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Phase I Trial of Nanoparticle Albumin-Bound Paclitaxel in Combination with Gemcitabine in Patients with Thoracic Malignancies

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Abstract

Background—Nab-paclitaxel has a different toxicity profile than solvent-based paclitaxel including a lower rate of severe neutropenia. This trial was designed to determine the maximum tolerated dose and dose limiting toxicities (DLT) of nab-paclitaxel in combination with gemcitabine.

Methods—Patients were required to have a performance status of 0 to 1, ≤three prior cytotoxic chemotherapy regimens, and preserved renal, hepatic, and bone marrow function. Patients received gemcitabine 1000 mg/m^2 on days 1, 8 in all cohorts, and nab-paclitaxel at doses of 260, 300, 340 mg/m^2 every 21 days depending on the treatment cohort (1 cycle = 21 days). DLT were assessed after the first cycle, and doses were escalated in cohorts of 3 to 6 patients.

Results—Eighteen patients were consented and 15 patients are evaluable [median age 62 years (range, 35–75); median number of prior treatments 3 (range, 1–4); tumor types: non-small cell lung cancer (NSCLC) (*n* = 8), small cell lung cancer (SCLC) (*n* = 6), and esophageal cancer (*n* = 1)]. At a nab-paclitaxel dose of 300 mg/m^2, 1 of 6 pts experienced a DLT (omission of day 8 gemcitabine due to absolute neutrophil count <500), and at an nab-paclitaxel dose of 340 mg/m^2 2 of 3 patients experienced a DLT (1 pt grade 3 rash and pruritus; 1 pt grade 3 fatigue and anorexia). Responses were observed in NSCLC and SCLC.

Conclusions—The maximum tolerated dose of nab-paclitaxel is 300 mg/m^2 in combination with gemcitabine 1000 mg/m^2 on days 1, 8 every 21 days. This combination demonstrated activity in previously treated NSCLC and SCLC patients.

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Keywords

Abraxane; Non-small cell lung cancer; Small cell cancer; Esophageal cancer; ABI-007; Taxane

Paclitaxel has demonstrated significant activity, either as a single agent or in combination with other chemotherapeutic or biologic agents in the treatment of breast, ovarian, lung, and squamous cell cancers of the head and neck. However, paclitaxel has several burdensome toxicities including hypersensitivity reactions, sensory neuropathy, myelosuppression, and mild nausea.1 Nanoparticle albumin-bound paclitaxel (nab-paclitaxel, ABI-007, Abraxane), a solvent-free formulation of paclitaxel, has recently been approved by the United States Food and Drug Administration for use in treatment of metastatic breast cancer, and has some practical advantages over standard formulation paclitaxel including a lack of hypersensitivity reactions and shorter infusion time. A phase III clinical trial compared paclitaxel with nab-paclitaxel in patients with metastatic breast cancer.[2] Patients who were treated with nab-paclitaxel experienced a significantly higher response rate, and time to tumor progression in comparison to paclitaxel. Patients who were treated with nab-paclitaxel experienced a significantly lower rate of grade 4 neutropenia, but had a higher rate of grade 3 sensory neuropathy in comparison to patients treated with paclitaxel. Phase II trials with single agent nab-paclitaxel and in combination with carboplatin have revealed significant activity in non-small cell lung cancer (NSCLC).[3–6] A phase III trial comparing carboplatin and paclitaxel versus carboplatin and nab-paclitaxel has been initiated in patients with advanced NSCLC.

Standard first-line chemotherapy for advanced NSCLC is a platinum-based doublet therapy; however, nonplatinum doublets are an acceptable alternative.7 Gemcitabine and paclitaxel is a nonplatinum combination that is used to treat advanced non-small cell lung cancer[8,9] and metastatic breast cancer.[10] However, there are significant differences in the standard doses and toxicities between nab-paclitaxel and paclitaxel, and thus the potential for additive toxicity with the combination of nab-paclitaxel and gemcitabine. Therefore, we performed a phase I trial to determine the maximum tolerated dose (MTD) and the dose limiting toxicities (DLT) of nab-paclitaxel in combination with a standard dose and schedule of gemcitabine.[8,9]

PATIENTS AND METHODS

Patients were required to have a cytologically or histologically confirmed advanced solid tumor, and a preserved functional status, organ function, a life expectancy of 8 weeks, and be able to provide informed consent. Patients who had received >3 lines of cytotoxic chemotherapy for metastatic disease or were considered heavily pretreated (as defined in Table 1) were excluded; however, there was no exclusion criterion related to prior taxane therapy. Patients were required to meet all the inclusion and exclusion criteria (Table 1). Toxicity was assessed after each cycle using the National Cancer Institute Common Terminology Criteria Adverse Events version 3.0. Dose limiting toxicities were determined after the first cycle, and were defined as on Table 1. Patients were evaluated with weekly complete blood cell count; liver function tests [aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and total bilirubin] and serum creatinine were evaluated before each cycle of chemotherapy. Efficacy was determined using the Response Evaluation Criteria in Solid Tumors.[11] Patients were assessed for response after every two cycles (6 weeks). All patients were required to sign informed consent before any study procedures being performed. This trial was reviewed by the protocol review committee of Lineberger Comprehensive Cancer Center and the Institutional Review Board of the University of North Carolina.

Study Design

This was a phase I single-center trial, and the primary objective was to determine the DLT and the MTD of nab-paclitaxel in combination with gemcitabine. The secondary objectives were to evaluate the efficacy and toxicity of the combination of nab-paclitaxel and gemcitabine. The trial used a standard 3-patient cohort dose escalation design. Three patients were treated at the initial dose level, and if no first cycle DLTs were observed, three additional patients were treated at the next dose level. If one of the three initial patients experienced a DLT at any given dose level, three additional patients were treated at the same dose level. If a DLT occurred in at least two patients at any dose level, dose escalation was halted, and the next three patients were enrolled at the next lower dose level. The MTD and the recommended treatment dose for phase II trials was defined as the highest dose levels that fewer than two of six patients experienced DLT in cycle one. The cohort at the MTD and recommended dose for phase II trials could be expanded to obtain additional efficacy and toxicity information about this dose level. The toxicities observed in the patients on the expanded cohort were not included in the determination of the DLT or MTD.

Study Treatment

Patients received gemcitabine 1000 mg/m^2 on days 1, 8 and nab-paclitaxel on day 1 every 21 days, and the dose of nab-paclitaxel depended on the patient's cohort. Patients received gemcitabine infused over 30 minutes, followed by a 30-minute infusion of nab-paclitaxel on day 1, and gemcitabine was infused over 30 minutes on day 8. Dose adjustments for the day 8 gemcitabine were as follows: 100% of the dose if absolute neutrophil count (ANC) was $\geq 1000 \times 10^6$/l and platelet count $\geq 100{,}000 \times 10^6$/l, and 75% of the dose if the ANC $500–999 \times 10^6$/l or platelet count 50,000 to $99{,}000 \times 10^6$/l. The day 8 dose of gemcitabine was not administered if the ANC was $<500 \times 10^6$/l or the platelet count $<50{,}000 \times 10^6$/l. The doses of nab-paclitaxel and gemcitabine were calculated using the patient's body surface area, with doses capped at a maximum body surface area of 2.0. Patients were treated until disease progression, unacceptable toxicity, two cycles after maximal response or a maximum of six cycles at the discretion of the treating physician.

Patients received antiemetic therapy with dexamethasone before each treatment with nab-paclitaxel and gemcitabine on day 1 and dexamethasone alone before treatment with single agent gemcitabine on day 8. No additional pre-medications for hypersensitivity reactions were given. Nab-paclitaxel (Abraxane) and gemcitabine (Gemzar) were supplied by the manufacturers. The use of growth colony stimulating factors was prohibited during the first cycle, and could be used after the first cycle if indicated following the American Society of Clinical Oncology guidelines.[12] The use of erythropoietin stimulating agents was permitted and based on the American Society of Clinical Oncology guidelines available at the time trial was performed.13

RESULTS

Eighteen patients were consented for this trial, and 15 patients are considered evaluable. Three patients are nonevaluable for the following reasons: progressive disease prior to initiating protocol therapy ($n = 1$), withdrawal of consent after cycle 1 day 1 therapy ($n = 1$), and inability to meet screening laboratory eligibility criteria ($n = 1$). The demographics of the evaluable 15 patients are presented in Table 2. The majority of the patients were: white ($n = 14$), male ($n = 8$) and had non-small cell or small cell lung cancer ($n = 14$). The median number of prior therapies was 3.

Determination of the Maximum Tolerated Dose

No DLT were observed in the first cohort (nab-paclitaxel 260 mg/m^2 every 21 days). At the second-dose level (nab-paclitaxel 300 mg/m^2 every 21 days), one of the 6 patients experienced DLT (omission of day 8 gemcitabine due to ANC <500 × 10^6/l). In the third dose cohort (340 mg/m^2 every 21 days), 2 of the first 3 patients experienced a DLT (grade 3 fatigue/asthenia and grade 3 anorexia in one patient, grade 3 rash and grade 3 pruritis in one patient). The MTD and recommended dose for phase II trials is nab-paclitaxel is 300 mg/m^2 on day 1 in combination with gemcitabine 1000 mg/m^2 on days 1, 8, every 21 days.

Toxicities

The hematological toxicities for all the cycles are summarized in Table 3. The rate of severe hematological toxicity was low with grade 4 neutropenia observed in one cycle, and one episode of febrile neutropenia. Growth colony stimulating factors supportive therapy was not used during any of the cycles. Grade 3 anemia and grade 3 thrombocytopenia were each observed in one cycle. Two patients were treated with erythropoietin stimulating agents for a total of 4 cycles, and one patient had transfusion of 2 units packed red blood cells. The main nonhematological toxicities consisted of sensory neuropathy, nausea, vomiting, fatigue, and alopecia. The nonhematological toxicities for all patients are summarized in Table 4. One patient in the expanded cohort developed grade 3 pneumonitis, which was attributed to the gemcitabine. The patient was treated with supplemental oxygen and corticosteroids with improvement of his dyspnea and oxygenation, and did not continue treatment due to evidence of disease progression and toxicity. Two patients discontinued therapy due to treatment related toxicity: one patient experienced grade 3 fatigue/asthenia and grade 3 anorexia after cycle 1 of nab-paclitaxel at a dose of 340 mg/m^2 and while eligible for further therapy after a dose reduction, elected not to continue and one patient experienced grade 3 sensory neuropathy which did not resolve after a 2 week treatment delay. This patient had underlying diabetes and had previously received paclitaxel: she received nab-paclitaxel 300 mg/m^2 on cycle 1 and 260 mg/m^2 on cycle 2. A second patient developed grade 3 sensory neuropathy after the second cycle, but did not have a history of diabetes or previous paclitaxel therapy, and discontinued therapy because of progressive disease.

Treatment Administration

A total of 59 cycles were administered and no patients experienced any treatment delays related to myelosuppression. Patients received treatment with nab-paclitaxel at 3 different doses of nab-paclitaxel: 260 mg/m^2 (17 cycles), 300 mg/m^2 (39 cycles), and 340 mg/m^2 (3 cycles). Four patients underwent dose reduction of the nab-paclitaxel; the 3 patients who experienced a DLT, and one patient who initiated therapy at 340 mg/m^2 had the nab-paclitaxel dose reduced when it was determined that the dose level has an unacceptable rate of toxicity. The day 8 gemcitabine was successfully administered on 58 of the 59 cycles. One patient had cycle 1 day 8 gemcitabine withheld due to neutropenia (and was considered a DLT), and after dose adjustment of the nab-paclitaxel received the day 8 gemcitabine on the second-cycle. On 7 cycles, the dose of the day 8 gemcitabine was adjusted from 1000 to 750 mg/m^2. The dose intensity of the gemcitabine, defined as the dose patients received divided by full dose prescribed per protocol, was 98%, and for the day 8 gemcitabine was 95%.

Response

Thirteen of the 15 patients are evaluable for response; 2 patients discontinued therapy and are nonevaulable since response was either not assessed or confirmed. The best response per patient recorded from the start of treatment until completion of protocol therapy that was confirmed on repeating imaging ≥4 weeks is reported on Table 5. Partial responses were

seen among patients with small cell lung cancer (SCLC) (n = 3), and NSCLC (n = 3); 4 patients experienced stable disease [NSCLC (n = 3) and esophageal cancer (n = 1)].

DISCUSSION

This phase I trial demonstrates that the MTD of nab-paclitaxel was 300 mg/m^2 on day 1 in combination with gemcitabine 1000 mg/m^2 on days 1, 8 on an every 21-day schedule. This result is concordant with the findings from other early phase trials of this agent alone or in combination.[14–16] This dose of nab-paclitaxel did not seem to significantly compromise the treatment administration of the day 8 gemcitabine.

Two patients did develop grade 3 sensory neuropathy on this trial; both after two cycles of treatment. The incidence of grade 3 sensory neuropathy was higher with nab-paclitaxel than paclitaxel in the phase III trial (10% versus 2%, respectively; $p < 0.001$).17 The incidence of sensory neuropathy is known to increase significantly after four cycles of carboplatin and paclitaxel,18 and the incidence of sensory neuropathy related to nab-paclitaxel may be cumulative or dose dependent. Given the variability in dose and number of cycles of nab-paclitaxel received in previous trials, it is difficult to make a definitive conclusion about the relationship between these factors and the rate of grade 3 sensory neuropathy. In a recent phase II dose escalation trial of carboplatin and nab-paclitaxel, the incidence of sensory neuropathy appeared to increase with increasing dose of nab-paclitaxel.[5] In this trial, all patients received carboplatin (area under the curve = 6), and patients received nab-paclitaxel 225, 260, 300, or 340 mg/m^2 every 21 days depending on the cohort. The incidence of grade 3 sensory neuropathy was 8%, 8%, 12%, and 24%, respectively. Future clinical trials that investigate the dose and schedule of nab-paclitaxel should include close monitoring for this toxicity. Preliminary evidence indicates that prolonging the infusion time of nab-paclitaxel from the standard 30 minutes to 2 hours may decrease the incidence of grade 2 and 3 sensory neuropathy, presumably by decreasing the peak plasma levels of nab-paclitaxel.[19]

This combination demonstrated significant activity: 6 patients experienced a partial response and 4 patients experienced stable disease in this previously treated population (median number of previous cytotoxic therapies = 3). However, these results should be interpreted with caution given the small sample size and the fact that gemcitabine and paclitaxel as single agents or in combination have demonstrated significant activity in second-line therapy for NSCLC and SCLC.[20–23] Phase II trials in specific patient populations will be required to assess the activity of this combination. This combination may prove to be a nonplatinum alternative regimen for patients with advanced NSCLC if phase II studies confirm the preliminary indications of activity observed in the previously treated patients enrolled in our trial.

The combination of gemcitabine and paclitaxel has demonstrated similar efficacy and toxicity in comparison to platinum-based doublet chemotherapy in advanced NSCLC in two large phase III trials.[8,9] The rate of neutropenia observed with gemcitabine and paclitaxel in these trials has been within acceptable limits. In the phase III trial by Kosmidis et al., the percentage of patients experiencing grade 3 and 4 neutropenia on gemcitabine and paclitaxel treatment arm (n = 239) was 10% and 5%, respectively.[9] In the phase III trial by Treat et al., the percentage of patients on the gemcitabine and paclitaxel treatment arm (n = 328) experiencing grade 3 and 4 neutropenia and febrile neutropenia was 12% and 9%, respectively, and 3% and 1%, respectively. A low incidence of grade 4 neutropenia (1 of 59 cycles) was observed in this trial. However, the clinical benefit of the substitution of nab-paclitaxel for paclitaxel in this combination to reduce the incidence of neutropenia, without a reduction of other toxicities or an improvement in efficacy, is debatable. The low incidence on neutropenia may make the combination of gemcitabine and nab-paclitaxel an

attractive chemotherapy combination to investigate with novel targeted agents that may be associated with severe neutropenia. For instance, the addition of bevacizumab to carboplatin and paclitaxel in advanced NSCLC resulted in a statistically significant increase in the rate of grade 4 neutropenia and febrile neutropenia in comparison to standard carboplatin and paclitaxel.[24] Multitargeted tyrosine kinase inhibitors, such as sunitinib or sorefenib, have demonstrated activity in NSCLC, but may cause myelosuppression as well.[25,26]

One deficiency in this trial was that a pharmacokinetic analysis was not performed. A phase I trial by Kroep et al. investigated the schedule of gemcitabine 1000 mg/m^2 on days 1, and 8 and escalating doses of paclitaxel (150 and 200 mg/m^2) on day 1 every 21 days in 18 patients with advanced NSCLC.[27] Paclitaxel did not affect the pharmacokinetics of gemcitabine, and nor did gemcitabine affect the pharmacokinetics of paclitaxel, and the conclusion of the trial was that no drug-drug interactions were seen with this combination. A phase I trial be Folgi et al. investigated for a potential pharmacokinetic interaction between the two drugs with a treatment schedule of paclitaxel 100 mg/m^2 and escalating doses of gemcitabine (1500, 1750, and 2000 mg/m^2) on days 1, 8, and 15 every 28 days in 15 patients with advanced NSCLC.[28] This trial demonstrated no interaction between the two drugs. A phase I trial by De Pas et al. investigated escalating doses of gemcitabine (800–2000 mg/m^2) and paclitaxel (60–100 mg/m^2) on days 1, 8, and15 every 28 days in 35 patients with advanced NSCLC.[29] No pharmacokinetic interactions were observed. All three of these phase I trials used the same gemcitabine infusion time (30 minutes) as our trial. On the basis of the data from these previous trials that had investigated the pharmacokinetics of gemcitabine and paclitaxel on several different schedules in a similar patient population, we determined that the probability of a drug-drug interaction between nab-paclitaxel and gemcitabine was low, and elected not to pursue a pharmacokinetic analysis of the two drugs.

In conclusion, the maximum tolerated dose and the dose recommended dose for phase II trials of nab-paclitaxel is 300 mg/m^2 on day 1 in combination with gemcitabine 1000 mg/m^2 on days 1, 8 every 21 days. In this previously treated patient population with NSCLC, SCLC, and esophageal cancer, the combination of gemcitabine and nab-paclitaxel revealed acceptable toxicity and encouraging preliminary evidence of activity.

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TABLE 1

Inclusion and Exclusion Criteria and Dose-Limiting Toxicities

Inclusion criteria	
1	Histologically or cytologically documented solid tumors
2	Measurable disease by RECIST
3	Patients must have progressed on standard therapy, not be a candidate for standard therapy, or have a disease or disease status for which there is no defined standard therapy
4	Age >18 yr
5	Eastern Cooperative Oncology Group (ECOG) functional status of 0–2
6	Adequate organ function defined as:
	Renal: serum creatinine ≤1.5 × ULN or Cockcraft calculated creatinine clearance of ≥60 ml/min
	Hepatic: transaminases ≤2.5 × ULN and total bilirubin in normal range
	Bone marrow: ANC ≥1.5 × 10^6/l, platelet count ≥100,000 × 106/l
7	Life expectancy of at least 8 wk
Exclusion criteria	
1	Previous anaphylactic reaction or severe allergic reaction to paclitaxel and/or docetaxel
2	Previous anaphylactic reaction or severe allergic reaction to gemcitabine
3	Symptomatic brain metastases
4	Inability to sign informed consent
5	Pregnant or lactating women
6	Active infectious process that will require treatment with antibiotics for greater than 4 wk
7	Uncontrolled congestive heart failure
8	Symptomatic coronary artery disease or heart block
9	Myocardial infarction within the last 3 months
10	Chemotherapy, radiation therapy or any other treatment for malignancy within the last 3 wk
11	Grade ≥2 peripheral neuropathy at baseline assessment from any cause
12	Irradiation of >25% of bone marrow
13	Prior exposure to nitrosureas
14	Prior exposure to >6 cycles of alkylating agents
15	Prior exposure to >2 cycles of mitomycin
16	Treatment with >3 previous lines of cytotoxic therapy for metastatic disease
Dose limiting toxicities based on first cycle toxicities*	
1	Grade ≥3 nonhematological toxicity
2	Grade 4 thrombocytopenia or anemia
3	Grade 4 neutropenia lasting ≥7 days
4	Dose delay of initiating the second cycle of >2 wk
5	Day 8 gemcitabine being held related to ANC <500 × 10^6/l or platelet count <50,000 × 10^6/L

ULN, upper limit of normal; ANC, absolute neutrophil count; RECIST, Response Evaluation Criteria in Solid Tumors.

*Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

TABLE 2

Patient Characteristics at Baseline

Characteristic	No.
Sample size	15
Median age (range) in years	62 (35–75)
ECOG performance status	
0	6
1	8
2	1
Gender	
Male	8
Female	7
Race	
White	14
Black	1
Median number of previous cytotoxic therapies	3
Malignancy	
Non-small cell lung cancer	8
Small cell lung cancer	6
Esophageal cancer	1

ECOG, Eastern Cooperative Oncology Group.

TABLE 3

Treatment-Related Hematological Toxicity[a]

Nab-Paclitaxel (mg/m^2)	No. Patients	No. Cycles	Neutropenia Grade				Anemia Grade				Thrombocytopenia Grade				Febrile Neutropenia Grade			
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
260	3	17	7	1	2	0	5	1	0	0	3	0	0	0	0	0	1	0
300	9	39	11	7	9	1	15	3	1	0	9	0	1	0	0	0	0	0
340	3	3	0	2	3	0	2	1	0	0	1	0	0	0	0	0	0	0

[a]Worst grade of individual toxicity per cycle reported.

TABLE 4

Treatment Related Nonhematological Toxicities[a]

Nab-paclitaxel	**260 mg/m^2**				**300 mg/m^2**				**340 mg/m^2**			
No. patients	**3**				**9**				**3**			
No. cycles	**17**				**39**				**3**			
Grade	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Sensory neuropathy	5	1	1	0	10	3	1	0	1	1	0	0
Nausea	0	1	0	0	11	4	0	0	2	1	0	0
Vomiting	0	0	0	0	5	2	0	0	0	0	0	0
Diarrhea	1	0	0	0	2	1	0	0	0	0	0	0
Mylagia	0	0	0	0	4	2	0	0	2	0	0	0
Arthralgias	0	0	0	0	2	1	0	0	1	1	0	0
Fatigue/asthenia	2	0	0	0	13	4	0	0	1	0	1	0
Fever[b]	0	0	0	0	4	0	0	0	2	0	0	0
Rash[c]	1	0	0	0	2	0	0	0	1	0	1	0
Pruritis	0	0	0	0	2	1	0	0	0	0	1	0
Peumonitis	0	0	0	0	0	0	1	0	0	0	0	0
Transaminitis	0	0	0	0	3	2	0	0	0	0	0	0
Electrolyte[d]	0	0	0	0	1	0	0	0	0	0	1	0
Dehydration	0	0	0	0	2	1	0	0	0	1	0	0
Alopecia[e]												

[a] Worst grade of individual toxicity per cycle reported.

[b] Fever in absence of neutropenia or identifiable infection.

[c] At nab-paclitaxel dose of 340 mg/m^2 grade 3 rash consisted of diffuse erythema over >50% of the body associated with grade 3 pruritis.

[d] At nab-paclitaxel dose of 300 mg/m^2 grade 1 hyponatremia; at nab-paclitaxel dose of 340 mg/m^2 grade 3 hyponatremia.

[e] All patients experienced grade 2 alopecia.

TABLE 5

Best Response as Assessed by RECIST[11]

Malignancy	PR	SD	PD	NE[a]
NSCLC	3	3	1	1
SCLC	3	0	2	1
Esophageal	0	1	0	0

RECIST, Response Evaluation Criteria in Solid Tumors; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; PR, partial response; SD, stable disease; PD, progressive disease; NE, nonevaluable.

[a]Two patients were nonevaluable due to toxicity; one patient had grade 3 asthenia and anorexia after the first cycle, one patient had grade 3 sensory neuropathy after the second cycle and response was not confirmed.