Phase I Clinical Trial of STA-4783 in Combination with Paclitaxel in Patients with Refractory Solid Tumors

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Abstract

Purpose: STA-4783 is a new compound that markedly enhances the therapeutic index of paclitaxel against human tumor xenograft models. A phase I clinical trial was undertaken to determine the maximum tolerated dose, toxicity profile, and pharmacokinetics of STA-4783 in combination with paclitaxel.

Experimental Design: Adults with refractory solid tumors concurrently received STA-4783 and paclitaxel as a 3-h i.v. infusion at starting doses of 44 and 135 mg/m^2, respectively. After increasing paclitaxel to 175 mg/m^2, the STA-4783 dose was escalated as permitted by dose-limiting toxicity during the first 21-day cycle.

Results: Thirty-five patients were treated with eight dose levels of STA-4783/paclitaxel. In patients receiving 175 mg/m^2 paclitaxel, the incidence of severe toxicity increased with escalation of the STA-4783 dose above 263 mg/m^2, and 438 mg/m^2 was the maximum tolerated dose. All toxicities were typical of paclitaxel, with neutropenia, mucositis, and myalgia/arthralgia being dose limiting. Partial responses were achieved in one patient with Kaposi's sarcoma and another with ovarian cancer that progressed during prior treatment with paclitaxel. STA-4783 exhibited linear pharmacokinetics characterized by rapid elimination from plasma (biological half-life, 1.06 ± 0.24 h) and a low steady-state apparent volume of distribution (25.1 ± 8.1 L/m^2). The total body clearance of paclitaxel decreased significantly with escalation of the STA-4783 dose.

Conclusions: The STA-4783/paclitaxel combination was well tolerated with a toxicity profile similar to single-agent paclitaxel. Enhanced systemic exposure to paclitaxel resulting from a dose-dependent interaction with STA-4783 was associated with increased toxicity. Objective responses in two heavily pretreated patients, both with taxane exposure, have encouraged further clinical evaluation of this regimen.

Introduction of the taxanes, paclitaxel, and docetaxel into clinical use has notably improved the treatment of patients with various solid tumors. In particular, both drugs have significant single-agent activity against metastatic breast cancer, advanced ovarian cancer, and advanced non–small cell lung cancer (1–3). Efficacy against ovarian cancer and non–small cell lung cancer is enhanced considerably when the taxanes are combined with cisplatin or carboplatin (2, 3). Taxane-platinum regimens are currently considered to be one of the preferred options for first-line treatment of these diseases. Unfortunately, despite the important advances that have been achieved with taxane-based chemotherapy in treatment outcomes, these regimens are generally not curative, as disease progression occurs eventually in all patients with advanced ovarian cancer and non–small cell lung cancer (2, 3). As with any other cytotoxic chemotherapeutic agent, the potential effectiveness of the taxanes is limited by the severity and frequency of host toxicities that occur at sufficiently high doses. Neutropenia is the principal dose-limiting toxicity (DLT) of both clinically approved taxanes. Peripheral neuropathy, arthralgia, and myalgia are also significant complications (4).

Ongoing efforts to further optimize the taxane-platinum regimens may improve tolerability, but it is unlikely that clinical efficacy can be significantly enhanced. This stimulated interest in identifying compounds that could favorably modulate the antiproliferative activity of paclitaxel against tumor cells without affecting host toxicity, thereby effectively increasing the therapeutic index of the drug. *N*-malonyl-bis(*N*′-methyl-*N*′-thiobenzoylhydrazide) (STA-4783; Fig. 1) is a compound that exhibits these characteristics. It was originally identified by empirically screening for compounds that

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Note: A. Berkenblit and J.P. Eder contributed equally to this work.

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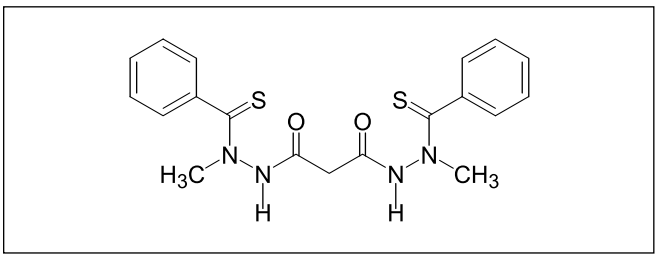

Fig. 1. Chemical structure of STA-4783.

enhanced the *in vitro* cytotoxicity of paclitaxel against human tumor cell lines. Preclinical studies done at the Southern Research Institute (Birmingham, AL) showed that the growth of human tumor xenografts in CD-1 nude mice is unaffected by treatment with STA-4783 alone. In contrast, administering STA-4783 in combination with paclitaxel dramatically enhanced the antitumor activity achieved with single-agent paclitaxel, in a dose-dependent manner, without increasing host toxicity. Synergistic activity with paclitaxel was shown against human tumor xenografts of breast cancer, lung cancer, and lymphoma cell lines. In addition, the number of animals with sustained tumor-free regressions after completing treatment was significantly greater in groups that received the STA-4783/paclitaxel combination compared with treatment with paclitaxel alone. The underlying mechanism responsible for the synergistic effect of STA-4783 on the antitumor activity of paclitaxel remains to be elucidated, although preliminary experiments suggest that it may be related to enhanced immune-mediated cytotoxicity. However, the effect is not simply a consequence of a pharmacokinetic interaction because the plasma pharmacokinetics of paclitaxel in mice was found to be unaffected by coadministration of STA-4783.

This report describes the results of the first phase I clinical trial of STA-4783. The study was designed to identify the maximum tolerated dose (MTD) of STA-4783 when given concurrently with the standard 175 mg/m^2 dose of paclitaxel as a 3-h i.v. infusion, repeated every 21 days, in adult patients with refractory solid tumors. Additional objectives of the study were to characterize the pharmacokinetic behavior of STA-4783 in humans and to assess whether it has any effect on the plasma pharmacokinetics of paclitaxel when coadministered.

Materials and Methods

Patient selection. Patients with histologically confirmed solid tumors that were metastatic or unresectable and for which no standard therapy existed were eligible for this study. They were required to be at least 18 years old, have an Eastern Cooperative Oncology Group performance status of 0 to 2, and have a life expectancy of >12 weeks. Acceptable hematologic (absolute neutrophil count ≥1,500 cells/μL, platelet count ≥100,000/μL), hepatic (aspartate aminotransferase and alanine aminotransferase ≤2.5 times the upper limit of normal, normal total bilirubin), and renal (serum creatinine <1.5 mg/dL or measured creatinine clearance >50 mL/min) function as well as an electrocardiogram without evidence of clinically significant conduction abnormalities or active ischemia were required. Patients with a history of treated brain metastases that were clinically stable for at least 4 weeks were eligible. Conditions resulting in exclusion from the study included any of the following: baseline neuropathy grade ≥2, history of significant neurologic problems, treatment with approved or investigational anticancer agents or radiation within 4 weeks (6 weeks for chloroethylnitrosoureas or mitomycin C), prior high-dose chemotherapy with autologous stem cell rescue or bone marrow transplantation, history of severe allergic reaction to taxanes, current pregnancy or breast-feeding, and an uncontrolled intercurrent medical condition or psychiatric illness that would limit compliance with study requirements. Patients whose tumors had progressed during previous treatment with a taxane were not excluded, although the efficacy of the STA-4783/paclitaxel combination has not been evaluated in taxane-resistant tumor models. The protocol for this clinical trial was approved by the Dana-Farber/Harvard Cancer Center (Boston, MA) Scientific Review Committee and Institutional Review Board. Patients signed a written informed consent document satisfying all institutional, state, and federal requirements as a condition of registration into the study.

Drug administration. Paclitaxel (Bristol-Meyers Squibb Co., Wallingford, CT) was obtained from commercial sources as the standard dosage form for injection. STA-4783 was provided by Synta Pharmaceuticals (Lexington, MA) as 75 and 300 mg of a dry powder, free of excipients, in 50 mL vials. Because of the poor water solubility of STA-4783, the drug was reconstituted by adding Paclitaxel Injection USP [sterile solution containing 6 mg paclitaxel, 527 mg of purified Cremophor EL, and 49.7% (v/v) dehydrated alcohol, USP in each mL] directly into a single STA-4783 vial. The paclitaxel/STA-4783 doses (mg/m^2) are reducible to whole number ratios, ranging from 4:1 to 1:3 at each dose level to be evaluated, allowing the precise volume of Paclitaxel Injection USP required to prepare any dose to be readily determined. The vial was manually shaken and placed in an ultrasonic bath at 25 ± 3°C for 5 min or until the solid was completely dissolved. In the event that multiple vials of STA-4783 were required for a given dose, this procedure was repeated sequentially by transferring the entire volume of paclitaxel/STA-4783 solution into another vial of STA-4783. For example, the ratio was 1:2 for dose level 6, 175 mg/m^2 paclitaxel, and 350 mg/m^2 STA-4783. To prepare the dosing solution for a patient with a bovine serum albumin of 1.60 m^2, 50 mL of Paclitaxel Injection USP (300 mg) were added to a 300 mg vial of STA-4783 and the resulting solution was transferred into another 300 mg vial of STA-4783. Following sonication, the appropriate volume of this 1:2 (w/w) paclitaxel/STA-4783 solution (46.7 mL) was added to 250 mL of 0.9% Sodium Chloride Injection USP in a non–polyvinyl chloride infusion bag for administration. The final dosing solution is stable for up to 7 h at ambient temperature.

Treatment was delivered on an outpatient basis whenever possible. All patients were premedicated with dexamethasone, diphenhydramine, and a histamine H_2-receptor antagonist to prevent hypersensitivity reactions to Cremophor EL in the paclitaxel vehicle as well as a 5-HT_3 receptor antagonist antiemetic. STA-4783/paclitaxel was administered as a 3-h continuous i.v. infusion using a non–polyvinyl chloride containing administration set with a 0.22-μm microporous membrane inline filter. Treatment with the same doses of STA-4783 and paclitaxel was repeated every 21 days, for a maximum of six cycles, for patients who did not experience a DLT, as defined below, if all eligibility requirements continued to be satisfied. Retreatment could be delayed for not more than 2 weeks to permit recovery from toxicity of the previous dose. Patients experiencing a DLT that resolved to grade ≤1 within 2 weeks received the next lower dose level of STA-4783/paclitaxel on retreatment. A one-time, discretionary, 25% reduction in the paclitaxel dose was permitted in the event of myelosuppression.

Erythropoietin and blood transfusions were permitted anytime as clinically indicated. The use of other hematopoietic growth factors was prohibited only during the first 21-day cycle of therapy. Treatment with any other approved or investigational chemotherapeutic agent and radiation was not permitted. Therapy was discontinued for any of the following reasons: progressive disease, life-threatening toxicity, incomplete recovery from toxicity, physician decision in consideration of other medical conditions, and patient request or noncompliance with the protocol.

Dose escalation. The starting doses of STA-4783 and paclitaxel were 44 and 135 mg/m^2, respectively. After increasing the paclitaxel dose to 175 mg/m^2 with 44 mg/m^2 STA-4783 (dose level 2), the paclitaxel dose was maintained at 175 mg/m^2 as the STA-4783 dose was escalated as follows in dose levels 3 to 8: 88, 175, 263, 350, 438, and 525 mg/m^2. STA-4783 could not be delivered at doses >525 mg/m^2 because of the practical limitation imposed by the solubility of the compound. The MTD was established by the occurrence of DLTs during the initial 21-day cycle of therapy. DLT was defined as any of the following adverse events: (*a*) absolute neutrophil count ≤500 cells/μL for ≥5 days; (*b*) febrile neutropenia (temperature ≥101°F with absolute neutrophil count ≤500 cells/μL); (*c*) platelet count ≤50,000 cells/μL for ≥4 days (without transfusion); (*d*) anemia grade ≥3 with erythropoietin; (*e*) nausea and/or vomiting grade ≥3 despite maximum antiemetic premedication; and (*f*) any other nonhematologic toxicities grade ≥3, including hypersensitivity reactions with premedication.

Groups of three patients were initially treated at each dose level. Escalation of the dose to the next scheduled level proceeded if there were no DLTs in any of the patients entered into the current dose level within 21 days after treatment. An additional three patients were entered into a given dose level in cases where a single patient experienced a DLT. Dose escalation proceeded in the absence of a DLT in these additional patients. The occurrence of a DLT in at least two patients from any cohort of three to six patients established the preceding dose level as the MTD. Additional patients were enrolled at this lower dose level only if fewer than six had been evaluated for confirmation of the MTD.

Patient evaluations. Preliminary evaluations done within 14 days of beginning treatment in the study included a medical history, physical and neurologic examinations, performance status determination, electrocardiogram, chest X-ray, complete blood count with platelet and differential counts, coagulation tests (prothrombin time and partial thromboplastin time), standard serum chemistry profile with electrolyte measurements, urinalysis, pregnancy test for women of childbearing potential, and radiographic tumor measurement. A physical examination with a neurologic evaluation and a complete blood count with differential and platelet counts was done within 72 h before and 72 h after each STA-4783/paclitaxel administration. These tests were repeated, together with a performance status evaluation, urinalysis, and determination of serum chemistry variables, on a weekly basis. Toxicities were characterized according to the National Cancer Institute Common Toxicity Criteria version 2.0.[6]

In patients with measurable disease, response was based on changes in the sum of the largest diameter of target tumor lesions determined by unidimensional measurement according to the Response Evaluation Criteria in Solid Tumors (5). Patients with Kaposi's sarcoma were evaluated by the AIDS Clinical Trial Group response criteria (6). A baseline assessment of measurable disease by computed tomography was done within 2 weeks of beginning therapy. Tumor markers were measured as appropriate. Evaluations to assess therapeutic response were done after completing every second cycle of therapy until relapse. The duration of a response was measured from the date that the response was first recorded to the date of documented disease progression. Complete response was defined as the disappearance of all target lesions. A 30% or greater reduction in the longest diameter of target lesions defined a partial response. A confirmatory disease measurement was done at least 4 weeks after documenting a complete or partial response. Progressive disease was defined as a 20% or greater increase in the longest diameter of target lesions. Stable disease was defined as a difference in the target lesions that could not be classified as either a partial response or a progressive disease.

Pharmacokinetic studies. Sampling to characterize the plasma pharmacokinetics of paclitaxel and STA-4783 was done during the first cycle of therapy. Blood specimens were drawn from a peripheral vein in the arm opposite to that used for dosing in tubes containing freeze-dried sodium heparin. Blood samples (7 mL) for paclitaxel pharmacokinetics were obtained at the following times relative to the start of the drug infusion: 10 min, 1.5 h, 3.0 h, 3.25 h, 4.0 h, 6.0 h, 8.0 h, 24 h, and 48 h. A second set of blood samples (3 mL) for STA-4783 pharmacokinetics was collected at 1.0, 3.0, 3.5, 4.0, 5.0, 7.0, and 8.0 h. Sample tubes were mixed by inversion and placed over wet ice until centrifuged (1,200 × *g*, 10 min, 4°C) within 10 min. Plasma was removed from the paclitaxel sample tubes and transferred directly into a polypropylene cryovial for storage at −70°C until assayed. For the STA-4783 samples, 1,000 μL plasma was pipetted into a 2 mL plastic tube containing 100 μL DMSO. The contents of the tube were mixed gently and stored at −70°C.

A validated analytic method based on isocratic reversed-phase high-performance liquid chromatography with electrospray ionization mass spectrometric detection was used to measure the concentration of paclitaxel in plasma as previously reported (7). During application for the analysis of samples from this study, the between-day accuracy and precision of the assay were 111.5% and 6.2%, respectively, at the 0.50 ng/mL lower limit of quantitation. At all other concentrations in the calibration curve, the between-day accuracy ranged from 95.3% to 102.6% and the precision ranged from 1.8% to 6.2%.

The concentration of STA-4783 in plasma was determined by high-performance liquid chromatography with tandem mass spectrometric detection. Pharmacokinetic plasma samples that contained 10% DMSO were thawed at room temperature. In a 96-deep-well polypropylene plate, 275 μL of each sample were mixed with 50 μL of internal standard solution [2.5 μg/mL of [$^{13}C_4$]STA-4783 in acetonitrile/water (1:9) containing 11 mmol/L DTT] and 750 μL acetonitrile. The plate was shaken, sonicated for 2 min, and then centrifuged at 3,520 rpm for 10 min. Approximately 800 μL of supernatant were transferred from each well into a clean 96-well plate, evaporated under nitrogen at 55°C, and reconstituted by adding 100 μL of formic acid/acetonitrile/water (0.1:10:90). The plate was shaken, centrifuged for 10 min, and placed into an autosampler. Sample solution (40 μL) was loaded onto a 3-μm Polaris C18-A, 2.0-mm internal diameter × 50 mm, high-performance liquid chromatography column (Varian, Inc., Palo Alto, CA), and separated by gradient elution using a mixture of acetonitrile and water containing 0.1% formic acid as the mobile phase at a flow rate of 0.5 mL/min. The amount of acetonitrile in the mobile phase was 5% from the beginning of the run to 0.5 min and then increased linearly to 95% over 1.2 min and held at 95% until 2.5 min, whereupon it was decreased back to 5%. The run time was ~3 min. A Perkin-Elmer Sciex API 3000 LC/MS/MS system with a turbo ionspray interface (Perkin-Elmer, Thornhill, Ontario, Canada), operated with a source temperature of 450°C, was used for detection. Multiple reaction monitoring with a dwell time of 100 ms was used to detect positive ions resulting from the *m/z* 399.0→165.1 and 402.9→165.0 transitions for STA-4783 and the internal standard, respectively. Quantitation was based on integrating peaks corresponding to elution of the drug and internal standard in the extracted product ion chromatograms.

The concentration range of the calibration standards of STA-4783 in human plasma was 1.00 to 500 ng/mL. Study samples were assayed together with a series of eight calibration standards and a three quality control samples. Standard curves were constructed by plotting the drug/internal standard chromatographic peak area ratio against the known drug concentration in each calibration standard. Linear least squares regression was done with weighting in proportion to concentration^{-2} of each calibration standard. Calibration curves exhibited excellent linearity with correlation coefficients of >0.981. Values of the slope and y-intercept of the best-fit line were used to calculate the drug concentration in study samples. Specimens with concentrations exceeding the upper range of the standard curve were reassayed on appropriate dilution with drug-free human plasma.

The analytic method was thoroughly validated according to current recommendations (8). Peaks that interfered with detection of the drug or internal standard were not evident in chromatograms of drug-free

[6] http://ctep.cancer.gov/forms/ctcv2nom-4-30-99-final3.pdf.

plasma from anonymous donors and plasma samples obtained shortly before the administration of STA-4783/paclitaxel from cancer patients participating in this clinical trial. STA-4783 was stable in human plasma containing 10% DMSO at −70°C for at least 63 days. Interday accuracy of the assay for measuring quality control samples of STA-4783 in human plasma at concentrations of 3.00, 40.0, and 300 ng/mL ranged from 96.7% to 102.0% of the known concentrations, and the precision, calculated as the coefficient of variation, was 7.8% to 15.4%.

Actual sample times were calculated relative to the beginning of the infusion. Individual patient plasma concentration-time data were analyzed by standard noncompartmental methods using WinNonlin Professional version 4.0.1 (Pharsight Corp., Cary, NC; ref. 9). Area under the plasma concentration-time curve (AUC) was estimated using the log-linear trapezoidal algorithm to the last data point, with extrapolation to time infinity using the estimated value of the slope of the terminal log-linear disposition phase. The area under the first moment curve was determined in an analogous manner after multiplying each observed plasma concentration by the sample time. The pharmacokinetic variables estimated by the program included total body clearance, half-life of the terminal disposition phase ($t_{1/2,z}$), mean residence time, and the apparent volume of distribution at steady-state (V_{ss}). Mean values of the pharmacokinetic variables were calculated as the geometric mean of the individual patient values (10–12). Parametric statistical tests (two tailed) of pharmacokinetic variables were done using log-transformed values of the variable values. Linear regression was used to assess dose-dependent trends in pharmacokinetic variables. $P < 0.05$ was considered to be significantly different.

Results

Patient characteristics. Characteristics of the 35 patients who were enrolled in the clinical trial and treated with STA-4783/paclitaxel are summarized in Table 1. The group was composed of 20 males (57%) and 15 females (43%) with a median age of 57 years (range, 33-72 years). Thirteen different tumor types were represented, with the most prevalent being melanoma in seven (20%) patients. The majority of patients were heavily pretreated, with 74% having received at least four prior therapies, including paclitaxel in 14 patients. Nevertheless, 91% of the patients were in good to excellent physical condition as indicated by an Eastern Cooperative Oncology Group performance status of 0 and 1.

Table 1. Patient characteristics

No. patients	35
Age (y)	
Median (range)	57 (33-72)
Gender	
Male	20 (57)
Female	15 (43)
ECOG performance status	
0	11 (31)
1	21 (60)
2	3 (9)
Histologic diagnosis	
Melanoma	7 (20)
Ovarian	5 (14)
Pancreatic	4 (11)
Colorectal	3 (9)
Gastroesophageal	3 (9)
Kaposi's sarcoma	3 (9)
Sarcoma	3 (9)
Other	7 (20)
No. prior therapies	
1-3	9 (26)
4-6	15 (43)
7-9	10 (29)
10	1 (3)

NOTE: Unless indicated otherwise, data are reported as number of patients, with the percentage relative to the entire group in parentheses.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Maximum tolerated dose. Groups of three patients were evaluated at each of the first five dose levels, in which the STA-4783/paclitaxel doses were increased from 44/135 mg/m^2 (dose level 1) to 263/175 mg/m^2 (dose level 5) without the occurrence of any DLT during the first cycle of therapy. Each of the three higher dose levels, 350 mg/m^2 STA-4783 (dose level 6), 438 mg/m^2 STA-4783 (dose level 7), and 525 mg/m^2 STA-4783 (dose level 8) with 175 mg/m^2 paclitaxel, was expanded due to DLTs in one of the initial three patients evaluated. These events were febrile neutropenia (dose level 6), grade 3 myalgia and arthralgia (dose level 7), and grade 4 neutropenia (dose level 8). In addition, a single patient in dose level 6 and another in dose level 7 were removed from the study for nontreatment-related causes before completing the first cycle and replaced with another patient. The three additional evaluable patients in dose levels 6 and 7 did not experience a DLT. Unacceptable grade 4 neutropenia occurred in two of six patients in dose level 8, establishing dose level 7, 448 mg/m^2 STA-4783 combined with 175 mg/m^2 paclitaxel, as the MTD.

Toxicity. A total of 86 cycles of STA-4783/paclitaxel was delivered to 33 evaluable patients during the course of this study. The number of treatment cycles received by individual patients ranged from one to six with a median of two cycles per patient. Clinically significant toxicities observed at each dose level that were categorized as being at least possibly related to treatment are summarized in Table 2. Twenty-five (76%) patients experienced at least one adverse event of grade ≥2, and grade 3 to 4 toxicities occurred in 13 (39%) patients. As indicated in Table 2, the frequency and severity of the toxicities tended to increase as the dose of STA-4783 was escalated, whereas the paclitaxel dose was maintained at 175 mg/m^2 in dose levels 2 to 8. The most frequently observed toxicities, occurring in at least three patients, included fatigue (33%), myalgia/arthralgia (21%), neutropenia (21%), leukopenia (15%), neuropathy (9%), and mucositis (9%). Myelosuppression was modest and consistent with that of single-agent paclitaxel given at a dose of 175 mg/m^2 once every 3 weeks. Nonhematologic toxicities were also similar to those expected for paclitaxel alone. Toxicities that occurred in single patients in dose levels 4 to 8, categorized as being possibly treatment related, included anorexia, hyperglycemia, hypophosphatemia, candidiasis infection, abdominal pain, hypoasthesia, pulmonary embolism, and pruritic rash. Each of these events was grade 2, with the exception of grade 3 pulmonary embolism and grade 3 abdominal pain in two patients in dose level 7.

Response. All three patients enrolled for treatment with the starting dose had Kaposi's sarcoma, which was considered to be appropriate because 135 mg/m^2 paclitaxel is the dose typically used in this disease. Among the 24 patients who were evaluable for response, two partial responses were observed: 1 in a patient with Kaposi's sarcoma and the other in an ovarian cancer patient. The former patient received six cycles of STA-4783/

Table 2. Summary of clinical toxicities for all cycles of therapy

	No. cycles with toxicity grade 2/3/4 at dose level							
	1	2	3	4	5	6	7	8
No. patients evaluated	3	3	3	3	3	6	6	6
No. cycles delivered	10	6	7	8	11	19	12	13
Hematologic								
Anemia		0/1/0	1/0/0		1/0/0			0/1/0
Leukopenia					2/1/0	0/2/0*		0/2/0
Neutropenia					0/3/2	0/1/0		0/1/3
Febrile neutropenia						0/0/1		0/1/0
Nonhematologic								
Fatigue	1/0/0		3/0/0	1/0/0	1/0/0	1/0/0	3/0/0	2/0/0
Hypersensitivity						1/0/0	0/1/0	
Mucositis						1/0/0		1/1/0
Myalgia/arthralgia			4/0/0			1/0/0	1/1/0	2/0/0
Nausea/vomiting		0/1/0					1/0/0	
Neuropathy			1/0/0			3/1/0		1/0/0
Transaminitis	0/1/0					1/0/0		

NOTE: Entries were not made for dose levels where the indicated toxicity was not observed.
*Includes lymphopenia in one cycle.

paclitaxel at dose level 1. Before entering this study, the patient had received six regimens of chemotherapy, including paclitaxel, bleomycin/vincristine, liposomal doxorubicin, IFN, and two other investigational agents. The other patient had endometrioid serous ovarian cancer that was initially treated with debulking surgery followed by adjuvant chemotherapy with a platinum/paclitaxel regimen. She then received four cycles of i.p. cisplatin for disease found at the time of a second-look laparoscopy followed by an investigational tumor vaccine at the time of complete clinical remission. When her disease began to progress once again, she was treated sequentially with carboplatin, an investigational cytotoxic anticancer agent, and liposomal doxorubicin. She was then enrolled in the present study and received eight cycles of 350 mg/m^2 STA-4783 and 175 mg/m^2 paclitaxel (dose level 6). A partial response associated with declining CA-125 was documented after the fourth cycle of therapy, with resolution of pleural effusion, diaphragmatic disease, and chest wall mass, with persistence of some perihepatic disease. After completing six cycles of therapy, the maximum permitted by the protocol, she received two additional cycles under a special exception, after which treatment was discontinued because of progressive sensory neuropathy. Only one other patient, a 58-year-old male with a parotid gland tumor who had previously received docetaxel, exhibited disease stabilization for six cycles of therapy.

Pharmacokinetics. Mean plasma concentration-time profiles for STA-4783 and paclitaxel for the group of seven patients evaluated at the MTD (dose level 7), 438 mg/m^2 STA-4783 and 175 mg/m^2 paclitaxel, are shown in Fig. 2. The STA-4783 concentration in the first plasma sample obtained 1 h after starting the infusion was 86% of the mean maximum concentration in plasma (C_{max}), which was 12.8 ± 2.6 μmol/L for the patients treated at this dose level. Plasma levels of the drug decayed ~2 orders of magnitude, in an apparent biexponential manner, during 5 h following the end of the 3-h i.v. infusion. The C_{max} (r = 0.898) and AUC (r = 0.889) of ST-4783 increased linearly as the dose was escalated from 44 to 438 mg/m^2. Thus, as shown in Fig. 3A, the clearance of the drug was independent of the dose, indicating that STA-4783 exhibits apparent linear pharmacokinetics within this dose range. Mean values of the pharmacokinetic variables for STA-4783 at each dose level and for the entire cohort of patients evaluated in the study are presented in Table 3. The compound was rapidly eliminated from plasma with a mean $t_{1/2,z}$ of 1.06 ± 0.24 h and a mean clearance of 28.6 ± 6.8 L/h/m^2 that corresponded to ~50% of normal hepatic blood flow in adults. The mean V_{ss}, 25.1 ± 8.1 L/m^2, was comparable with total body water.

The pharmacokinetics of the drug in patients treated with 525 mg/m^2 STA-4783 in dose level 8 was inconsistent with the lower doses. The mean C_{max} and AUC were >2-fold lower than expected based on linear extrapolation of the data, although the $t_{1/2,z}$ was within the range of values observed at the lower doses. An abrupt departure from linear pharmacokinetics at a

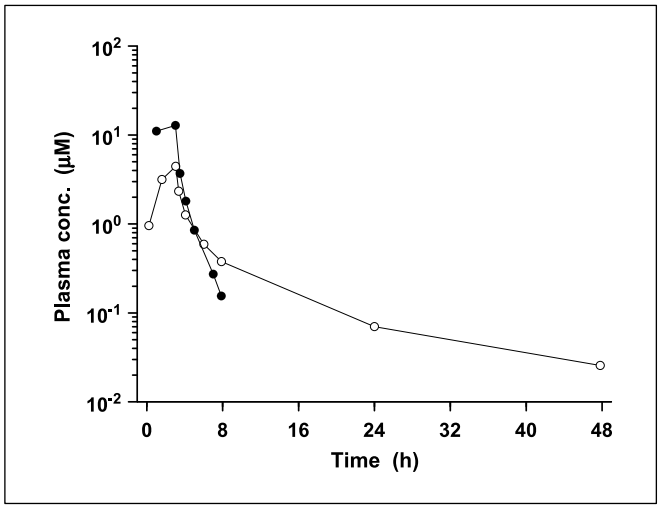

Fig. 2. Mean plasma concentration-time profiles for the group of seven patients receiving 175 mg/m^2 paclitaxel (○) in combination with 438 mg/m^2 STA-4783 (●) given as a 3-h i.v. infusion.

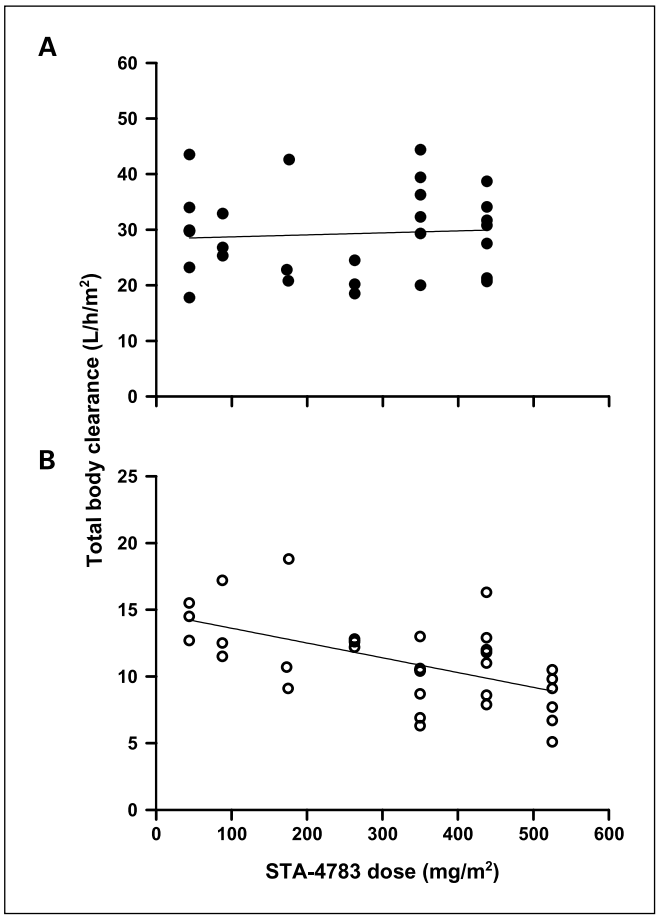

Fig. 3. Relationships between the total body clearance of STA-4783 (*A*) and paclitaxel (*B*) and the dose of STA-4783. Points, observed values in individual patients; solid lines, generated from linear regression analysis of the data sets. *A*, $r = 0.071$, $P = 0.72$. *B*, $r = 0.56$, $P < 0.001$.

higher dose of this nature, suggestive of enhanced clearance, is highly unusual. It seems likely that these aberrant results are the result of an indeterminate error introduced during analysis of the plasma samples. In any event, data from dose level 8 were excluded for calculating overall mean values of the pharmacokinetic variables for STA-4783.

Data on the pharmacokinetics of paclitaxel were obtained from 34 of the 35 patients entered into the clinical trial. Regression analysis to evaluate associations between paclitaxel pharmacokinetic variables and the dose of STA-4783 was done using data for the 32 patients who received 175 mg/m^2 paclitaxel in dose levels 2 to 8. As illustrated in Fig. 3B, there was a significant trend toward a decrease in the clearance of paclitaxel, with escalation of the STA-4783 dose from 44 to 438 mg/m^2 ($r = 0.56$; $P < 0.001$), such that there was a 20% difference ($P = 0.064$) between the clearance in patients in dose levels 2 (14.2 ± 1.5 L/h/m^2; $n = 3$) and 7 (11.2 ± 2.7 L/h/m^2; $n = 7$). The C_{max} ($r = 0.188$; $P = 0.37$), V_{ss} ($r = 0.157$; $P = 0.45$), and $t_{1/2,z}$ ($r = 0.245$; $P = 0.25$) of paclitaxel were not significantly correlated with the STA-4783 dose. Overall mean values of these pharmacokinetic variables for the 25 patients treated with 175 mg/m^2 paclitaxel in dose levels 2 to 7 were as follows: C_{max}, 4.90 ± 1.20 μmol/L; $t_{1/2,z}$, 15.9 ± 3.8 h; V_{ss}, 79.4 ± 25.6 L/m^2; mean residence time, 6.7 ± 1.9 h.

Discussion

This phase I study established the MTD of STA-4783 as 438 mg/m^2 when coadministered with 175 mg/m^2 paclitaxel by i.v. infusion over 3 h once every 3 weeks in patients with advanced malignancies. The incidence and severity of toxicity increased as the STA-4783 dose was escalated in dose levels 2 to 8, although patients received the same 175 mg/m^2 dose of paclitaxel. DLTs observed at the three highest dose levels of STA-4783, neutropenia, febrile neutropenia with mucositis, and myalgia/arthralgia, were similar to those expected for single-agent paclitaxel. Toxicities other than those characteristic of paclitaxel were not observed. It seems likely that the increased incidence of treatment-related toxicities at the higher doses of STA-4783 is the consequence of a pharmacokinetic interaction between the two drugs, as there was a progressive, statistically significant decrease in the clearance of paclitaxel when given together with increasing doses of STA-4783. These findings were not predicted by preclinical evaluation of the combination regimen, as the concurrent administration of STA-4783 did not produce greater toxicity than single-agent paclitaxel or alter the

Table 3. Mean pharmacokinetic variables for STA-4783

Variable	Dose level								Entire cohort*
	1	2	3	4	5	6	7	8	
Dose (mg/m^2)	44	44	88	175	263	350	438	525	
No. patients	3	3	3	3	3	6	7	6	28
C_{max} (μmol/L)	1.32 (0.19)	1.38 (0.65)	2.96 (0.29)	5.61 (1.92)	10.79 (1.73)	9.55 (3.04)	12.84 (2.57)	6.66 (3.31)	
$t_{1/2,z}$ (h)	0.85 (0.01)	0.80 (0.11)	0.89 (0.15)	1.07 (0.39)	0.85 (0.08)	0.94 (0.22)	1.06 (0.24)	0.93 (0.38)	0.92 (0.11)
AUC (μmol·h/L)	3.83 (0.77)	3.87 (1.87)	7.80 (1.04)	16.0 (5.7)	31.4 (4.4)	26.8 (8.6)	38.2 (9.0)	19.2 (10.5)	
CL (L/h/m^2)	28.7 (5.4)	28.4 (12.9)	28.2 (4.0)	27.2 (12.1)	20.9 (3.1)	32.6 (8.5)	28.6 (6.8)	68.2 (35.9)	27.8 (3.5)
V_{ss} (L/m^2)	24.2 (3.1)	16.9 (11.4)	22.1 (7.0)	21.2 (7.8)	14.2 (1.1)	31.2 (31.2)	25.1 (8.1)	130 (97)	22.1 (5.6)
MRT (h)	0.84 (0.23)	0.59 (0.13)	0.78 (0.13)	0.78 (0.19)	0.68 (0.07)	0.97 (0.60)	0.88 (0.27)	1.90 (0.90)	0.79 (0.13)

NOTE: Numbers in parentheses are the SD of the mean.
Abbreviations: CL, clearance; MRT, mean residence time.
*Data from dose level 8 was excluded from calculation of overall mean values for the entire group.

plasma pharmacokinetics of paclitaxel in laboratory animals.[7] Nevertheless, the disposition of STA-4783 in cancer patients seems to be generally similar to the available data from pharmacokinetic studies in rats and dogs.

Competitive inhibition of paclitaxel metabolism by STA-4783 is a plausible mechanism to account for this interaction. Hepatic metabolism catalyzed by CYP2C8 and CYP3A4 is a significant route of elimination for paclitaxel (13, 14). Studies done under the direction of the sponsor of this clinical trial revealed that STA-4783 is a substrate of CYP2C9, CYP2C19, and CYP3A4.[7] Moreover, STA-4783 inhibited the metabolism of paclitaxel by human liver microsomes. The interaction would be expected to be greatest during the infusion of the two drugs, when plasma levels of STA-4783 are relatively high, and diminish on completing the infusion because STA-4783 is eliminated much more rapidly than paclitaxel. The average of the mean AUC values for 175 mg/m^2 paclitaxel when given as a 3-h i.v. infusion from three previously published studies of the drug in adult cancer patients single-agent paclitaxel is 18.9 $\pm$ 2.3 μmol·h/L (15–17). This was very similar to the mean AUC of paclitaxel in the group of seven patients evaluated at the MTD of the combination in the present investigation (18.3 $\pm$ 4.5 μmol·h/L). In contrast, the mean AUC of paclitaxel was 33% greater (25.8 $\pm$ 6.9 μmol·h/L) in the cohort treated with the next higher dose level of 525 mg/m^2 STA-4783.

Partial responses were observed in two patients, one with Kaposi's sarcoma and another with ovarian cancer, both of whom had previously received paclitaxel. Although response was not a primary end point of this phase I trial, evidence of objective antitumor activity in a very heavily pretreated patient population is considered to be very encouraging and suggests that the regimen merits further clinical evaluation. Phase II trials of STA-4783/paclitaxel have been initiated in patients with melanoma, sarcoma, and non–small cell lung cancer.

[7] N. Tatsuta, unpublished data.

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