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ORIGINAL ARTICLE

A phase I trial of SJG-136 (NSC#694501) in advanced solid tumors

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Abstract
Purpose SJG-136 is a pyrrolobenzodiazepine dimer that forms DNA crosslinks and has demonstrated broad antitumor activity. We undertook this trial to determine the maximum-tolerated dose (MTD), toxicities and pharmacokinetic (PK) profile of SJG-136 in patients with an advanced solid tumor.
Patients and methods In this phase I study, patients were treated with SJG-136 on days 1, 8 and 15 of a 28-day cycle. Dose levels studied were 10, 20, 40 and 60 μg/m^2. PK parameters of SJG-136 were assessed following the intravenous administration of SJG-136 on days 1 and 15 of cycle 1.
Results Twenty-one patients with advanced solid tumors were treated. Patients had a median of two prior chemotherapy regimens. Fatigue was dose-limiting with SJG-136 60 μg/m^2/day administered on days 1, 8 and 15 of a 28-day cycle. Grade 3 thrombocytopenia and delayed onset liver toxicity were seen in one patient each. PK parameters of SJG-136 indicated dose-proportional increases in systemic exposure with increasing doses. No objective responses were seen.
Conclusion For patients with advanced solid tumors, the MTD of SJG-136 is 40 μg/m^2/day administered on days 1, 8 and 15 of a 28-day cycle. The major dose limiting toxicity was fatigue. Alternative dosing strategies are now being evaluated.

Keywords Phase I · SJG-136 · Solid tumors · Lung cancer

Introduction

Many antitumor therapies, including alkylating agents and antibiotics, target DNA. Recently, interest in small molecules that target precise DNA sequences has increased, due to their potential to alter the transcription of specific genes. Pyrrolobenzodiazepine dimers (PBD) are a family of antitumor antibiotics derived from *Streptomyces* species that act by forming DNA crosslinks, interfering with endonuclease–DNA interactions and inhibiting RNA polymerase activity [1–3]. SJG-136 is pyrrolobenzodiazepine dimer with an optimized chemical structure at the C2/C2′-positions, rationally designed to produce more efficient and selective covalent interactions with guanine in the minor groove of DNA [3, 4]. The SJG-136 pyrrolobenzodiazepine dimer (MW 556) spans six DNA base pairs and forms sequence-specific intrastrand crosslinks at Pu-GATC-Py sites, in which the recognition sequence is the central GATC string.

Results of the National Cancer Institute's (NCI's) in vitro 60 cell line screen indicate that SJG-136 has a multi-log

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differential pattern of activity [5]. Antitumor activity has been demonstrated in human tumor xenografts (LOX and UACC-62 melanoma, OVCAR-3 and OVCAR-5 ovarian cancer, MDA-MB-435 breast cancer, SF-295 and C-6 glioma, and LS-174T colon cancer) [6]. In addition, SJG-136 was also active in mice bearing cisplatin-resistant ovarian cancer xenografts (CH1cisR) [7].

We report the results of a phase I trial of SJG-136 in patients with refractory solid tumors. The primary objective was to establish the maximum tolerated dose (MTD) for intravenous SJG-136 administered on days 1, 8 and 15 of a 28-day cycle. Pharmacokinetic parameters of SJG-136 were determined following intravenous administration of SJG-136 on days 1 and 15 to assess the dose proportionality and the impact of repeated SJG-136 dosing on SJG-136 pharmacokinetics.

Patients and methods

All patients had pathologically confirmed unresectable or metastatic cancer with a measurable indicator lesion. They were ≥18 years old and had a Karnofsky Performance Status of ≥60%. Patients were required to have absolute neutrophil count of (ANC) ≥1,500/μL, platelets ≥100,000/μL, serum creatinine ≤1.4 mg/dl, total bilirubin ≤1.0 mg/dl, and AST and ALT <2× upper limit of normal. There were no exclusions based on the number or duration of prior therapies, but the patient must have recovered from the acute toxicities of any prior therapy and not received chemotherapy, radiation therapy or other investigational anticancer drug for at least 4 weeks prior to entry into the study. The protocol was approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center (MSKCC).

Study design

All patients who received at least one dose of SJG-136 were assessed for toxicity. Dose-limiting toxicity (DLT) was defined as grade 4 neutropenia, febrile neutropenia (ANC < 1,000/μL and temperature >38°C), grade 4 thrombocytopenia or any grade ≥3 treatment-related non-hematologic toxicity excluding nausea, vomiting, allergic reaction and alopecia. Patients were assessed for toxicity according to the National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0. Tumor response was assessed by response evaluation criteria in solid tumors (RECIST).

Based on murine and canine studies, the recommended clinical starting dose of SJG-136 has been defined. Based on the dog as the most sensitive species with an MTD of 24 μg/m^2 per day, the recommended clinical starting dose daily for a 5-days schedule is 1/6 of the dog MTD, or 4 μg/m^2 per day. As we were interested in evaluating a days 1, 8 and 15 of every 28-day schedule, the starting dose chosen was 10 μg/m^2 per day. The planned dose escalation increment was 100% until a DLT occurred or if two or more patients experienced grade 2 toxicity where after dose escalation would follow a modified Fibonacci scheme (dose increments of 50%, 40%, 33% and 25% for further dose escalations). Three patients were enrolled at each dose level starting at dose level 1. If no DLT was observed after one treatment cycle (4 weeks), three patients were enrolled at the next dose level. If one DLT was observed, the dose level was expanded to six patients. If two DLTs were observed at a dose level, there were no further dose escalations as the MTD had been exceeded. The dose level that follows was considered the MTD, provided a DLT was observed in less than two of six treated patients at that dose level.

Drug and treatment

SJG-136 (NSC #694501) was distributed by the Pharmaceutical Management Branch/NCI in 10 μg (1 mL) and 50 μg (5 mL) sterile single-use vials at a concentration of 10 μg/mL. The drug was administered over 20 min without corticosteroid or antihistamine premedication on days 1, 8 and 15 of a 28-day cycle. All patients had a medical history, physical examination and laboratory work at baseline and before each dose of SJG-136. A complete blood count was performed weekly for the first and second cycle and then on days 1, 8 and 15 of all subsequent cycles. A comprehensive metabolic panel (electrolytes, serum creatinine, liver function tests and calcium) was performed on days 8, 15 and 21 of cycle 1 and days 1, 8, 15 and 21 of cycle 2, and days 1 and 15 of all subsequent cycles. Before administration of SJG-136, ANC ≥1,500/μL and platelets ≥ 100,000/μL were required. All non-hematologic toxicities had to recover to grade 0–1 or baseline (except alopecia). Up to 4 weeks (one cycle) of treatment, delay was permitted to allow sufficient time for recovery. If dosing was held for more than 4 weeks as a result of toxicity, the patient was removed from the study. Dose reductions by one or two dose levels were permitted for toxicities. Filgrastim was not used prophylactically. Patients continued treatment with SJG-136 until development of progressive disease or intolerance to treatment.

Pharmacokinetic (PK) analysis

PK studies of SJG-136 were performed on days 1 and 15 of cycle 1. Serial blood samples were collected at 10, 20 min (end of infusion), 22, 25, 30, 50, 65, 80, 110, 140 and 260 min following intravenous SJG-136 administration.

The plasma samples were separated by centrifugation and stored at −80°C until analysis.

Determination of SJG-136 plasma concentration levels was performed using a recently validated liquid chromatography mass spectrometry analytical method [8]. Non-compartmental PK parameters were obtained using the WinNonlin software package, version 4.1 (Pharsight Corp., Palo Alto, CA). The area under the concentration–time curve from time 0 to the last time point (260 min) (AUC_{last}) was calculated using the linear trapezoidal method. The remaining area under the curve from the last time point to infinity was calculated using the equation $AUC_{last-\infty} = C_{last}/K_{el}$, where C_{last} is the last measured plasma concentration and K_{el} is the slope of the concentration versus time plot during the log-linear terminal phase. Total clearance (CL) and volume of distribution at steady state (V_{ss}) were calculated as follows: CL = dose/AUC; V_{ss} = mean residence time (MRT) × CL.

Results

Patients

Between 30 November 2004 and 13 February 2007, 21 patients were enrolled in this single-institution study. The pretreatment characteristics are summarized in Table 1. The majority of patients had lung cancer (42%) and melanoma (38%). Patients received a median of two prior chemotherapy regimens.

Table 1 Patient characteristics, $n = 21$

Age (years)	
Median	65
Range	45–78
Sex	
Female	10 (47%)
Male	11 (52%)
Karnofsky Performance Status	
≥80%	18 (86%)
70%	3 (14%)
Primary site	
Lung	9 (42%)
Melanoma	8 (38%)
Colon	2 (9%)
Bladder	1 (5%)
Ovarian	1 (5%)
Number of prior chemotherapy regimens	
Median	2
Range	0–4
Prior radiotherapy	3 (14%)

Adverse events

Adverse events were assessed in all 21 patients. Treatment was initiated at 10 μg/m^2 per day with patients being observed for 4 weeks before escalation to the next dose level was allowed. The SJG-136 dose was escalated to 20, 40 and 60 μg/m^2 in consecutive patient cohorts.

A median of one cycle (range 1–8) was completed for all patients (Table 2). Doses were not reduced. Therapy was discontinued due to progression of disease in 18 of 21 patients (86%); 3 of 21 patients (14%) discontinued treatment due to treatment-related toxicity.

Table 3 summarizes adverse events at all dose levels that were assessed by the investigator as related or possibly related to treatment with SJG-136. At the first dose level, three patients were treated with SJG-136 10 μg/m^2 per day. Grade 2 toxicities that occurred in one patient each were nausea, leukopenia and neutropenia. Two patients experienced grade 1 transaminitis. Other grade 1 toxicities that occurred once included hypoalbuminemia, dyspepsia, diarrhea, fatigue, pruritus, nail changes and mucositis. One patient underwent dose escalation to 20 μg/m^2 per day on cycle 8, day 8.

At the second dose level, three patients were treated with SJG-136 20 μg/m^2 per day. One patient experienced grade 3 transaminitis in the beginning of cycle 4, probably related to the investigational treatment. Because the grade 3 transaminitis did not occur during cycle 1, expansion of the patient cohort at the second dose level was not required. Grade 2 toxicities, occurring in one patient each were: transaminitis and hypoalbuminemia. Grade 1 transaminitis, hypoalbuminemia, hyperbilirubinemia, alkaline phosphatase elevation, nausea and fatigue each occurred in one patient.

At the third dose level, three patients were treated with SJG-136 40 μg/m^2 per day. One patient experienced grade 2 fatigue. Two patients experienced grade 1 fatigue and one patient experienced grade 1 neuropathy. No DLTs occurred at this dose; therefore, dose escalation was permitted.

After dose level 3, the protocol was amended to allow a more conservative dose escalation. As such, subsequent patients were escalated with a standard dose escalation study design with a modified Fibonacci scheme (dose increments of 50, 40, 33 and 25% for further dose escalation). In

Table 2 SJG-136 exposure

SJG 136 dose[a] (μg/m^2 per day)	No. of patients treated	Median no. of cycles	DLT
10	3	7	0
20	3	1	0
40	8	2	0
60	7	1	3

[a] No dose reductions were done

Table 3 Treatment-related toxicities of SJG-136 (all doses)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Bone marrow				
Leukopenia	1	1	0	0
Neutropenia	0	1	0	0
Anemia	3	0	0	0
Thrombocytopenia	0	1	1	0
Cough	1	0	0	0
Depression	1	0	0	0
Dyspnea	0	1	0	0
Edema/limb	1	3	0	0
Fatigue	1	4	3	0
Gastrointestinal				
Constipation	1	0	0	0
Diarrhea	2	1	0	0
Nausea	9	1	0	0
Vomiting	3	0	0	0
Hemorrhage, other	1	0	0	0
Hepatic				
Bilirubin elevation	2	0	0	0
ALT elevation	6	1	1	0
AST elevation	8	1	0	0
Alkaline phosphatase elevation	1	1	0	0
Hypoalbuminemia	12	6	0	0
Hypocalcemia	2	0	0	0
Hyponatremia	1	0	0	0
Mental status change	0	1	0	0
Mucositis	4	0	0	0
Neuropathy	2	0	0	0
Nail changes	1	0	0	0
Pain (extremity)	0	1	0	0
Pruritus	1	0	0	0
Rash, desquamation	1	0	0	0
Weight gain	1	0	0	0

addition, due to delayed liver toxicity reported by investigators elsewhere, the patients were observed for toxicity for 8 weeks prior to dose escalation.

Seven patients were treated at the fourth dose level (SJG-136 60 μg/m^2 per day). Initially, three patients were enrolled. The first patient experienced grade 2 fatigue and grade 3 thrombocytopenia during cycle 1. Although grade 3 thrombocytopenia was not defined in the protocol as a DLT, it precluded this patient from receiving further SJG-136 treatment. She subsequently developed disease progression and was taken off the study. The second patient experienced grade 3 fatigue during cycle 1, and therefore the dose level was expanded. The third patient experienced grade 2 diarrhea and grade 2 fatigue during cycle 1. During cycle 2, the patient experienced grade 2 hypoalbuminemia, grade 2 myalgias/thigh swelling and persistent grade 2 fatigue precluding further therapy. He subsequently developed progression of disease and was taken off the study. The fourth patient experienced grade 3 fatigue during cycle 1. That patient had a fatal CNS hemorrhage in his tumor 4 days later, unrelated to SJG-136 therapy. Grade 3 fatigue was attributed to CNS metastatic disease progression and therefore this patient was replaced. The fifth patient experienced dose-limiting grade 3 fatigue on completion of cycle 1 and was taken off the study shortly thereafter due to disease progression. The sixth patient experienced grade 2 lower extremity edema, grade 2 fatigue and grade 2 hypoalbuminemia during cycle 1. The patient gained 10 pounds during cycle 1 of SJG-136 therapy. Initiation of cycle 2 was delayed by 3 weeks in this patient due to persistent grade 2 lower extremity edema and hypoalbuminemia. The patient received furosemide with improvement in his lower extremity edema to grade 1 and reinstitution of SJG-136 therapy. At the end of cycle 2, the patient experienced grade 2 dyspnea. Computed tomography of the chest 1 week later revealed numerous patchy alveolo-interstitial nodules scattered throughout both lung fields, suggestive of pneumonitis. This was determined to be possibly related to the study drug and the patient was removed from the study. The seventh patient experienced grade 2 hand swelling and tenderness possibly related to SJG-136 infusion. She was subsequently taken off the study for disease progression. The following grade 2 toxicities occurred once in the fourth dose level cohort: alkaline phosphatase elevation, fatigue, thrombocytopenia and mental status change.

Because three patients at the fourth dose level experienced dose-limiting toxicity, grade 3 fatigue, the MTD was exceeded and dose level 3 (SJG-136 40 μg/m^2 per day) was expanded to include five additional patients. Based on preclinical data demonstrating activity in colon cancer, the cohort was further expanded to five instead of three patients to include two additional patients with colon cancer. One patient experienced grade 2 fatigue. Two patients experienced grade 2 hypoalbuminemia. Grade 1 transaminitis and hypoalbuminemia occurred in three patients each. Grade 1 nausea occurred in two patients. Grade 1 mucositis, depression, vomiting, fatigue, limb edema and hyperbilirubinemia occurred in one patient each.

Antitumor activity

Thirteen patients were assessed for tumor response using RECIST criteria. No objective tumor responses were noted for any of the patients. One patient with metastatic melanoma achieved stable disease for eight cycles. The patient was initially treated with SJG-136 10 μg/m^2 per day and underwent intra-patient dose escalation on day 8, cycle 8.

She tolerated the treatment well, but was subsequently taken off the study after day 15, cycle 8 for progression of disease.

Pharmacokinetic data

PK data were obtained from 19 patients (Fig. 1; Table 4). The plasma concentrations of SJG-136 were above the assay detection limit at all the time points and at all dose levels tested. The pre-dose concentrations of SJG-136 on day 15 were below the detection limit of our assay in all the patients, indicating no significant accumulation of SJG-136 on day 15. SJG-136 pharmacokinetics appears to be linear in the dose range tested (10–60 μg/m^2 per day) based on the dose-proportional increases in SJG-136 systemic exposure (i.e., AUC_{last} and C_{max}; Fig. 1b; Table 4). Other PK parameters such as clearance (CL) and volume of distribution at steady state (V_{ss}) did not show any statistically significant differences across different doses and between days 1 and 15 (Table 4).

Discussion

SJG-136 targets precise DNA sequences and has shown activity in cisplatin-resistant tumor xenografts. Preclinical data showed the best activity in animal models using repeated SJG-136 dosing. The current study determined an MTD of SJG-136 given on days 1, 8 and 15 of a 28-day cycle in patients with advanced solid tumors. Grade 3 toxicities of fatigue, thrombocytopenia and transaminitis were observed. When SJG-136 was given at a dose of 60 μg/m^2 per day, the MTD was exceeded with dose-limiting fatigue occurring in 42% (three of seven) of patients. Additionally, 14% (one of seven) of patients experienced grade 3 thrombocytopenia during cycle 1. Delayed grade 3 transaminitis was seen in 33% (one of three) of the patients at dose level 3 (SJG-136 20 μg/m^2 per day), similar to the experience from published phase I data. Although, edema, transaminitis and hypoalbuminemia were not determined to be DLTs in our study, these toxicities were frequently experienced by our patients. Grade 2 hypoalbuminemia and transaminitis were seen in 33% (one of three) of patients at dose level 2. Grade 2 hypoalbuminemia and edema were seen in 25% (two of eight) of patients at dose level 3 and 28% (two of seven) of patients at dose level 4. PK parameters of SJG-136 indicated dose-proportional increases in systemic exposure of SJG-136 with increasing doses of SJG-136.

Investigators at Vanderbilt-Ingram Cancer Center (Nashville, TN, USA) conducted a phase I study of SJG-136 in patients with refractory solid tumors [9]. SJG-136 was initially administered daily for 5 days every 21 days. Grade 3 DLT of edema, dyspnea and fatigue was observed in cycle 1 at 48 μg/m^2 per day. Similar toxicity was

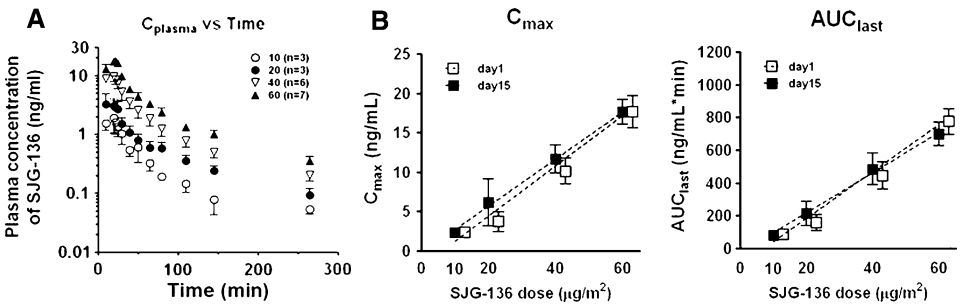

Fig. 1 **a** Average plasma concentration versus time profiles of SJG-136 following intravenous administration of SJG-136 at 10, 20, 40 and 60 μg/m^2 on day 1 in cycle 1. **b** Comparison of AUC_{last} and C_{max} obtained on days 1 and 15 following intravenous SJG-136 administration at increasing doses

Table 4 Pharmacokinetic parameters of SJG-136 following intravenous SJG-136 administration of 10, 20, 40 or 60 μg/m^2 per day

		Dose level (μg/m^2 per day)			
		10 (n = 3)	20 (n = 3)	40 (n = 6)	60 (n = 7)
C_{max} (ng/mL)	Day 1	2.3 (1.2)	3.7 (2.2)	10.1 (4.0)	17.7 (5.4)
	Day 15	2.3 (0.5)	6.2 (5.2)	11.6 (4.3)	17.6 (4.2)
AUC_{last} (ng min/mL)	Day 1	83.1 (36.7)	156.5 (84.0)	443.8 (201.8)	773.8 (207.2)
	Day 15	81.0 (10.5)	211.7 (124.9)	484.9 (231.8)	698.4 (194.4)
$AUC_{infinity}$ (ng min/mL)	Day 1	88.5 (40.7)	166.0 (219.5)	459.6 (207.3)	809.4 (216.1)
	Day 15	87.4 (13.2)	219.5 (122.0)	504.4 (244.7)	727.2 (194.2)
CL (mL/min per m^2)	Day 1	134.5 (64.2)	160.0 (111.8)	100.2 (34.4)	80.6 (28.0)
	Day 15	116.6 (19.1)	118.4 (75.9)	102.6 (57.9)	87.9 (22.8)
V_{ss} (mL/m^2)	Day 1	8,171 (4,833)	12,090 (10,810)	5,837 (3,226)	4,977 (1,637)
	Day 15	7,769 (749)	8,761 (8,604)	5,736 (2,759)	5,525 (2,320)

observed in cycle 2 at 24 μg/m^2 per day study. Grade 4 delayed liver toxicity was also reported with this schedule. Investigators were unable to dose escalate; therefore, the protocol was amended to shorten daily administration to 3 days with dexamethasone premedication and diuretic support to reduce the vascular leak syndrome manifestations. As much as 14 patients were treated with SJG-136 administered intravenously daily for 3 days in a 21-day cycle at the initial dose level of 20 μg/m^2 per day. Soft tissue edema, dyspnea and fatigue were the DLTs in one of the two patients enrolled at 35 μg/m^2 per day dose and transaminitis in the second patient. No significant myelosuppression was observed. The recommended phase II dose from this study was determined to be 30 μg/m^2 per day administered daily for 3 days in a 21-day cycle. Pharmacokinetic (PK) analysis revealed dose-dependent increases in SJG-136 systemic exposure [9]. In another phase I study of 16 refractory solid tumor patients, SJG-136 was administered at escalating doses (15–240 μg/m^2 per day) intravenously once every 21 days. The major DLTs were delayed onset vascular leak syndrome (peripheral edema, hypoalbuminemia, pleural effusions and ascites) and liver toxicity. SJG-136 demonstrated biphasic clearance and linear PK across the dose range tested. The investigators determined the MTD for SJG-136 to be 45 μg/m^2, but a recommended phase II dose was not identified [10].

In summary, SJG-136 administered on days 1, 8 and 15 of a 28-day cycle was associated with fatigue, thrombocytopenia and hypoalbuminemia and delayed transaminitis. The maximum tolerated dose of SJG-136 administered at this dosing schedule was 40 μg/m^2 per day. Although the increases in C_{max} and AUC values were dose proportional at the SJG-136 levels examined (10–60 μg/m^2 per day), a larger study would be necessary to further verify dose-linear pharmacokinetics of SJG-136. No objective tumor responses were noted. Alternative dosing strategies that include dexamethasone premedication and diuretic support are now being evaluated.

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