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Phase I study of *continuous* MKC-1 in patients with advanced or metastatic solid malignancies using the modified Time-to-Event Continual Reassessment Method (TITE-CRM) dose escalation design

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Abstract

Background—MKC-1 is an oral cell-cycle inhibitor with broad antitumor activity in preclinical models. Clinical studies demonstrated modest antitumor activity using intermittent dosing schedule, however additional preclinical data suggested continuous dosing could be efficacious with additional effects against the mTor/AKT pathway. The primary objectives were to determine the maximum tolerated dose (MTD) and response of continuous MKC-1. Secondary objectives included characterizing the dose limiting toxicities (DLTs) and pharmacokinetics (PK).

Methods—Patients with solid malignancies were eligible, if they had measurable disease, ECOG PS 1, and adequate organ function. Exclusions included brain metastases and inability to receive oral drug. MKC-1 was dosed twice daily, continuously in 28-day cycles. Other medications were eliminated if there were possible drug interactions. Doses were assigned using a TITE-CRM algorithm following enrollment of the first 3 pts. Disease response was assessed every 8 weeks

Results—Between 5/08-9/09, 24 patients enrolled (15 M/9 F, median 58 years, range 44-77). Patients 1-3 received 120 mg/d of MKC-1; patients 4-24 were dosed per the TITE-CRM algorithm: 150 mg [n=1], 180 [2], 200 [1], 230 [1], 260 [5], 290 [6], 320 [5]. The median time on drug was 8 weeks (range 4-28). The only DLT occurred at 320 mg (grade 3 fatigue). Stable disease occurred at 150 mg/d (28 weeks; RCC) and 320 mg/d (16 weeks; breast, parotid). Escalation halted at 320 mg/d. Day 28 pharmacokinetics indicated absorption and active metabolites.

Conclusion—Continuous MKC-1 was well-tolerated; there were no RECIST responses, although clinical benefit occurred in 3/24 pts. Dose escalation stopped at 320 mg/d, and this is the MTD as defined by the CRM dose escalation algorithm; this cumulative dose/cycle exceeds that determined from intermittent dosing studies. A TITE-CRM allowed for rapid dose escalation and was able to account for late toxicities with continuous dosing via a modified algorithm.

Keywords

MKC-1; TITE-CRM; Solid malignancy; Novel dose escalation designs

INTRODUCTION

MKC-1 (formerly known as Ro 31-7453) is a novel, orally active cell cycle inhibitor. Several proteins have been identified as binding targets of MKC-1, including microtubules

(colchicine binding site) and members of the importin- β family (involved in nuclear transport and spindle formation). In vivo, MKC-1 demonstrated efficacy in a broad range of tumor models, including paclitaxel resistant cell lines, and demonstrated possible synergy with other tubulin-interacting agents.

Phase I studies have been conducted with MKC-1 with a variety of dosing schedules for patients with solid tumors (see Table 1). Partial responses and disease stabilization were reported from these and other studies with MKC-1.¹⁻⁵ However, preclinical studies suggested continuous dosing could be efficacious with additional effects against the mTor/AKT pathway. Therefore, the University of Wisconsin Carbone Cancer Center conducted a Phase I study with the primary objective of defining the MTD and efficacy of continuous MKC-1. Secondary objectives included the safety and pharmacokinetic characteristics of continuous MKC-1.

This study also employed a novel, model-based dose escalation design. Because of the wealth of pre-existing toxicity data and need to account for late toxicity, a Time to Event Continual Reassessment Method (TITE-CRM), was used to escalate the doses.^{6,7} The CRM was modified to suit the oral doses available with MKC-1 as well as the possibility of late chronic toxicity due to continuous oral dosing.⁸ Using a CRM is reasonable when extensive Phase I data already exists and a reasonable estimate of the MTD on a new dosing schedule can be made. A model-based dose escalation design such as the CRM design tends to estimate the true MTD more accurately than standard 3+3 designs if the model assumptions (e.g., a monotone dose-toxicity relationship) are correct.⁹ The results of a Phase I study to define the MTD of continuous MKC-1 using a TITE-CRM dose escalation design are presented.

METHODS

Patient Accrual

A phase I, single center, open-label design was used to find the MTD of MKC-1 when given continuously, as well as to assess the safety, pharmacokinetic characteristics and efficacy of continuous MKC-1. This study was conducted at the University of Wisconsin Carbone Comprehensive Cancer Center after institutional review board approval. Patients were required to have a histologically confirmed malignancy that was metastatic or unresectable for which standard curative measures did not exist or was no longer effective. Patients ≥ 18 years old, a life expectancy ≥ 3 months, ECOG performance status of 2 or better; and unresectable or metastatic solid malignancy were eligible. Inclusion criteria included at least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST).¹⁰

Patients were excluded for hematopoietic (ANC $< 1500/\text{mm}^3$, platelets $< 100,000/\text{mm}^3$), hepatic (total bilirubin outside institutional upper limit of normal [ULN]), AST or ALT > 2.5 times ULN, albumin $< 3 \text{ g/dL}$) or renal (Cr > 1.5 times ULN) dysfunction. Patients were also excluded for prior MKC-1 exposure, brain metastases, use of other anticancer agents, radiotherapy or surgery within the previous four weeks, radiotherapy to more than 25% of bone marrow, and any condition that might impair the ability to swallow and retain MKC-1 capsules. All patients provided written informed consent prior to enrollment.

Study Design

The first 3 patients received 60 mg twice daily, given orally, continuously. This was empirically chosen as the starting dose because it represented roughly half the MTD of MKC-1 when administered 14 days on/14 days off.² Although prior studies with MKC-1 had utilized body surface area (BSA) calculations to derive final dosing, this study elected to

use a flat dose, which was not altered based on BSA. After the first 3 patients were enrolled and treated for 4 weeks each, further patients were allowed to enroll. The modified TITE-CRM algorithm was used to assign doses of MKC-1 after the first 3 patients for up to 21 additional patients.^{7,8} A dose expansion at the MTD was planned for a further 12 patients.

The planned chronic, continuous, oral nature of drug administration mandated that toxicities be defined as either acute (occurring during cycle 1) or late (occurring during cycle 2 or 3). Both acute and late toxicities were incorporated into the TITE-CRM algorithm in order to determine future patient doses, if the toxicity met dose-limiting toxicity (DLT) criteria. Toxicity had to be at least possibly related to MKC-1 administration in order to be considered a DLT. Hematologic DLTs included ANC<750/mm³, neutropenic fever, or platelets < 25,000/mm³. Clinically significant bleeding (requiring transfusion) in the setting of platelets < 50,000/mm³ lasting 7 days or more was also considered a DLT. Nonhematologic DLTs included any event ≥ 3 or a subjectively intolerable Grade 2 toxicity, which did not resolve within 14 days. Nausea, vomiting, and diarrhea had to be persistent despite maximal supportive care in order to be considered DLTs. Toxicity was graded according to CTCAE Version 3.0. Patients not completing the initial 28-day treatment period for reasons other than DLT were deemed unevaluable for toxicity and were replaced.

Treatment Plan and Patient Follow Up

The study sponsor, EntreMed, Inc. (Rockville, MD) supplied MKC-1. Drug was supplied as 30 or 100 mg capsules. This study employed a flat dose, which was not altered based on patient BSA.

Patients received the study drug in two divided daily doses continually throughout a 28-day cycle. Patients who completed the initial treatment cycle without evidence of DLT or symptomatic disease progression were eligible for additional cycles. Patients were assessed on day 1 of subsequent cycle with clinical exam, chemistries and complete blood counts; chemistries and complete blood counts were also assessed on Day 15 of Cycle 1 only. Patients who discontinued study drug were followed for 30 days subsequently, or until the resolution of toxicity to baseline or less than grade 1.

Dose modifications

Development of a DLT that did not resolve within 14 days mandated that patients discontinue study drug. If the toxicity resolved in 14 days, the patient resumed therapy at the next lower dose level. Treatment otherwise continued until withdrawal of consent or progressive disease.

Pharmacokinetic Analyses and Correlative Studies

Trough levels of MKC-1 and its 2 active metabolites (Ro 27-4006 and Ro 27-0431) were assessed.

Tumor Response

Tumor response was assessed using RECIST¹⁰ at baseline and again before every odd numbered cycle.

Statistical Analyses

Dose escalation of MKC-1 was performed using the TITE-CRM algorithm. The primary goal is to estimate the MTD, which was defined as the dose of MKC-1 at which 33% of the patients experience DLTs by 12 weeks. The TITE-CRM method assumes a parametric model for the time to occurrence of toxic response as a function of dose, and thereby allows

information from all patients enrolled to be employed when assigning a dose to new patients entering the study. Specifically, the estimates of the probabilities of DLTs were continuously updated using a single-parameter logistic dose-toxicity model with a fixed intercept and an unknown dose-toxicity parameter β , after each new patient entered the study. While the standard TITE-CRM algorithm is based on pre-specified dose levels, the modified version of TITE-CRM algorithm used in this trial allowed for the calculation of continuous oral medication dosages. Patients who had not experienced a DLT were included in the probability calculation with a weight equal to the proportion of the 3 cycles (12 weeks) toxicity observation period they had completed. Patients who had experienced a DLT or completed the observation period of 3 treatment cycles (12 weeks) without DLT were assigned full weight. Each new patient was assigned to the estimated target dose, defined as the dose having an estimated DLT probability of 33%. In order to avoid an overly rapid dose escalation, the maximum dose increment was restricted to 30 mg/daily. Before initiating the study, simulation studies were conducted to determine an appropriate prior distribution specification for the dose-toxicity parameter β (normal distribution with mean zero and scale 1.2) under various scenarios about the true relationship between dose and toxicity. The TITE-CRM algorithm was implemented using R software version 2.3.1.¹¹

Patient's baseline characteristics were summarized using standard descriptive statistics. Toxicities were summarized by type and severity in tabular format. The final estimates of DLT probabilities were computed for MKC-1 doses ranging from 120mg to 320mg based on the final posterior distribution of the dose-toxicity parameter mean and reported along with the corresponding 90% posterior probability intervals.

RESULTS

Baseline Patient Characteristics

Between May 2008 and September 2009, a total of 24 patients enrolled. Table 2 summarizes their baseline characteristics.

Treatment

All 24 patients completed at least one cycle of continuous MKC-1, and 21 (88%) completed at least 2 cycles of continuous MKC-1. The median number of weeks on drug was 8 (range 4-28 weeks). Reasons for discontinuation included disease progression (n=19) and MD discretion (n=5). No patients withdrew secondary to inability to tolerate drug.

The CRM algorithm calculated patient doses based on acute (Cycle 1) and late (Cycle 2 and 3) toxicities. A cap was placed on the total amount by which the algorithm could increase the dose (e.g. if patient Y had received 160 mg, and the algorithm calculated the dose as 500 mg for patient Z, a predetermined cap dictated that the starting dose for patient Z was no higher than some fraction of patient Y's dose.) Also, because of the CRM design, the final dose of MKC-1 could not be escalated above 460 mg/d. The investigators had predetermined that doses above that level would not be of interest, as these doses would significantly exceed the MTD defined by prior studies using intermittent dosing.

Patients 1 through 3 received 120 mg/d of MKC-1; while patients 4-24 were dosed per the TITE-CRM algorithm (see Table 3). No study drug related DLT was seen until 320 mg/d, when patient 18 developed grade 3 fatigue during cycle 1. Drug was held and symptoms improved; treatment was resumed at 290 mg/d. Patient 17 also experienced intolerable grade 2 fatigue, and drug was held for one week. The CRM algorithm thus calculated a dose reduction to 290 mg/d. Patients 19, 20 and 21 did not experience DLTs, and the dose was re-escalated to 320 mg/d. No further DLTs were seen at 320 mg/d. Dose escalation was stopped at 320 mg/d, because the pre-specified number of patients had been enrolled (n=24).

This dose was judged to be a reasonable stopping point by study investigators, as the cumulative dose of MKC-1 per cycle exceeded that reached with the intermittent dosing schedules. Thus, based on rules of the CRM dose escalation algorithm, 320 mg/d is defined as the MTD of continuous MKC-1.

Toxicity

Treatment was generally very well tolerated. The most frequent toxicities are listed along with grade in Table 4. The most common treatment-related toxicities were fatigue (n=6) and urine color change (n=4).

A number of grade 3 or higher events occurred on study, only 2 of which were judged at least possibly attributable to study drug. Only one of these occurred during Cycle 1, and was judged to be an acute DLT (Patient 18, grade 3 fatigue) at 320 mg/d. Table 5 shows the estimated probabilities for a DLT with the corresponding 90% posterior intervals for the various dose levels. These probabilities were estimated from the posterior dose-toxicity distribution which is based on the conditional distribution of the dose-toxicity parameter β , given the observed toxicities in the 24 patients. The estimated DLT rate for 320 mg/daily was 28% with a 90% posterior probability interval ranging from 8 to 54%.

In Cycle 2, Patient 1 developed a grade 3 elevation in INR judged unrelated to study drug. Patients 2 and 9 developed grade 3 hyponatremia in Cycle 2, judged unrelated to study drug. Patient 5 developed grade 3 hyperkalemia in Cycle 2, judged unrelated to study drug. Patient 10 developed grade 4 dyspnea in Cycle 2, felt to be possibly related to study drug. Drug was delayed, and symptoms improved and drug was later resumed without dose reduction and without further difficulties. Patient 11 developed grade 3 hyperglycemia, judged unrelated to study drug. Patient 12 had grade 3 abdominal pain, and grade 3 LOC, unrelated to study drug. In Cycle 2, Patient 13 developed grade 3 hyperglycemia, possibly related to study drug. Patient 21 developed grade 3 abdominal pain and vomiting – this pain was judged related to underlying ovarian cancer, but MKC-1 was delayed due to these symptoms.

Tumor Response Evaluation

All enrolled patients had measurable disease; all patients receiving 2 or more cycles of continuous MKC-1 were evaluated for tumor response (see Table 6). There were no confirmed complete or partial responses by RECIST. Three patients had prolonged stable disease. Patient 2 had renal cell carcinoma and demonstrated stable disease for 28 weeks at 150 mg/d of continuous MKC-1. Patient 17 and 22 each had 16 weeks of stable disease at 320 mg/d (these patients had breast and parotid carcinomas respectively).

DISCUSSION

MKC-1 is a novel, orally active cell cycle inhibitor. Previous phase I studies have been conducted with MKC-1 using a variety of intermittent dosing schedules for patients with solid tumors. Myelosuppression and mucositis are the dose limiting toxicities with the intermittent schedules. Partial responses and disease stabilization were reported from these and other studies with MKC-1.^{2,3} Because the efficacy of MKC-1 was postulated to improve with sustained exposure, the University of Wisconsin conducted a Phase I study with the primary objective of defining the MTD of continuous MKC-1 using the modified TITE-CRM algorithm. This statistical design was chosen as an optimal method for incorporating toxicity and tolerability, both being important for a continuously administered oral regimen. Dose escalation was stopped at 320 mg/d when the cumulative dose of MKC-1 per 28-day cycle exceeded that reached with the intermittent dosing schedules.

Given that human BSA generally ranges from 1.5 to 2.2 m², the MTDs defined on the intermittent dosing schedules (540 mg/m²/day for 4 days of 21-days cycle; 400 and 250 mg/m²/day for 7- and 14-days of a 28 day cycle) translate into roughly 150 - 275 mg/day. The majority of patients on this study received cumulative doses in excess of 150 mg/day. Despite this, treatment of continuous MKC-1 was very well tolerated with few side effects. The only DLT was grade 3 fatigue. Myelosuppression or mucositis did not occur, unlike with the intermittent dosing schedules. Day 28 pharmacokinetics indicated absorption and active metabolites at levels consistent with known efficacious doses of MKC-1.

The prolonged exposure with continuous oral administration avoided high peak drug concentrations, and likely explains the lack of myelosuppression.¹² Two other potential explanations exist for the general lack of toxicity. First, analysis of prior studies suggested that low albumin levels predicted greater toxicity with MKC-1; therefore, unlike prior studies, we required an albumin ≥ 3.0 g/dL. This might have improved the toxicity profile compared with other Phase I trials. Another explanation is that previous studies used BSA, while this study used a flat dose. Using a flat dose can lead to under-dosing of larger patients and hence, less toxicity. However, the BSAs on this study fall in the expected range 1.6 to 2.2 m².

Despite evidence that continuous MKC-1 dosing achieved levels of active metabolites consistent with known efficacious doses of MKC-1, the efficacy was very modest. Three patients (1 renal cell carcinoma, 1 parotid adenocarcinoma and 1 breast cancer) achieved stable disease for 28, 16 and 16 weeks respectively. Given the nature of these disease types, the stable disease seen on continuous MKC-1 may have simply indicated slowly progressive disease. The study did include patients with disease types that had previously demonstrated signs of clinical activity with MKC-1 (3 ovarian, 2 breast, 1 lung, 1 pancreatic cancer); however, these patients were relatively heavily pretreated, as is typical for a Phase I trial.

Our study employed a novel dose-escalation design which modeled DLTs during the first three cycles along with discontinuation due to intolerability rather than the traditional 3+3 dose-escalation of most Phase I trials. A traditional 3+3 design emphasizes toxicity during cycle 1 – a paradigm that works fairly well for intermittently administered intravenous drugs. A traditional 3+3 design cannot easily account for chronic intolerable symptoms (such as persistent grade 2 nausea) or late toxicities (such as hand-foot symptoms in cycle 3). Both chronic and late toxicities are of significant concern with a continuous oral medication. Moreover, simulations have shown that CRM-based methods more accurately find the true MTD and treat more patients at optimal dose levels – both of which are highly desirable outcomes.

However, the 3+3 design remains the most common design for Phase I studies, because it is well understood by oncologists.^{6,8,9,13} Few examples exist in the literature of a CRM being used for an oral anticancer agent in a Phase I study. Although a modified CRM was employed safely on our study and functioned well overall, a few difficulties were encountered and are notable. We report these here for the benefit of those wishing to employ a CRM in place of a 3+3 design.

First, a CRM requires significant statistical support, far more than a traditional 3+3 design. Simulation studies should be conducted before initiating a study to evaluate the operating characteristics for various dose-toxicity relationships. Based on the results of these simulation studies, an appropriate prior distribution for the dose-toxicity relationship should be identified. Moreover, the implementation of such a CRM dose-escalation design is a logistically challenging endeavor requiring continuous communication with the study statistician. Second, despite occurring at a single, academic institution, with extensive

briefing on the study design, the referring clinicians remained uncomfortable with CRM dose escalation.

In summary, continuous MKC-1 is well tolerated at 320 mg/d, and this is the MTD as defined by the CRM dose escalation algorithm. A modest efficacy signal was observed. A CRM algorithm was used safely to assign doses for the Phase I study of an anti-cancer agent and study late or chronic toxicities.

Statement of Clinical Relevance

This manuscript describes the results of a phase I study of MKC-1 in patients with advanced solid malignancies. Preclinical and clinical studies of MKC-1 have demonstrated activity in a variety of tumors including breast and lung cancer. Here, we evaluate the safety and tolerability of continuously dosed MKC-1, which may provide additional mechanisms of antitumor activity over intermittent dosing strategies. We also describe the application of an unusual dose-escalation design and important considerations for applying reassessment models to continuous oral chemotherapy in which extended drug tolerability (in addition to toxicity) is important.

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Table 1

Summary of Prior Phase I Studies with Single-agent MKC-1

	Schedule	MTD	Toxicities
Dupont et al ³	4 days on 21 day cycle	560 mg/m ² /day	*Myelosuppression, *stomatitis, diarrhea, nausea/vomiting, fatigue, alopecia, elevated LFTs [#]
Salazar et al ²	7 days on 28 day cycle	400 mg/m ² /day	*Myelosuppression, *mucositis nausea/vomiting, diarrhea fatigue
Salazar et al ²	14 days on 28 day cycle	250 mg/m ² /day	*Myelosuppression, *mucositis nausea/vomiting, diarrhea fatigue

* DLT

[#] LFTs = liver function tests

Table 2**Patient Demographics**

Sex	15 male, 9 female
Ethnicity (n)	Caucasian (24)
Median age, years (range)	58 yo (44-77 yo)
ECOG PS, median (range)	1 (0-1)
Number prior therapies, median (range) *	3 (0-8)
Tumor Type (n)	Pancreas (1) Renal cell carcinoma (6) Gallbladder (1) Hepatocellular carcinoma (1) Colorectal or small intestine (4) Sarcoma (2) Bladder carcinoma (1) Breast (2) Ovarian (3) Parotid adenocarcinoma (1) Neuroendocrine tumor (2) Non-small Cell lung cancer (1)

* Includes the following: cytotoxics, antibody and/or immunologic therapies but not endocrine therapies

Table 3

Dose Escalation of MKC-1 as per TITE-CRM algorithm

Patient Number	Assigned dose of continuous MKC-1	Dose Determined By
1-3	120 mg/d	Fixed dose, not calculated by algorithm
4	150 mg/d	
5, 6	180 mg/d	
7	200 mg/d	
8	230 mg/d	
9-13	260 mg/d	Because of rapidity of patient enrollment, CRM continued to calculate 290 mg/d as dose, due to lack of further data regarding late toxicity.
14- 16	290 mg/d	Because of rapidity of patient enrollment, CRM continued to calculate 290 mg/d as dose, due to lack of further data regarding late toxicity.
17, 18	320 mg/d	Patient 17 had DLT (grade 3 fatigue); Patient 18 had grade 2 intolerable fatigue and had delay starting subsequent cycle. CRM calculated need for dose reduction.
19- 21	290 mg/d	No DLTs seen at 290 mg/d. Six total patients treated at 290 mg/d. CRM calculated need for dose escalation back to 320 mg/d
22-24	320 mg/d	No further DLTs seen at 320 mg/d. Five total patients treated at 290 mg/d.

Table 4

Adverse events (at least possibly study drug related) on continuous MKC-1

Dose	Adverse events	Grade 1		Grade 2		Grade 3		Grade 4	
		N	%	N	%	N	%	N	%
260 mg	Neurology	0	0	0	0	1	4	0	0
	Dyspnea	0	0	0	0	0	0	1	4
	Vomiting	0	0	0	0	1	4	0	0
290 mg	Pain-Abdomen	0	0	0	0	1	4	0	0
	Fatigue	0	0	0	0	1*	4	0	0
320 mg	Pain-Chest/thorax	0	0	1	4	0	0	0	0

* DLT

Table 5

Final estimates of DLT probabilities based on TITE-CRM

Dose (mg/daily)	N	Number of DLTs	Estimated probability of DLT (90% posterior probability interval)
120 mg	3	0	0% (0% - 1%)
150 mg	1	0	0% (0% - 1%)
180 mg	2	0	0% (0% - 2%)
200 mg	1	0	0% (0% - 3%)
230 mg	1	0	1% (0% - 7%)
260 mg	5	0	4% (1% - 20%)
290 mg	6	0	12% (1% - 35%)
320 mg	5	1 (Grade 3 fatigue)	28% (8% - 54%)

Table 6

Summary of Best Confirmed Overall Tumor Response

Category of Response	Dose of continuous MKC-1 in mg/d										Total
	120	150	180	200	230	260	290	320			
Complete Response	0	0	0	0	0	0	0	0	0	0	0
Partial Response	0	0	0	0	0	0	0	0	0	0	0
Stable Disease	0	1	0	0	0	0	0	2	3		3
Progressive Disease	3	0	2	1	1	5	6	3	21		21
Not evaluable	0	0	0	0	0	0	0	0	0		0
TOTAL treated at dose level	3	1	2	1	1	5	6	5	24		24