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A Phase 2 Study of Oral MKC-1 in Patients with Unresectable or Metastatic Pancreatic Cancer

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Abstract

Background—MKC-1 is an orally available cell cycle inhibitor with downstream targets that include tubulin and the importin- β family. We conducted an open-label Phase II study with MKC-1 in patients with advanced pancreatic cancer.

Methods—Eligibility criteria included unresectable or metastatic pancreatic cancer, performance status of 1 or better, and failure of at least one prior regimen of chemotherapy. MKC-1 was administered orally, twice daily, initially at 100mg/m² dosing for 14 consecutive days of a 28-day

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cycle. This schedule was modified during the trial to fixed and continuous dosing of 150mg per day.

Results—20 of an original target of 33 patients were accrued, with a median age of 61 (range 44 to 81). No objective responses were observed, with one patient demonstrating stable disease. Overall survival was 101 days from the start of MKC-1 administration, and median time to progression was 42 days. The most common adverse events listed as related or possibly related to MKC-1 administration were hematologic toxicities and fatigue. One patient developed grade 5 (fatal) pancytopenia. Grade 3 and 4 events included cytopenias (lymphopenia, anemia), hyperbilirubinemia, pneumonia, mucositis, fatigue, infusion reaction, anorexia, and hypoalbuminemia.

Conclusions—MKC-1 administration was associated with substantial toxicity and did not demonstrate sufficient activity in patients with advanced pancreatic cancer to justify further exploration in this patient population.

Keywords

Pancreatic cancer; Phase II; MKC-1; importin; tubulin

Introduction

Pancreatic cancer is currently the fourth leading cause of cancer-related death in the United States, with an expected 43,140 cases and 36,800 deaths in 2010 [1]. The overall 5-year survival for all stages is 5.6% [2]. In patients with local disease, less than 20% are candidates for curative surgery, and the five year survival is only 22%. In patients with metastatic disease at presentation, who constitute over half of all patients diagnosed with pancreatic cancer, survival is exceedingly poor, with a 5 year survival of just 1.9% [2]. In patients with advanced disease, chemotherapy response rates are low (generally 10% or less), and median survival is only 6–11 months [3, 4]. First-line chemotherapy for locally advanced or metastatic pancreatic cancer has traditionally been single-agent gemcitabine on the basis of several Phase III trials, which has a low response rate of 5–10% and a median survival of 5–7 months [5–9]. More recently, the use of a combination chemotherapy regimen consisting of fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) in patients with good performance status appears promising, with improvements in progression free and overall survival [10]. However, the regimen was associated with higher toxicity than conventional regimens used in pancreatic cancer, with nearly half of patients developing Grade 3 or 4 neutropenia, and thus the applicability to patients with a less robust performance status is unknown. Given the poor outcomes of patients with pancreatic cancer, and particularly with advanced pancreatic cancer, it is imperative to study new agents that may target important signaling pathways in pancreatic tumors and improve outcomes.

MKC-1, formerly referred to as Ro 31-7453, is a novel, orally available small molecule cell cycle inhibitor. MKC-1 has several targets, including the importin- β family of proteins, which function in transnuclear protein transport. Other targets include tubulin, causing destabilization of microtubules, and the Akt/mTOR signal transduction cascade. The first two actions of MKC-1 serve to inhibit the formation of the mitotic spindle and hence chromosomal segregation, ultimately leading to hyperploidy and apoptosis. MKC-1 has demonstrated activity in a wide range of preclinical tumor models, including multi-drug resistant cell lines [11]. In the first published Phase I study of this compound, 37 patients with refractory locally advanced or metastatic solid tumors were treated with MKC-1 twice daily for 7 or 14 consecutive days. Myelosuppression and mucositis were the dose-limiting toxicities (DLT), with mild fatigue and gastrointestinal side effects most commonly

observed. The maximal tolerated dose (MTD) was 200mg/m² twice daily for the 7-day consecutive dosing schedule and 125mg/m² twice daily for the 14-day consecutive dosing schedule. One patient with non-small cell lung cancer achieved a partial response, and multiple patients achieved stable disease [12]. In another Phase I study performed in 48 patients with advanced solid tumors, MKC-1 was administered at doses ranging from 25 to 800mg/m² per day for four consecutive days, either as a single dose or in divided equal doses. The four-day regimen was administered every three weeks. The MTD was 560mg/m² per day, and the DLTs were myelosuppression and stomatitis, occurring at the 800mg/m² per day dose level. No complete or partial responses were observed, but one patient with pancreatic cancer had stable disease for six cycles, and two patients with breast and two patients with non-small cell lung cancer, demonstrated minor responses or stable disease [13]. Subsequently, several Phase I/II and Phase II evaluations have been performed with MKC-1, in advanced non-small cell lung cancer [14], breast cancer [15], and ovarian or endometrial cancer [16], with one patient demonstrating a complete response (metastatic breast cancer previously treated with anthracycline and taxane) and approximately 20 patients with stable disease. Most recently, a Phase I study was performed with MKC-1 using continuous twice daily dosing in 24 patients with advanced or metastatic solid tumors, with a model-based dose escalation design. The only DLT was observed at 320mg per day (grade 3 fatigue), and this was the MTD as specified by the dose-escalation algorithm. There were no clinical responses, but three patients (with renal cell carcinoma, parotid carcinoma, and breast cancer) demonstrated stable disease [17]. The current study was proposed as a Phase II open-label study of MKC-1 in patients with non-resectable or metastatic pancreatic cancer after progression on prior chemotherapy.

Methods

Eligibility

Eligible patients were at least 18 years of age with histologically confirmed pancreatic cancer and measurable disease who had failed at least one prior chemotherapy regimen in the neoadjuvant, adjuvant, or metastatic settings. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or better, with a hemoglobin ≥ 9 g/dL, absolute neutrophil count $\geq 1.5 \times 10^9$ cells/L, platelet count $\geq 75 \times 10^9$ cells/L, serum creatinine ≤ 1.5 times the upper limit of normal, aspartate and alanine transaminases ≤ 2.5 times the upper limit of normal, total bilirubin $\leq$ the upper limit of normal, and serum albumin ≥ 3.0 g/dL. Patients were excluded if they were pregnant or breast-feeding or had the following medical conditions or history: central nervous system metastases (unless under treatment, clinically stable, and without steroid use), significant bowel obstruction, active uncontrolled malabsorption syndromes, history of total gastrectomy, uncontrolled hypercalcemia (serum calcium-corrected greater than 12 mg/dL), class III/IV heart failure, acute myocardial infarction within the prior six months, previous malignancies (unless basal cell carcinoma or carcinoma in-situ of the cervix or unless free of recurrence for at least five years), any medical condition that would impose excessive risk to the patient, or on treatment with anti-retroviral therapy metabolized through CYP3A4.

Treatment regimen

All subjects signed informed consent and were treated at Massachusetts General Hospital, Dana Farber Cancer Institute, or Faulkner Hospital (all in Boston, MA). Initially, subjects received 100mg/m² of MKC-1, twice daily for 14 consecutive days in 28-day cycles. Unpublished data that emerged during the study indicated possible improved efficacy in leukemia patients when treated with a continuous dosing schedule, therefore, an amendment to the protocol was created changing the dosing schedule to continuous twice daily dosing (Part B). In Part B, MKC-1 was administered twice daily in 28-day cycles, with a fixed daily

total dose of 150 mg per day in divided doses of 90 mg every morning and 60 mg every evening. Patients originally enrolled at twice daily dosing for 14 out of 28 days were considered to have been enrolled in Part A. For both Part A and B, MKC-1 was discontinued upon disease progression or unacceptable adverse events interpreted to be linked to MKC-1 administration, or death.

Response and safety evaluation

Diagnostic imaging with CT or MRI was performed after each two cycles of treatment to assess the primary endpoint, overall response rate, which was calculated on the basis of response evaluation criteria in solid tumors (RECIST). In the event of discontinuation, a subject was considered evaluable for response if at least 14 days of dosing with MKC-1 had been completed. Serial sampling of carbohydrate antigen 19-9 (CA19-9) was performed every 28 days. All subjects who received MKC-1 were evaluated for safety. Toxicity assessments were conducted according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). Adverse events were summarized by the total number of subjects experiencing any event at highest grade, by system organ class, and preferred term.

Statistical analysis

The study was designed for a total accrual goal of 33 subjects, with a primary endpoint of overall response rate based on tumor measurements by RECIST. The null hypothesis specified that the response rate of MKC-1 would be 10%, and the study was powered at 80% to detect at 30% response rate, with an α of 0.025. Time to progression was defined as the interval between the day of first administration of MKC-1 and the date of the first documentation of progressive disease or the date of death. For radiographic progression, the date of the imaging modality was utilized, while the date of last clinic visit was utilized for clinical progression. Subjects who withdrew from the study without documented progression were censored at the last date the subjects were known to be progression free. Tumor response was also measured based on the change from baseline of the surrogate marker for pancreatic cancer, CA19-9. Overall survival was defined as the interval between the day of first administration of MKC-1 and the date of death. Tabular summaries were generated for treatment-emergent adverse events, including relationship to study drug. If the same adverse event occurred on multiple occasions, the highest severity and least complementary relationship was assumed. Time to progression and overall survival were estimated using the Kaplan-Meier method. Statistical analyses were conducted using SAS software version 9.2 (SAS Institute Inc. Cary, NC).

Results

Patient characteristics

Between December 2007 and February 2009, 20 patients were enrolled in the trial. 16 patients were enrolled in Part A, receiving 100 mg/m² for 14 days in 28-day cycles. Four patients were enrolled in Part B, with continuous, twice daily dosing (90 mg qam and 60 mg qpm). Accrual was discontinued after 20 patients given the lack of responses by RECIST criteria and the toxicities observed; therefore, the target of 33 patients was not achieved.

Demographic characteristics of the enrolled patients are listed in Table 1. All of the enrolled patients had pancreatic adenocarcinoma, with the exception of one patient with ampullary carcinoma. 70% of the patients had been treated with two or more chemotherapy regimens (not inclusive of chemotherapy received during radiation treatment), 40% had received prior radiation, and 95% of patients had received prior treatment for metastatic pancreatic cancer. Most of the patients enrolled had an ECOG performance status of 1.

Efficacy

One patient discontinued the study for treatment of a brain metastasis after receiving four doses of MKC-1. 19/20 patients were considered in the analysis for time to progression and overall survival, though one of these 19 patients completed only 7 days of dosing before being hospitalized with grade 4–5 adverse events. There were no radiographic responses as assessed by RECIST, although one patient demonstrated stable disease and was on study for 104 days. This patient had been enrolled under Part B, which utilized fixed continuous dosing. The median time on study for all 20 patients was 42 days, median overall survival was 101 days (Figure 1), and median time to progression was 42 days (Figure 2).

The tumor antigen, CA19-9, was measured for all patients at baseline and for 14 of the 19 patients completing at least two weeks of MKC-1. CA19-9 values were categorized as a 50% or greater decrease, 50% or greater increase, or less than a 50% increase or decrease. No patients had a 50% or greater decrease in CA19-9 levels, while half of patients demonstrated no change or progressive disease.

Toxicity

The adverse event profile of toxicities interpreted as likely or possibly related to MKC-1 administration is indicated in Table 3. Notably, there were multiple patients who developed cytopenias, including one patient with grade 5 pancytopenia. Other grade 4 events were fatigue and mucositis, each occurring in the same patient that developed grade 5 pancytopenia.

Discussion

MKC-1 is an orally available small molecule cell cycle inhibitor, binding to both microtubules and importin- β . The administration of MKC-1 in the current study was associated with substantial toxicity, including one death in the setting of severe cytopenias. Prior reports of myelosuppression in other studies were observed on intermittent dosing schedules (reviewed in [17]). Interestingly, in a Phase I study of MKC-1 with continuous dosing, this myelosuppression was not observed at doses up to 320 mg per day [17]. In the current study, the four patients dosed continuously (Part B) appeared to have fewer toxicities, with two patients developing grade 1/2 lymphopenia. However, there were no grade 3, 4, or 5 toxicities of any kind in this small subset of patients. The reason for the lack of myelosuppression with continuous dosing has been attributed to multiple potential mechanisms, including the avoidance of high peak concentrations of MKC-1 with this dosing schedule, a minimum albumin of 3 or greater, and the use of a fixed dose instead of one based on BSA [17]. In the current study, the median albumin was greater than 3, and the same small group of patients that received continuous dosing of MKC-1 also received a fixed dose instead of one based on BSA. Since only four patients received continuous dose MKC-1 (Part B) in this study, we cannot draw any definitive conclusions about lower toxicity in the continuous dosing group.

In the current study, there were no responses by RECIST criteria, and only one patient demonstrated stable disease. The one patient with stable disease was enrolled to the continuous dosing part of the protocol. The reason for the lack of response in this study is unclear, but may relate to the refractory nature of the patients on this protocol, where 70% of patients had received two or more chemotherapy regimens. It is unknown whether additional patients treated with a fixed and continuous dose of MKC-1, as performed during Part B of the protocol, would have demonstrated disease stabilization in additional patients. In summary, this study using MKC-1 in patients with advanced pancreatic cancer did not demonstrate sufficient activity to warrant further studies in this patient population.

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Figure 1.
Overall survival in patients with advanced pancreatic cancer who received MKC-1.

Figure 2.
Time to progression in patients with advanced pancreatic cancer who received MKC-1.

Table 1

Demographic characteristics of enrolled patients

Median Age		61 (range 44–81)
Gender	Female	8 (40%)
	Male	12 (60%)
Race	Caucasian	20 (100%)
ECOG Performance Status	0	3 (15%)
	1	17 (85%)
Location of Primary Mass	Head/Uncinate	7 (35%)
	Body/Tail	12 (60%)
	Ampulla of Vater	1 (5%)
History of Whipple surgery/distal pancreatectomy		6/20 (30%)
Prior Therapy	Radiation	8 (40%)
	Adjuvant CT	4 (20%)
	Neoadjuvant	2 (10%)
	Chemotherapy for Metastatic Disease	19 (95%)
# Prior Chemotherapy Regimens	1	6 (30%)
	2	14 (70%)
Albumin (median)		3.8
Creatinine (median)		0.81

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; Hx = history.

Table 2Overall Survival[/] and Time to Progression[/]

Median Overall Survival (OS)	101 days (range 19–506) CI=(57–151)
Time to Progression (TTP)	42 days (range 14–104) CI=(22–49)

[/] Overall survival and time to progression in evaluable patients, n=19

Table 3

Adverse Events considered to be at least possibly related to MKC-1 administration, worst grade per patient, based on National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0)

Toxicity	Grade 1/2 (%)	Grade 3/4 (%)	Grade 5 (%)
Allergic Reactions			
Allergic reaction		1 (5)	
Pruritus	1 (5)		
Constitutional			
Fatigue	5 (25)	2 (10)	
Weight loss	1 (5)		
Gastrointestinal			
Abdominal Cramping/Bloating	3 (15)		
Anorexia		1 (5)	
Constipation	2 (10)		
Diarrhea	1 (5)		
Dysphagia	1 (5)		
Nausea	2 (10)		
Odynophagia	1 (5)		
Stool color change	1 (5)		
Taste alteration	2 (10)		
Genitourinary			
Erectile dysfunction	1 (5)		
Urine color change	4 (20)		
Hematologic			
Anemia	2 (10)	1 (5)	
Leukopenia	1 (5)		
Lymphopenia	5 (25)	1 (5)	
Pancytopenia			1 (5)
Infectious Disease			
Cellulitis	1 (5)		
Infection			1 (5)
Pneumonia		1 (5)	
Liver Function Tests			
Hyperbilirubinemia		1 (5)	
Increased alk phosphatase	1 (5)		
Increased SGOT/SGPT	1 (5)		
Oral Symptoms			
Mucositis		1 (5)	
Pain – sore tongue	2 (10)		
Other			
Decreased bicarbonate	1 (5)		
Hypertension	1 (5)		
Hypoalbuminemia		1 (5)	

Toxicity	Grade 1/2 (%)	Grade 3/4 (%)	Grade 5 (%)
Pain – muscle	1 (5)		