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ORIGINAL ARTICLE

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Clinical and pharmacokinetic study of TNP-470, an angiogenesis inhibitor, in combination with paclitaxel and carboplatin in patients with solid tumors

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Abstract *Purpose*: Preclinical studies have demonstrated a synergistic effect with the angiogenesis inhibitor TNP-470 and several cytotoxic agents. A recent clinical trial with the combination of paclitaxel and TNP-470 has shown promising effects. The present study was designed to determine the toxicity and pharmacokinetics of carboplatin in combination with TNP-470 in comparison with the doublet regimen of paclitaxel and carboplatin in patients with solid tumors. *Experimental design*: Enrolled in the study were 17 patients with lung (11), head/neck (3), sarcoma (2) and thymoma (1). The patients received intravenous paclitaxel and carboplatin on day 1 followed by TNP-470 (60 mg/m^2 i.v. over 1 h administered thrice weekly on Monday, Wednesday, and Friday). Each cycle of therapy consisted of 3 weeks. The initial cohort of three patients received carboplatin at AUC 5 mg/ml×min. No dose-limiting toxic effects occurred, thus the subsequent cohort received carboplatin at AUC 6 mg/ml×min. In addition to toxicity, the pharmacokinetics of carboplatin were evaluated, and tumor response and patient survival rates were assessed. *Results*: The administered regimen of paclitaxel (225 mg/m^2 i.v. over 3 h) and carboplatin (AUC 6 mg/ml×min i.v. over 1 h) on day 1 followed by TNP-470 (60 mg/m^2 i.v. over 1 h administered thrice weekly on Monday, Wednesday, and Friday) was defined as both the maximum tolerated and optimal dose. Hematological toxic effects were similar to those expected with the chemotherapy doublet. All neurocognitive impairments were graded as mild to moderate and reversed after discontinuation of TNP-470 administration. No alterations in the pharmacokinetic disposition of carboplatin were noted. Overall, the median survival duration was 297 days. Four patients (24%) had a partial response, and eight (47%) had stable disease. *Conclusions*: The combination of TNP-470, paclitaxel, and carboplatin is a reasonably well tolerated regimen. Further randomized studies of TNP-470 with this doublet regimen are now warranted for non-small-cell lung carcinoma and other solid tumors.

Keywords Lung cancer · TNP-470 · Angiogenesis inhibitor

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Introduction

TNP-470 is a synthetic analogue of fumagillin with antiangiogenic activity, blocking the growth of new blood vessels by inhibiting endothelial cell proliferation [1, 13]. The mechanism of TNP-470 appears to be inhibition of the intracellular enzyme methionine aminopeptidase-2 (MetAP2) [7, 27, 33]. In vitro studies have shown growth-inhibitory activities of TNP-470 in a variety of cancer cell lines [7]. Additionally, investigators have demonstrated the activity of TNP-470 as a single agent and in combination with cytotoxic agents in a variety of animal tumor models, showing significant tumor growth delay [10, 14, 29–32].

In several phase I/II clinical studies, TNP-470 has shown promising activity as a single agent in several solid tumors including melanoma, sarcoma, and prostate and breast cancer [3, 16–18, 21]. The dose-limiting toxic effects of TNP-470 in these studies were shown to be neurological symptoms, including dizziness, confusion, anxiety and agitation, which resolved upon discontinuation of the TNP-470 therapy. The maximum tolerated dose in these studies appeared to be 180 mg/m^2 per week administered as a single infusion of 60 mg/m^2 administered three times weekly. Two recent phase I studies combining TNP-470 with paclitaxel have shown promising results [2, 11]. Our experience at M. D. Anderson has shown this regimen to be safe with no clinically observed drug interactions [11]. The recommended dose level of TNP-470 and paclitaxel is 60 mg/m^{2}administered three times a week and 225 mg/m^{2}administered every 3 weeks, respectively. The next step for this regimen was to add carboplatin to this cytotoxic antiangiogenic combination therapy. The doublet of paclitaxel and carboplatin is one combination that has become a widely accepted regimen in the treatment of various solid tumors, including non-small-cell lung cancers (NSCLC) [8, 9, 25]. The purpose of this present study was to document the tolerability and pharmacokinetic interactions, if any, of carboplatin when added to the paclitaxel/TNP-470 combination.

Patients and methods

Patient eligibility

All patients were required to have a histologically confirmed diagnosis of an advanced solid tumor and to have received no more than one prior chemotherapy regimen. Patients were also required to (a) have at least one measurable unirradiated tumor site, (b) be at least 18 years old, (c) have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1, (d) have a life expectancy of >16 weeks, and (e) not have undergone radiation therapy within 3 weeks of enrollment. Additionally, all of the patients were required to have adequate hepatic, renal, and bone marrow function, with a white blood cell count of $\geq 3000\ \mu l^{-1}$, absolute neutrophil count of $\geq 1500\ \mu l^{-1}$, platelet count of $\geq 100{,}000\ \mu l^{-1}$, hemoglobin value of ≥ 10 g/dl, serum creatinine value of <1.5 mg/dl or estimated creatinine clearance of ≥ 50 ml/min, total bilirubin level not more than twice the upper limit of normal, and alanine aminotransferase level less than 1.5 times the upper limit of normal. This clinical research study was approved by our institution's clinical research and institutional review boards. All patients were required to give signed informed consent according to federal and institutional guidelines before entering the study.

Treatment protocol

This study was conducted at The University of Texas M. D. Anderson Cancer Center. At the time of the study, the optimal dose of paclitaxel and TNP-470 was determined to be 225 mg/m^2 administered every 3 weeks and 60 mg/m^2 administered three times a week, respectively. Because no clinical data were available for TNP-470 plus the doublet combination, there was a single dose escalation of carboplatin to target an area under the curve (AUC) of first 5 and then 6 mg/ml×min. Paclitaxel and carboplatin were administered as a 3-h and a 1-h infusion, respectively, on day 1 of each 3-week cycle, while TNP-470 was administered as a 1-h infusion 3 days a week, usually on Monday, Wednesday, and Friday (Fig. 1). On day 1 of cycle 1, carboplatin was administered after the completion of paclitaxel administration to allow for pharmacokinetic sampling of carboplatin. In cycle 2 and thereafter, the study drugs were administered in the following sequence: paclitaxel, TNP-470, and carboplatin.

Safety evaluations

Prior to study entry and at the end of each treatment cycle, patients were evaluated with a medical history, physical examination, electrocardiogram, and assessment of neurological and neuropsychological function. Hematology and chemistry panels were evaluated weekly during the first two cycles and once per cycle thereafter. An ophthalmological examination was performed at baseline and at study termination. The neurological examinations were performed at baseline and repeated after two cycles of treatment. Details of these tests have been described elsewhere [11].

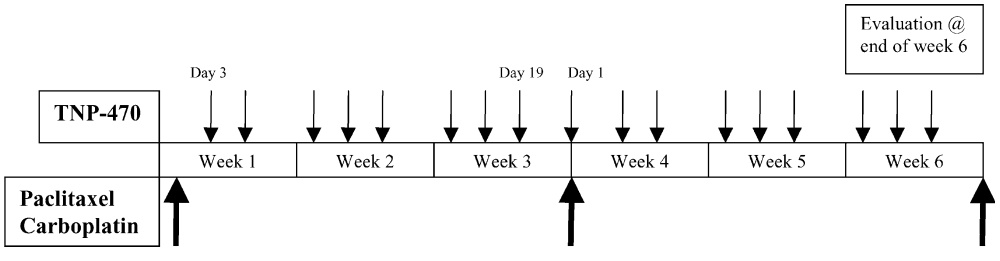

Fig. 1 Schematic representation of the trial design. In the first cycle, TNP-470 was held on day 1 to allow for collection of blood samples for the analysis of carboplatin and on day 19, the pharmacokinetic effects were examined for TNP-470 alone. On day 1 of cycle 2, TNP-470 was assessed in the presence of paclitaxel and carboplatin

Tumor response was assessed after every two cycles of treatment and at termination of the study via bidimensional tumor measurement. The tumor type dictated which imaging modality was appropriate for determining the location, size, and type of the lesion: chest radiography or computed tomography, magnetic resonance imaging, or bone scanning. Response was defined as a ≥50% decrease in the tumor measurements that was maintained for at least 4 weeks. Progression was defined as a >25% increase in tumor size or the appearance of a new lesion. Tumor shrinkage of <50% or growth of <25% represented stable disease.

Pharmacokinetic and statistical methods

Blood and plasma samples for the pharmacokinetic study of carboplatin without and in combination with TNP-470 were obtained on day 1 of cycle 1 and day 1 of cycle 2, respectively. Paclitaxel was the first agent administered during each treatment cycle. Samples were collected on day 19 of cycle 1 for assessment of TNP-470, and its metabolites M-IV and M-II without chemotherapy and on day 1 of cycle 2 for assessment with chemotherapy.

Blood samples for determination of the plasma concentrations of TNP-470, M-IV and M-II were drawn via venipuncture into evacuated glass tubes containing a citric acid solution at the following time points: 0 (predose), and 10, 25, 40, 55, 65, 75, 85, 95, 105, 120 and 150 min after the start of the 1-h TNP-470 infusion. Blood samples for determination of the plasma ultrafiltrate concentrations of carboplatin were drawn via venipuncture into heparinized tubes at the following time points: 0 (predose), and 30, 60, 90 and 360 h after the start of the 1-h carboplatin infusion. After processing, samples were transferred into appropriately labeled vials and stored frozen (−80°C) until analysis.

The concentrations of TNP-470, M-II, and M-IV in plasma were determined at Covance Laboratories (Madison, Wis.) using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantitation of 0.250 ng/ml for TNP-470, 0.500 ng/ml for M-IV, and 2.500 ng/ml for M-II [34]. Concentrations of carboplatin in plasma ultrafiltrate samples obtained during carboplatin treatment were analyzed for the presence of platinum at M. D. Anderson Cancer Center using validated flameless atomic absorption spectroscopy (FAAS) (SPECTRAA-300; Varian, Sugar Land, Tx.) with a graphite tube atomizer assay as described by Madden et al. with minor modifications [19]. Briefly, standards, controls, and samples were injected at 20 µl into the graphite tube at a temperature of 25°C. The furnace temperature was increased from 25°C to 1300°C in five steps over 1.5 min, held at 1300°C (ashing) for 2 min, raised to 2700°C over 1 min (atomization), and held at for 5 s. The argon gas flow was 3 l/min. In addition, the hollow cathode lamp current was 10 mA, and the spectral bandwidth was 0.7 nm at a monochromator wavelength of 265.9 nm with a signal integration time of 5 s and background correction with a deuterium lamp. A linear standard curve covering the platinum range of 50–400 ng/ml was run at the start of each assay day and after each change to a new graphite tube. Plasma ultrafiltrate samples were diluted in 0.1 *N* HCl; all samples were diluted to achieve concentrations within the linear portion of the standard curve. Sample concentrations were determined by comparing sample peak concentrations with those of external standards using linear least-squares regression analysis. The FASS was operated under conditions that maximized sensitivity. This method detected elemental platinum only, but did not indicate the chemical form of the metal. Thus, all of the values calculated from the calibration curve were converted to an equal molar amount of carboplatin. Pharmacokinetic parameters for TNP-470, M-IV, M-II, and carboplatin were estimated using standard noncompartmental methods (WinNonlin, version 3.1; Pharsight Corporation, Mountain View, Calif.). The survival rate was measured using the standard Kaplan-Meier method [15].

Results

Safety and tolerability

Enrolled in the study were 17 patients; their characteristics are detailed in Table 1. Overall, a total of 163 cycles of therapy were administered (median 4 cycles). There were no dose-limiting toxic effects observed in the initial cohort of three patients who received carboplatin at AUC 5 mg/ml×min in combination with paclitaxel and TNP-470 as described above. Therefore, escalation of carboplatin to AUC 6 mg/ml×min proceeded without

Table 1 Patient characteristics. The values are number of patients, except age in years

Age (years)	
Median	58
Range	31–71
Gender	
Male	12
Female	5
Previous therapy[a]	
None	5
Chemotherapy	11
Radiation therapy	10
Combination of therapy	1
Tumor type	
Lung (NSCLC)	11
Head and neck	3
Sarcoma	2
Thymoma	1
Performance status (ECOG)	
0	5
1	12
Median	1

[a]Patients may have received more than one type of treatment prior to study enrollment

Table 2 Summary of overall hematological toxicities

Patients ($n=17$)	Grade 3	Grade 4
Anemia	2 (12%)	0 (0%)
Thrombocytopenia	1 (6%)	1 (6%)
Neutropenia	6 (35%)	7 (41%)

Hematological toxicities grading definition were as follows: anemia: grade 3 $\leq$ 7.9 g/dl, grade 4 $\leq$ 6.5 g/dl; thrombocytopenia: grade 3 $\leq$ 50,000 mm^{-3}, grade 4 $\leq$ 25,000 mm^{-3}; neutropenia: grade 3 $\leq$ 900 mm^{-3}, grade 4 $\leq$ 500 mm^{-3}

Table 3 Summary of significant neurotoxic adverse events

Event	All grades	Grade 3/4
Neuromotor	11 (65%)	3 (18%)
Neuropathy	0	0
Cognitive dysfunction	8 (47%)	0
Anxiety and depression	5 (29%)	0
Dizziness	7 (41%)	1 (6%)
Fatigue/weakness	11 (65%)	1 (6%)

Table 4 Neuropsychological effects of TNP-470 plus paclitaxel plus carboplatin ($n=12$)

Neuropsychological evaluation (domain)	Mean *Z*score (SD)	
	Baseline	After two cycles of treatment
Attention span	0.16 (1.29)	−0.27 (1.07)[a]
Graphomotor speed	0.11 (1.15)	−0.24 (1.18)
Visual scanning	−1.76 (2.36)	−3.21 (4.82)
Verbal fluency	−0.45 (1.26)	−0.97 (1.03)[b]
Immediate recall	−1.14 (1.22)	−2.10 (1.63)[b]
Delayed recall	−1.72 (2.03)	−1.52 (1.39)
Recognition memory	−0.64 (2.57)	−0.67 (1.48)
Motor dexterity (dominant)	−2.91 (7.96)	−3.35 (4.14)
Motor dexterity (non-dominant)	−2.47 (5.63)	−4.13 (4.55)
Executive functions	−1.63 (5.36)	−2.73 (3.29)
Quality of life	−0.25 (1.06)	−0.52 (0.77)

[a]Approaching statistical significance at $P=0.08$
[b]$P<0.05$

any problems. A total of 14 patients were treated at this dose level.

Hematological toxicities included grade 3 anemia and thrombocytopenia and grade 3/4 neutropenia, and these are summarized in Table 2. There were also significant nonhematological toxicities observed in this trial, and these are summarized in Table 3. Fatigue and arthralgia were the two most prevalent adverse events observed in this study. Other adverse events included peripheral neuropathy, nausea, diarrhea, vomiting, insomnia, and dizziness.

A total of 12 patients were available for the assessment of the changes in cognitive and motor function from baseline to after completion of two cycles of therapy. The data are summarized in Table 4. Declines in both cognitive and motor function were observed in nearly all of the patients after they had received two cycles of therapy in the context of an expected practice effect (e.g., better performance at the second assessment due to prior exposure to the tests). Declines in verbal fluency and immediate recall were statistically significant ($P<0.05$). Changes In attention span approached statistical significance ($P=0.08$). Further statistical significance likely was not achieved due to the small number of subjects and resulting low statistical power. Furthermore, the mean scores were actually in the impaired range for a number of tests at baseline including visual scanning, delayed recall, motor dexterity and executive functions. Scores ≥1.5 standard deviations (SDs) below the mean were considered to be impaired (e.g., only 6.7% of the general population would be expected to score in this range), and the follow-up scores indicated a significant prevalence of severe impairments that would have a major impact on the patient's ability to function normally in their usual daily activities.

Pharmacokinetic analysis

The mean pharmacokinetic parameters determined for carboplatin, TNP-470, M-IV, and M-II are presented in Tables 5and 6. Sequential administration of paclitaxel, TNP-470, and carboplatin resulted in a decrease in the dose-normalized mean maximum plasma concentration (C_{max}) of TNP-470 of approximately 6.25% and a decrease in the dose-normalized mean AUC_t for TNP-470 of 17.7% when compared with the values obtained following the administration of TNP-470 alone. However, increases in the dose-normalized mean C_{max} and AUC_t were observed for M-IV and M-II metabolites. Ten patient sample sets were available for carboplatin analysis. No significant alterations in the mean carboplatin clearance were seen in this study: 54.0 and 57.1 ml/min/m^2 without and with TNP-470, respectively.

Treatment outcomes

Of the 17 patients enrolled, 3 had the best tumor response of a partial response, while 9 had stable disease

Table 5 Mean (±SD) carboplatin pharmacokinetic parameters after administration alone or in combination with TNP-470 and paclitaxel (C_{max} maximum concentration, $T_{1/2}$, half-life, *AUC* area under the concentration–time curve, *CL* clearance)

Treatment	C_{max}(μg/ml)	$T_{1/2}$(h)	AUC (mg/ml×min)	CL(ml/m^2/min)
Carboplatin plus paclitaxel	36.6	1.0 ± 0.1	6.9 ± 1.9	54.0 ± 8.5
Carboplatin plus TNP-470/paclitaxel	36.7	1.0 ± 0.1	7.3 ± 2.3	57.1 ± 21.8

Table 6 Summary of the pharmacokinetic parameters of carboplatin, TNP-470, M-IV, and M-II (T_{max} time to maximum concentration, C_{max} maximum concentration, $T_{1/2z}$ harmonic mean half-life, AUC area under the concentration-time curve, values are mean ± standard deviation)

Treatment	T_{max}(min)	C_{max}(ng/ml)	AUC_T(ng/ml/h)	$T_{1/2z}$(min)
TNP-470 parameters				
TNP-470 alone	35 ± 15	477 ± 255	372 ± 224	3.2
TNP-470 plus carboplatin plus paclitaxel	40 ± 13	233 ± 91	126 ± 48	11.0
M-IV parameters				
TNP-470 alone	52 ± 11	16 ± 5	15 ± 5	16.0
TNP-470 plus carboplatin plus paclitaxel	52 ± 13	29 ± 11	24 ± 8	16.0
M-II parameters				
TNP-470 alone	68 ± 8	455 ± 239	583 ± 288	52.0
TNP-470 plus carboplatin plus paclitaxel	64 ± 8	508 ± 206	721 ± 305	53.0

Table 7 Best tumor response overall and among patients with lung cancer

Best tumor response	Overall ($n = 17$)	NSCLC ($n = 11$)	Second-line therapy for NSCLC ($n = 9$)
Complete response	0 (0%)	0 (0%)	0 (0%)
Partial response	3 (24%)	2 (33%)	2 (22%)
Stable disease	9 (47%)	8 (73%)	4 (44%)
Disease progression	5 (29%)	1 (6%)	1 (62%)

(Table 7). Overall, the median survival duration was 297 days (95% confidence interval, 181–502 days). Of the 11 patients with a NSCLC, 2 had a partial response and 8 had stable disease. Nine of the patients with NSCLC received this regimen as second-line therapy.

Discussion

This phase I dose escalation study was designed primarily to assess the safety and pharmacokinetics of TNP-470 in combination with paclitaxel and carboplatin. The optimal dose was 60 mg/m^2 administered three times a week for TNP-470, paclitaxel and carboplatin at 225 mg/m^2 and AUC 5 mg/ml×min, respectively, administered every 3 weeks. The addition of TNP-470 to this paclitaxel and carboplatin doublet did not result in significant additional adverse events with respect to nonhematological toxicities compared to those reported with the TNP-470 and paclitaxel combinations [2, 11]. Specifically, the neurological adverse events were higher but not worse than those expected with a standard regimen of paclitaxel alone. These findings are similar to those reported previously for administration of TNP-470 as a single agent [3, 16].

Certain neurocognitive functions declined during treatment in our study. These included hand dexterity (dominant and nondominant), executive function, and verbal fluency. However, attention, graph-motor speed, verbal recall, and recognition memory were all unchanged. In comparison with our prior study with TNP-470 in combination with paclitaxel; the declines in function were in different skill categories. This can be attributed to the small sample size. The etiology of the TNP-470-associated neurological toxic effects may have been due to the ability of TNP-470 to penetrate the central nervous compartment. The neurological symptoms observed in this and other clinical studies of TNP-470 are similar to those seen in patients receiving paclitaxel. Furthermore, TNP-470-associated neuropathy is thought to be due to the accumulation of TNP-470 in central nervous system tissues. These adverse events often resolve within 2 weeks after discontinuation of TNP-470 treatment.

In this study, no changes in the mean clearance of carboplatin were observed when given in combination with paclitaxel and TNP-470. In our prior study, a minor decrease in the clearance of paclitaxel was shown when paclitaxel was given in combination with TNP-470. The decrease in paclitaxel clearance was not statistically significant [11]. As noted, the high variability in the disposition of TNP-470 can lead difficulties when attempting to determine drug interactions in any study.

There are an increasing number of agents that have entered the clinic that target various step(s) in the angiogenic process. These includes the matrix metalloproteinase inhibitors (MMPi), inhibitors of endothelial cell signaling via vascular endothelial growth factor and its receptor, inhibitors of angiogenesis and direct inhibitors of integrins and existing endothelial cells [28]. Two phase III studies with AG3340 (prinomastat) in combination with the chemotherapy doublet of paclitaxel and carboplatin or gemcitabine and cisplatin in patients with advanced NSCLC did not show any survival benefits [5, 27]. Similar findings have been reported in two randomized placebo-controlled trials of BAY12-9566 as adjuvant therapy in patients with small-cell and NSCLC [22].

Squalamine is a synthetic aminosterol which selectively inhibits new blood vessel formation. Herbst et al. have recently reported a phase I/IIA trial of squalamine in

combination with paclitaxel and carboplatin in 45 patients with advanced NSCLC. They found good tolerability and no drug interactions of the combination [12]. Of the 43 evaluable patients from this study, there were 12 patients with partial responses and 8 patients with stable disease, with an overall median survival of 10 months and a 40% 1-year survival. Preliminary data from a phase I/II study has shown that the combination of the recombinant humanized monoclonal anti-VEGF antibody bevacizumab (rhu-Mab VEGF, Avastin, Genentech) and the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib (OSI744, Tarceva, Genetech) is a promising therapeutic strategy for combining two noncytotoxic agents in patients with NSCLC [20].

The mechanism of action of TNP-470 is believed to be the inhibition of intracellular MetAP2 [7, 26, 33]. TNP-470 undergoes almost immediate enzymatic degradation via epoxide hydrolase leading to a very short circulating half-life. Preclinical data have suggested that continuous exposure to TNP-470 may enhance antiangiogenic activities while reducing toxicities. This hypothesis has been suggested following two clinical trials of TNP-470 as a single agent and combined with paclitaxel and carboplatin, with promising results [4, 6]. In a preliminary study, Blumenschein et al. have demonstrated that TNP-470 administered as a continuous infusion in combination with paclitaxel and carboplatin is a safe and well-tolerated regimen with few neurocognitive effects [6]. In all, the combination of TNP-470 with chemotherapeutic agent(s) does seem to offer additive efficacy with tolerable but significant adverse effects. With continuing interest in TNP-470 and MetAP2 as a target in cancer therapeutic, Satchi-Fainaro et al. have reported a novel formulation for delivery of TNP-470 involving its conjugation to a water-soluble hydroxy-propyl-methacrylamide copolymer. These investigators showed in animal models that this new conjugated TNP-470 formulation has enhanced and prolonged activity with little or no drug-related toxicity as compared to nonconjugated TNP-470 [23, 24]. It was proposed that the conjugated TNP-470 has selective disposition properties and may provide a therapeutic approach with this active compound.

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