Phase I Trial of Hepatic Arterial Infusion of Nanoparticle Albumin–Bound Paclitaxel: Toxicity, Pharmacokinetics, and Activity

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Abstract

Because liver involvement in patients with metastatic cancer has limited options and poor outcomes, we conducted a phase I study to determine the safety, activity, and pharmacokinetic characteristics of hepatic arterial infusion of nanoparticle albumin–bound paclitaxel (HAI nab-paclitaxel). Cohorts of three patients having predominant hepatic metastases received HAI nab-paclitaxel at three dose levels (180, 220, and 260 mg/m^2, respectively) infused for more than 1 hour every 3 weeks (3 + 3 design). Some patients participated in comparative pharmacokinetic studies (i.v. vs. HAI), receiving their first course i.v., to determine peak concentrations and effect of first-pass hepatic extraction compared with subsequent courses administered by HAI. The highest dose level was expanded to determine the safety and activity of HAI nab-paclitaxel. Thirty-eight patients were treated. There were no dose-limiting toxicities at doses up to 260 mg/m^2. Common adverse events included alopecia, fatigue, myelosuppresion, nausea, and vomiting. Three patients had stable disease for 4 or more months and 2 patients (1 of 12 with breast cancer and 1 of 1 with cervical cancer) achieved a partial response lasting for 5 and 15 months, respectively. Peak concentrations were lower (~50%) with greater hepatic extraction of drug (~42%) following HAI than i.v. infusion based on area under the curve comparison of drug exposure. HAI nab-paclitaxel showed partial hepatic extraction. At doses 260 mg/m^2 or less given for 1 hour every 3 weeks, the treatment was well-tolerated and showed activity in advanced cancer patients with predominant liver metastases. *Mol Cancer Ther; 10(7); 1300–7. ©2011 AACR.*

Introduction

The liver is a common site of metastatic involvement in patients with gastrointestinal, breast, ovarian, cervical, melanoma, and other solid tumors, often the predominant site of metastatic disease (1, 2). Except for a minority of patients with resectable isolated hepatic lesions, the overall prognosis for patients with malignant tumors involving the liver is dismal (3). Because liver metastases derive their blood supply from the hepatic artery, unlike hepatocytes, which are perfused predominantly from the portal vein (4), hepatic arterial infusion (HAI) of a therapeutic agent has been explored as a treatment strategy for patients with unresectable liver metastases. Direct infusion of a therapeutic agent by HAI produces higher drug concentrations at the tumor site while circumventing high-dose, chemotherapy-related systemic side effects to normal tissue (5).

Different agents have been used to treat hepatic metastasis from various tumor types: cisplatin (6–9), oxaliplatin (10–14), paclitaxel (15, 16), floxuridine (FUDR; refs. (17–21), interleukin-2 (22, 23), 5-fluorouracil/leucovorin (24), and IFN (25–28). Although many studies have shown higher response rates for HAI treatment than for i.v. infusion, most have not shown an overall survival advantage for HAI (29). However, a randomized phase III trial of HAI with FUDR plus i.v. fluorouracil resulted in improved overall survival (72.2 vs. 59.3 months) and progression-free survival (37.4 vs. 17.2 months) in 74 colorectal cancer patients compared with 82 similar patients receiving systemic chemotherapy alone (4). A similar study showed a greater response rate, time to hepatic progression, and overall survival in patients with hepatic metastases from colorectal cancer treated with HAI versus i.v. chemotherapy (30). Considering these combined results, it seems that this procedure deserves further exploration.

Paclitaxel has been used as regional arterial chemotherapy for various neoplasms at their primary sites: squamous cell carcinoma of the tongue through external carotid artery infusion, non–small-cell lung cancer

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through the bronchial artery, breast cancer through the internal mammary artery, and hepatic metastases through the hepatic artery. At The University of Texas MD Anderson Cancer Center, 10 patients with liver-predominant metastases of breast cancer received once monthly 24-hour continuous HAI of paclitaxel at 200 mg/m^2 for a total of 56 cycles, resulting in a 30% partial remission rate, including 1 patient with a 48-month response (16).

Nanoparticle albumin–bound paclitaxel (nab-paclitaxel) might be more suitable than paclitaxel for HAI because of the ability to deliver more drug over a shorter frame of time and greater extent of tissue distribution as a result of a greater first-pass hepatic extraction (31–33). In a pilot study assessing the feasibility, maximum tolerated dose (MTD), and toxicities of nab-paclitaxel administered by intra-arterial infusion, 31 patients with advanced head and neck cancer and 12 with recurrent anal canal squamous cell carcinoma were treated via transfemoral infusion into branches of the external carotid artery and internal iliac artery with nab-paclitaxel every 4 weeks for 3 cycles (32). Most dose levels showed considerable antitumor activity: 42 evaluable patients achieved a combined complete response (CR) and partial response (PR) rate of 80.9%. To explore the safety and preliminary evidence of activity of nab-paclitaxel, we conducted a phase I trial of HAI nab-paclitaxel for patients with liver-predominant metastases, including a self-comparison pharmacokinetic study to compare HAI versus i.v. administration in which the patients who participated acted as their own controls.

Patient and Methods

Patient eligibility

Eligible patients included those with a diagnosis of an advanced solid tumors and predominant hepatic metastases, defined as at least 40% of the total tumor burden involving the liver, and who had failed standard-of-care therapy. The patients were required to have an Eastern Cooperative Oncology Group performance status of 2 or greater; absolute neutrophil counts (ANC) 1,500/mm^3 or more, platelets 100,000/mm^3 or more; creatinine level 2 mg/dL or less, or a calculated glomerular filtration rate based on the Cockcroft–Gault equation of more than 40 mL/min if creatinine level was more than 2 mg/dL; alanine aminotransferase level 5 times or less upper limit of normal; bilirubin 2 mg/dL or less; the ability to understand and willingness to sign an Institutional Review Board approved informed consent; and full recovery from all previous therapies. Exclusion criteria included clinically significant ascites, pregnancy or breast-feeding, hypersensitivity to nab-paclitaxel, untreatable bleeding diathesis, evidence of portal vein thrombosis and clinically significant peripheral vascular disease, neuropathy grade 2 or more, and a known history of central nervous system metastasis except for patients who were neurologically stable after treatment with surgery and/or radiation therapy. Caution was exercised when administering nab-paclitaxel concomitantly with known substrates or inhibitors of CYP2C8 and CYP3A4.

Study design

This phase I study was conducted at MD Anderson and approved by the MD Anderson Cancer Center Institutional Review Board. Informed consent was obtained from all subjects before enrollment. The first part of the study was a dose escalation based upon a standard 3 + 3 design to define the MTD of HAI nab-paclitaxel. Three dose levels were included (180, 220, and 260 mg/m^2, respectively, the latter being the highest dose level approved by the Food and Drug Administration (FDA) for i.v. use (Table 1). The second part was a dose expansion phase designed to enroll additional patients treated at the MTD or dose level 3 if the MTD was not defined. The MTD was defined as the highest dose level at which 6 patients were treated, with 1 or more patients experiencing a dose-limiting toxicity (DLT) occurring during the first 4 weeks. A hematologic DLT was defined as platelet count of less than 25,000/mm^3 or bleeding associated with platelet count of less than 50,000/mm^3, ANC level of less than 500/mm^3 for more than 7 days, neutropenic fever, or more than 14 days of delay in initiation of subsequent treatment because of inadequate hematologic parameters, whereas a nonhematologic DLT was defined as a grade 3 or more nonhematologic toxicity according to National Cancer Institute (NCI) CTCAE v3.0 toxicity criteria (34) other than nausea, vomiting, fatigue, or elevated levels of hepatic enzymes only.

All patients were evaluated both for toxicity for all cycles, using NCI CTCAE v3.0 toxicity criteria, and for efficacy, using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 guidelines (35). Descriptive statistics were used to describe the toxicity profile, including the grade and type of toxicity by dose level. The RECIST guidelines defined a CR as complete disappearance of all lesions, a PR as a 30% or more decrease in the sum of the longest diameter of target lesions, progressive disease (PD) as a 20% or more increase in the sum of the longest diameter of target lesions, and stable disease as small changes not meeting the criteria for a PR or PD. Descriptive statistics were used to assess clinical responses and their covariates of interest. Cox proportional hazards regression models were used to describe the associations among each type of survival and covariates of interest. Statistical analyses were carried out using GraphPad Prism (GraphPad Software) and a value of $P < 0.05$ was considered statistically significant.

Treatment and dose adjustment

After completing the informed consent process and registration, eligible patients were admitted after consultation with the interventional radiology service. On the day of treatment, patients underwent angiographic placement of the catheter for HAI. Arteriography (using

Table 1. Baseline characteristics of treated patients ($N = 38$ patients)

Baseline characteristics	*n*	%
Age, y		
Mean	59.2	
SD	10.7	
Gender		
Female	24	63.2
Male	14	36.8
Number of prior chemotherapy regimens		
Median	5	
Range	2–12	
ECOG performance status		
0	10	26.3
1	25	65.8
2	3	7.9
Race		
White	31	81.6
Black	4	10.5
Others	3	7.9
Diagnosis		
Breast cancer	12	
Colorectal cancer	8	
Melanoma	4	
Esophageal cancer	3	
Cholangiocarcinoma	3	
Ovarian cancer	2	
Sarcoma	2	
Others (carcinoid tumor, cervical, angiosarcoma, leiomyosarcoma, prostate, and pancreatic cancer each)	4	
Number of patients per dose level		
Dose level 1 (180 mg/m^2)	3	7.9
Dose level 2 (220 mg/m^2)	3	7.9
Dose level 3 (260 mg/m^2)	32	84.2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; and SD, standard deviation.

noniodinated contrast media) of the celiac axis and superior mesenteric artery was conducted to delineate anatomy, identify accessory arteries, and confirm adequacy of portal venous flow and adequate positioning of the catheter. If indicated, embolization was done to alter collateral blood flow patterns or to protect gastrointestinal organs (36). After catheter placement, patients were taken to the nuclear medicine department for a catheter flow study. Once patients were transported to the designated floor, treatment was initiated with the assigned dose of nab-paclitaxel plus 1,500 IU of heparin intra-arterially over 60 minutes without prophylactic medications. The hepatic intra-arterial catheter was removed once the intra-arterial infusion was completed. The treatment was repeated once every 3 weeks.

To be eligible to participate in a subsequent treatment cycle, patients had to meet minimum retreatment criteria, including an ANC level of greater than 1,500/mm^3, platelet count of greater than 100,000/mm^3, and the resolution of toxicity to less than grade 2 or to the pretherapy baseline level.

In general, anemia was not an indication for dose reduction. Patients who experienced grade 3 or greater thrombocytopenia and/or neutropenia had a dose reduction of 25% and prophylactic granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor were used in subsequent cycles. Grade 3 or greater neuropathy required interruption of nab-paclitaxel until adverse effects resolved. Grade 2 neuropathy or other grade 3 or greater nonhematologic toxicities resulted in a 25% dose reduction in subsequent cycles. Abnormal hepatic enzyme values alone did not require dose reduction.

Pharmacokinetic studies

Pharmacokinetic comparison studies were conducted for patients enrolled in the dose escalation phase. Two sets of pharmacokinetic studies were conducted to compare peak drug concentrations and systemic drug exposure of i.v. and HAI nab-paclitaxel, both given over 60 minutes.

Samples of 4-mL whole blood were obtained in sodium heparin tubes from an in-dwelling venous catheter placed in the arm (in the contralateral arm if i.v. nab-paclitaxel is given) at the following 12 time points: 0 (predose), 5, 10, 20, and 40 minutes, and 1 (within 5 minutes before the end of infusion), 1.5, 2, 3, 4, 6, and 24 hours immediately after initiation of the infusion. The collected samples were stored at −70°C for future analyses, using tandem mass spectrometry (33, 37, 38).

All drug concentration–time data were analyzed as individual patient data sets. Pharmacokinetic parameter estimates for the individual data sets were generated by noncompartmental analysis by using WinNonlin Version 5.2 software (Pharsight Corporation). The peak paclitaxel concentration (C_{max}) and the corresponding peak time were observed values. The elimination rate constant was obtained by log-linear regression analysis of the terminal phase of the whole-blood paclitaxel concentration versus time profile. The elimination half-life was calculated as ln 2 divided by the elimination rate constant. The area under the curve (AUC) from time 0 to infinity (AUC_{inf}) was obtained by summation of AUC from time 0 to last measurable concentration (calculated by the log-linear trapezoid rule) and AUC of extrapolated area (estimated by dividing the last measurable concentration by the elimination rate constant). The dose–area relationship (i.e., total drug dose divided by AUC_{inf}) was used to determine total-body clearance. The volume of distribution was calculated as total-body clearance divided by the elimination rate constant.

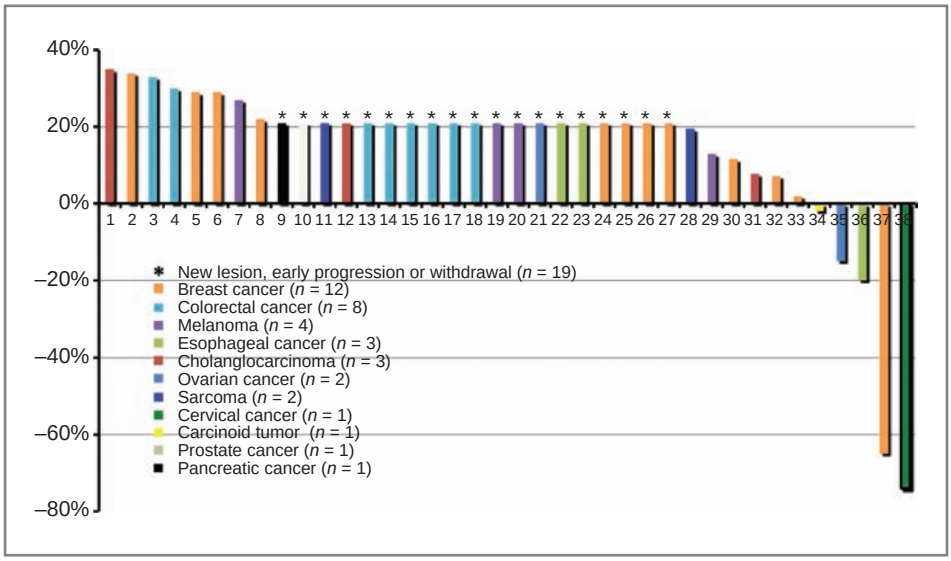


Figure 1. The waterfall plot displays best tumor responses by RECIST criteria. All 38 patients were evaluated. Patients denoted by asterisk (*) had new lesions or early progression or early withdrawal for other reasons. They were arbitrarily designated as having a 21% progression rate.

Results

Patient characteristics

A total of 38 patients (median age, 61 years; range, 38–77 years) who met the inclusion and exclusion criteria were recruited into the study, as described in Table 1. These patients had metastatic breast cancer ($n = 12$ patients), colorectal cancer ($n = 8$ patients), melanoma ($n = 4$ patients), esophageal cancer ($n = 3$ patients), cholangiocarcinoma ($n = 3$ patients), ovarian cancer ($n = 2$ patients), and sarcoma ($n = 2$ patients), and 1 patient each with cervical, pancreatic, prostate cancer, angiosarcoma, leiomyosarcoma, and carcinoid tumor ($n = 6$ patients). All 38 patients were evaluable for toxicity and considered evaluable for response, including 26 patients who were evaluable by RECIST criteria as shown in Fig. 1. Eight patients showed clinical progression, 2 patients received 1 cycle of the treatment with early withdrawal for hospice care, and 2 patients died, as described in the following text. These patients were considered treatment failures.

Toxicity

No DLTs were observed in the 38 patients evaluable for toxicity. The most common adverse events included alopecia and fatigue. One patient with metastatic colorectal cancer was admitted for neutropenic fever on day 8 of cycle 1 at a dose of 260 mg/m^2. She was one of the patients who received her first course of therapy by i.v. infusion, not by HAI, and developed toxic epidermal necrolysis and died on day 23. The relationship between this toxicity and the study drug was unclear because the patient had also been treated with other medications that can cause this reaction, including antibiotics such as tigecycline, meropenem, ciprofloxacin, cefepime, and fluconazole. Another patient with melanoma developed diarrhea, dehydration, and fatigue on cycle 1, day 6, of HAI at a dose of 260 mg/m^2 and was removed from the study on day 15 after rapid tumor progression. The patient died on day 16 after HAI nab-paclitaxel treatment. Other grade 2 or greater toxicities included rash, nausea, vomiting, diarrhea, mucositis, hematuria, neutropenia, and thrombocytopenia, as shown in Table 2.

Antitumor activity

Among 38 patients, 4 patients withdrew after 1 cycle of treatment because of rapid tumor progression and/or adverse events. Three patients had stable disease for 4 months or more (7.9%). Two patients (1 of 12 with breast cancer and 1 of 1 with cervical cancer) achieved a PR (5.3%), as shown in Fig. 2, lasting for 5 and 15 months, respectively. Another patient with metastatic esophageal carcinoma had liver lesions successfully resected after 10 cycles of HAI nab-paclitaxel, achieving tumor reduction by 11%. This patient showed no evidence of disease, with the latest follow-up at 12 months postsurgery.

Pharmacokinetic studies

Pharmacokinetic analyses were conducted to determine whether hepatic extraction of nab-paclitaxel administered through HAI was greater than that from i.v. nab-paclitaxel infusion. To decrease intersubject variability, each patient assessed from the 180 mg/m^2 cohort ($n = 2$) and the 220 mg/m^2 cohort ($n = 3$) underwent 2 sets of pharmacokinetic studies. Patients first received an i.v. infusion of nab-paclitaxel in 1 arm while having blood taken from the contralateral arm during and after distribution of the drug into venous and arterial endothelial cells and lung parenchyma. Three weeks later, the patients went on to receive HAI nab-paclitaxel while having samples of venous and arterial endothelial

Table 2. Grade 2 or greater drug-related toxicity profile

	Toxicity grade			
	2	3[a]	4	5
Dose level 1 (180 mg/m^2, $n = 3$ patients with 31 total cycles assessed)				
Alopecia	3 (100%)			
Rash	1 (33%)			
Dose level 2 (220 mg/m^2, $n = 3$ patients with 9 total cycles assessed)				
Alopecia	3 (100%)			
Edema	1 (33%)			
Dose level 3 (260 mg/m^2, $n = 32$ patients with 80 total cycles assessed)				
Alopecia	30 (93.8%)			
Edema	1 (3.1%)			
Hyperbilirubinemia	1 (3.1%)	1 (3.1%)		
Nausea/vomiting	1 (3.1%)	2 (6.3%)		
Diarrhea		2 (6.3%)		
Mucositis			1 (3.1%)	
Hematuria	1 (3.1%)			
Urinary tract infection	1 (3.1%)			
Thrush		1 (3.1%)		
Confusion		2 (6.3%)		
Fatigue		3 (9.4%)		
Toxic epidermal necrolysis[b]				1 (3.1%)
Thrombocytopenia	1 (3.1%)	1 (3.1%)	1 (3.1%)	
Neutropenia		2 (6.3%)	1 (3.1%)	

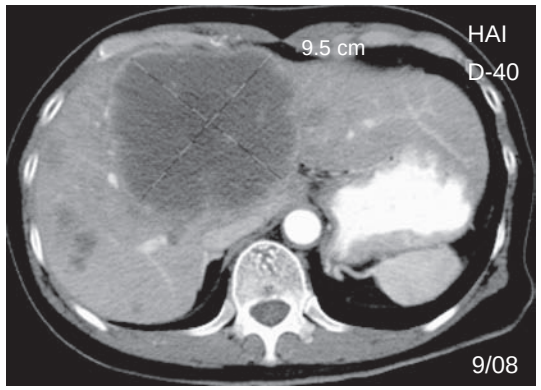
[a]No grade 3 or higher toxicity occurred during the initial 4 weeks, thus no DLT was observed.
[b]The relationship with the study drug has not been clearly established. Also, the first course of the drug was given i.v. (not HAI) in patients who developed this complication.

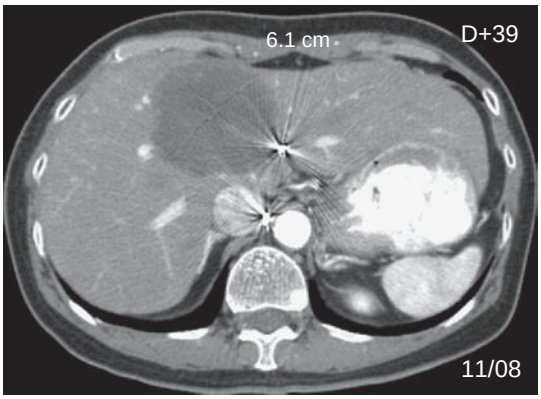
cells and lung parenchyma taken during and after the drug distribution into the hepatic parenchyma. Thus, the difference between these 2 routes of administration is the uptake of HAI nab-paclitaxel by the hepatic parenchyma in addition to the other loci. Whole-blood concentrations of paclitaxel were measured and plotted for each dose level as shown in Fig. 3. At the dose level of 220 mg/m^2 ($n = 3$), we observed mean peak concentrations (C_{max}) of 6.3 and 3.1 μg/mL and calculated drug exposures (AUC) of 17,924 and 10,288 h μg/L for i.v. and HAI nab-paclitaxel, respectively. Similar findings were confirmed at 180 mg/m^2 ($n = 2$) about mean peak concentrations, but drug exposure declined linearly in a dose-dependent fashion. Hepatic extraction is the relative amount of nab-paclitaxel delivered directly to the liver, thereby bypassing systemic exposure, which is calculated as 1 − [AUC (HAI)/AUC (i.v.)]. At the dose level of 180 mg/m^2, hepatic extraction rate was 41.7%, whereas at the dose level of 220 mg/m^2, hepatic extraction rate was 41.5%, indicating that hepatic extraction of nab-paclitaxel was saturated at the dose levels described earlier.

Discussion

Patients with advanced solid cancers and liver metastases have poor outcomes and limited treatment options. Local therapy, including surgical resection, radiation, and transcatheter arterial chemoembolization, is largely ineffective for patients with extensive hepatic metastases. HAI chemotherapy takes advantage of the fact that malignant hepatic lesions derive most of their blood supply from the hepatic artery in contrast to normal hepatic parenchyma, which derive their blood supply from both the hepatic artery and the portal venous circulation (39). Thus, HAI of cytotoxic agents results in higher local concentrations than those achieved by i.v. infusion (40) and fewer systemic toxicities (41).

The current clinical trial of HAI nab-paclitaxel in patients with predominant liver metastases showed that this regimen was well tolerated, with no DTLs observed up to the dose level of 260 mg/m^2 over 60 minutes once every 3 weeks. Pharmacokinetic analyses revealed a moderate hepatic extraction rate of approximately 42%





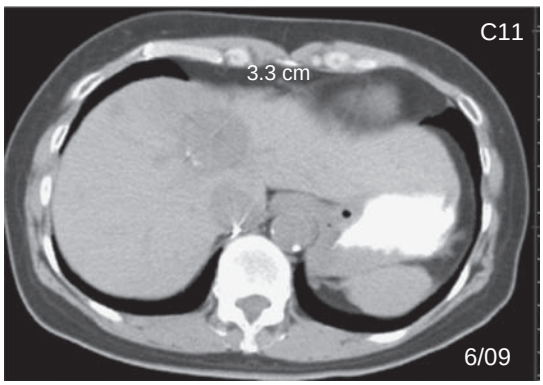


Figure 2. Computed tomographic (CT) scans of the abdomen showing hepatic lesions in a patient with metastatic cervical cancer. Top, CT scan taken pretherapy; middle and bottom, CT scans done after 2 and 11 cycles of HAI nab-paclitaxel, respectively. There was a 65% decrease in the size of liver lesions by RECIST. The patient remained on study for a total of 15 months, with the best response being a 74% overall decreased tumor burden when other metastatic lesions were included.

when HAI nab-paclitaxel was administered over a 1-hour period of time.

The results of this trial provide several interesting observations. First, HAI nab-paclitaxel can be given safely at doses up to 260 mg/m^2, which is the maximum FDA-approved i.v. dose. Second, there is approximately a 42% hepatic extraction rate for nab-paclitaxel. Third, because MTD was not defined, it is possible that raising the dose further is feasible and safe. We plan to explore whether prolonged HAI nab-paclitaxel might result in higher hepatic extraction because the hepatic uptake achieved during the 60-minute HAI infusion was saturated at different doses. Finally, HAI nab-paclitaxel combined with other anticancer agents may provide even more efficacious anticancer regimens than HAI nab-paclitaxel alone.

An intense dose-dependent tumor response was seen in the patient with metastatic cervical cancer. She achieved a PR after 2 cycles of HAI nab-paclitaxel at 180 mg/m^2 and continued to respond until cycle 16 when her tumor progressed. At the higher dose of HAI nab-paclitaxel (260 mg/m^2) given after disease progression, the patient's tumor burden decreased further by 18% after only 2 cycles of the HAI treatment. She remained on study for a total of 19 cycles.

Clinical data showed that C_{max} and AUC were well correlated with toxicities (42). When the pharmacokinetic data of HAI nab-paclitaxel were compared with those from i.v. nab-paclitaxel, C_{max} and AUC were reduced by more than 50% in patients who received HAI nab-paclitaxel. These data suggest that higher doses of HAI nab-paclitaxel might be safer than the FDA-approved i.v. dosages and are consistent with the notion that the C_{max} and AUC of i.v. nab-paclitaxel are correlated with clinical toxicities. Of course, the lower systemic exposure could also attenuate response in nonhepatic sites, hence supporting the idea that further increasing the dose of HAI nab-paclitaxel or combining it with systemic agents should be studied.

Nab-paclitaxel capitalizes upon albumin binding to its receptor (gp60) on endothelial cells, which initiates transcytosis across the endothelial cell into the extravascular space via caveolae (43–45) and then into tumor cells mediated by secreted protein acidic rich in cysteine (SPARC; ref. 46). Previous studies showed that the administration of paclitaxel directly into the hepatic artery resulted in a 95% mean hepatic extraction rate during the infusion and a 61% mean extraction rate from 5 to 9 hours after completion of the infusion (16, 47). In contrast, this trial showed approximately a 42% mean hepatic extraction rate following HAI nab-paclitaxel when administered over a 60-minute period of time. The moderate hepatic extraction rate associated with HAI nab-paclitaxel over 60 minutes could be explained by the short infusion time, saturating SPARC-mediated intracellular uptake of nab-paclitaxel (48, 49). Accumulating evidence indicates that constitutive activation of multiple signaling pathways in cancer cells requires a multitargeted approach for optimal results. Therefore, it is likely that HAI nab-paclitaxel will need to be combined with other therapeutic agents to optimize therapeutic effects. Finally, because it is well tolerated with an excellent safety profile, further study with increased dosages

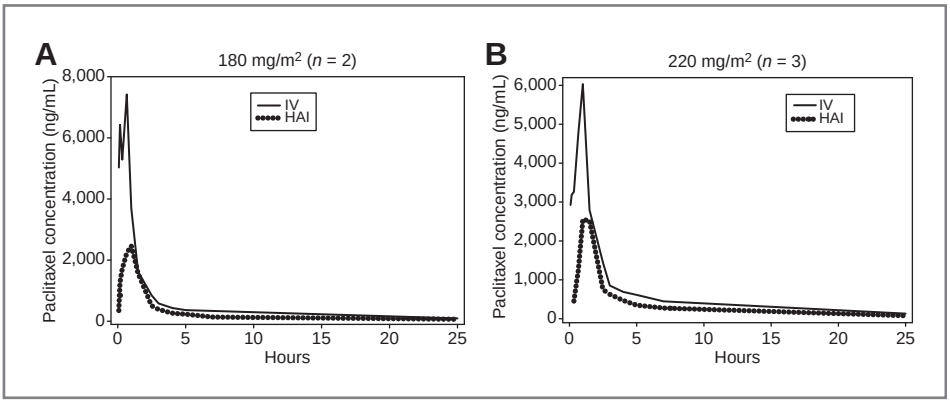


Figure 3. Comparison of time course of plasma paclitaxel concentrations between i.v. infusion and HAI at dose levels of 180 mg/m^2 (A: $n = 2$) and 220 mg/m^2 (B: $n = 3$) showed moderate hepatic extraction. Each patient had 2 sets of pharmacokinetic analyses for self-comparison (i.v. vs. HAI).

of HAI nab-paclitaxel, and prolonged infusion times to increase hepatic extraction as well as its combination with other agents, is planned.

Disclosure of Potential Conflicts of Interest

D.C. Madoff is on the consultant/advisory board of Biosphere Medical.

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