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Clinical study

KW-2149-induced pulmonary toxicity is not prevented by corticosteroids: a phase I and pharmacokinetic study

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KW-2149 is a new, semisynthetic, *C*-7-*N*-Substituted, mitomycin C analog showing antitumor activity both *in vitro* and *in vivo*, equal or superior to mitomycin C. In a phase I study, KW-2149 was administered as an i.v. bolus injection every 21 days and at a dose of 100 mg/m^2 pulmonary toxicity was dose limiting. Animal studies have indicated since that KW-2149-induced pulmonary toxicity can be prevented by pretreatment with corticosteroids. This paper presents the results of a further phase I study of KW-2149 with corticosteroid pretreatment. Patients were treated with oral dexamethasone 8 mg every 12 h, starting 24 h before KW-2149 administration, for 5 days. KW-2149 was given as an i.v. bolus injection every 21 days. Seventeen patients were treated with a total of 48 courses. Six patients received 60 mg/m^2 and 11 patients 75 mg/m^2. Two courses were not evaluable for toxicity. Significant lung toxicity was observed in at least three patients treated with a dose of 75 mg/m^2 KW-2149 and pulmonary toxicity was therefore considered the dose-limiting toxicity at 75 mg/m^2. No other important side effects were noted. One partial response was observed in a patient with colorectal cancer. Pretreatment with dexamethasone failed to suppress KW-2149-induced lung toxicity. [© **1999 Lippincott Williams & Wilkins.**]

Key words: KW-2149, mitomycin C analog, pharmacokinetics, phase I, pulmonary toxicity.

Introduction

KW-2149 is a new, semisynthetic, *C*-7-*N*-substituted, mitomycin C analog showing antitumor activity both *in vitro* and *in vivo* assays, equal or superior to mitomycin C.[1–3] In terms of preclinical activity profile, hematological toxicity data in rodents[2,4] and water solubility, the compound compares favorably to mitomycin C. In an initial phase I study, 37 patients were treated with KW-2149 as an i.v. bolus injection every 21 days and pulmonary toxicity (dyspnea, pleural effusions, decreases in lung diffusion capacity) was dose limiting, with grade 3 toxicity occurring in all three patients treated at a dose of 100 mg/m^2,[5] and in one of two patients treated with 60 mg/m^2. Pathological examination of the lungs showed interalveolar widening, with increased deposition of collagen and elastin, and fibrosis. It was also noted that treatment with corticosteroids improved the clinical symptoms. Increasing the infusion duration to 24 h again led to pulmonary toxicity at a cumulative dose of 100 mg/m^2.[6] However, antitumor activity was observed in patients. Subsequent animal studies confirmed this pulmonary pathology; rats treated with KW-2149 developed perivascular edema, alveolar hemorrhages and telangiectasia of the alveolar walls. Pretreatment with dexamethasone could prevent KW-2149-induced pulmonary toxicity.

This paper describes a further phase I study commencing with 60 mg/m^2 KW-2149, the dose at which pulmonary toxicity was first seen,[5] preceded by dexamethasone. The objectives were to determine the maximum tolerated dose (MTD) of KW-2149 when administered as bolus every 3 weeks, combined with oral dexamethasone 8 mg every 12 h, starting 24 h before KW-2149 administration, and continuing for a total of 5 days; to determine the qualitative and quantitative toxic effects of KW-2149, and to study the

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predictability, duration, intensity, onset and reversibility of toxic side effects; to propose a safe dose for phase II evaluation; to study the pharmacokinetics of KW-2149 at the different dose levels; to document any possible antitumor activity; and to determine whether pretreatment with dexamethasone prevents pulmonary toxicity.

Patients and methods

The study was approved by the medical ethics committees of both institutions in Antwerp and Lyon. All patients gave written informed consent prior to the start of the study.

Patients

All patients had a pathologically confirmed diagnosis of a solid tumor not amenable to standard treatment. They were older than 18 years, had a good performance status (WHO < 2),[8] a life expectancy of at least 3 months, and adequate renal (creatinine < 1.4 mg/dl), liver (bilirubin < 1.5 mg/dl, other liver function tests less than twice the upper limit of normal, unless liver metastases were present), bone marrow (white blood cells > 4000/mm^3, platelets > 100 000/mm^3), and cardiac and pulmonary function (normal lung function tests and arterial blood gas tensions). Coagulation (prothrombin time) was within normal limits. Patients had no other significant medical conditions affecting compliance with the protocol. Prior radiotherapy or chemotherapy was discontinued for at least 4 weeks, 6 weeks in the case of extensive radiotherapy or nitrosurea treatment). Patients receiving drugs with hepatic, renal, cardiac or pulmonary toxicities were excluded, as were those who were pregnant or breast-feeding, had acute infections, severe psychological disorders, brain or meningeal disease, or pulmonary impairment. Prior treatment with mitomycin C was not allowed.

Treatment protocol

KW-2149 was supplied as a lyophilized grey-green colored powder of 50 mg KW-2149, which was reconstituted with 2 ml of sterile water. The finished product was administered within 3 h after reconstitution, through a sideline of an infusion of 0.9% sodium chloride or 5% dextrose, by slow bolus injection over at least 10 min. KW-2149 was given every 3 weeks or after full recovery from the previous treatment. The starting dose was 60 mg/m^2 and doses were escalated according to a fixed dose escalation scheme (75 and 90 mg/m^2). Dexamethasone 8 mg was administered orally every 12 h, starting 24 h before KW-2149 administration and continuing for 5 days.

The MTD was defined as the highest dose without common toxicity criteria grade 3 in two out of six patients. The recommended dose for phase II testing was the dose one step below the MTD, provided at least five patients were treated at this dose level without developing dose-limiting toxicity. A fixed number of patients was allocated to each dose level depending on toxicity. At the dose level of 60 mg/m^2, initially three patients would be treated and if no toxicity occurred the dose would be escalated to 75 mg/m^2. At this dose schedule initially six patients were planned. If no toxicity occurred in at least four evaluable patients with at least four courses per patient, two further patients would be entered into the study. If no toxicity occurred in these six evaluable patients during four courses per patient, six patients would be treated at 90 mg/m^2, according to the same accrual schedule.

Patients were scheduled to receive at least four courses and a maximum of six courses. Treatment could be continued at the same dose, in the case of response, provided no serious toxicity was observed. In case of progressive disease, patients were removed from the study. Treatment was discontinued if patients developed impaired lung diffusion capacity, a Common Toxicity Criteria (CTC) (9) grade greater than 2 and/or pulmonary symptoms (dyspnea and cough greater than grade 2) and/or any drug-related clinically significant abnormalities on chest X-ray or CT scan.

Toxicity evaluation

Patients were evaluable for toxicity after one course of therapy. Toxicity was evaluated by the CTC (9). Grade 9 toxicity was defined as the deterioration of at least one CTC grade of a pre-existent abnormality or adverse event after treatment. Each patient was assessed clinically prior to starting treatment and weekly thereafter. Hematological and biochemical profiles, and urinalysis, were performed weekly. Arterial blood gas analysis, creatinine clearance, electrocardiogram, chest X-ray, lung function tests with carbon monoxide lung diffusion capacity (DLCO) were carried out prior to each course, with a CT scan of the lungs every two courses. An assessment of left ventricular function by MUGA scan or ultrasound was performed at baseline, after three courses and before

the start of each subsequent course. All tests were repeated at the end of the study.

Tumor response

Patients were evaluable for response if disease measurements were recorded over at least a 6 week period from the day of first treatment. Tumor measurements were performed before each course and at the end of the study. Response evaluation was according to WHO criteria. A complete response indicated the complete resolution of all known lesions and no reappearance of new lesions, determined in two assessments no less than 4 weeks apart. A partial response showed a reduction of the sum of the products of the two longest perpendicular diameters, equal to or more than 50%, no progression in any non-measured evaluable or non-evaluable lesion, and no appearance of new lesions, determined in two assessments no less than 4 weeks apart. Patients with stable disease showed no progression of their lesions. Progressive disease was defined either by appearance of new lesions or an increase of greater than 25% of the sum of the products of the two longest perpendicular diameters. When progression was observed after 3 or 6 weeks after study entry, it was considered early progression.

Pharmacokinetics

Clinical pharmacokinetic studies were performed during the first treatment course in 14 patients. Blood samples were collected from the arm contralateral to the infusion, in heparinized polypropylene tubes containing oxidized gluthatione, at −10 min (pre-treatment), 0, 5, 10, 15, 30 and 60 min, and then at 2, 4, 6, 9, 12, 24, 36 and 48 h. Each sample was centrifuged at 4000 *g* for 15 min, and plasma was isolated and stored at −20°C until analysis. Concentrations of KW-2149 and its metabolites M-16 and M-18 were determined by high-performance liquid chromatography and UV spectrophotometry as described earlier.[10]

Results

Demographics

Seventeen patients, 11 male and six female, were entered into the trial with a mean age of 57.5 years (range 35–72 years). Performance status was 0 and 1 in two and 15 patients, respectively. Patient characteristics are presented in Table 1. All patients were considered eligible for the study, although one had a slight prolongation of the activated partial thrombo-

Table 1. Patient characteristics

Patient no.	Sex	Age	Tumor	Prior treatment			No. of courses
				Chemo-therapy	Surgery	Radio-therapy	
Dose level: 60 mg/m^2							
1	M	59	pancreas	+	+	−	6
2	F	55	colorectal	+	+	−	2
3	M	59	head and neck	+	+	+	2
4	M	65	colorectal	+	+	−	2
5	M	42	kidney	−	+	−	3
6	F	59	colorectal	+	+	−	1
Dose level: 75 mg/m^2							
7	M	66	peritoneum	+	−	−	2
8	F	60	colorectal	+	+	+	4
9	F	70	colorectal	+	+	+	4
10	M	58	duodenum	−	+	−	2
11	F	66	ureter	+	+	+	3
12	M	43	head and neck	+	−	−	3
13	M	63	primary unknown	−	−	−	4
14	M	64	stomach	+	+	+	1
15	F	72	colorectal	−	+	−	3
16	F	42	breast	+	+	+	3
17	M	35	kidney	−	+	−	3

plastin time (APTT), with a normal prothrombin time (PT), due to liver metastases, four had minor abnormalities in the DLCO and one had received limited radiotherapy to the right shoulder for pain relief just prior to inclusion in the study.

Treatment administration

Seventeen patients were treated with a total of 48 courses. Six received 60 mg/m^2 and 11 received 75 mg/m^2. The treatment interval was greater than 21 days in six courses, with a maximum delay of 14 days.

Toxicity results

Overall toxicity. There were no toxic deaths in the study. One patient was withdraw following a sub-endocardial infarction during the second cycle of 60 mg/m^2 KW-2149 and one died at home with symptoms of pulmonary embolism on day 8 of the second course of 75 mg/m^2; both events were thought to be unrelated to KW-2149 administration. One patient developed brain metastases during the third course and died on day 8 from disease progression. Autopsy revealed no signs of lung fibrosis. The last cycles of these three patients were not evaluable for toxicity.

Hematological toxicity. Following 60 mg/m^2 of KW-2149, two patients developed grade 1 thrombocytopenia. Grade 1 falls in hemoglobin were reported in two patients and one grade 9 anemia was seen in one. One case of grade 3 and four grade 9 lymphopenia occurred. The hematological toxicity per cycle is shown in Table 2. At 75 mg/m^2, three patients developed thrombocytopenia and leukopenia of greater than grade 2, and grade 4 neutropenia was observed in one patient. The incidence of anemia and lymphopenia was similar to that seen in patients treated at the 60 mg/m^2 dose level.

Hematological toxicities seemed dose limiting with persistent thrombocytopenia and was of late onset in one patient who had received extensive prior chemotherapy. Bone marrow damage from extensive prior chemotherapy (epirubicin, cyclophosphamide, cisplatin, etoposide and vinblastine) probably contributed.

Non-hematological toxicity.

Pulmonary toxicity. The effects of KW-2149 on the DLCO, arterial blood gasses and the development of clinical symptoms are shown in Table 3.

Table 2. Hematological toxicity per cycle

Toxicity	Common toxicity criteria				
	0	1	2	3	4
Dose level: 60 mg/m^2 (16 evaluable cycles)					
hemoglobin	2	5	6	3	0
white blood cells	16	0	0	0	0
neutrophils	16	0	0	0	0
platelets	14	2	0	0	0
Dose level: 75 mg/m^2 (30 evaluable cycles)					
hemoglobin	1	14	11	3	1
white blood cells	22	4	2	2	0
neutrophils	27	1	0	1	1
platelets	19	8	1	1	1

Table 3. Pulmonary toxicity per patient

Clinical sign or symptom	Common toxicity criteria					
	0	1	2	3	4	9
Dose level: 60 mg/m^2 (six patients)						
DLCO	2	1	3	0	0	0
PO_2	3	2	0	0	0	1
dyspnea	6	0	0	0	0	0
Dose level: 75 mg/m^2 (11 patients)						
DLCO	5	0	5	1	0	0
PO_2	7	2	0	0	1	1
dyspnea	9	0	1	0	1	0

Grade 9: pre-existent adverse event/abnormality which deteriorates at least one grade CTC.

At 60 mg/m^2 there were grade 1 and 2 decreases in DLCO in one and three patients, respectively. Two patients developed a grade 1 reduction in PO_2 and one a grade 9 PO_2 abnormality. The dose was escalated to 75 mg/m^2, according to the protocol, as at this time the patients with the most severely impaired DLCO had only reached grade 1 and had not yet progressed to grade 2 toxicity. Only one case of dyspnea was reported at 60 mg/m^2. This was considered a direct result of progression of lung disease and a relationship with KW-2149 was considered unlikely (excluded from toxicity tables).

At 75 mg/m^2, five patients developed grade 2 and one grade 3 DLCO toxicities, all of which were considered related to KW-2149. Grades 4, 1 and 9 changes in arterial PO_2 in one, two and one patients, respectively. Three patients, experienced dyspnea, which was not considered related to KW-2149 in one. Post-mortem revealed lung fibrosis in two patients.

Cardiovascular toxicity. Constrictive pericarditis, with compensatory myocardial thickening in the remaining heart tissue, was found at autopsy in one

patient; no alternative explanation other than the administration of KW-2149 was identified.

Gastrointestinal toxicity. Two patients suffered grade 1 nausea and one grade 2 vomiting at 60 mg/m^2. Two patients reported mild anorexia. More prominent gastrointestinal toxicity was present in patients given 75 mg/m^2: five patients experienced mild nausea; one grade 2 nausea accompanied by grade 1 vomiting; and one patient transient grade 3 vomiting during the first course and grade 3 nausea and grade 2 vomiting during the second course, both lasting 10 days. Four patients reported mild anorexia.

Hepatic toxicity. Elevated transaminases (grade 1) were observed after the first drug administration in one patient, returning to baseline 1 week later. It was also observed during the second course and to a lesser degree during the third and the fourth courses. During the fourth course there also was a transient grade 1 elevation of the alkaline phosphatase. These changes were considered related to KW-2149 administration. In another patient, there were non-significant, transient elevations of AST and ALT, LDH and bilirubin. No other hepatic toxicities were reported.

Renal toxicity. In three patients treated with 60 mg/m^2 KW-2149, elevations in blood urea were observed. One patient had a transient grade 2 uraemia during the first course, but the creatinine remained unchanged. During the second and the fifth courses, transient grade 1 elevations of urea were observed. Isolated grade 1 uremia was also seen during the second course in another patient. One patient had a marginally increased urea level at baseline (46 mg/dl, normal range 19–45 mg/dl) and during the first course a transient increase to 108 mg/dl was observed (grade 9), which did not resolve.

At 75 mg/m^2, elevated urea blood levels were seen in five patients, four experiencing grade 1 and one grade 2 toxicities. No change in serum creatinine level was observed.

Toxicity conclusion. Significant lung toxicity was observed in at least three patients treated with 75 mg/m^2 KW-2149. Therefore pulmonary toxicity was considered the DLT. After a thorough evaluation of the pulmonary events, it was concluded that pretreatment with dexamethasone failed to prevent lung toxicity and the study was closed.

Two patients developed important hematological toxicity and in one this was dose limiting. However, in view of the late onset and the presence of other etiological factors, a relationship to treatment with KW-2149 is not definite.

Efficacy

One partial response was observed in a patient with colorectal cancer. Five patients had stable disease and nine had disease progression at the first evaluation. In two patients response was not evaluable due to early death.

Pharmacokinetic analysis

Pharmacokinetic data were obtained from 14 patients, four receiving 60 mg/m^2 and 10 receiving 75 mg/m^2 (Tables 4 and 5). The KW-2149 data was best fitted to a bolus input one-compartment model. It was possible to estimate the concentration at time 0 (C_0) of KW-2149 in two patients receiving 60 mg/m^2 and in seven patients receiving 75 mg/m^2. C_0 was estimated by back extrapolation of the log concentration-time curve. The mean α half-life of KW-2149, calculated in patients in whom there were sufficient data points, was 3.1 min and the terminal elimination half-life calculated in all patients, using the last two data points, was 11.8 min.

Table 4. Pharmacokinetic parameters of KW-2149 on cycle 1 [mean (SD)]

Dose (mg/m^2)	C_0 (ng/ml)	$t_{1/2}$		AUC (ng.min/ml)	AUMC (ng.min^2/ml)	CL (ml/min/m^2)	V_{ss} (ml/m^2)
		α (min)	β (min)				
All		3.1	11.8	5973	36223	5973	36223
		(0.8)	(10.8)	(5278)	(19596)	(5278)	(19596)
		n=9	n=14	n=9	n=9	n=9	n=9
60	1167			4755	20455		
	n=2			n=2	n=2		
75	4288			19378	120335		
	(2869)			(11011)	(67199)		
	n=7			n=7	n=7		

Table 5. Pharmacokinetic parameters of M-16 and M-18 [mean (SD)]

Dose (mg/m^2)	M-16			M-18		
	$t_{1/2\beta}$ (min)	AUC (ng.min/ml)	AUMC ($ng.min^2/ml$)	$t_{1/2\beta}$ (min)	AUC (ng.min/ml)	AUMC ($ng.min^2/ml$)
All	53.3 (23.6) n=14			15.9 (18.0) n=10	12787	994961
60		50063 (55055) n=4	4164319 (5294764) n=4		36809 (42273) n=4	4714674 (5557023) n=4
75		30460 (13690) n=10	2189230 (1436311) n=10		12787 (19422) n=10	994961 (1913916) n=10

The areas under the concentration-time curve (AUC) and the first moment curve (AUMC) were calculated using the trapezoidal rule when concentrations values were increasing and the log-trapezoidal rule when concentrations values were decreasing after the maximum concentration. In those patients in whom it was possible to estimate C_0, AUC and AUCM were calculated from C_0 to infinity.

Clearance (CL) of KW-2149 was calculated as CL=dose/AUC and the volume of distribution of KW-2149 at steady state (V_{ss}), in those patients in whom $AUC_{0-\infty}$ was known, calculated as V_{ss}=dose × AUMC/AUC^2.

Mean clearance of KW-2149 was 5973 ml/min/m^2 and mean V_{ss} 36 223 ml/m^2. The terminal elimination half-life, AUC and AUMC of the metabolites M-16 and M-18 were calculated as described above in all patients. The mean elimination half-lives were 53.2 and 15.9 min for M-16 and M-18, respectively.

Three patients receiving 75 mg/m^2 KW-2149 were studied on more than one cycle, with two sampled also on their second cycle and one on his third cycle. There was a trend to a longer elimination half-life of M-18 with subsequent courses (18.1 to 32.9 and 6.7 to 227.2 min, cycles 1 to 2; and 20.9 to 88.7 min, cycle 1 to 3). A similar trend was seen with the AUC of M-18 (18 676 to 57 027, and 1821 to 36 611 ng.min/ml, cycles 1 to 2; and 40 522 to 130 102 ng.min/ml, cycle 1 to 3). These results suggest that the capacity to generate M-18 is increased with repeated exposure to KW-2149.

Urinay excretion data is available in three patients. The amount of KW-2149 excreted in the urine on the first cycle varied from 37 to 41% (two patients) and during the second 14% (one patient). Respective values for urinary excretion of M-16:KW-2149 molar ratios during the first cycle was 2.33 (two patients) and in the second cycle 3.56 (one patient), and for M-18, expressed as M-18:KW-2149 molar ratios, 0.0253 and 0.0596.

Discussion

Earlier phase I studies of KW-2149 established pulmonary toxicity as dose limiting and this was also the case in the present study at a dose of 75 mg/m^2 (cumulative dose 150 mg/m^2), despite pretreatment with corticosteroids. It was also observed in patients with 60 mg/m^2 in whom one showed clinical signs of dyspnea. In the group patients treated with 75 mg/m^2, two patients experienced dyspnea, related to KW-2149. Six of 11 patients developed significant changes in their lung diffusion capacity. At autopsy, two patients had lung fibrosis. As in the first phase I study, hematological toxicity was only pronounced in heavily pretreated patients.

The pharmacokinetic data show lower KW-2149 AUC values and higher rates of clearance compared to those described previously by Dirix *et al.*,[5] e.g. at a dose of 75 mg/m^2 a mean AUC of 19 378 ng.min/ml was obtained compared to 46 831 ng.ml/ml, and a clearance of 5 973 ml/min/m^2 against values of 1138 to 1694 ml/min/m^2. Higher mean M-16 AUC values were seen in comparison to those of Dirix *et al* (18 593 ng.min/ml after 60 mg/m^2 KW-2149 and 24 157 ng.min/ml after 75 mg/m^2 KW-2149[5]). The present study also suggests that the capacity to generate M-18 is increased with repeated exposure to KW-2149.

In conclusion, KW-2149-induced lung toxicity was not prevented by dexamethasone pretreatment and the study was terminated. Although antitumor activity was observed with KW-2149, further development of i.v. KW-2149 has been suspended.

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