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

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ABSTRACT

Since 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 (HAI) of nanoparticle albumin-bound paclitaxel (nab-paclitaxel). Cohorts of three patients having predominant hepatic metastases received HAI nab-paclitaxel at three dose levels (180 mg/m², 220 mg/m² and 260 mg/m²) infused over 1 hour every three weeks (3 + 3 design). Some patients participated in comparative pharmacokinetic studies (IV versus HAI), receiving their first course IV, to determine peak concentrations and effect of first-pass hepatic extraction compared to 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/m². Common adverse events included alopecia, fatigue, myelosuppression, nausea and vomiting. Three patients had stable disease > 4 months and 2 patients (1/12 breast and 1/1 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 compared to IV infusion based on AUC comparison of drug exposure. HAI nab-paclitaxel demonstrated partial hepatic extraction. At doses < 260 mg/m² given for 1 hour every 3 weeks, the treatment was well tolerated and showed activity in advanced cancer patients with predominant liver metastases.
Key Words: hepatic arterial infusion, nanoparticle albumin-bound paclitaxel, hepatic extraction, pharmacokinetics, liver metastasis, phase I trial, regional therapy
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), flouxuridine (FUDR) (17-21), interleukin-2 (22, 23), 5-fluorouracil (5-FU)/leucovorin (24), and interferon (25-28). Although many studies demonstrated higher response rates for HAI treatment compared to intravenous (IV) infusion, most have not shown an overall survival advantage for HAI (29). However, a randomized phase III trial of HAI with flouxuridine plus IV fluorouracil resulted in improved overall survival (72.2 versus 59.3 months) and progression-free survival (37.4 versus 17.2 months) in 74 colorectal cancer patients compared to 82 similar patients receiving systemic chemotherapy alone (4). A similar study demonstrated a greater rate of response, time to hepatic progression, and overall
survival in patients with hepatic metastases from colorectal cancer treated with HAI versus IV chemotherapy(30). Considering these combined results, it appears 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 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 (MD Anderson), 10 patients with liver predominant metastases of breast cancer received once monthly 24-hour continuous HAI paclitaxel at 200 mg/m² for a total of 56 cycles, resulting in a 30% partial remission rate, including one 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 intraarterial 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) 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 IV 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 (ECOG) performance status ≥ 2; absolute neutrophil counts (ANC) ≥ 1500/mm³, platelets ≥ 100,000/mm³; creatinine ≤ 2 mg/dL or a calculated glomerular filtration rate (GFR) based on the Cockcroft-Gault Equation > 40 mL/min if creatinine was > 2 mg/dL; alanine aminotransferase (ALT) ≤ 5 times upper limits of normal; bilirubin ≤ 2 mg/dL; the ability to understand and willingness to sign an IRB-approved informed consent; and full recovery from all previous therapies. Exclusion criteria included clinically significant ascites, pregnancy or breastfeeding, hypersensitivity to nab-paclitaxel, untreated bleeding diathesis, evidence of portal vein thrombosis and clinically significant peripheral vascular disease, neuropathy ≥ grade 2, 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 mg/m², 220 mg/m² and 260 mg/m², the latter being the highest dose level approved by the FDA for IV 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 six patients were treated with ≤ 1 patient experiencing a DLT occurring during the first 4 weeks. A hematologic DLT was defined as platelets < 25,000/mm³ or bleeding associated with platelets < 50,000/mm³, ANC < 500/mm³ for > 7 days, neutropenic fever, or > 14 days of delay in initiation of subsequent treatment because of inadequate hematologic parameters, while a non-hematologic DLT was defined as a ≥ grade 3 non-hematologic toxicity using NCI CTCAE v3.0 toxicity criteria(34) other than nausea, vomiting, fatigue or elevated hepatic enzymes only.

All patients were evaluated for toxicity for all cycles using NCI CTCAE v3.0 toxicity criteria and for efficacy using the 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 (SD) 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 utilized to describe the association among each type of survival and covariates of interest.
Statistical analyses were carried out using GraphPad Prism (San Diego, CA) and a p-value < 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 non-iodinated contrast media) of the celiac axis and superior mesenteric artery was performed 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 1500 IU of heparin intraarterially over 60 minutes without prophylactic medications. The hepatic intraarterial catheter was removed once the intraarterial 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 > 1500/mm$^3$, platelet count > 100,000/mm$^3$, and the resolution of toxicity to < grade 2 or to the pre-therapy baseline level.
In general, anemia was not an indication for dose reduction. Patients who experienced ≥ grade 3 thrombocytopenia and/or neutropenia had a dose reduction of 25% and prophylactic granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) 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 non-hematologic 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 performed for patients enrolled in the dose escalation phase. Two sets of pharmacokinetic studies were performed to compare peak drug concentrations and systemic drug exposure of IV and HAI nab-paclitaxel, both given over 60 minutes.

Samples of 4 mL whole blood were obtained in sodium heparin tubes from an indwelling venous catheter placed in the arm (in the contralateral arm if IV nab-paclitaxel is given) at the following 12 time points: 0 (predose), 5, 10, 20, 40 minutes, and 1 (within 5 minutes prior to 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 (LC/MS/MS) (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 non-compartmental analysis (NCA) using WinNonlin version 5.2 software (Pharsight Corporation, Mountain View, CA). The peak or maximum paclitaxel concentration (Cmax) 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 \( \ln 2 / \) the elimination rate constant. The area under the curve (AUC) from time 0 to infinity (AUC\(_{\text{inf}}\)) 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\(_{\text{inf}}\)) was used to determine total-body clearance. The volume of distribution was calculated as total-body clearance divided by the elimination rate constant.
RESULTS

Patient Characteristics

A total of 38 patients (median age, 61 years; range, 38 to 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), sarcoma (n=2 patients) and one patient each with cervical, pancreatic, prostate cancer, angiosarcoma, leiomyosarcoma, and carcinoid tumor (n=6 patients). All 38 patients were evaluable for toxicity. All 38 patients were considered evaluable for response, including 26 patients who were evaluable by RECIST criteria as shown in Figure 1. Eight patients showed clinical progression, two patients received 1 cycle of the treatment with early withdrawal for hospice care, and two patients died, as described below. 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 dose 260 mg/m². She was one of the patients who received her first course of therapy by IV infusion, not 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/m², 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 ≥2 grade toxicities included rash, nausea, vomiting, diarrhea, mucositis, hematuria, neutropenia and thrombocytopenia, as shown in Table 2.

**Antitumor Activity**

Among 38 patients, four patients withdrew after 1 cycle of treatment because of rapid tumor progression and/or adverse events. Three patients had SD > 4 months (7.9%). Two patients (1/12 breast cancer, and 1/1 cervical cancer) achieved PR (5.3%) as shown in Figure 2, lasting for 5 months 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 post-surgery.

**Pharmacokinetic Studies**

Pharmacokinetic analyses were conducted to determine whether hepatic extraction of nab-paclitaxel administered through HAI was greater than that from IV nab-paclitaxel infusion. To decrease intersubject variability, each patient assessed from the 180 mg/m² cohort (n=2) and the 220 mg/m² cohort (n=3) underwent two sets of pharmacokinetic studies. Patients first received an IV infusion of nab-paclitaxel in one 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 cells and lung parenchyma taken during and after the drug distribution into the hepatic parenchyma. Thus, the difference between these two 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 Figure 3. At the dose level of 220 mg/m² (n=3), we observed mean peak concentrations (Cmax) of 6.3 and 3.1 mcg/mL and calculated drug exposures (AUC) of 17,924 and 10,288 hr-mcg/L for IV and HAI nab-paclitaxel, respectively. Similar findings were confirmed at 180 mg/m² (n=2) in regards to 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 (IV)]. At the dose level of 180 mg/m², hepatic extraction was 41.7% while at the dose level of 220 mg/m², hepatic extraction was 41.5%, indicating that hepatic extraction of nab-paclitaxel was saturated at the dose levels described above.
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 IV administration (40) and fewer systemic toxicities (41).

The current clinical trial of HAI nab-paclitaxel in patients with predominant liver metastases demonstrated that this regimen was well tolerated with no DTLs observed up to the dose level of 260 mg/m² over 60 minutes once every 3 weeks. Pharmacokinetic analyses revealed moderate hepatic extraction of approximately 42% when HAI nab-paclitaxel was administered over a one-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/m², which is the maximum FDA approved IV dose. Second, there is approximately a 42% hepatic extraction for nanoparticle albumin-bound paclitaxel. Third, since an 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 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 intensity 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/m², and continued to respond until cycle 16 when her tumor progressed. At the higher dose of HAI nab-paclitaxel (260 mg/m²) 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 Cmax and AUC were well correlated with toxicities (42). When the pharmacokinetic data of HAI nab-paclitaxel were compared with those from IV nab-paclitaxel, Cmax 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 IV dosages, and are consistent with the notion that the Cmax and AUC of IV nab-paclitaxel are correlated with clinical toxicities. Of course, the lower systemic exposure could also attenuate response in non-hepatic 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)[46]. Previous studies showed that administration of paclitaxel directly into the hepatic artery resulted in a 95% mean hepatic extraction during the infusion and a 61% mean extraction from 5 to 9 hours after completion of the infusion (16, 47). In contrast, this trial demonstrated approximately a 42% mean hepatic extraction following HAI of 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 multi-targeted 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 of HAI nab-paclitaxel, and prolonged infusion times to increase hepatic extraction as well as its combination with other agents is planned.
REFERENCES

Acknowledgements

The authors thank Vivianne Velez-Bravo and Rhonda Clement in the Department of Investigational Cancer Therapeutics at MD Anderson Cancer Center for coordinating the study, Yan-Ping Zhang in the Department of Pharmacy Research at MD Anderson Cancer Center for technical support on pharmacokinetic studies, and Joann Aaron in the Department of Investigational Cancer Therapeutics at MD Anderson Cancer Center for editing our manuscript.
Table 1. Baseline Characteristics of Treated Patients (n=38 patients)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>No.</th>
<th>%</th>
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<tbody>
<tr>
<td><strong>Age, years</strong></td>
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<td></td>
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<tr>
<td>Mean</td>
<td>59.2</td>
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<tr>
<td>SD</td>
<td>10.7</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Female</td>
<td>24</td>
<td>63.2%</td>
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<tr>
<td>Male</td>
<td>14</td>
<td>36.8%</td>
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<tr>
<td><strong>No. of prior chemotherapy regimens</strong></td>
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<td>Range</td>
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<tr>
<td>0</td>
<td>10</td>
<td>26.3%</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>65.8%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>7.9%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
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<td>White</td>
<td>31</td>
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<td>Black</td>
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<td>7.9%</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
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<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>12</td>
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</tr>
<tr>
<td>Colorectal Cancer</td>
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<tr>
<td>Melanoma</td>
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<td>Esophageal Cancer</td>
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<tr>
<td>Cholangiocarcinoma</td>
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</tr>
<tr>
<td>Ovarian Cancer</td>
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<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2</td>
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<tr>
<td>Others (carcinoid tumor, cervical, Angiosarcoma, leiomyosarcoma, prostate and pancreatic cancer each)</td>
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<tr>
<td><strong>No. of patients per dose level</strong></td>
<td></td>
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<tr>
<td>DL1 (180 mg/m²)</td>
<td>3</td>
<td>7.9%</td>
</tr>
<tr>
<td>DL2 (220 mg/m²)</td>
<td>3</td>
<td>7.9%</td>
</tr>
<tr>
<td>DL3 (260 mg/m²)</td>
<td>32</td>
<td>84.2%</td>
</tr>
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Abbreviations: DL, dose level; ECOG, Eastern Cooperative oncology group; No., number; and SD, standard deviation.
Table 2. Grade 2 Drug-related Toxicity Profile

<table>
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<th>Toxicity Grade</th>
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<td><strong>Dose level 1</strong> (180 mg/m², n = 3 patients with 31 total cycles assessed)</td>
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<tr>
<td>Alopecia</td>
<td></td>
<td>3 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>1 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose level 2</strong> (220 mg/m², n = 3 patients with 9 total cycles assessed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td>3 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td></td>
<td>1 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose level 3</strong> (260 mg/m², n = 32 patients with 80 total cycles assessed)</td>
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<tr>
<td>Alopecia</td>
<td></td>
<td>30 (93.8%)</td>
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<tr>
<td>Edema</td>
<td></td>
<td>1 (3.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1 (3.1%)</td>
<td>1 (3.1%)</td>
<td></td>
<td></td>
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<tr>
<td>Nausea/Vomiting</td>
<td>1 (3.1%)</td>
<td>2 (6.3%)</td>
<td></td>
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</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>2 (6.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
<td>1 (3.1%)</td>
<td></td>
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<tr>
<td>Hematuria</td>
<td></td>
<td>1 (3.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine tract infection</td>
<td>1 (3.1%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Thrush</td>
<td></td>
<td>1 (3.1%)</td>
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<tr>
<td>Confusion</td>
<td></td>
<td>2 (6.3%)</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Toxic epidermal necrolysis*</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Neutropenia</td>
<td>2 (6.3%)</td>
<td>1 (3.1%)</td>
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</table>

* The relationship to the study drug has not been clearly established. Also, the first course of the drug was given IV (not HAI) in patients who developed this complication.

** No grade 3 or higher toxicity occurred during the initial 4 weeks, thus no DLT was observed.
Figure Legends

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

Figure 2. Computed tomography (CT) scans of the abdomen showing hepatic lesions in a patient with metastatic cervical cancer. The upper CT scan was taken pretherapy; the middle and lower CT scans were done after 2 and 11 cycles of HAI nanoparticle albumin-bound 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.

Figure 3. Comparison of time course of plasma paclitaxel concentrations between IV infusion and HAI at dose levels of 180 mg/m$^2$ (Panel A: n = 2) and 220 mg/m$^2$ (Panel B: n = 3) demonstrated moderate hepatic extraction. Each patient had 2 sets of pharmacokinetic analyses for self-comparison (IV versus HAI).
Figure 1
Figure 2
Figure 3

Panel A

Panel B

Figure 3
Molecular Cancer Therapeutics

Phase I Trial of Hepatic Arterial Infusion of Nanoparticle Albumin-Bound Paclitaxel in Cancer Patients with Predominant Hepatic Metastases: Toxicity, Pharmacokinetics, and Activity.

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