:

$$P = X \text{ (reduced model)}$$

or

$$P = (\text{PROG}) \times X + (1 - \text{PROG}) \times Y \text{ (full model)}$$

where P denotes the parameter, PROG is either 1 (if progesterone was used) or 0 (if not) and X, Y are estimated parameters.

Based on the NONMEM objective function [4], for each of the structural model parameters, we have investigated whether the extra parameter (compared to the reduced model $P = X$) improves the fit significantly with the likelihood-ratio test ([4], pp 47–49). For the parameters listed in Table 3, progesterone was a significant covariate.

Based on the typical parameter values and the variance of the final model, bayesian estimates of the individual pharmacokinetic parameters were obtained. The structural model incorporating progesterone effects identified by examination of the bayesian parameters was then reevaluated using the NONMEM objective function, and final empirical bayesian estimates of the individual pharmacokinetic parameters were obtained. From the resulting continuous description of the time course of the concentration, relevant end points (peak paclitaxel concentration, area under the time versus concentration curve) were estimated for each individual [27] according to standard methods [21].

Results

Patients

Twenty-nine patients (18 women, 11 men) were entered in the study. Nine patients (5 women, 4 men) were excluded from the analysis because they withdrew from the study before they could be treated with the combination of progesterone and paclitaxel. The remaining 20 patients were evaluable for toxicity and response to treatment, and their characteristics are summarized in Table 1. All patients had received prior chemotherapy with agents other than paclitaxel. The 20 evaluable patients received a median of two courses of single-agent paclitaxel before being identified as having progressive disease. Following the addition of high-dose progesterone to the regimen, the patients received a median of three additional cycles of combination treatment (range, 2 to 11).

Table 1 Patient characteristics

Characteristics	(*n*)
Patients entered on trial	29
Patients crossed over to progesterone + paclitaxel	20
Assessable patients	20
Males/females	7/13
Median age (range)	64.5 (44–75) years
Tumor type	
Ovarian cancer	6
Head and neck cancer	5
Breast cancer	3
Large cell malignant lymphoma	1
Endometrial cancer	1
Other cancers	4

Hematological Toxicity

In the patients without concomitant G-CSF, the nadir of the absolute neutrophil count on the last cycle of single drug paclitaxel was not significantly different from the nadir count on the first cycle of combined progesterone and paclitaxel treatment (2007 ± 1388 vs. 2643 ± 1869 (SD), $P = 0.10$, paired two-sided t test). Four patients required treatment with G-CSF while receiving single-drug paclitaxel. An additional four patients were treated with G-CSF after the addition of progesterone to their therapy. Multivariate logistical regression analysis was used to model the probability of using G-CSF with patient identifier, cycle number on the present study, and use of progesterone serving as covariates. The only statistically significant covariate was the number of chemotherapy cycles, but not the use of progesterone. In this heavily pretreated patient population, the use of G-CSF demonstrates that paclitaxel caused substantial hematological toxicity even at the low dose used, but there is no evidence that progesterone may have augmented the myelotoxicity of paclitaxel. There were no reports of significant nonhematological toxic effects.

Pharmacokinetics

Blood samples for pharmacokinetic analysis were available from paired courses of paclitaxel alone and paclitaxel in combination with progesterone from eight patients (five women and three men). Four different three-compartment models (one linear and three nonlinear) were considered after a preliminary analysis showed that a linear two-compartment model was significantly biased (data not shown). Based on the Akaike information criterion (Table 2), the model shown in Fig. 1 proved superior to both a simpler all-linear model (linear intercompartmental drug exchange), a model with saturable elimination and linear intercompartmental drug exchange, and a more complex model with saturable elimination as proposed by Gianni [8].

The parameters estimates are summarized in Table 3. In spite of the high variability of the pharmacokinetic variables, we found that for two parameters of the nonlinear intercompartmental drug exchange process ($k31$, V_m) the use of progesterone was a significant covariate ($P = 0.04$), i.e. these parameters were significantly affected by the treatment with progesterone.

From the continuous description of the time–concentration curve, relevant end points were estimated for each individual and summarized in Table 4. Progesterone led to a 38% increased peak concentration of paclitaxel at the end of the 3-h infusion and to a 21% increase in the area under the time–concentration curve (AUC). However, the mean plasma concentration of paclitaxel after 24 h was not significantly altered by progesterone (0.26 ± 0.16 vs. 0.24 ± 0.10 μM/l; mean ± SD). As expected [8, 24], there was no corre-

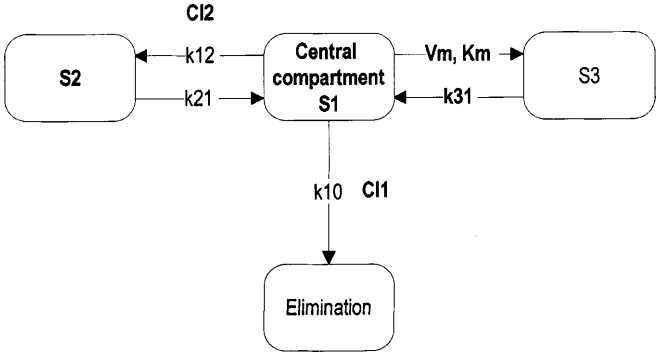

Fig. 1 Proposed model for the pharmacokinetics of paclitaxel. The parameters in *bold print* were estimated using NONMEM

Table 2 Evaluation of three-compartment models

Models	Parameters (*n*)	Minimum value of objective function	Akaike information criterion (AIC)
1 All linear	6	−454.006	AIC model 1 vs. 4 = 55
2 Nonlinear elimination and transfer to compartment 3 [8]	8	−509.463	AIC model 2 vs. 4 = 3.5
3 Nonlinear elimination, linear transfer to compartment 3	7	−465.494	AIC model 3 vs. 4 = 45.5
4 Linear elimination and nonlinear inter-compartmental drug exchange (Fig. 1)	7	−510.985	

Table 3 Pharmacokinetic parameters of paclitaxel as estimated by NONMEM analysis

Parameters[a]	V_1 (l)	V_2 (l)	Cl_2 (l/h)	Cl_1 (l/h)	$k31$ (h^{-1})	V_m (μM/h)	K_m (μM/l)
Paclitaxel	6.63	757	21.5	3.55	1.28	149	7.49
Progesterone + paclitaxel					1.88*	119*	
Coefficient of variation	0.52	0.59	0.44	0.63	0.33	0.0055	0.14

[a] See Fig. 1
* $P = 0.04$

Table 4 Pharmacokinetic parameters of paclitaxel as a single drug and in combination with progesterone (mean ± SD)

Paclitaxel (μM/l)				$AUC_{(0-24\ h)}$ (μmol/l × h)	
End of infusion		24 hours after the start of infusion			
Paclitaxel	Progesterone + paclitaxel	Paclitaxel	Progesterone + paclitaxel	Paclitaxel	Progesterone + paclitaxel
3.00 ± 0.94	4.15 ± 1.63	0.26 ± 0.17	0.24 ± 0.10	14.32 ± 4.75	17.33 ± 5.59
$P = 0.029$[a]		$P = 0.84$		$P = 0.006$	

[a] Paired two-sided t test

lation between either area under the time–plasma concentration curve or peak concentration and hematological toxicity (absolute neutrophil count: $\rho = 0.38$ for peak plasma concentration, $\rho = 0.37$ for $AUC_{(0-24h)}$; platelet count: $\rho = 0.25$ for peak plasma concentration, $\rho = 0.30$ for $AUC_{(0-24\ h)}$; Spearman rank correlation coefficient, all $P > 0.14$). We did not detect a correlation between the time above a certain threshold concentration of paclitaxel and neutropenia [8, 10, 25, 27], but any such correlation was obscured by the use of G-CSF and the high variability of the kinetics of paclitaxel.

Response

Three of the 20 patients (15%) achieved a partial remission with the combination treatment. The partial responses were observed in one patient with large cell lymphoma with predominantly cutaneous manifestations and in two patients with ovarian adenocarcinoma. The partial responses lasted between 2 and 6 months. Two additional patients suffering from head and neck squamous cell cancer and ovarian adenocarcinoma, respectively, experienced a minor decrease in tumor size without achieving a partial response.

Discussion

This study was designed to investigate the effect of adding high-dose intravenous progesterone to single agent paclitaxel. The main effect was that, similar to other modulators of P-glycoprotein function, progesterone produced statistically significant changes in the plasma pharmacokinetics of the paclitaxel. When compared to classical P-glycoprotein modulators [3, 23], these changes were of minor magnitude, and they did not translate into an increased toxicity.

In this study, the pharmacokinetics of paclitaxel were found to be nonlinear. Similar findings were reported in serveral studies [8, 25, 27]. Contrary to the findings of Gianni et al. [8], our data were best described using a nonlinear intercompartmental drug transfer and a linear rather than a nonlinear elimination step. This finding is more in line with the observation of Sonnichsen et al. [24], who described a similar predictive precision for several models that combine linear and nonlinear elimination and intercompartmental drug transfer. The most likely explanation for the apparently linear elimination of paclitaxel is the low dose used in this study. It is conceivable that this dose did not nearly saturate the metabolism of paclitaxel and that higher doses might have revealed nonlinearity for the elimination of paclitaxel. High-dose progesterone had a measurable effect on some pharmacokinetic parameters of paclitaxel. The progesterone-induced 39% increase of the end-of-infusion concentrations of paclitaxel reflects both the lower V_{max} of the transfer from the central to the peripheral compartment and the higher transport rate constant in the opposite direction. The $AUC_{(0-24\ h)}$ of paclitaxel was augmented by an average of 21%. It is obvious that high-dose progesterone has a measurable effect on the pharmacokinetics of paclitaxel. However, in contrast to the findings from studies of other inhibitors of P-glycoprotein, which have consistently demonstrated substantial alterations in the area under the concentration–time curve [15], clearance, or volume of distribution [15] of the cytotoxic drugs including paclitaxel [3], the pharmacokinetic interactions of progesterone and taxol appear to be of minor importance. This is underscored by the lack of differential bone marrow and extramyeloic toxicity in the present study.

Bone marrow stem cells express P-glycoprotein [13], and high-dose progesterone increases the myelotoxicity of doxorubicin in vitro and in vivo, presumably through inhibition of P-glycoprotein [6]. In this study, comparison of the blood counts during the last cycle with paclitaxel and the first cycle of combined progesterone and paclitaxel did not reveal an enhancement of

the bone marrow toxicity. While some patients required G-CSF with single-drug paclitaxel, G-CSF was needed in additional patients when progesterone was added. This was most likely due to cumulative toxicity of paclitaxel in the later cycles of therapy and to the protocol-specified rules for the use of G-CSF. In agreement with most other publications, we found no correlation between either maximum concentration or area under the time–concentration curve of paclitaxel and bone marrow toxicity. A relationship between the myelotoxicity of paclitaxel and the time above a certain threshold serum concentration has been described by various authors [8, 10, 25, 27]. We were unable to find a correlation between the time above various threshold concentrations of paclitaxel and neutropenia. However, any such correlation was obscured in the present study by the use of G-CSF and the long intervals between neutrophil counts. The main metabolite of paclitaxel, 6-hydroxypaclitaxel, was not measured in the present study; therefore, an effect of progesterone on the formation of the relatively nontoxic metabolite cannot be excluded.

In this study, a clinical response after the addition of high-dose progesterone to paclitaxel was observed in only a small subset (15%) of the patients progressing on single-agent paclitaxel alone. Such a modest response rate to the addition of an inhibitor of P glycoprotein function is typical for this type of study [19]. It is possible that inadequate progesterone plasma concentrations accounted for the failure of the remaining tumors to respond; however, we have previously documented that a lower dose of progesterone (2 g) administered over 24 h produces mean plasma concentrations of 2.3 μM [6]. In addition, reversal of P glycoprotein-mediated multidrug resistance in vitro has been demonstrated at concentrations as low as 2 μM [29]. Overexpression of *MDR1* can produce paclitaxel resistance, and progesterone was selected for this study because of its ability to block P glycoprotein function [11, 26]. Thus it is possible that the tumors that responded were resistant based on high levels of P glycoprotein, although the expression of P glycoprotein was not determined in this study. It is likely that tumors utilize several different defense strategies to protect themselves against paclitaxel [9]. In each of the responding cases, the tumor was well documented to be progressing during single agent treatment; however, the conclusion that progesterone at least partially reversed paclitaxel resistance is unproven, as progesterone alone could have had some cytotoxic activity [16].

In summary, combined treatment with high-dose intravenous progesterone and paclitaxel is feasible in patients with advanced tumors. Combined treatment had a therapeutic effect in a small subset of patients with tumors that were clinically resistant to single-agent paclitaxel. This was accomplished with a dose of progesterone that by itself produced no major toxicity. Further trials will be needed to define the clinical efficacy of progesterone and paclitaxel.

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