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Cediranib (AZD2171) in Patients with Advanced Hepatocellular Carcinoma: A Phase II North Central Cancer Treatment Group (NCCTG) Clinical Trial¹

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Abstract

Objectives—Vascular endothelial growth factor (VEGF) has been shown to be overexpressed in several studies of hepatocellular carcinoma (HCC). Cediranib is a potent inhibitor of VEGF signaling. We assessed the efficacy and toxicity of cediranib in patients with HCC.

Methods—Twenty-eight patients with unresectable or metastatic HCC were enrolled on this study. Patients received 45 mg of cediranib orally, once daily, for 28 day cycles. The primary objective of this Phase II study was to assess six-month survival. Secondary objectives were to assess tumor response, time-to-progression, and toxicity.

Results—All 28 patients were evaluable for efficacy outcomes. Twelve patients (42.9%) survived 6 months, 15 (53.6%) died within 6 months, and one (3.6%) was lost to follow-up before 6 months. The median overall survival was 5.8 months (95% CI: 3.4–7.3 months). No patients experienced confirmed response. The median time-to-progression was 2.8 months (95% CI: 2.3 – 4.4 months). Twenty-six patients (93%) experienced a grade 3+ adverse event (AE) with the most common AEs being fatigue (46%), anorexia (25%), hypertension (21%), and elevated alanine aminotransferase (ALT) (18%).

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Conclusions—Due to toxicity, cediranib at this dose and schedule is not an effective treatment in patients with unresectable or metastatic HCC.

Keywords

AZD2171; cediranib; hepatocellular carcinoma; phase II; VEGF

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer deaths worldwide. The majority of HCC patients present with advanced disease that is not amenable to surgery, local modalities of therapy, or liver transplantation. For patients with more advanced disease few effective options are available. Chemotherapy, in particular, has been of limited benefit for patients with unresectable or metastatic HCC.¹ Given the limitations of chemotherapy treatments, recent trials have focused on targeted agents. Out of this work the drug sorafenib recently gained approval for use in HCC based on a survival advantage over best supportive care.² However, despite the benefits obtained with the use of sorafenib, it is clear that additional therapeutic agents are needed for the treatment of HCC.

Targeting the hypervascularity that develops in HCC has been an area of interest in recent clinical trials. Overexpression of VEGF has been noted in several studies of HCC in which a comparison was made to surrounding non-tumorous liver. These findings correlate with the observation that HCC is in general a hypervascular tumor. In one of these studies, involving a series of 60 patients with HCC, immunohistochemical staining showed more intense staining of VEGF₁₆₅ in the cytosol of tumor cells compared to stromal cells or hepatocytes in the nontumorous liver.³ In addition, there also appeared to be a correlation between VEGF levels in tumor cells and VEGF concentrations measured in the serum.³

Cediranib (AZD2171, Receptin; AstraZeneca, Wilmington, Delaware) is an orally available potent small molecule inhibitor of receptor tyrosine kinases (RTKs) which influences the effects of a key angiogenic factor, vascular endothelial growth factor-A (VEGF-A or VEGF).⁴ VEGF is implicated in tumor blood vessel formation and in disease progression in a wide range of solid tumor malignancies.⁵ Expression of this factor is increased by diverse stimuli which include proto-oncogene activation and hypoxia, with the hypoxic state frequently occurring in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature and thereby potentially contributes to tumor progression – a leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor cell migration during metastasis. With the goal of suppressing neovascularization and thus inhibiting tumor growth and metastasis, numerous antiangiogenic agents have been developed.⁶

Based on the growing body of literature indicating the importance of angiogenesis in HCC a phase II trial of cediranib in patients with HCC was undertaken.

Materials and Methods

Eligibility

Patients with histologic confirmation of locally advanced or metastatic HCC (Barcelona-Clinic Liver Cancer Stage C)⁷ deemed unresectable, not amenable to local modalities of treatment, and not candidates for liver transplant were eligible for enrollment in this phase II trial. Evidence of disease progression by imaging on serial exams or by biochemical evidence of a rising alpha-fetoprotein (AFP) on serial testing was required. Patients were required to be at least 18 years and to have an Eastern Cooperative Oncology Group

(ECOG) performance score of 0 or 1. Hematologic and chemistry parameters were to be in the following ranges: absolute neutrophil count (ANC) $\geq 1200/\text{mm}^3$ (cells/uL), platelets (PLT) $\geq 75,000/\text{mm}^3$, hemoglobin (Hgb) ≥ 10.0 g/dL, total bilirubin ≤ 3 times the institutional upper normal limit (UNL), aspartate aminotransferase (AST) ≤ 5 times the UNL, alkaline phosphatase ≤ 5 times the UNL, and urine protein $<1+$ by urine dip stick. Prior biologic, hormonal, or immunologic therapy was allowed if greater than 4 weeks of study entry. Prior chemoembolization, radiofrequency ablation (RFA), or other local ablative therapies were permissible if ≥ 6 weeks from procedure with evidence of progression or new metastatic disease.

Prior use of systemic chemotherapy regimens for HCC, prior external beam radiation to the primary site, or prior radiation to $>25\%$ of bone marrow were not allowed. Any history of prior malignancy diagnosed within 5 years was not allowed, with the exception of basal or squamous cell carcinoma of the skin and cervical carcinoma *in situ*. Other contraindications included patients with fibrolamellar HCC or mixed cholangiocarcinoma/HCC. Patients were not allowed to be pregnant or lactating and were required to use adequate contraception methods to prevent pregnancy during treatment. Finally, patients with uncontrolled blood pressure, QTc prolongation > 500 msec or other significant electrocardiogram (ECG) abnormality, New York Heart Association classification III or IV, or with conditions requiring use of drugs or biologics with proarrhythmic potential were not eligible.

This trial was approved by the Mayo Institutional Review Board (IRB) and by the IRBs of the individual memberships of the North Central Cancer Treatment Group (NCCTG) that elected to participate in this trial. A signed written informed consent was obtained from all patients prior to initiating therapy. This trial was funded through the NCCTG grant from the National Cancer Institute. There was no direct industrial funding of this trial.

Treatment

Patients received an oral daily dose of 45 mg cediranib for 28 days. Cycles were repeated every 4 weeks if patients met criteria for further therapy. Dose reduction steps for cediranib were as follows: Starting Dose = 45 mg, Dose Level – 1 = 30 mg, Dose Level – 2 = 20 mg, Dose Level – 3 = 10 mg, and no dose reduction was allowed below 10 mg so patients discontinued treatment if further reductions were required. Dose adjustments were made depending on the type and severity of treatment related toxicities.

Patient Evaluation

Tumor assessment via computer tomography (CT) or magnetic resonance imaging (MRI) and a chest x-ray was required within 28 days prior to enrollment. Within 14 days prior to enrollment, patients were required to undergo the following tests and procedures: complete history and exam, blood pressure, hematology group and blood chemistry group, serum thyroid stimulating hormone (sTSH) and thyroxine (T4), urinalysis for proteinuria, troponin, AFP, and ECGs. An Echo/MUGA was also required within 14 days prior to enrollment for patients at an increased risk of left ventricular ejection fraction (LVEF). A negative serum pregnancy test was required within 7 days prior to enrollment.

During the course of treatment, blood pressure was monitored twice daily and hematologic parameters and urinalysis for proteinuria were collected weekly. Prior to the next course of treatment, a history of adverse events (AEs) experienced was collected and all blood tests listed above, except serum pregnancy test, were repeated. AEs were collected using the National Cancer Institute's Common Toxicity Criteria for Adverse Events Version 3.0 (NCI CTCAE V3.0, <http://ctep.cancer.gov/reporting/ctc.html>). All AEs were reported, regardless of attribution to study treatment. Tumor measurements were repeated prior to every other

cycle (i.e., every 8 weeks). Following the discontinuation of study treatment, patients were observed for disease progression every 3 months for 1 year, then every 6 months for up to 4 years past their registration date. At the time of disease progression, patients were monitored for their status for a maximum of 5 years post-registration.

Disease Assessment

Measurable disease was defined as at least one lesion that could be accurately measured in at least one dimension (longest diameter [LD] recorded) as ≥ 2.0 cm or ≥ 1.0 cm if spiral CT is used. Clinical lesions were only considered measurable when they were superficial (e.g., skin nodules, palpable lymph nodes). Lesions on chest x-rays were acceptable as measurable lesions when they were clearly defined and surrounded by aerated lung.

Response was defined as two consecutive evaluations at least 4 weeks apart showing total disappearance of tumor (complete response [CR]), or a reduction of at least 30% in the sum of the LD of target lesions (partial response [PR]), taking as reference the baseline sum LD. Progression (PD) was defined as the appearance of new lesions or a $\geq 20\%$ increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since treatment started. Stable disease (SD) was the failure to meet the criteria for PR or PD taking as references the smallest sum LD.

Patients were also considered to have progressed in cases of significant clinical deterioration that could not be attributed to study treatment or other medical conditions. These conditions included worsening of tumor-related symptoms, $\geq 10\%$ weight loss, or a decline in PS of > 1 level. Subsequent treatment was at the treating physician's discretion and included treatments provided in clinical practice.

Time to disease progression was calculated from the date of registration to the date of disease progression (or last tumor assessment). If a patient died without a documentation of disease progression, the patient was considered to have had tumor progression at the time of their death unless there is sufficient documented evidence to conclude no progression occurred prior to death. Time to death was calculated from the date of registration to the date of death (or last contact). Patients lost to follow-up were counted as having no progression (alive) on their date of last tumor assessment (contact).

Statistical Considerations

A two-stage Fleming⁸ design with 20 patients in the first stage and an additional 20 patients in the second stage was used to test the null hypothesis that the true success proportion in a given patient population is at most 40%. In stage 1, of the first 20 eligible patients, if ≤ 8 successes were observed the regimen was considered ineffective and terminated; if 9–12 successes were observed, the study proceeded to stage 2, and if ≥ 13 successes were observed the study was terminated and this regimen was to be recommended for further testing in subsequent studies in this patient population. In stage 2, of the first 40 eligible patients, if ≤ 21 successes were observed the regimen was considered ineffective and if ≥ 22 successes were observed this regimen was to be recommended for further testing in subsequent studies in this patient population. The trial design did not require a halt in accrual between the first and second stage.

The primary endpoint for this trial was six-month survival in patients with locally advanced or metastatic HCC treated with cediranib. Secondary endpoints included assessing tumor response, time to disease progression, and AEs. Kaplan-Meier methodology⁹ was used to describe the distribution of time to disease progression and overall survival.

Results

Patient characteristics

Twenty eight patients were enrolled between January 31, 2006 and August 31, 2006. Patient accrual was halted after the interim analysis of the first 20 patients became available. At this point a total of 28 patients had been accrued. The patient baseline demographics, disease characteristics, and previous treatment are summarized in Table 1.

Outcome measures

All 28 patients were evaluable for efficacy outcomes. Twelve patients (42.9%) survived 6 months, 15 patients (53.6%) died within 6 months, and one patient (3.6%) was lost to follow-up before 6 months. No confirmed responses were observed, seven patients (25%) had SD, seven patients (25%) developed PD, and 14 patients (50%) did not have a post-baseline evaluation during treatment. Twenty-six patients developed disease progression and 24 patients have died. Twelve of these 24 patients died without radiologic evidence of progression. Lacking any additional information all 12 were assumed to have progressed at the time of their death. As shown in Figure 1, the median time-to-progression was 2.8 months (95% CI: 2.3 – 4.4 months), and the median survival was 5.8 months (95% CI: 3.4–7.3 months). The four (21%) patients still alive at last follow-up have a median follow-up of 19.2 months. Two of the four patients still living were lost to follow-up with follow-up of 0.9 and 10.9 months.

Treatment Summary

A median of two cycles of therapy with cediranib were given (mean [SD]: 2.9 [5.0] cycles; range: 1 – 28 cycles). The median percent dose of the target 45 mg per day was 63.7% (cycle 1), 57.1% (cycle 2), 52.4% (cycle 3), 64.3% (cycle 4), and 48.8% (cycle 5+). All patients have ended treatment. Patients went off treatment early due to disease progression (13/28; 46.4%), refused further treatment (8/28, 28.6%), AEs (5/28, 17.9%), death (1/28, 3.6%), and for reason of other (1/28, 3.6%).

Adverse Event Summary

All 28 patients were evaluable for AEs. Table 2 provides all grade 3+ AEs. Twenty-six patients (93%) experienced a grade 3+ AE. Five patients (18%) experienced a grade 4+ AE. The grade 4+ AEs included: valvular heart disease, hypoglycemia (unlikely related to treatment), anemia, dehydration, liver infection, increased AST and ALT, and fatigue. Two patients had grade 5 disease progression, with one death not related to study treatment.

Two late AEs occurred within 30 days of going off treatment. One patient experienced a grade 5 event (death, not otherwise specified) unlikely related to study treatment and another patient experienced a grade 3 fatigue that was possibly related to study treatment.

Adverse events resulted in 5 patients being taken off-study. An additional eight patients refused further therapy, primarily because of toxicities related to therapy.

DISCUSSION

This phase II trial examined the efficacy and toxicity of cediranib in patients with unresectable, locally advanced or metastatic HCC not amenable to local modalities of therapy. At the time this trial was conducted the initial phase I trial of cediranib in patients with solid tumors showed cediranib monotherapy was well tolerated at a daily oral dose of 45 mg or less.¹⁰ However, in this trial, cediranib at this dosing schedule was poorly tolerated in HCC patients. One possible explanation is that many of the HCC patients in this

trial had cirrhosis (53.6%) or history of hepatitis (42.9%), which may have reduced patient tolerability of the drug and its side effects. Thyroid function was also assessed (data not shown) based on the prior observation that cediranib use may be associated with clinical hypothyroidism in a small number of patients. With limited data there was no apparent change in thyroid function. Subsequently reported phase I trial now recommend the use of a lower dose.^{11, 12}

Consistent with early evidence of potential activity in HCC (stable disease in 2 patients)¹⁰, this phase II trial showed stable disease in 25% of the patients treated. No partial or complete responses were observed. However, given the poor tolerance and lower rate of response compared to sorafenib, cediranib did not have sufficient activity to justify further development in HCC with the dose and schedule used in this trial. In the SHARP trial the use of sorafenib resulted in a 71% rate of stable disease.² The outcome with cediranib occurred despite the protocol directed use of reduced doses following the development of treatment related toxicities.

Multiple challenges continue to exist in the treatment of HCC. Clearly, improved screening methods for earlier detection of this disease are needed given the limited benefit of available therapies for advanced disease. In addition, predicting treatment tolerability may be complicated in HCC patients due to pre-existing hepatic dysfunction, such as viral infection or cirrhosis. Lastly, HCC is a heterogeneous disease with multiple molecular and genetic abnormalities making single-targeted treatments only minimally effective. The use of agents with a broader range of molecular targets may be more likely to succeed. The use of drugs such as sorafenib or the combination of bevacizumab and erlotinib have been successful in producing stable disease and have shown improvements in increase overall survival.^{2, 13, 14}

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Figure 1. Kaplan-Meier curves of 15-month follow up for time to disease progression (dashed line) and overall survival (solid line) in 28 HCC patients being treated with cediranib.

Table 1

Patient Baseline Characteristics

Baseline characteristic	Number of patients (N=28)	% of patients
Age (years)		
Mean (range)	69 (48–84)	
Gender		
Female	3	10.7
Male	25	89.3
Performance Score (ECOG)		
0	8	28.6
1	20	71.4
Race		
White	25	89.3
African American	2	7.1
Asian	1	3.6
Current Disease Status		
Hepatic	11	39.3
Extrahepatic	17	60.7
Liver Disease		
Viral Hepatitis B or C	12	42.9
Hemochromatosis	1	3.6
Alcoholic cirrhosis	2	7.1
Cirrhosis, NOS	12	42.8
Differentiation (Grade)		
Well	7	25
Moderate	13	46.4
Poor	6	21.4
Unknown	2	7.1
Prior Surgery		
Prior Resection/Recurrent	6	21.4
Unresected	22	78.6
Prior Chemoembolization		
Yes	9	32.1
No	19	67.9
Prior Radiation Therapy		
Yes	4	14.3
No	24	85.7
Prior Therapy		
Yes	4	14.3
No	24	85.7

Table 2

Maximum Grade 3–4 Adverse Events at Least Possibly Related to Treatment

Body System	Toxicity	Grade			
		3		4	
		N	%	N	%
Hematology	Anemia			1	4
	Neutropenia	1	4		
Hepatic	SGPT (ALT)	3	11	1	4
	SGOT (AST)	2	7	1	4
	Bilirubin	2	7		
Infection/Febrile Neutropenia	Liver infection			1	4
Metabolic/Laboratory	Hyperkalemia	2	7		
	Hypokalemia	1	4		
	Hyponatremia	2	7		
	Leg weakness	1	4		
Musculoskeletal	Confusion	2	7		
Neurology	Somnolence	1	4		
	Dizziness	1	4		
	Abdominal	2	7		
Pain	Dyspnea	1	4		
Pulmonary	Proteinuria	1	4		
Renal /Genitourinary	Hypertension	6	21		
Cardiovascular	Hypotension	1	4		
	Valvular heart disease			1	4
Constitutional Symptoms	Fatigue	10	36	1	4
	Weight loss	1	4		
Dermatology/Skin	Hand-foot syndrome	1	4		
	Pruritis	1	4		
Gastrointestinal	Anorexia	5	18		
	Dehydration	3	11	1	4

Body System	Toxicity	Grade			
		3		4	
		N	%	N	%
	Diarrhea	3	11		
	Nausea	2	7		
	Vomiting	2	7		
	Stomatitis	3	11		