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A phase I trial of MK-0731, a Kinesin Spindle Protein (KSP) inhibitor, in patients with solid tumors

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Summary

Purpose—The kinesin spindle protein (KSP) is essential for separation of spindle poles during mitosis. Its inhibition results in mitotic arrest. This phase I trial examined safety, tolerability, dose-limiting toxicity (DLT), maximum tolerated dose (MTD), pharmacokinetic parameters, and anti-tumor activity of MK-0731, a potent inhibitor of KSP.

Experimental design—In part 1, patients with advanced solid tumors received MK-0731 intravenously over 24 h every 21 days starting at 6 mg/m², escalating until MTD was reached. In part 2, patients with taxane-resistant tumors received the MTD. Plasma samples were collected to

analyze the pharmacokinetics of MK-0731. Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0.

Results—In part 1, 21 patients (median age 63 years) were treated with MK-0731 at doses ranging from 6 to 48 mg/m²/24 h for median four cycles. The dose-limiting toxicity was neutropenia and the MTD was 17 mg/m²/24 h. At the MTD, AUC (±SD) was 10.5 (±7.3) μM × hour, clearance (±SD) was 153 mL/min (±84), and t_{1/2} was 5.9 h. In part 2, 22 patients received the MTD and there were no DLTs. Although there were no objective tumor responses, four patients (with cervical, non-small cell lung, and ovarian cancers) had prolonged stable disease.

Conclusions—MK-0731 at the MTD of 17 mg/m²/day every 21 days in patients with solid tumors had few grade 3 and 4 toxicities with the major DLTs at higher doses being myelosuppression. Anti-tumor efficacy was suggested by the length of stable disease in selected patients with taxane-resistant tumors.

Keywords

Kinesin spindle protein; Oncology; Neutropenia

Introduction

A variety of chemotherapeutic agents target the mitotic spindle, including the vinca alkaloids, epothilones, and taxanes [1–3]. These mitotic inhibitors can be potent anti-cancer drugs, although they are associated with toxicity and drug resistance. In the case of the taxanes, drug resistance can develop due to export of the drug from cancer cells by the p-glycoprotein multi-drug resistance transporter or due to inhibition of taxane binding to β-tubulin that occurs because of mutations of the β-tubulin gene in the cancer cells. Further, the dose administered of taxanes and other mitotic inhibitors can be limited by the development of significant neurotoxicity [4]. Thus, a novel method of targeting the mitotic spindle assembly that leaves microtubules intact and avoids the p-glycoprotein transporter could lead to a more effective and less neurotoxic chemotherapeutic agent.

The kinesin spindle protein (KSP) represents an alternative drug target. Mitotic kinesin proteins are closely aligned with microtubules during cell division [5]. These proteins aid in mitotic segregation of chromosomes, are expressed only during mitosis, and are unlikely to induce adverse effects in non-dividing cells such as post-mitotic neurons. KSP binds microtubules and directs the energy derived from the hydrolysis of ATP toward the separation of mitotic spindle poles. KSP is most abundant in proliferating human tissues [6], and a number of KSP inhibitors have been examined for their potential as anti-cancer agents [5–11].

MK-0731 (Fig. 1) is a 460 Da inhibitor of KSP with an IC₅₀ of 2.2 nM and >20,000-fold selectivity for KSP compared with other kinesins. MK-0731 is not competitive with either ATP or microtubules, suggesting an allosteric mechanism of action. MK-0731 inhibits spindle pole separation (leading to the formation of the star-like mitotic spindles characteristic of KSP inhibition [12]) in treated human ovarian carcinoma cells. MK-0731 inhibits proliferation of several tumor cell lines, including A2780 (ovarian cancer), HCT116 (colon cancer), KB-3-1 (cervical cancer), and multi-drug-resistant derivatives of KB-3-1 that over-express p-glycoprotein [13–15]. The growth of xenograft tumors in mice was inhibited to a similar degree by MK-0731 and paclitaxel following a multi-dose regimen. Based on results of the xenograft tumor models, a 24-hour continuous infusion was predicted to be necessary for sufficient exposure of MK-0731 to promote tumor cell death while best controlling toxic effects [15, 16].

The current phase I, first-in-human trial was performed to evaluate the safety and tolerability of MK-0731, determine dose-limiting toxicities, measure the pharmacokinetics of MK-0731 administered as a 24-hour continuous IV infusion, and obtain a preliminary assessment of anti-tumor activity.

Patients and methods

This was a 2-part, first-in-human, multicenter, open-label study (protocol #002). In part 1, pharmacokinetic data were collected and the maximum tolerated dose (MTD) was established for MK-0731 in patients with advanced solid tumors. In part 2, patients with measurable taxane-resistant cancer received the drug at or below the MTD, with serial radiologic assessments.

Patients

Patients were 18 years old, had Eastern Cooperative Oncology Group (ECOG) performance status 2, and had a life-expectancy of at least 12 weeks. For part 1, enrolled patients had metastatic or locally advanced solid tumors with progression after standard therapy, or had tumors for which no standard therapy was available. For part 2, enrolled patients with measurable metastatic or locally advanced taxane-resistant cancer (defined as progression of disease after receiving a total dose 350 mg/m² of paclitaxel or 150 mg/m² of docetaxel, or having relapse within 3 months of taxane therapy completion). Patients were required to have tumor biopsy material available for baseline evaluations. Patients could not have hematological malignancy; bone marrow or stem cell transplantation; active and uncontrolled infection; or uncontrolled congestive heart failure, angina, or myocardial infarction for 3 months preceding the trial. Patients could not be pregnant or breast feeding. Patients could not receive any products known to influence CYP3A4 during the study and until 2 weeks after the last dose of study medication. Patients were not excluded for neuropathy. All patients provided written informed consent to participate in the study. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies.

Treatment

Patients were treated with a 24-hour continuous intravenous (CIV) infusion in 21-day cycles. In part 1, cohorts consisting of at least one new patient per dosing level were treated sequentially at rising dose levels (6, 12, 24, or 48 mg/m²/24 h MK-0731) using an accelerated titration design of cohorts of at least one new patient per dose level and double dose steps [17]. One patient was enrolled at the first dose. Enrollment in the next dose group began once the first patient completed 24 h of dosing and 21 days of follow-up to assess safety. If no toxicity greater than grade 1 occurred, dosing was escalated by 2-fold. If a single toxicity of grade 2 occurred, then the current cohort was expanded to a total of three patients, and dosing was escalated by 2-fold in subsequent cohorts of three. If two episodes of grade 2 toxicity or any non-dose limiting toxicity (DLT) of grade 3 or higher occurred, dosing was escalated by 40% in subsequent cohorts of three. If at any dose level a DLT occurred, a total of six patients were treated at that dose level. If one out of six patients experienced a DLT, dosing was escalated by 40% in subsequent cohorts of six. If > two out of six patients experienced DLT, the next patients were treated with the previous dose level. A DLT was defined as any of the following: a grade 4 neutropenia for 5 days, a grade 3 or 4 neutropenia with fever >38.5°C, a grade 4 thrombocytopenia (< 25,000 mm³), any grade 3 or 4 non-hematologic toxicity (except alopecia and inadequately treated diarrhea, nausea, or vomiting), a grade 3 or greater transaminase elevation lasting 1 week, or any toxicity that required holding treatment for >3 weeks.

If two or greater out of six patients experienced a treatment-related DLT, the maximum tolerated dose (MTD) was exceeded and patients were entered at the dose level below. If < two of six patients experienced a DLT at that lower dose, and this occurred within the phase of 40% dose escalations, that lower dose was be considered the MTD. However, if < two of six patients experienced a DLT at that lower dose, and this occurred within the phase of 100% dose escalations, one additional dose escalation of 40% was given to a cohort of six patients. If < two of six patients developed a treatment-related DLT, this was considered the MTD.

In Part 2, 22 new patients with measurable taxane-resistant cancer of a variety of tumor types were treated at or below the MTD established in Part 1.

Assessments

Bioanalytical methods used to quantify—MK-0731 Two hundred microliters of plasma samples were pretreated with 50 μ L of sodium bicarbonate—sodium carbonate buffer (pH=10.7) and methyl-*t*-butyl ether (MTBE): hexane (50:50, *v/v*) for liquid-liquid extraction in a 96-well plate. The upper organic layer was transferred and evaporated to dryness under a heated N₂ stream. The dried residue was reconstituted in 100 μ L of 30% ACN in 10 mM ammonium acetate (pH=5.5, *v/v*) and 10 μ L was injected into the HPLC-MS/MS system in the positive ion mode with a heated nebulizer ion source. The concentration range of the standard curve was from 1 to 200 ng/mL. The coefficient of variation of the assay, based on the analysis of replicate standards prepared using five different lots of control human plasma, was 6.1% at all concentrations within the standard curve range. The assay accuracy was 98.0 to 101.5% of nominal standard concentrations.

Pharmacokinetic methods—Pharmacokinetic parameters of MK-0731 included AUC_(0-∞) (area under the plasma concentration-time curve), t_{1/2} (half life), C_{eo}i (end of infusion concentration), Cl (clearance), and V_{dss} (volume of distribution at steady state). The software package WinNonlin Enterprise Version 5.0.1 was used for calculation. The terminal t_{1/2} was estimated from the best-fit parameters of a single exponential to the log-linear portion of the plasma concentration-time curve using unweighted linear regression. AUC_(0-∞) was calculated using the linear up/log down method up to the last measured concentration, the additional area was estimated from that concentration, and the value of terminal t_{1/2} was estimated for that administration. C_{eo}i was obtained by inspection of the concentration-time data. Cl was calculated as the ratio of dose to AUC_(0-∞). V_{dss} was calculated as

$$V_{dss} = Cl \cdot MRT = \frac{\text{Dose}_{iv}}{AUC_{(0-\infty)}} \left[\frac{AUMC}{AUC_{(0-\infty)}} - \frac{\tau}{2} \right]$$

where MRT is the mean residence time and τ is the infusion time.

Urinary MK-0731 concentrations and urine volumes from individual collection intervals were used to calculate the total recovery of MK-0731 in urine (expressed as percentage of dose) for subjects following the highest dose levels of MK-0731.

Plasma samples for pharmacokinetic and pharmacodynamic measurements were collected predose, within 1 h prior to the infusion (0), and during the infusion at 1, 3, 6, 12, and 16 h, immediately before the end of the infusion (24 h—Day 2), and after the infusion was complete at, 24.5, 25, 27, 29, 31, 34, 38, 42, 48, 72, and 96 h from the start of the infusion.

Urine samples were collected at 0–4, 4–8, 8–12, 12–24 h during the 24-hour interval of the drug infusion and again after the infusion was complete at 24–28, 28–32, 32–36, 36–48 h from the start of the infusion.

Analysis of tumor response—For each patient, the sum of the longest diameters of lesions (up to five lesions per organ and ten lesions in total) that could be accurately measured in at least one dimension (with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scanning) was calculated at baseline. Tumor response and progression were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [18].

Safety—Vital signs, physical examinations, ECOG performance status, electrocardiograms (ECGs), and laboratory safety tests (complete blood count [CBC], serum chemistries, urinalysis) were obtained or assessed prior to drug administration and at designated intervals throughout the study. Toxicity was graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events-CTCAE, Version 3.0.

Statistical analysis—Summary statistics are provided for pharmacokinetic parameters, response criteria, and adverse experiences. The primary aim of the first part of the study was to determine the MTD of MK-0731. In part 1, the total number of patients was dependent on the number of dose levels tested, so an estimation of power was not appropriate. In part 2, the 22-patient cohort size was selected to provide more precision around the degree of toxicity and to provide additional clinical response data.

Results

Patients

Out of a total of 47 patients enrolled, 43 patients received treatment. Of the four patients who were not treated, one acquired a periodontal infection prior to treatment, one was accidentally enrolled although he had a high laboratory value that should have precluded his enrollment, one withdrew consent, and one died. Enrolled patients ranged from 23 to 75 years of age (median 63 years), 58% male, with a median of three prior chemotherapy regimens. Nine patients had an ECOG performance status of 0, 29 had a performance status of one, and five had a performance status of two. Baseline patient characteristics were similar among patients in part 1 ($n=21$) and part 2 ($n=22$) of the trial. Tables 1 and 2 lists selective baseline characteristics, including type of cancer and number of prior systemic treatments.

Dose escalation and dose limiting toxicities

As seen in Table 1 and 2, in part 1 of the study, the starting dose of MK-0731 was 6 mg/m^2 . One patient was treated at this dose level and had no grade 2 or higher toxicities; therefore, the next cohort was dosed at 12 mg/m^2 . No toxicities were noted in two patients enrolled at this dose level, and the next patient received 24 mg/m^2 . Again, there were no toxicities. Two patients were enrolled at 48 mg/m^2 and both experienced grade 4 neutropenia lasting more than 5 days, which met criteria for DLT. This led to the expansion of cohorts at lower dose levels. As more patients were enrolled at 24 mg/m^2 , two more patients had DLTs of grade 4 neutropenia lasting greater than 5 days. Thus, the dose was again de-escalated to 12 mg/m^2 . When more subjects were enrolled at 12 mg/m^2 , no further toxicities were observed. An intermediate dose of 17 mg/m^2 was subsequently tested. Six patients were treated at this dose level, and none experienced DLT; therefore, the maximum tolerated dose was determined to be 17 mg/m^2 .

In part 2 of the study, all patients received MK-0731 17 mg/m². There were no DLTs.

Pharmacokinetics

MK-0731 concentrations appear to decline monoexponentially or possibly biexponentially after the end of infusion (Fig. 2a), with individual terminal half-life estimates ranging from approximately 2 to 22 h. Preliminary results suggest that steady-state concentrations may not be achieved for all patients within 24 h after the start of the infusion, consistent with the longer terminal half-life values for some patients. Taken together, individual end of infusion concentrations and AUC values appear to increase approximately dose proportionally (Fig. 2b and c). Clearance estimates were consistently low and averaged approximately 100 to 250 mL/min, independent of dose (Table 3). On average, less than 4% of the dose was recovered in urine as unchanged drug at the highest dose levels, indicating that renal excretion plays a minimal role in the elimination of MK-0731.

PK/PD relationship

Absolute neutrophil count data are shown plotted versus individual Area Under the Curve (AUC) and End of Infusion Concentration (C_{eo}i, Fig. 3a and b, respectively). It appears that patients with the higher AUC and C_{eo}i values were generally those experiencing the reduced neutrophil counts (the dose-limiting toxicity), though due to the small number of patients analyzed, these relationships are not conclusive.

Efficacy

There were no partial or complete responses in this study according to RECIST. Four subjects receiving 17 mg/m²/24 h had prolonged stable disease for at least 5 months (Table 2,) including two patients with non-small cell lung cancer (NSCLC). One was on study drug for 12 cycles after progression of disease on four prior chemotherapy regimens, and the other was on study drug for eight cycles after progression of disease on three prior regimens. The other two subjects with stable disease had cervical and ovarian cancer and were on study drug for 9 and 11 cycles of therapy, respectively. No decreases were seen in levels of the Ca125 antigen in the ovarian cancer patient with prolonged stable disease. However, a greater than 50% reduction in serum Ca125 and PSA antigens were seen in patients treated with 17 mg/m² MK-0731 who had fallopian tube cancer and prostate cancer, respectively (data not shown).

Adverse experiences

Overall, there were few clinically relevant toxicities noted on study drug (Table 4). There were no reported occurrences of neuropathy. The DLTs were uniformly neutropenia. Other toxicities that occurred included anemia, lymphopenia, and thrombocytopenia, as well as nausea, vomiting, fatigue, anorexia, and syncope. The hematologic toxicities were mainly grade 2 with four grade 3 episodes of anemia. The few non-hematologic toxicities included one report each of grade 3 nausea, grade 3 vomiting, and a grade 3 syncopal event likely related to dehydration. Other toxicities consisted of clinically insignificant events or laboratory abnormalities.

Discussion

This is the first study to establish the safety, tolerability, and pharmacokinetics of the novel kinesin spindle protein inhibitor MK-0731 as a 24-hour IV infusion in patients with heavily pretreated and chemotherapy-resistant advanced solid tumor malignancies. MK-0731 was well tolerated with a maximum tolerated dose of 17 mg/m². Neutropenia was the dose-limiting toxicity at higher dose levels and significant non-hematologic toxicities, particularly

neurotoxicities that are typically seen with microtubule targeting agents, were uncommon. Thus, MK-0731 was able to affect rapidly proliferating cells (eg, neutrophils) and likely spare microtubule function unrelated to mitosis. It may also be reasonable in future studies, given the favorable side effect profile of MK-0731, to consider dose escalation with G-CSF support.

The neutropenia seen with MK-0731 has been noted with other kinesin spindle protein inhibitors in the clinic. In fact, neutropenia has been the single most common cause for halting further escalations [7, 11, 19–21]. This effect has been so common that neutropenia could be considered a pharmacodynamic marker of effect on the mitotic spindle. Unfortunately, this neutropenia has made it difficult to achieve a wide therapeutic window and has somewhat limited the development of these agents.

Evidence of the clinical efficacy of MK-0731 was seen in the form of prolonged disease stabilization of greater than 5 months in heavily pretreated patients, including two patients with NSCLC previously treated with a taxane. Although considerable tumor shrinkage was not seen, this result was not surprising given the inherent design and heavily pretreated patient population of phase I trials.

Both the AUC and C_{coi} of MK-0731 increased approximately proportionately to the dose administered. There was a fairly wide range of terminal half-lives and clearance values for MK-0731, but this was not unexpected given the small number of patients in the study. Based upon recovery in urine at the highest doses, MK-0731 appeared to have minimal renal excretion as unchanged drug. The levels of MK-0731 achieved were comparable, if not higher, than levels seen in animals with anti-mitotic effects [15].

In summary, administration of the novel kinesin spindle protein inhibitor MK-0731 at doses sufficient to modulate neutrophil counts resulted in prolonged disease stabilization without the development of neuropathy. Further evaluation of MK-0731 efficacy endpoints might be of value in a population of patients that are less heavily pre-treated.

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Fig. 1.
Molecular structure of MK-0731

Fig. 2.
Pharmacokinetics

Fig. 3.
Effects of MK-0731 on neutrophil count

Table 1

Summary of drug exposure. Part 1 of study—determining the maximum tolerated dose

Treatment Group (Dose MK-0731, mg/m ² /24 h)	Age (yrs)	Diagnosis	Gender	Number of prior systemic treatments	Number of cycles	DLT ^a
6	59	Ovarian cancer	Female	3	3	
12	75	Bladder cancer	Male	3	2	
12	63	Carcinoma, esophageal	Male	2	2	
12	72	Carcinoma, neuroendocrine	Male	3	2	
12	67	Endometrial cancer	Female	4	4	
12	63	Pancreatic cancer	Female	1	1	
12	45	Renal cell cancer	Male	2	5	
17	72	Carcinoma, adeno NOS	Female	2	2	
17	53	Carcinoma, adeno NOS	Male	3	2	
17	69	Colorectal cancer	Male	3	8	
17	54	Head and neck cancer	Male	3	1	
17	63	Prostate cancer	Male	5	6	
17	63	Prostate cancer	Male	4	6	
24	62	Gastrointestinal stromal tumor	Male	4	1	
24	54	Prostate cancer	Male	5	6	
24	51	Prostate cancer	Male	5	2	
24	74	Prostate cancer	Male	3	8	X
24	56	Sarcoma NOS	Male	3	4	
24	60	Vaginal cancer	Female	4	10	X
48	48	Carcinoid	Female	5	5	X
48	72	Liver cancer	Male	4	8	X

^aDose-limiting toxicity (DLT)

Table 2Summary of drug exposure. Part 2 of study—treatment at the maximum tolerated dose (17 mg/m²/24 h)

Age (yrs)	Diagnosis	Gender	Number of prior systemic treatments	Number of cycles
69	Bladder cancer	Male	1	2
72	Bladder cancer	Female	3	2
64	Breast cancer	Female	6	2
46	Breast cancer	Female	4	3
67	Carcinoma, adeno NOS	Male	2	4
67	Carcinoma, adeno NOS	Female	2	1
59	Carcinoma, adeno NOS	Female	3	4
53	Carcinoma, cystadeno	Female	2	2
60	Cervical cancer	Female	2	9 ^a
57	Fallopian tube cancer	Female	3	2
61	Gastric cancer	Female	2	1
60	Head and neck cancer	Male	3	2
23	Malignant hemangioma	Male	2	2
58	Non-small cell lung cancer	Male	4	12 ^a
56	Non-small cell lung cancer	Female	3	2
71	Non-small cell lung cancer	Male	3	8 ^a
57	Ovarian cancer	Female	2	11 ^a
64	Prostate cancer	Male	5	4
66	Prostate cancer	Male	6	2
65	Prostate cancer	Male	4	7
70	Prostate cancer	Male	6	2
70	Unknown	Female	4	4

^aPatient had stable disease, defined as stable for at least 5 months (eight cycles)

Table 3

Mean pharmacokinetic parameters (parts 1 & 2)

Dose mg/m ² /24 h	C _{eof} nM (SD)	Cl mL/min (SD)	V _{dss} L (SD)	t _{1/2} hr	AUC _{0-∞} μM × hr (SD)
6 (n=1)	71	251	102	4.0	1.44
12 (n=6)	288 (161)	154 (69)	80 (21)	5.9	6.96 (3.85)
17 (n=25)	429 (240)	153 (84)	79 (29)	5.9	10.52 (7.32)
24 (n=6)	851 (339)	98 (66)	68 (26)	9.9	23.56 (10.04)
48 (n=2)	1,223 (125)	122 (10)	94 (31)	8.4	26.59 (3.18)

^aHarmonic mean, C_{eof} = End of infusion concentration, V_{dss} = volume of distribution at steady state, t_{1/2} = half life, AUC = area under the plasma concentration-time curve

Table 4

Grade 2 and higher treatment-related toxicities by dose level, all cycles (n=47)

Dose (mg/m ² /24 h)	Adverse experience:	Grade 2		Grade 3		Grade 4	
		n	%	n	%	n	%
6	Abdominal Pain	1	2.1				
6	Anorexia	1	2.1				
12	Leukopenia	1	2.1				
12	Neutropenia	1	2.1				
12	Vomiting	1	2.1				
17	Anemia	2	4.3	4	8.5		
17	Anorexia	1	2.1				
17	Fatigue	2	4.3				
17	Hypoalbuminemia	1	2.1				
17	Hypophosphatemia	1	2.1				
17	Leukopenia	6	12.8	1	2.1		
17	Lymphopenia	2	4.3	1	2.2		
17	Neutropenia	2	4.3	5	10.7		
17	Thrombocytopenia	1	2.1				
17	Pruritus	1	2.1				
17	Pyrexia						
17	Syncope			1	2.1		
24	Fatigue	1	2.1				
24	Leukopenia	1	2.1				
24	Neutropenia	1	2.1	1	2.1	2	4.3
24	Pyrexia	2	4.3				
48	Alopecia	2	4.3				
48	Anemia	1	2.1				
48	Hyperglycemia			1	2.1		
48	Hypocalcemia	1	2.1				
48	Hypophosphatemia	1	2.1				
48	Leukopenia	1	2.1	1	2.1		
48	Mucosal Inflammation	1	2.1				

Dose (mg/m ² /24 h)	Adverse experience:	Grade 2		Grade 3		Grade 4	
		n	%	n	%	n	%
48	Nausea			1	2.1		
48	Neutropenia					2	4.3
48	Thrombocytopenia			1	2.1		
48	Vomiting			1	2.1		