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Cediranib in patients with malignant mesothelioma: A phase II trial of the University of Chicago Phase II Consortium

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Abstract

Introduction—Malignant mesothelioma (MM) is an aggressive disease with limited therapeutic options. In preclinical models, vascular endothelial growth factor (VEGF) stimulates MM proliferation. In MM patients, higher plasma VEGF levels correlate inversely with survival. Cediranib is an orally administered tyrosine kinase inhibitor of VEGF receptors -1, -2, and -3.

Methods—We conducted a multi-center phase II trial of cediranib in patients with unresectable, histologically-confirmed MM who had received ≤1 prior regimen of chemotherapy. The primary endpoint was objective response rate. Initial cediranib dosing was 45 mg daily during a 28-day cycle. Due to substantial toxicity, the starting dose was subsequently lowered to 30 mg daily.

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Results—Fifty-one patients enrolled at 9 centers; 50 were evaluable for response. Partial responses were observed in 10% of patients; stable disease was seen in 34%. Disease control (PR + SD) was higher at the 45 mg cediranib dose level (67% vs. 34%, p=0.04). Median progression-free survival was 1.8 months (95% CI 0.1, 14.2); median overall survival (OS) was 4.4 months (95% CI 0.9, 41.7). The 1-year survival rate was 15%. Grade 3/4 toxicities were more frequent in the 45 mg dose level group (87% vs. 43%, p=0.002). These included fatigue, hypertension, pulmonary embolism, angioedema, and reversible posterior leukoencephalopathy. Median OS was superior in patients who developed ≥ grade 3 hypertension (8.5 vs. 4.1 months, p=0.024).

Conclusion—This trial did not meet its pre-specified response endpoint. A higher cediranib dose level was associated with improved disease control, but this dose was poorly tolerated.

Keywords

Mesothelioma; cediranib; vascular endothelial growth factor; hypertension

Introduction

Malignant mesothelioma, a malignancy caused by asbestos exposure, is diagnosed in about 3,300 patients annually in the United States[1]. Cisplatin plus pemetrexed has become the standard of care based on a phase III trial that reported improvements in response rate (41% vs. 17%, p<0.001), time to progression (5.7 vs. 3.9 months, p=0.001), overall survival (OS) (12.1 vs. 9.3 months, p=0.020), and quality of life for patients randomized to the combination compared to single-agent cisplatin, respectively[2]. There are no approved agents for patients who do not respond to pemetrexed-platinum therapy or for those who progress following initial disease control[1, 3].

Vascular endothelial growth factor (VEGF), a key regulator of tumor angiogenesis, is an autocrine growth factor for mesothelioma[4-5]. Inhibition of VEGF signaling decreases proliferation of mesothelioma cell lines in preclinical models[1, 6]. In mesothelioma patients, high pretreatment plasma VEGF levels are associated with an inferior survival, [7-8] and declining serum VEGF levels during treatment are associated with a longer survival[8].

Cediranib (AZD2171, Recentin, AstraZeneca) is an orally administered, small molecule, selective inhibitor of the receptor tyrosine kinases for VEGF-1, -2, and -3. Cediranib has demonstrated broad activity in multiple human cancer models[9]. In a phase I trial, the 45 mg daily dose as monotherapy was generally well tolerated; hypertension was the most common dose-limiting toxicity. Encouraging single agent activity that appeared to be dose-dependent was observed in several tumor types[10].

Due to the important role of VEGF signaling in mesothelioma biology and the VEGF inhibitory properties of cediranib, we evaluated this drug in a multi-center phase II trial in patients with advanced malignant mesothelioma (ClinicalTrials.gov identification number NCT00309946).

Materials and Methods

Eligibility Criteria

Eligible patients had histologically- or cytologically-confirmed malignant mesothelioma not amenable to potentially curative surgical resection, and an Eastern Cooperative Oncology Group performance status of 0 to 1. Measurable disease was required, as defined by either Response Evaluation Criteria in Solid Tumors (RECIST)[11] for non-pleural tumors, or by modified RECIST[12] for pleural-based disease. Normal bone marrow (granulocytes ≥ 1,500/μL, platelets ≥ 100,000/μL), hepatic (normal total bilirubin and transaminases ≤ 2.5 times institutional upper limit of normal) and renal function (serum creatinine within normal institutional limits or creatinine clearance ≥ 60 mL/min/1.73 m^2) were required. Patients could have received no more than one prior regimen of cytotoxic chemotherapy. Prior radiation therapy was allowed if measurable disease was located outside of the radiation port. More than 4 weeks must have elapsed since completion of any previous treatment. Exclusion criteria included prior treatment with a VEGF inhibitor, pregnancy or lactation, uncontrolled inter-current illnesses, or immunodeficiency. All subjects provided written informed consent according to federal and institutional guidelines.

Study treatment and evaluation

Pretreatment evaluation included a medical history and physical exam, complete blood count and differential, chemistry panel, pregnancy test, and a computed tomography (CT) scan of the chest, abdomen, and pelvis if relevant. A history and physical exam were repeated every 14 days and laboratory evaluations including a complete blood count with differential, serum chemistry panel, and urinalysis were repeated every 7 days. Patients were provided with a blood pressure monitoring device and a diary to record their blood pressure readings twice daily.

Patients received a minimum of 2 cycles unless unacceptable toxicity or rapid clinical progression of disease occurred. Response was evaluated by CT imaging every two cycles. Confirmatory scans were to be obtained at least 4 weeks after initial documentation of an objective complete or partial response.

Cediranib was administered orally once daily on days 1 through 28 of a 28-day cycle. Cediranib was initially dosed at 45 mg daily, but due to substantial rates of toxicity the protocol was amended in June 2007 to decrease the starting dose to 30 mg daily. Cediranib was taken 1 hour before or 2 hours after meals. Only one dose modification was permitted. When the starting cediranib dose was 45 mg, dose level -1 was 30 mg daily. After the protocol amendment, dose level -1 was 20 mg daily. Further dose reductions were allowed at the discretion of the investigator only if the patient had received clinical benefit from cediranib for > 3 months.

Adverse effects were graded according to National Cancer Institute Common Toxicity Criteria version 3.0. The dose was reduced for grade 3 or greater non-hematologic toxicity attributable to cediranib or grade 4 hematologic toxicity if the toxicity lasted for > 5 days and did not resolve to ≤ grade 2. Maximal antihypertensive therapy was defined as taking 4 antihypertensive agents for > 2 weeks at full dosage. For patients on antihypertensive

therapy who had an elevation in systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg on 2 separate readings during a 48 hour period, the dose of cediranib was maintained without interruption while the dosage of current antihypertensive therapy was increased or an additional antihypertensive agent was started. If 2 readings reported a SBP ≥ 180 mmHg or a DBP ≥105 mmHg during a 1 week period, cediranib was held and there was either an increase in the dosage of current antihypertensive therapy or an additional antihypertensive agent was added. Resumption of cediranib was allowed only after the blood pressure was < 140/90 mmHg. If 2 blood pressure readings recorded an SBP ≥ 160 mmHg or a DBP ≥ 105 mmHg 1 hour apart during a 48 hour period in a patient already on maximal antihypertensive therapy, cediranib was held and treatment was resumed at 1 dose level lower when the blood pressure was < 160/105.

Statistical methods

The primary endpoint of this study was objective response rate (complete response [CR] + partial response [PR]). Secondary endpoints included progression-free survival (PFS), defined as the time to disease progression or death from any cause, overall survival, and toxicity. The trial was conducted using a Simon optimal two-stage design to test the null hypothesis that the response rate was less than or equal to 10% versus the alternative that it was at least 25%[13]. Twenty-one evaluable patients were to be enrolled in the first stage. If two or fewer patients had an objective response, the trial would be terminated for lack of efficacy. Otherwise, an additional 29 subjects would be accrued, and if 8 or more responses were observed among the total 50 patients, the regimen would be considered worthy of further study. This design yielded a 90% probability of a positive result if the true response rate was at least 25%. Progression-free and overall survival were calculated using the Kaplan-Meier product-limit estimate and expressed as probabilities with a 95% confidence interval (CI)[14].

Results

Patients

Fifty-one patients were enrolled at 9 centers between March 2006 and September 2010. One patient withdrew consent before receiving treatment; all other patients were evaluable for response and toxicity and are included in this analysis. Patient characteristics are summarized in Table 1. As expected in this occupationally-related cancer, eighty-four percent of the subjects were male. The median age was 64 (range 44-81). The majority of patients (70%) had an ECOG performance status of 1. Most (88%) had received one prior regimen of cytotoxic chemotherapy. Pleural mesothelioma was the most frequent site of origin (94%). The most common histologic sub-type was epithelial (72%). Thirty-five patients (70%) started cediranib at the 30 mg daily dose. The characteristics of the patients at the 45 mg and 30 mg starting doses were comparable.

A total of 164 cycles of cediranib were delivered. The median number of treatment cycles administered was 2 (range 1-14). Patients who initiated treatment at 45 mg daily received a median of 3 cycles (range 1-14); those who initiated treatment at 30 mg daily received a median of 2 cycles (range 1-8).

Toxicity

Grade 3 and 4 toxicities are summarized in Table 2. Fatigue and hypertension were the most commonly observed side effects. More of the patients whose starting dose was 45 mg experienced at least one grade 3 or greater toxicity than those who started at the lower, 30 mg dose (87% vs. 43%, p=0.002). There was a trend for an increased rate of grade 3 and 4 hypertension in patients who initiated cediranib at the 45 mg dose (40% vs. 14%, p=0.09).

There were five grade 4 events: two patients developed pulmonary embolism and one patient each experienced fatigue, angioedema, and reversible posterior leukoencephalopathy syndrome (RPLS). There were no grade 5 toxicities. There was only one hematologic toxicity grade 3 or greater noted in a patient: lymphopenia. Twenty-six percent of patients experienced grade 1 or 2 proteinuria.

Dose reductions and delays due to toxicity were common. Twenty-eight percent of all patients required at least 1 dose reduction of cediranib; more patients required such reductions at the 45 mg initial dose compared to the 30 mg initial dose (60% vs. 14%, p=0.002). More patients also discontinued cediranib due to toxicity at the 45 mg initial dose than at the 30 mg initial dose (47% vs. 17%, p=0.05).

Response and Survival

Response data are available for 50 patients. Five patients (10%) achieved a partial response with a median duration of 6.5 months (range, 4.0-9.8 months). Twenty percent of patients who received cediranib at the initial 45 mg dose achieved a partial response compared with 6% at the 30 mg dose (p=0.12). There were no responses observed in any patient with sarcomatoid or biphasic histology.

Seventeen patients (34%) had stable disease (SD) as their best response: 47% for the 45 mg initial dose group and 28% for the 30 mg initial dose group (p=0.22). Stable disease was maintained for a median of 4.4 months (range, 3.4-5.3 months). The rate of disease control for all patients (PR + SD) was 44%; the disease control rate was higher for those who initiated treatment with cediranib at the 45 mg dose compared to the 30 mg dose (67% vs. 34%, p=0.04). More patients who started cediranib at the 45 mg dose were on study for 6 months or longer compared to those at the 30 mg dose (40% vs. 9%, p=0.02). The median progression-free survival was 1.8 months (95% CI: 0.1, 14.2 months) (Figure 1). The median overall survival was 4.4 months (95% CI: 0.9, 41.7 months) (Figure 2). The one-year survival rate was 15%. Patients who initiated cediranib at the 45 mg dose survived a median of 5.5 months compared to 4.1 months for those who initiated treatment at the 30 mg dose (p=0.069). Chemo-naive patients survived a median of 12.4 months compared to 4.4 months for those who received cediranib as second-line treatment (p=0.052). There was a trend for improved median overall survival in those patients with epithelial histology compared to all other histologies (6.6 vs. 4.4 months, p=0.15). Median overall survival was statistically superior in those patients who experienced grade 3 or 4 hypertension (8.5 vs. 4.1 months, p=0.024) (Figure 3).

Discussion

We evaluated cediranib, an oral VEGF tyrosine kinase inhibitor, in a multicenter phase II trial in patients with advanced malignant mesothelioma, based on preclinical data suggesting a key role for VEGF signaling inhibition in this disease. Unfortunately, the study did not meet its pre-specified response endpoint.

Although disease control was better in patients who initiated cediranib at the 45 mg dose, this higher dose was poorly tolerated. The initial dose of 45 mg daily yielded superior disease control (67% versus 34%, p=0.04), and a trend for an improvement in response (20% vs. 6%, p=0.12), compared to the 30 mg dose. This observation supports previous phase I data in which the anti-tumor activity of cediranib was dose-dependent in this range[10]. The cost for such activity was clear: 87% of patients in the 45 mg daily initial dose group experienced a grade 3 or greater event, compared to 43% in the 30 mg group (p=0.002). While 26% of all study patients discontinued cediranib due to toxicity, almost half of the patients who initiated treatment at the 45 mg dose (47%) were required to do so. Despite the higher drop-out rate, those patients who could tolerate the higher doses of cediranib appeared to benefit from it. Forty percent of patients who started cediranib at the 45 mg dose were on trial for 6 months or longer, compared to just 9% of those at the 30 mg dose (p=0.02).

Inhibition of VEGF signaling decreases nitric oxide production, which causes vasoconstriction, decreased sodium ion renal excretion, and resultant hypertension[15]. Our study demonstrated that patients who developed grade 3 or 4 hypertension had a statistically significant improvement in median overall survival. The utility of hypertension as a pharmacodynamic biomarker for effective VEGF signaling inhibition has been assessed in several malignancies, including renal[16], breast[17], colorectal[18], and non-small cell lung cancer[19] – without any clear results confirming its potential value. In theory, cediranib could be titrated based on the development of hypertension. In reality, given the toxicities we observed with cediranib even at lower doses, this approach is not feasible with this agent.

Our results are comparable to those reported in the SWOG S0509 cediranib study,[20] though the conclusions differ somewhat. The primary endpoint in both studies was objective response rate. In the SWOG trial, 54 pleural mesothelioma patients who were previously treated with one platinum-containing chemotherapy regimen received cediranib at 45 mg daily. In the 47 evaluable patients, 9% achieved a partial response, and 34% had stable disease. These numbers are nearly identical to the 10% partial response rate and 34% rate of stable disease that we report in this trial. SWOG investigators found these data sufficiently compelling to develop this agent further in this disease, and they are currently accruing to a phase I/randomized phase II trial of cisplatin/pemetexed plus either cediranib or placebo for patients with previously untreated pleural mesothelioma. Cediranib is given at 20 mg daily, the lowest dosage at which the agent is thought to have biologic activity[10].

In conclusion, the limited activity and substantial toxicity we observed with cediranib in this study adds to the increasing body of phase II trials in mesothelioma patients that have demonstrated very modest activity of VEGF inhibitors in this disease[7, 20-25]. As trial

development for mesothelioma moves forward, we would advocate looking beyond VEGF inhibition, and focusing on other, more promising molecular targets.

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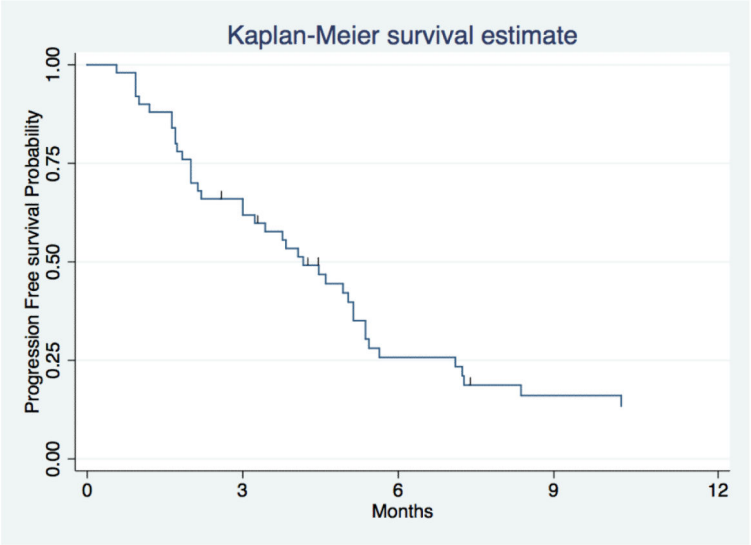

Figure 1.
Progression-free survival

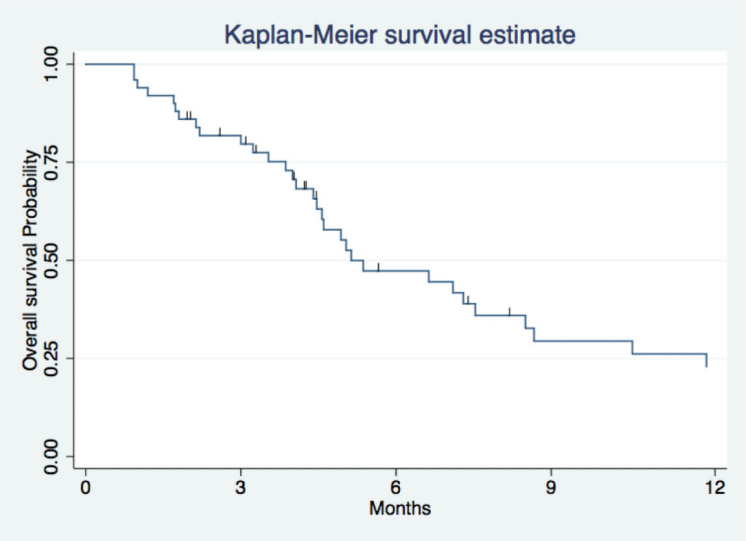

Figure 2.
Overall survival

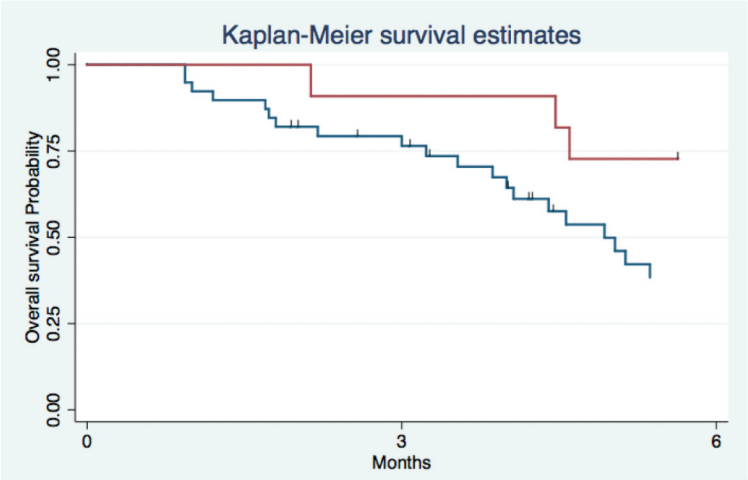

Figure 3. Overall survival by development of grade 3 and 4 hypertension

Red bold line: Developed grade 3 or 4 hypertension

Blue bold line: Did not develop grade 3 or 4 hypertension

Table 1

Patient Characteristics

Characteristics	45 mg ID N =15 (%)	30 mg ID N = 35 (%)	Overall N = 50 (%)
Gender			
Male	12 (80)	30 (86)	42 (84)
Female	3 (20)	5 (14)	8 (16)
Age (years)*			
<50	1 (7)	2 (6)	3 (6)
50-69	9 (60)	24 (69)	33 (66)
70+	5 (33)	9 (26)	14 (28)
Histology			
Epithelial	11 (73)	25 (71)	36 (72)
Biphasic	2 (13)	4 (11)	6 (12)
Sarcomatoid	0 (0)	2 (6)	2 (4)
Indeterminate	2 (13)	4 (11)	6 (12)
Tumor site			
Pleura	14 (93)	33 (94)	47 (94)
Peritoneum	1 (7)	2 (6)	3 (6)
Previous Chemotherapy			
Yes	13 (87)	31 (89)	44 (88)
No	2 (13)	4 (11)	6 (12)
Performance status			
0	8 (53)	7 (20)	15 (30)
1	7 (47)	28 (80)	35 (70)
Thrombocytosis†			
Yes	6 (40)	7 (20)	13 (26)
No	9 (60)	28 (80)	37 (74)

*median age for all groups was 64 years

†defined as ≥ 400,000/μL

Abbreviations: ID = initial dose

Table 2

NCI CTC Grade 3 and 4 Toxicities on Cediranib

	45 mg ID n (%)		30 mg ID n (%)		Overall n (%)	
Toxicity	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Non-Hematologic						
Fatigue	4 (27)	1 (7)	7 (20)	0 (0)	11 (22)	1 (2)
Hypertension	6 (40)	0 (0)	5 (14)	0 (0)	11 (22)	0 (0)
Diarrhea	2 (13)	0 (0)	2 (6)	0 (0)	4 (8)	0 (0)
Hyponatremia	0 (0)	0 (0)	3 (9)	0 (0)	3 (6)	0 (0)
Thrombosis	0 (0)	0 (0)	1 (3)	2 (6)	1 (2)	2 (4)
Acute renal failure	1 (7)	0 (0)	1 (3)	0 (0)	2 (4)	0 (0)
Mucositis	1 (7)	0 (0)	1 (3)	0 (0)	2 (4)	0 (0)
RPLS	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (2)
Angioedema	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (2)
Headache	1 (7)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Seizure	0 (0)	0 (0)	1 (3)	0 (0)	1 (2)	0 (0)
Hematologic						
Lymphopenia	0 (0)	0 (0)	1 (3)	0 (0)	1 (2)	0 (0)

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Abbreviations: ID = initial dose; RPLS = reversible posterior leukoencephalopathy syndrome.