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ORIGINAL ARTICLE

A phase 2 study of weekly albumin-bound paclitaxel (Abraxane®) given as a two-hour infusion

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Abstract
Purpose Paclitaxel is an effective therapy for patients with solid tumors. While the albumin-bound formulation eliminates the hypersensitivity reaction caused by the Cremaphor solvent, significant peripheral neuropathy persists when given over the standard 30-min infusion time. We sought to determine if the incidence and severity of peripheral neuropathy could be reduced when the infusion time is lengthened to 2-h.
Methods This was an open-label, single-arm, phase 2 study of albumin-bound paclitaxel given over 2 h. Twenty-five patients with advanced non-small-cell lung cancer were enrolled to determine whether the longer infusion reduced the severity of neuropathy compared to data from an earlier cohort of 40 similar patients treated over 30 min Patients received 125 mg/m^2 of albumin-bound paclitaxel IV over 2 h without premedication on days 1, 8, and 15 of a 28-day cycle. Radiologic assessment was performed every 8 weeks.
Results There was a significant 0.45 grade decrease in average peripheral neuropathy experienced by patients in the 2-h group versus the 30-min group (90% CI, 0.03-0.87). There was, in addition, a significant decrease in grade $\geq$2 peripheral neuropathy in patients treated over 2 h versus 30 min (28% vs. 55%, 2-sided $P = 0.04$). A decrease in grade $\geq$2 neutropenia (20% vs. 48%, 2-sided $P = 0.07$) was also observed. The median survival, 11 months, was the same for both groups.
Conclusion Increasing the infusion time of albumin-bound paclitaxel from 30 min to 2 h resulted in a significant reduction in both average and grade $\geq$2 peripheral neuropathy without affecting survival.

Keywords Albumin-bound paclitaxel · Abraxane · Neuropathy · Non-small-cell lung cancer

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Introduction

Paclitaxel is used alone and in combination with other chemotherapeutics in the treatment of many solid tumors [12, 14]. The treatment-limiting adverse events associated with paclitaxel are neuropathy, neutropenia, and hypersensitivity reactions. While the predominant peripheral neuropathy associated with paclitaxel is sensory, a distinct motor neuropathy is also recognized [3]. In addition to the inherent neurotoxicity of the active agent [15], the lipid-based Cremophor solvent required to dissolve the compound appears to contribute independently to the development of neuropathy [9].

To reduce both the neurotoxicity and the severe hypersensitivity reactions caused by Cremophor or Tween 80 (the solvent used with docetaxel), an albumin-bound solvent-free version of paclitaxel was developed [6]. This

formulation, albumin-bound paclitaxel (Abraxane®), eliminates solvent-associated toxicity. Moreover, because albumin-bound paclitaxel causes no severe hypersensitivity reactions, premedication with steroids or antihistamines is not required.

Albumin-bound paclitaxel is generally used in patients with metastatic breast cancer at 260 mg/m^2 over 30 min every 3 weeks. When compared to paclitaxel in a randomized phase III trial in patients with metastatic breast cancer, albumin-bound paclitaxel improved time to progression, was associated with a decreased incidence of neutropenia, but appeared to cause an increased incidence of severe neuropathy [4]. Albumin-bound paclitaxel has also been studied in patients with NSCLC. When administered at 260 mg/m^2 over 30 min once every 3 weeks, grade 2 peripheral neuropathy developed in 12% of patients, grade 3 peripheral neuropathy in 5% of patients, grade 4 neutropenia in none [5].

In our phase I/II study of weekly albumin-bound paclitaxel in patients with NSCLC, the maximum tolerated dose (MTD) was determined to be 125 mg/m^2 over 30 min on days 1, 8, and 15 of a 28-day cycle [13]. In the phase II portion of the study, there was a 30% objective response rate. However, 23% of patients developed grade 3 peripheral neuropathy (combined sensory and motor), which emerged as a treatment limiting toxicity. To date, all published studies with albumin-bound paclitaxel have used a 30-min infusion [1, 4, 6, 7, 10].

Prior clinical trials evaluating the relative contributions of dose and schedule to the development of paclitaxel-induced neuropathy produced mixed results. Comparison of a 24-h infusion (24 h) to a 3-h infusion (3 h) was addressed in three studies. In the NSABP B-26 trial, paclitaxel was given at 250 mg/m^2 once every 3 weeks to 563 patients; neuropathy $\geq$ grade 3 arose in 13% in 24 h compared to 22% in 3 h ($P = 0.005$) [17]. Eisenhauer et al. evaluated 135 or 175 mg/m^2 once every 3 weeks in 391 patients; neuropathy at any grade arose in 40% in 24 h compared to 49% in 3 h ($P = 0.84$) while grade 3 neuropathy arose in 0.6% in 24 h compared to 0.7% in 3 h (P = NS) [2]. Peretz et al. described paclitaxel given at 175 mg/m^2 or larger doses (per study escalation) once every 3 weeks to 521 patients; neuropathy occurred in 65% in 24 h compared to 78% in 3 h ($P = 0.001$), however, the 3-h group had more dose escalations and thus received more paclitaxel [11]. Subsequently, two studies compared the 3-h infusion to an even shorter 1-h infusion. Mielke et al. treated 92 patients with paclitaxel at 100 mg/m^2 weekly for 12 weeks [9]. They used a clinical scoring system (range, 0-12) to evaluate peripheral neuropathy and describe the probability of developing a score >3 at 12 weeks as 47% in 3 h compared to 68% in 1 h ($P = 0.66$). No patients treated with 3 h had a score >6 whereas 3 patients treated with 1 h did. Lastly, CALGB 9840 evaluated 572 patients treated with two different regimens: paclitaxel at 175 mg/m^2 over 3 h every 3 weeks or 80 mg/m^2 over 1 h weekly [16]. Grade 2 neuropathy was identical at 21% in the 3-h and 1-h groups. Grade 3 neuropathy developed in 12% in 3 h but in 24% in 1 h ($P = 0.0003$). Grade 4 neuropathy occurred in no patient in 3 h and 1 patient in 1 h. Because the two groups differed in dose, in infusion time, and in schedule, it is difficult to know which variable was responsible for the differences in the adverse events reported in this study.

While some of these data demonstrate statistically significant differences and others trends, all five studies comparing longer infusions to shorter infusions agreed that shorter infusions of paclitaxel are associated with increased severity of neuropathy.

Based on these observations and studies suggesting that peripheral neuropathy may develop from peak plasma levels during infusion [9], we hypothesized that lengthening the infusion time would reduce the incidence and/or severity of peripheral neuropathy. We therefore, conducted a single-arm, phase 2 study of weekly albumin-bound paclitaxel at 125 mg/m^2 over 2 h, in order to assess the incidence and severity of peripheral neuropathy and anti-tumor efficacy when compared to a cohort treated over 30 min This comparison group of 40 patients was treated on a protocol identical to that of the current study, with the length of albumin-bound paclitaxel infusion the only difference [13].

Patients and methods

Study design

The primary study endpoint was to determine whether a 2-h infusion would reduce the severity of neuropathy compared to a 30-min infusion. The study was designed so that treatment of 25 patients would allow us to detect an average one half-grade difference in peripheral neuropathy with 80% power at a 2-sided $P = 0.10$ significance level, when compared with patients in our earlier study treated with albumin-bound paclitaxel over 30 min, as described above [13].

In addition to the analysis planned by the protocol, we compared the two treatment groups using an adapted Mantel–Haenszel method [20]. This is used for 2-by-c tables when the response variable is ordinal, and tests for the tendency for patients in one treatment group to have higher scores than patients in another treatment group. Further, we compared the two treatment groups with

respect to the rate of clinically significant toxicities (grade $\geq$ 2) using Fisher's exact test.

Patients

We expanded the phase 2 portion of our study to enroll an additional 25 patients who received albumin-bound paclitaxel over 2 h. Patients with stage IV or recurrent NSCLC who had not received prior chemotherapy for advanced NSCLC were eligible. Patients may have received chemotherapy in the adjuvant or neoadjuvant setting. Patients with peripheral neuropathy grade more than 1 were excluded. All patients who had received any drug were evaluable for efficacy and toxicity. All patients underwent a medical history, physical examination, complete blood count with differential (CBC), and chemistry panel. The CBC and chemistry panel were repeated before each cycle, and the CBC was performed before each dose. All patients had a CT scan of the chest every 2-cycles.

The protocol and informed consent documents were approved by the Institutional Review Board at Memorial Sloan–Kettering Cancer Center. All patients signed informed consent prior to enrollment onto this trial.

Data from patients in the comparison 30-min infusion group, treated on an otherwise identical protocol, were obtained from our prior study of albumin-bound paclitaxel as reported previously [13].

Drug and treatment

Albumin-bound paclitaxel (Abraxane®, Abraxis BioScience Inc., Los Angeles, CA) was supplied in 50-ml vials containing 100 mg of paclitaxel and human albumin albumin-bound paclitaxel was reconstituted with normal saline and diluted in a PVC infusion bag. The drug was administered over 2 h intravenously on days 1, 8, and 15 of a 28-day cycle. At the beginning of each cycle, laboratory values were checked with a requirement to meet baseline eligibility criteria. Prior to drug administration on days 8 and 15, an ANC $\geq 1 \times 10^9$ cells/L was required. Patients continued on treatment until progressive disease or treatment intolerance.

Dose reductions were allowed by 25 mg/m^2 to a minimum dose of 100 mg/m^2 for grade 3 or 4 thrombocytopenia or any grade 3 or 4 non-hematologic toxicity. The use of filgrastim or peg-filgrastim was encouraged in patients developing fever during drug-induced neutropenia, and as prophylaxis in patients who had developed fever and neutropenia in previous cycles or neutropenia causing a delay in previous treatments.

Toxicity, including neuropathy, was evaluated at the start of each treatment cycle and graded according to NIH CTCAE v3.0.

Results

Patient characteristics

Between March 2006 and September 2007, 25 patients were treated with 125 mg/m^2 of albumin-bound paclitaxel over 2 h on days 1, 8, and 15 of a 28-day cycle. Table 1 lists the patient characteristics of this group and the earlier 30-min infusion cohort. There were no significant differences in median age, gender, performance status, smoking history, race, tumor histology, prior chemotherapy, or baseline neuropathy.

Drug delivery

The median number of administered doses was 11 (range, 2–30) for the 2-h infusion and 11 (range, 1–40) for the 30-min infusion (Table 2). Six patients in each group required dose reduction for the following toxicities: hematologic (2 in 2 h, 1 in 30 min), grade 3 or 4 neuropathy (2 in 2 h, 3 in 30 min) and other grade 3 or 4 toxicity (2 in 2 h, 2 in 30 min). The outlier patient who received 40 treatments in the 30-min infusion group required no dose modifications, having experienced only grade 1 sensory neuropathy and grade 1 anemia. The median cumulative dose was 1375 mg/m^2 for the 2-h infusion and 1225 mg/m^2 for the 30-min infusion. No hypersensitivity reactions were reported with either schedule. No premedications were administered.

Toxicity

Therapy was stopped in 5 patients (20%) for treatment-related neuropathy in the 2-h group as compared to 14 patients (36%) in the 30-min group. The average neuropathy grade (the primary endpoint of the study) was 1.2 for the 2-h infusion and 1.65 for the 30-min infusion. This 0.45 grade difference was not significantly different from the pre-specified 0.5 grade endpoint, and reflected a statistically significant decrease in the average grade neuropathy experienced by patients (90% CI; 0.03-0.85, $P = 0.08$).

An evaluation of distinct toxicity grades also revealed a significantly higher proportion of clinically relevant toxicities (grade $\geq$ 2) in the 30-min group as compared to the 2-h group (Table 3). In the 2-h group, grade 2 neuropathy occurred in 12% of patients (3/25) and grade 3 neuropathy in 16% of patients (4/25) (combined rate, 28%). In contrast, in the 30-min group, grade 2 neuropathy occurred in 33% of patients (13/40) and grade 3 neuropathy in 23% of patients (9/40) (combined rate, 55%). One patient in the 30-min group developed grade 3 motor neuropathy, and one patient in the 2-h group developed grade 1 motor neuropathy. Both the ordinal test across the

Table 1 Baseline characteristics of patients treated with 125 mg/m^2 albumin-bound paclitaxel

Characteristic	2-hour infusion ($N = 25$)		30-minute infusion ($N = 40$)	
	No.	%	No.	%
Age, years				
Median	66		70	
Range	49–83		43–84	
Sex				
Female	14	56	21	53
Male	11	44	19	48
Karnofsky performance status				
90–100%	5	20	10	25
70–80%	20	80	30	75
Smoking history, pack-years				
Never	0	0	2	5
0–15	5	20	7	18
>15	20	80	31	78
Histology				
Squamous	7	28	8	20
Adenocarcinoma	18	72	32	80
Baseline neuropathy				
Grade 0	20	80	30	75
Grade 1	5	20	10	25

Table 2 Albumin-bound paclitaxel administration and responses

Doses and responses	2-hour infusion ($N = 25$)		30-minute infusion ($N = 40$)	
	No.	%	No.	%
Number cycles given				
Median	4		4	
Minimum, maximum	1, 10		1, 14	
Number doses given				
Median	11		11	
Minimum, maximum	2, 30		1, 40	
Dose reductions	6	24	6	15
Hematological toxicity	2	8	1	3
Grade 3 neuropathy	2	8	3	8
Number evaluable for response	25	100	40	100
Responses				
Complete	0	0	1	3
Partial	4	16	11	28
Median PFS, months	5.3		5.3	
95% CI	3.4–7.3		2.3–8.9	
Median overall survival, months	11		11	

PFS progression-free survival; *CI* confidence interval

four toxicity scores and the exact test comparing the difference in clinically significant toxicities (grade ≥ 2) between the two treatment groups were statistically significant (two-sided $P = 0.04$). There was a similar, but not significant, trend towards a decrease in grade ≥ 3 neuropathy favoring the 2-h infusion (16% vs. 23%, $P = 0.75$).

Finally, we noted a trend towards a reduction in neutropenia. Neutropenia grade 2 or greater occurred in 6 (24%) patients in the 2-h group in contrast to 19 patients (48%) in the 30-min group ($P = 0.071$). Grade ≥ 3 neutropenia showed a similar, though not significant, trend favoring the 2-h infusion (12% vs. 20%, $P = 0.51$).

Table 3 Toxicities of albumin-bound paclitaxel by infusion duration and grade

Toxicity	2-hour infusion ($N = 25$)					30-minute infusion ($N = 40$)				
	Number (%)					Number (%)				
	0	1	2	3	4	0	1	2	3	4
Neuropathy	6 (24)	12 (48)	3 (12)	4 (16)	–	5 (13)	13 (33)	13 (33)	9 (23)	–
Neutropenia	16 (64)	3 (12)	3 (12)	1 (4)	2 (8)	16 (40)	5 (13)	11 (28)	6 (15)	2 (5)
Leukopenia	11 (44)	6 (24)	5 (20)	2 (8)	1 (4)	15 (38)	9 (23)	8 (20)	8 (20)	–
Fatigue	7 (28)	2 (8)	8 (32)	8 (32)	–	4 (10)	14 (35)	13 (33)	9 (23)	–
Diarrhea	12 (48)	9 (36)	3 (12)	1 (4)	–	20 (50)	11 (28)	4 (10)	5 (13)	–
Myalgia	17 (68)	4 (16)	3 (12)	1 (4)	–	28 (70)	8 (20)	4 (10)	–	–
Alopecia	8 (32)	5 (20)	12 (48)	–	–	8 (20)	4 (10)	28 (70)	–	–
Constipation	15 (60)	6 (24)	4 (16)	–	–	16 (40)	16 (40)	8 (20)	–	–
Anemia	3 (12)	18 (72)	4 (16)	–	–	3 (8)	25 (63)	9 (23)	3 (8)	–
Edema	17 (68)	5 (20)	3 (12)	–	–	26 (65)	8 (20)	6 (15)	–	–
Nausea	11 (44)	13 (52)	1 (4)	–	–	20 (50)	16 (40)	3 (8)	1 (3)	–
Rash	15 (60)	9 (36)	1 (4)	–	–	23 (58)	15 (38)	2 (5)	–	–
Anorexia	19 (76)	5 (20)	1 (4)	–	–	29 (73)	7 (18)	4 (10)	–	–
Hypersensitivity	25 (100)	–	–	–	–	40 (100)	–	–	–	–

Highest drug-related adverse events reported at any time on study

Filgrastim or peg-filgrastim was administered to 2 patients in the 30-min group and to 3 patients in the 2-h group. In all cases, these agents were administered subsequent to the development of neutropenia. There were no other significant differences between adverse event groups.

Response/survival

Of the 25 patients in the 2-h cohort, 4 (16%) experienced a partial response (PR) and none a complete response (CR) (95% CI: 5-36%) (Table 2). This was not significantly different from the 30% response rate (PR + CR) seen in the 30-min cohort (95% CI: 16-44%).

Concordant with these results, the median progression-free survival (PFS) was 5.3 months for both groups. The median survival was 11 months for the 2-h infusion and 11 months for the 30-min infusion (Table 2). The Kaplan–Meier survival curves for the two groups overlapped (Fig. 1).

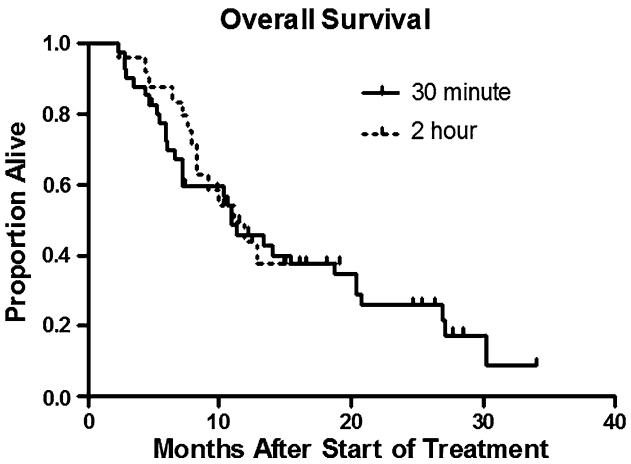

Fig. 1 Kaplan–Meier survival curves of patients treated with weekly albumin-bound paclitaxel (Abraxane®) over 2 h versus 30 min

Discussion

Administering paclitaxel over shorter periods of time (1 h versus 3 h, 3 h versus 24 h) has generally led to increased neuropathy (see introduction as well as review by Lee and Swain) [8]. Studies of albumin-bound paclitaxel have thus far evaluated only 30-minute infusions, however.

In an attempt to reduce the severity of peripheral neuropathy, we studied a longer infusion schedule. Our findings demonstrate that by prolonging the infusion time from 30 min to 2 h, study participants experienced a statistically significant reduction in the degree and incidence of peripheral neuropathy.

The trial was designed to use, as a primary endpoint, the difference in average grade of neuropathy between the two groups. The 2-h infusion was associated with a significant reduction in average neuropathy of 0.45 grade points when compared to the 30-min infusion, meeting the trial's primary objective. We also noted a 51% decrease (from 56% to 28%) in the frequency of grade ≥ 2 neuropathy favoring the 2-h group, which was statistically significant. This observation underscores the marked difference in

neuropathy seen between the two groups, one that an unweighted average of all toxicities has a tendency to under-represent (e.g., four grade 1 toxicities, when averaged, is not equivalent to one grade 4 toxicity in a cohort of 4 patients).

In addition, we observed a 50% reduction in the frequency of grade ≥ 2 neutropenia when albumin-bound paclitaxel was administered over 2 h that trended towards, but did not reach, statistical significance. Because filgrastim or peg-filgrastim was administered after the onset of neutropenia, it is unlikely that this impacted the incidence of neutropenia. The identical median PFS and overall survival, along with the overlapping survival curves (Fig. 1), suggest that efficacy is unaffected by infusion duration.

The significant reduction in neuropathy coupled to a clinically important improvement in neutropenia is striking, in light of previous studies of long-versus short infusion times with paclitaxel, in which longer infusion times led to a reduction in peripheral neuropathy countered by an increase in neutropenia [2, 17].

While studies of albumin-bound paclitaxel in lung cancer have been uncommon, Socinski et. al. recently reported data from a randomized phase III study of carboplatin (AUC = 6) plus either paclitaxel or albumin-bound paclitaxel (100 mg/m^2 over 30 min) in untreated patients with advanced NSCLC [18]. We note that the incidence of grade ≥ 3 sensory neuropathy associated with albumin-bound paclitaxel plus carboplatin was 3%, which is considerably lower than that found in our study. Part of this may be attributable to the lower dose of albumin-bound paclitaxel that was used by Socinski et. al. Support for this can be found in their preceding dose finding trial, where the incidence of grade ≥ 3 peripheral neuropathy doubled when the dose was increased from 100 to 125 mg/m^2 (16% vs. 8%) [19].

Finally, we note that while the overall response rate (ORR) reported in the phase III study was higher in the albumin-bound paclitaxel arm than in the paclitaxel arm (33% vs. 25%, $P = 0.005$), the ORR was highest in patients with squamous-cell histology (41% vs. 24%, $P < 0.001$). Unfortunately, the smaller sample size of our study did not provide sufficient power to allow for a meaningful histologic subgroup comparison, as only 15 patients (23%) held diagnoses of squamous-cell carcinoma (squamous vs. non-squamous RR 13% vs. 24%, $P = 0.49$).

In summary, our data suggest that a change in the infusion time of albumin-bound paclitaxel from 30 min to 2 h may lead to a significant reduction in the frequency and severity of peripheral neuropathy experienced by patients without affecting efficacy. Given the wide range of solid tumor malignancies for which albumin-bound paclitaxel is used, the resulting clinical impact that this alteration could have has the potential to be substantial, and is a maneuver that warrants consideration in patients who experience peripheral neuropathy while being treated with this drug.

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Conflict of interest None.

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