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ORIGINAL ARTICLE

A phase I, pharmacokinetic and pharmacodynamic dose escalation trial of weekly paclitaxel with interferon-α2b in patients with solid tumors

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Abstract *Purpose*: Paclitaxel and interferon have demonstrated anti-angiogenic activity in vitro and in vivo. The toxicity, pharmacokinetics, and pharmacodynamics of paclitaxel with interferon-α2b (IFN-α2b) were assessed in patients with solid tumors to assess the feasibility of this novel anti-angiogenic regimen. *Methods*: IFN-α2b (1 million units) was administered twice daily by subcutaneous injection. Paclitaxel was given weekly over 1 h starting at 30 mg/m^2 and increased to 50 mg/m^2. Cycles were repeated every 4 weeks. *Results*: Nineteen patients with a variety of solid tumors were enrolled. Dose-limiting toxicity in cycle 1 was observed at 50 mg/m^2. Eleven patients were treated at 40 mg/m^2 with no undue toxicity. Pharmacokinetic parameter comparison studies were completed in 11 patients who received days 1 and 29 paclitaxel. Mean paclitaxel clearance and area under the curve (0–∞) were not statistically different from days 1 to 29. There was a 50% increase in the average C_{max} from days 1 to 29. There was also a 73% decrease of matrix metalloproteinase-9 (MMP-9) levels in these 11 patients from days 1 to 29 ($p < 0.0005$). All three patients with cutaneous angiosarcomas experienced clinically meaningful remissions. In addition, minor responses were observed in one patient with heavily pretreated ovarian cancer and another with adrenocortical carcinoma. *Conclusion*: This trial details the inability to dose escalate to the maximum tolerated dose of weekly paclitaxel when combined with low-dose interferon. However, this low-dose regimen caused a significant decrease in MMP-9 and demonstrated anti-cancer activity in cutaneous angiosarcomas.

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Introduction

Paclitaxel plays an important role in the treatment of many solid tumors. Paclitaxel binds to microtubules and prevents depolymerization and thus causes G2/M arrest and apoptosis [1, 2]. Additionally, it has been demonstrated that lower doses of paclitaxel have anti-angiogenic properties [3–5]. Interferon-α (IFN-α) is an immune modulating agent that is widely used in the treatment of metastatic renal cell carcinoma [6, 7] and as adjuvant therapy for high-risk melanoma [8–11]. Interferon has also been shown to exert anti-angiogenic activity [12]. This apparent anti-angiogenesis effect of IFN-α may partially explain its anti-tumor activity [13–15]. There are preclinical data

which suggest the combination of paclitaxel and IFN-α provide synergistic activity [16]. In one study, the combination was more effective in decreasing angiogenesis and inhibiting the growth of a human ovarian carcinoma cell line than either agent alone. The combination also produced significant inhibition in the expression of proangiogenic molecules' basic fibroblast growth factor (bFGF) and matrix metalloproteinase-9 (MMP-9) [16]. There is also evidence suggesting that interferon may affect metabolism mediated by the cytochrome P450 enzymes [17]. As such, there is the potential for a drug–drug interaction as paclitaxel is metabolized to the inactive metabolite, 6α-hydroxytaxol, by CYP2C8 and CYP3A4 [18]. The safety of weekly and three-weekly paclitaxel with both interferon and 13-*cis*-retinoic acid has been previously demonstrated in phase I trials [19, 20]. A phase II trial of this combination in renal cell carcinoma demonstrated safety with minimal efficacy [21].

A variety of angiogenesis-associated proteins found in the blood have been correlated with a poor prognosis for many tumor types. These proteins are easily assessed in peripheral blood and may serve as surrogate markers that detail the efficacy of a new therapy's ability to decrease cancer-related angiogenesis. For example, VEGF is a potent and specific stimulator of endothelial cell proliferation and angiogenesis [22]. Other molecules are also important in angiogenesis including vascular cell adhesion molecule (VCAM), bFGF [13], MMP-2, and MMP-9, among others [23–26]. It has previously been demonstrated in the preclinical setting that MMP-9 expression (along with other markers of angiogenesis) is down-regulated in the treatment with a variety of tumor types with use of interferon alone [27–29], or in combination with other cytotoxic agents such as gemcitabine [30], docetaxel [31], or paclitaxel [16]. In addition, this anti-angiogenic activity has also translated into anti-tumor activity [16, 29, 30].

This study was designed to assess the safety and to determine the toxicity profile of low-dose interferon-α2b (IFN-α2b) and weekly paclitaxel in combination. In addition, we evaluated the influence of IFN-α2b on the disposition of paclitaxel. Finally, the influence of this combination on the process of angiogenesis was evaluated in an exploratory fashion by ascertaining the expression of proposed markers of angiogenesis, MMP-9, MMP-2, VEGF, bFGF, and VCAM.

Patients and methods

Patient selection

Patients were eligible if they had histological or a cytological diagnosis of cancer with no standard available therapies. Patients had to be ≥ 18 years with an adequate hematologic, renal, and hepatic function, defined as: absolute neutrophil count ≥ 1,500 cells/mm^3, hemoglobin ≥ 9 g/dL (may be post-transfusion), platelet count ≥ 100,000 mm^{-3}, creatinine ≤ 1.5 mg/dL, bilirubin ≤ 1.5 × upper limit of normal, AST (SGOT) ≤ 2 × upper limit of normal. Patients had to have an ECOG performance status ≤ 2 and women of child-bearing potential were required to use appropriate barrier contraception for the duration of the study (negative pregnancy test required at baseline). Patients with prior weekly taxane therapy were excluded. All patients gave written informed consent, and this study was approved by the Indiana University and Purdue University at Indianapolis Institutional Review Board.

Patients were excluded if they were pregnant, nursing, or if they had been treated with chemotherapy within 4 weeks of study drug administration. Other exclusion criteria included active infection requiring parenteral antibiotics at study entry, a documented abnormal central nervous system exam with seizure disorder, major neuropsychiatric problems or uncontrolled depression, or other uncontrolled medical or psychiatric illnesses. Patients taking drugs that significantly altered the CYP 3A enzymes (e.g. cyclosporin, terfenadine, erythromycin, ketoconazole, trolendamycin) were also excluded.

Trial design

This was a phase I, open-label, non-randomized, dose-finding study of weekly paclitaxel in combination with a fixed dose of IFN-α2b. The study was conducted at Indiana University, and all patients were registered through the Clinical Research Office at Indiana University. This trial was approved by the IRB at Indiana University.

Dosing and drug administration

Paclitaxel was administered to patients by an intravenous catheter over 1 h on days 1, 8, 15, and 22 of a 28-day cycle. Hypersensitivity prophylaxis consisted of dexamethasone (20 mg intravenously) 1 h prior to paclitaxel administration along with ranitidine (150 mg orally twice daily on the day of paclitaxel dosing) and benadryl (50 mg orally prior to dosing). The initial starting dosage of paclitaxel was 30 mg/m^2 with a planned escalation scheme to 90 mg/m^2. Dose-limiting toxicity (DLT) was based on events in the first 4 weeks, and was defined as follows: (1) any grade 3 or greater toxicity or (2) any toxicity (due to the drugs) requiring a dose delay of greater than or equal to 1 week of either the paclitaxel or the

interferon. If one of three patients experienced a DLT, then an additional three patients were accrued to that dose level. When two or more patients in a cohort experienced any of the specified toxicities, the previous dose level was deemed to be the maximum tolerated dose (MTD) and expanded to treat ten patients. IFN-α2b was administered subcutaneously (SQ) at a dose of 1 million units (MU) twice daily starting on day 1. Any patients developing grade 3 or greater toxicity felt to be possibly related to IFN-α2b had their interferon held until resolution to grade 1 or less toxicity. Following resolution of the toxicity, IFN-α2b was permitted to be resumed at a dosage of 0.5 MU SQ twice daily. Dose adjustments of paclitaxel for hematological toxicities are detailed in Table 1. Any patient that required dose delays of paclitaxel or IFN-α2b for greater than 2 weeks within a single cycle of therapy or more than two dose reductions of paclitaxel or two dose reductions of IFN-α2b over the course of the study were removed from study.

Treatment plan

All patients were expected to participate in the mandatory pharmacokinetic studies on days 1 and 29 of course #1. All patients not experiencing DLT in the first 28 days (first cycle) or not having overt disease progression were to continue therapy with scheduled disease re-evaluations as follows: (1) clinically every 4 weeks and (2) radiographically every 8 weeks. Patients with stable or responding disease were permitted to remain on paclitaxel/IFN-α2b until objective disease progression or patient intolerance of therapy. Evaluation for tumor response was by two-dimensional criteria when measurable disease was present.

Pharmacokinetics

Serial blood samples for paclitaxel were collected on days 1 and 29. Blood samples were collected prior to the dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 12, and 24 h after paclitaxel intravenous administration.

Paclitaxel concentrations were quantified by a validated atmospheric pressure chemical ionization liquid chromatography–mass spectrometry (APCI LC–MS) method. The standard curve ranged from 5 to 1,000 ng/mL with docetaxel as the internal standard. The coefficient of variation for the low control (75 ng/mL) and the high control (500 ng/mL) was less than 10%. Patient plasma samples were prepared by solid-phase extraction. Fifty microliters of docetaxel solution (1 μg/mL) was added to 1 mL of plasma and the sample was vortexed. Solid-phase extraction cartridges were Strata C18E 1 mL/30 mg sorbent material (Phenomenex, Torrance, CA). The column was washed with 1 mL of acetonitrile followed by 1 mL of water. The sample was loaded and the column was washed with 1 mL of 5% acetonitrile in acetic acid water (0.05% acetic acid). The drug was eluted with 1 mL of 0.05% acetic acid in acetonitrile, dried under a stream of nitrogen, and reconstituted with 100 μL of a 50:50 mix of water and acetonitrile. Twenty microliters of each sample was injected onto the LC–MS system. The column used was a Synergi 4 micron 250 × 2 mm Polar RP column (Phenomenex, Torrance, CA). The mobile phase consisted of 1% formic acid in acetonitrile (solution A) and 1% formic acid in deionized water (solution B) with a flow rate of 0.2 mL/min. The system started at a mix of 50% solution A, 50% solution B, and was held at this ratio for 4 min. From 4 to 5 min, solution A was increased linearly to 100% and held for four additional minutes. Then the ratio returned to the original mix. The retention time for the internal standard, docetaxel, was 10 min and the retention time for paclitaxel was 10.5 min. The ions monitored and used for quantitation for docetaxel were 508.9 and 527.25, and for paclitaxel were 854.2 and 734.3.

Plasma concentration versus time profiles were analyzed using Adapt II software. (ADAPT II user's guide. Biomedical Simulations Resource, University of Southern California, Los Angeles, 1992.) The pharmacokinetic models that were evaluated included: (1) 2-compartment model, (2) 2-compartment model with Michaelis–Menton (MM) elimination, (3) 2-compartment model with MM distribution, and (3) 2-compartment model with MM distribution and MM elimination. The pharmacokinetic model was fit to each individual's paclitaxel concentration time data. The model was fit to the data using maximum likelihood estimation as implemented in ADAPT II software. Each observation was weighted by the inverse of the variance for the model prediction. Visualization of concentration versus, time plots, residuals, and comparison

Table 1 Management of hematological toxicity

Absolute neutrophil count	Paclitaxel dose	Platelet count
≥1,500	No change	>100,000
≥1,000 but < 1,500	Reduce one dose level[a]	≥75,000 but < 100,000
<1,000	Hold until ANC ≥ 1,000 and platelet count > 75,000 then reduce one dose level[a]	<75,000

ANC, absolute neutrophil count

[a] If a dose is reduced, it was maintained for all future treatments

of the Akaike's Information Criterion and estimator criterion values were utilized to determine the best pharmacokinetic model.

Pharmacodynamics

Serologic, plasma, and urinary quantification of the chosen markers of angiogenesis were performed via enzyme-linked immunosorbent assay (ELISA) in the patients who received both courses of therapy. Human VEGF Quantikine ELISA Kit (R&D Systems, Inc., Minneapolis, MN, USA) was used to measure plasma VEGF levels. Human FGF basic Quantikine HS ELISA Kit was utilized for the measurement of urinary and serum bFGF levels (R&D Systems, Inc.). Human sVCAM-1/CD106 Quantikine ELISA Kit (R&D Systems, Inc.) was used to measure serum VCAM-1 levels. Serum MMP-2 and MMP-9 levels were assessed by the Matrix Metalloproteinase 2 ELISA Kit and the Matrix Metalloproteinase 9 ELISA Kit, respectively (EMD Biosciences, Inc., San Diego, CA, USA). All samples were run in duplicate and a standard curve was run for each 96-well plate.

Statistical analysis

Pharmacokinetic parameters were compared for samples taken at days 1 and 29 of treatment. This comparison was performed with an unpaired *t* test with Welch correction using GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, San Diego, CA, USA) with a two-sided *p* value. For patients who completed one full cycle of therapy, the blood levels of each angiogenic marker from baseline were compared with their corresponding level at day 29 using the same statistical analysis.

Results

Patient characteristics

Nineteen patients were enrolled in this study and 18 patients received treatment. The patient that did not receive therapy died of sudden cardiopulmonary death prior to therapy. Paclitaxel pharmacokinetic parameters were determined in 18 patients on day 1, and 11 patients on day 29. Thirteen patients were evaluable for response. The patient characteristics for the 18 patients who received treatment are detailed in Table 2.

Drug delivery, dose escalation, and toxicity

The MTD was 40 mg/m^2 of paclitaxel weekly with 1 MU twice per day of IFN-α2b. The first three patients enrolled were treated at 30 mg/m^2 of paclitaxel and there were no DLTs experienced. Subsequent patients were treated in the 40 mg/m^2 cohort. None of the first three patients enrolled experienced a DLT. Three patients were then enrolled at 50 mg/m^2 of paclitaxel. The first two patients were not evaluable (one from sudden death prior to therapy and one from symptomatic progression in first week of therapy). These non-evaluable patients were replaced, and DLT was experienced in two of the first three evaluable patients. One patient developed prolonged grade 3 neutropenia which prevented repeat dosing and this patient was deemed a DLT. The second patient's DLT included both grade 3 anemia and grade 3 fatigue. Thus, the prior dose level (40 mg/m^2) was expanded to include ten evaluable patients (11 were ultimately enrolled as one progressed during cycle 1). Two of the ten evaluable patients experienced DLT (grade 3 neutropenia requiring dose reductions in cycle 1). Thus the MTD was defined as 40 mg/m^2 of paclitaxel weekly with 1 MU twice per day of IFN-α2b.

In general, the patients who experienced DLT and required dose reduction per protocol in cycle 1 had received substantial amounts of prior therapy. In the 40 mg/m^2 paclitaxel cohort, two patients experienced DLT (as stated above). The first patient had ovarian cancer and experienced DLT secondary to grade 3 neutropenia. This patient had previously received radiation therapy to the pelvis as well as the combination of carboplatin/paclitaxel on two separate occasions and then received topotecan. The second patient had fallopian tube cancer and experienced grade 3 neutropenia. This patient had previously received pelvic radiation and the combination of carboplatin/paclitaxel. She

Table 2 Patient characteristics ($N = 18$)

Median age (years)	61
Range	30–80
Median weight (kg)	66.0
Range	47.6–164.6
Median body surface area (m^2)	1.75
Range	1.49–3.02
Male/female	4/14
Race	
Caucasian	16
African American	2
ECOG performance status	
0/1/2	9/8/1
Tumor types	
Sarcoma	5 (3 cutaneous angiosarcomas)
Ovarian	3
Non-small cell lung	2
Colorectal	2
Other	6

later received pegylated liposomal doxorubicin. In the 50 mg/m^2 cohort, two patients also experienced DLTs. The first had esophageal cancer and experienced grade 3 anemia and grade 3 fatigue. This patient had previously been treated with carboplatin/paclitaxel, then 5-fluorouracil, and then the combination of 5-fluorouracil/methotrexate. The second patient in this cohort had cervical cancer and had a DLT of grade 3 neutropenia. This patient had previously received pelvic and left femoral radiation therapy as well as four cycles of cisplatin/etoposide. Of note, this patient later tolerated 80 mg/m^2 of weekly single-agent paclitaxel as subsequent therapy after discontinuation of this study.

As stated above, both hematological and non-hematological toxicities were minimal at the first two dose levels. Toxicities are summarized in Tables 3 and 4. Toxicities that were reported as not being drug-related have been carefully evaluated and have not been included if they were clearly not related to the experimental therapy.

Pharmacokinetic analysis

Eighteen patients had pharmacokinetic studies performed on day 1 of therapy. Eleven patients were able to continue therapy and had pharmacokinetic studies performed on day 29 of therapy. A two-compartment linear model best described the paclitaxel concentration time data. Pharmacokinetic parameters for the 18 patients who received the first dose of paclitaxel (day 1) are summarized in Table 5. Paclitaxel clearance was highly variable, ranging from 15.9 to 76.0 L/h. Eleven of the 18 total patients were able to receive day 1 of the second cycle (day 29) of paclitaxel with IFN-α2b therapy. All 11 patients received the same dosage of paclitaxel that they received on day 1. The results for these 11 patients are summarized in Table 6. The mean paclitaxel clearance from day 1 (mean 42.6 L/h) was not statistically different from day 29 (mean 47.9 L/h). Paclitaxel clearance decreased greater than 50% in three patients. In six of 11 patients (55%), paclitaxel clearance was within 25% of the value from the day 1 clearance. The area under the curve (AUC) for the day 1 of paclitaxel (mean 1,988 ng h/mL) was not different from the AUC for the day 29 value (mean was 2,389 ng h/mL). The average maximum concentration (C_{max}) increased by 50% from mean of 372.0 ng/mL on day 1 to a mean of 559.0 ng/mL on day 29. Despite this being numerically different, it did not reach statistical significance ($p = 0.134$).

Pharmacodynamic analysis

The pharmacodynamic assessment included the 11 patients who received therapy on day 1 of the first cycle (day 1) and day 1 of the second cycle (i.e. day

Table 3 Non-hematologic toxicity (all cycle-related events)

Grade toxicity	Paclitaxel dose											
	30 mg/m^2 ($n = 3$)				40 mg/m^2 ($n = 10$)				50 mg/m^2 ($n = 4$)			
	1	2	3	4	1	2	3	4	1	2	3	4
Fatigue	1	1	0	0	3	2	0	0	1	1	1	1
Nausea	2	0	0	0	1	1	0	0	1	0	0	0
Proteinuria	0	0	0	0	0	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	0	0	0	0	0	0
Rash	0	0	0	0	0	0	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhea	1	0	0	0	1	0	0	0	1	0	0	0
Vomiting	0	0	0	0	0	1	1	0	0	0	0	0

Interferon dose: 1 MU subcutaneously twice daily (for all)

Table 4 Hematologic toxicity (all cycle-related events)

Grade toxicity	Paclitaxel dose											
	30 mg/m^2 ($n = 3$)				40 mg/m^2 ($n = 10$)				50 mg/m^2 ($n = 4$)			
	1	2	3	4	1	2	3	4	1	2	3	4
Neutropenia	1	1	0	0	0	1	2	0	1	0	1	0
Thrombocytopenia	0	0	0	0	1	0	0	0	0	0	0	0
Anemia	0	1	0	0	2	0	0	0	0	1	1	0

Interferon dose: 1 MU subcutaneous twice daily (for all)

29). Samples were collected prior to therapy. The pharmacodynamic parameters studied included plasma VEGF, urine and serum bFGF, serum MMP-2, serum MMP-9, and serum VCAM-1 levels. The ELISA assay revealed that there were no decreases in VEGF, bFGF, VCAM-1, and MMP-2. There was, however, a 73% decrease in the MMP-9 levels. The MMP-9 value decreased from an average of 429 ng/mL (SE ± 64) to 111 ng/mL (SE ± 17) in absolute terms and was statistically significant ($p < 0.0005$) (Fig. 1). Eight of the 11 had a > 50% decrease in MMP-9 level from baseline. Of note, there was no correlation between decrease in MMP-9 and dose level.

Response data

There were three clinically meaningful remissions of cutaneous angiosarcomas. The first patient had involvement of the face. The patient previously had excision with recurrence followed by radical excision and nodal neck dissection and parotidectomy with evidence of nodal involvement. She also had adjuvant radiation therapy at that time. She later had progressive disease in the peri-orbital region with marked narrowing of her orbital diameter. This patient experienced a nearly complete clinical response after five cycles of therapy with paclitaxel and IFN-α2b with an improved ability to open the involved eye. The response lasted 6 months. The second patient had a radiation-induced angiosarcoma of the chest wall after therapy for a stage I breast cancer. The patient had several excisions of local recurrences. The last recurrence required excision with a skin graft because of bleeding from the tumor. The patient again experienced local recurrence and was enrolled in this trial. This patient experienced a partial response by two-dimensional measurement which lasted 7 months. The third patient had a metastatic angiosarcoma to the second palmar interdigit webspace. This patient also had a radiation-induced angiosarcoma on the chest wall after therapy for a breast cancer. She had re-excision after local recurrence and later developed a metastatic lesion on the hand (the site of evaluable disease on this study). On trial, this patient had an almost a complete clinical response which last more than 2 months and then she was lost follow-up. Minor responses were also observed in one patient with heavily pretreated ovarian cancer and another with adrenocortical carcinoma.

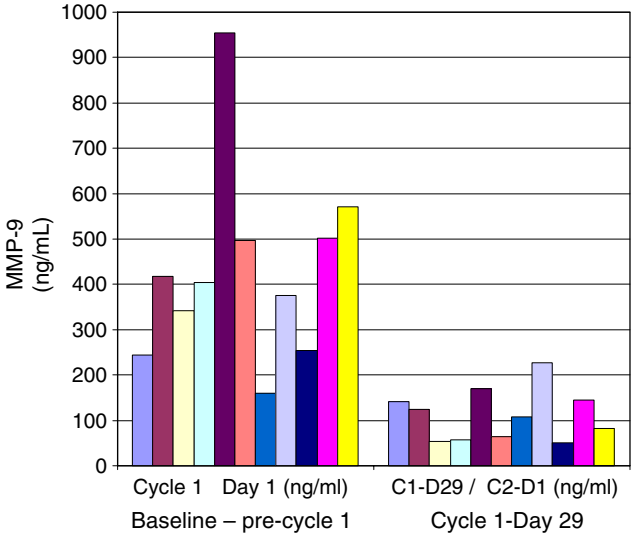

Fig. 1 Each of the 11 differently colored bars represents an MMP-9 level from that patient during day 1 of cycle 1 versus day 29. MMP-9 levels decreased from an average of 429 to 111 ng/mL ($p < 0.0005$)

Table 5 Pharmacokinetic parameters for paclitaxel on day 1 ($n = 18$)

	Mean (SD)	Range
$AUC_{0-\infty}$ (ng h/mL)	1668.8 (687.6)	818.1–3564.6
Elimination rate constant, k_e (h^{-1})	0.65 (0.46)	0.21–1.93
Clearance, Cl (L/h)	38.7 (15.6)	15.9–76.0
Maximum concentration, C_{max} (ng/mL)	438.7 (184.4)	156.0–946.0
Volume of distribution, V_d (L)	82.6 (46.2)	13.3–200.0

Table 6 Pharmacokinetic parameter for paclitaxel on day 1 versus day 29 ($n = 11$)

	Mean (SD)		p Value (two-sided)
	Day 1	Day 29	
$AUC_{0-\infty}$ (ng h/mL)	1988 (947)	2389 (1793)	0.522
k_e (h^{-1})	0.716 (0.475)	0.658 (0.268)	0.729
Cl (L/h)	42.6 (19.1)	47.9 (36.3)	0.679
C_{max} (ng/ml)	372 (129)	559 (364)	0.134
V_d (L)	71.5 (24.9)	79.3 (74.5)	0.745

Discussion

There was substantial variability in paclitaxel pharmacokinetic parameters when administered with IFN-α2b in this patient population. The coefficient of variation for paclitaxel clearance increased from 44% on day 1 to 75.7% on day 29 after twice daily dosing of IFN-α2b.

Although no clear pharmacokinetic interaction was seen between IFN-α2b and paclitaxel, there was an increase in the mean C_{max}. Of note, three patients had a greater than 50% reduction in paclitaxel clearance on day 29. However, our data were potentially biased by not reanalyzing the seven patients who could not receive all five doses of paclitaxel because of toxicity or early progression. Specifically, in this analysis, only 11 patients' data were used to compare the pharmacokinetic parameters between days 1 and 29. Thus it is possible that the patients removed for excess toxicity had a more substantial increase in their drug exposure. It is also of note, in a Phase II study conducted by the CALGB in advanced lung cancer, that the pharmacokinetic parameters (AUC, Cl, nor duration of time that plasma paclitaxel concentration exceeded 0.05 μM) of weekly paclitaxel were not significantly different in the first, third, or fifth week [32].

Nonetheless, the inability to dose escalate paclitaxel to its single-agent MTD provides evidence of a drug–drug interaction between paclitaxel and IFN-α2b. Although there were generally minimal hematologic toxicities at 30 and 40 mg/m^2, the toxicities substantially increased with further attempts to escalate the paclitaxel dose which prevented repeat dosing in cycle 1. Furthermore, the fact that a patient who experienced DLT at 50 mg/m^2 (when combined with IFN-α2b) was later able to be treated with single-agent weekly paclitaxel at 80 mg/m^2 further supports the possibility of a drug–drug interaction. However, the inability to dose escalate may also have been due to a pharmacodynamic interaction. Specifically, both single-agent IFN-α2b and weekly paclitaxel are only mildly myelosuppressive, but myelosuppression was unexpectedly worse with the combination. Other potential etiologies for this degree of myelosuppression include: (1) heavily pretreated population (both prior cytotoxic therapies and pelvic radiation) being more prone to myelosuppression from IFN-α2b and (2) potential pharmacodynamic interaction with additive myelosuppression of IFN-α2b combined with paclitaxel with no alteration of drug exposure. Our review of the literature reveals a low rate of grade 3/4 myelosuppression for single-agent IFN-α2b [33].

In an exploratory analysis, we also analyzed the pharmacodynamic effect of this combination on multiple serologic and urinary markers of angiogenesis. The novel finding from this study was that combined low doses of both drugs were able to suppress MMP-9 but none of the other angiogenic factors tested. It is not clear why this was the only parameter which was suppressed and what implications this might have from an efficacy standpoint.

This low-dose regimen has anti-cancer activity. In particular, there was activity in patients with cutaneous angiosarcomas. Indeed, this may be secondary to the highly vascular nature of the disease and the successful inhibition of angiogenesis by this combination. It is important, however, to recognize that higher doses of single-agent paclitaxel have been shown to have activity in this disease sub-type. In a retrospective analysis, specifically evaluating the use of single-agent paclitaxel in angiosarcomas of the scalp/face, eight of the nine patients had a major response and one of the nine had a minor response [34]. Three schedules of paclitaxel were used: (1) 250 mg/m^2 over 24 h every 3 weeks; (2) 175 mg/m^2 over 3 h every 3 weeks; and (3) 90 mg/m^2 over 1 h every week. Although taxane sensitivity alone may explain the responses seen in our trial, the dose intensity of paclitaxel used in our trial was significantly less, implying a contribution from the combination. It is not clear, however, that what proportional benefit is gained by the combination of interferon with paclitaxel as compared to a single-agent taxane regimen. Further evaluation of this low-dose combination for cutaneous angiosarcoma is warranted.

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