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A Phase I Trial of Escalating Doses of Cixutumumab (IMC- A12) and Sorafenib in the Treatment of Advanced Hepatocellular Carcinoma

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Abstract

Purpose: The insulin-like growth factor (IGF) pathway is activated in hepatocarcinogenesis. Cixutumumab is a monoclonal antibody against human insulin-like growth factor-1 receptor (IGF-1R). Given the cross-talk between the IGF and VEGF pathways, we performed a phase I study of the combination of cixutumumab and sorafenib in hepatocellular cancer (HCC).

Methods: Eligible patients with no prior systemic therapy for advanced HCC and Child-Pugh A to B7, were treated with sorafenib 400 mg BID and escalating doses of cixutumumab (2, 4, or 6 mg/kg IV weekly) in a 3+3 design. Dose limiting toxicity (DLT) was defined as treatment related grade 3 or 4 non-hematologic toxicity (except for a subset of manageable toxicities) or any grade 4 hematologic toxicities.

Results: In 21 patients enrolled, there were 3 DLTs; grade 3 hyperglycemia, grade 3 hypophosphatemia, and grade 5 peritonitis. The maximum tolerated dose of cixutumumab was 4 mg/kg IV weekly with standard-dose sorafenib. Eighteen of 21 (86%) patients had grade 3 or above toxicities attributed to treatment. One patient also experienced grade 4 colonic perforation and grade 5 peritonitis. The median number of cycles completed was 4 (0–26). Of 16 patients

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Compliance with ethical standards

Conflict of interest: Dr. Anthony El-Khoueiry and Dr. Heinz-Josef Lenz both have received honoraria for advisory board participation from Bayer. No potential conflicts of interest were disclosed by other authors.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants involved in the study.

evaluable for response, 81% achieved stable disease. The median progression free survival was 6.0 months (95% CI 3.6 – undefined) and the median overall survival was 10.5 months (95% CI 7.1 – undefined).

Conclusions: While the combination of cixutumumab and sorafenib had a toxicity profile similar to that of sorafenib monotherapy, it manifested limited clinical efficacy in unselected patients with HCC.

Keywords

Hepatocellular cancer; Sorafenib; IMC-A12; Cixutumumab; Phase I

Introduction

Due to its widespread incidence and generally poor outcome, hepatocellular carcinoma (HCC) is an international public health problem. Based on improved median overall survival in 2 multicenter, Phase III, double-blind, placebo-controlled trials in patients that had not received prior systemic therapy, sorafenib is an accepted systemic treatment option [1, 2]. Despite this sentinel therapeutic advance, the prognosis of unresectable HCC remains dismal and the development of novel treatment strategies for HCC represents a major unmet need. As sorafenib is the most promising drug yet found for the treatment of HCC, combining sorafenib with other potentially active or synergistic agents is a strategy to improve treatment outcomes.

The insulin-like growth factor (IGF) pathway is a family of receptors (IR/IGF-1R, IGF-2R, IGF-1R, IR-A, IR-B) and ligands (IGF-I, IGF-II, insulin) [3, 4]. Signaling through the IGF-1R pathway has been implicated in many tumors through its role in regulating cellular proliferation, apoptosis and motility [3]. The expression and activity of IGF-1R is up-regulated in HCC. In addition, increased expression of IGF by HCC tumors is thought to potentiate their development and growth [5]. Genetic abnormalities, such as loss of heterozygosity of the IGF-2R gene and reduction of the IGF-2R expression occur in as many as 80% of patients with HCC [6]. Indeed, pre-clinical studies using a variety of anti-IGF-1R strategies have resulted in growth inhibition and apoptosis in HCC cell lines [7–9]. Moreover, IGF signaling can induce the secretion of vascular endothelial growth factor (VEGF), and studies suggest the presence of an angiogenic component to the biological activity of the IGF-1R signaling cascade [10]. Therefore, anti-IGFR therapy may enhance the activity of anti-VEGF treatment by further suppressing the secretion of tumor-associated VEGF.

Cixutumumab (formerly IMC-A12, ImClone Systems, Inc) is a recombinant human IgG₁ monoclonal antibody directed at IGF-1R. Cixutumumab binds IGF-1R with high affinity (K_d=0.04 nM), blocks the interaction between IGF-1R and its ligands, IGF-I and IGF-II, and induces internalization and degradation of IGF-1R [11]. In vitro studies demonstrated that cixutumumab can decrease cell viability and proliferation in IGF-1R activated HCC cell lines [12]. In this study, we hypothesized that the combination of sorafenib and cixutumumab would be safe and feasible in patients with advanced HCC with the goal of future development of this combination.

Methods

This phase I study was sponsored by the National Cancer Institute and conducted by the California Cancer Consortium. Cixutumumab was provided through a Cooperative Research and Development Agreement between NCI Cancer Therapy Evaluation Program (CTEP) and ImClone/Lilly. The institutional review board at each participating site approved the study protocol and written informed consent was obtained from each enrolled patient. The study was registered at www.clinicaltrials.gov with the identifier NCT01008566.

Patients

Eligible patients were aged 18 years and older with unresectable or metastatic HCC and a Zubrod performance status of 0–1. The diagnosis of HCC was based on standard imaging criteria of arterial phase enhancement and venous or delayed phase wash out in the setting of liver cirrhosis or hepatitis, or on histologic confirmation (which was not mandatory if the imaging criteria were satisfied). No prior systemic treatment for HCC was allowed; however, patients may have had prior embolization, chemoembolization, intra-arterial chemotherapy infusion, ethanol injection, radiofrequency ablation or cryosurgery. Further inclusion criteria included the ability to give informed consent, assent to adequate contraception, no evidence of hepatic encephalopathy in the preceding 6 months and acceptable end-organ function defined by an absolute neutrophil count $> 1,000/\text{mm}^3$, platelet count $> 65,000/\text{mm}^3$, total bilirubin ≤ 2 times the institutional upper limit of normal (ULN), ALT and AST < 5 times the ULN, prothrombin time < 4 seconds of prolongation above the ULN, and creatinine < 1.5 mg/dl or calculated creatinine clearance > 50 mL/min using the Cockcroft-Gault formula.

Exclusion criteria included Child-Pugh C cirrhosis or Child-Pugh B cirrhosis with more than 7 points, local therapy for HCC within 4 weeks prior to treatment on this study or those who have not recovered from adverse events related to therapy administered more than 4 weeks earlier, receipt of other investigational agents, inability to swallow sorafenib whole and any component of fibrolamellar histology. Patients were also excluded for brain metastases, fasting blood glucose > 160 mg/dL, esophageal or gastric variceal bleeding within the last 6 months, clinically evident ascites (minimal, medically controlled ascites detectable on imaging studies only was allowed). Further exclusion criteria included cardiac comorbidities including clinically significant and uncontrolled cardiac dysrhythmia, New York Heart Association class II or greater congestive heart failure, unstable angina, myocardial infarction within the past 6 months, and systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg on two occasions within two weeks of beginning therapy. Patients with active hepatitis B infection were required to be on appropriate antiviral therapy.

Study Procedures

Prior to registration, patients underwent a history and physical examination that included assessment of height, weight, performance status, and vital signs. Baseline laboratory studies, including a pregnancy test for women of child bearing potential were performed within 2 weeks of registration. Radiographic tumor assessment was required within 4 weeks of registration. Tumor measurements by CT or MRI (whichever was the pre-therapy

radiologic study) were subsequently performed every 8 weeks. History and physical examination were performed by the treating physician weekly during the first 4-week cycle and then once every 4 weeks.

Treatment Plan

Patients were enrolled using a standard 3 + 3 design. The starting dose of sorafenib was fixed at the approved treatment dose for HCC (400 mg by mouth twice per day). The initial cixutumumab dose was 2 mg/kg IV over 1 hour once weekly with planned escalation to 4 and 6 mg/kg in successive dose levels. Dose modification of both sorafenib and cixutumumab for grade 3 or higher toxicity was allowed according to a defined schedule. Specific recommendations were provided for appropriate patient education and for supportive care of hand foot skin reaction.

Toxicity was graded according to the NCI common terminology criteria for adverse events version 3.0 until July 31, 2010 and version 4.0 beginning August 1, 2010. The data originally collected in version 3.0 was converted to 4.0. Dose limiting toxicity (DLT) was defined as any treatment related grade 3 or 4 non-hematologic toxicity except grade 3 or 4 nausea or grade 3 vomiting occurring without maximal antiemetic therapy. Further exceptions included toxicities typical of sorafenib monotherapy including hypertension, hand-foot skin reaction, rash, hypertension and fatigue that were manageable with the appropriate medical therapy and dose modification. Additionally, asymptomatic grade 3 elevation of bilirubin, asymptomatic grade 3 or 4 elevation of AST or ALT lasting ≥ 7 days, and asymptomatic grade 3 electrolyte abnormalities that were easily correctable with oral or intravenous replacement were excluded. Finally, during the study it became apparent that hyperglycemia was a common and frequently manageable toxicity of cixutumumab. We therefore excluded asymptomatic grade 3 hyperglycemia typical of cixutumumab from DLT criteria if it was manageable with medical therapy (including insulin) to a fasting glucose 160 mg/dL (grade 1) within 7 days. Grade 4 thrombocytopenia and grade 4 neutropenia were hematologic criteria for DLT. To be eligible for DLT assessment, a patient must have completed 28 days of treatment including all doses of cixutumumab and ≥ 75% of the oral doses of sorafenib, or have experienced DLT. All patients enrolled were followed for toxicity, but patients who were not evaluable for DLT were replaced.

Treatment was continued in 4-week cycles until unacceptable adverse event(s), progression of disease, the patient withdrew consent, intercurrent illness preventing further drug administration occurred, or general or specific changes in the patient's condition rendered them unacceptable for further treatment in the judgment of the investigator.

Correlative Studies

Blood specimens were collected in 10-mL EDTA tubes at baseline. Plasma was isolated and stored in aliquots at -80°C. Specimens were analyzed in duplicate for levels of hepatocyte growth factor (HGF), IGF-1, IGF-2, and IGF binding protein 3 (IGFBP-3) using commercially available ELISA kits following the manufacturer's instructions by technicians blinded to study results. HGF was measured using the R&D Systems Quantikine ELISA

Cat# DHG00, IGF-1 by R&D Systems Quantikine ELISA Cat# DG100, IGF-2 by Mediagnost E30, and IGFBP-3 by R&D Systems Quantikine ELISA Cat# DGB300.

Statistical Analysis

Data analysis included descriptive summaries of baseline and demographic information. Toxicities attributed to treatment were summarized in terms of type and grade. Rates and 95% Clopper Pearson confidence limits were provided for tumor response determined based on RECIST 1.0 criteria [13]. Kaplan Meier methods were used to estimate median progression free survival and overall survival. Results of baseline ELISAs of plasma markers were transformed using a natural logarithm (ln) and Cox proportional hazards models were used to assess if they were predictive of progression free or overall survival. Slopes of the ln transformed markers (HGF, IGF-1, IGF-2 and IGFBP-3) over time were calculated and assessed for a relationship to progression and survival. Given their exploratory nature, all correlative analyses are considered hypothesis generating.

Results

Patient Characteristics

Between August 13, 2009 and November 21, 2012 a total of 21 patients were enrolled on this phase I study at the University of Southern California – Norris Comprehensive Cancer Center, the University of California Davis Cancer Center, the City of Hope Comprehensive Cancer Center, Penn State Cancer Institute, and the University of Pittsburgh Comprehensive Cancer Center. The median age was 61 years (range 43–85); 81% of patients were male. Ninety percent of patients had Child-Pugh A cirrhosis and 10% had a score of Child-Pugh B7. The majority of patients had Barcelona Clinical Liver Cancer (BCLC) stage C disease as defined by the presence of extrahepatic metastases (57%) and/or macrovascular invasion (19%). Prior treatment for HCC included Transarterial Chemoembolization (TACE) in 19% and surgery in 24%. Demographics of the entire cohort are summarized in Table 1.

Treatment and Adverse Events

Of the eight patients who entered treatment at dose level 1, six were deemed evaluable for dose escalation decisions (Table 2). One patient experienced a dose limiting toxicity (DLT) (grade 3 hyperglycemia), prior to amendment excluding grade 3 hyperglycemia that was manageable with medical therapy from the DLT criteria. A decision was made to escalate. Subsequently it was determined that one of six evaluable patients had missed one of the weekly doses of cixutumumab per physician decision but still had no DLT. Three patients accrued to dose level 2 with no DLTs. Seven patients entered dose level three, two were not evaluable for dose escalation decision, and two experienced DLTs (grade 3 hypophosphatemia; grade 5 peritoneal infection). Based on the rules of the 3+3 design, dose level 3 was declared above the maximum tolerated dose and three further patients were entered at dose level 2. Of those patients, one was not evaluable; the remaining patients did not experience DLTs, giving a total of 5 evaluable patients at that dose with no DLTs. Dose level 2 was deemed to be the maximum tolerated dose. Reasons for not being evaluable for dose escalation decisions included: less than the minimum required administration of one or both drugs as a result of toxicities that did not meet DLT definition (3 patients), patient

choice not to continue with study therapy (2 patients) and disease-related complication of bronchopulmonary hemorrhage in one patient.

Eighteen of 21 (86%) patients had grade 3 or above toxicities attributed to treatment (Table 3). Treatment related grade 3 adverse events that occurred in 2 or more patients were hypertension (24%), diarrhea (19%), thrombocytopenia (14%), palmar-plantar erythrodysesthesia syndrome (10%), hyperglycemia (10%), and fatigue (10%). There was also 1 grade 4 colonic perforation and 1 grade 5 peritoneal infection in the same patient. Of the sixteen patients that completed one or more cycles of treatment, the sorafenib dose was reduced in 7 (44%), cixutumumab was reduced in 3 (19%) and one patient (6%) had both treatments reduced. Only 1 patient discontinued study therapy due to toxicity.

Treatment and Response

The median number of cycles completed was 4 (0–26). Sixteen of the 21 participants completed 2 cycles, which allowed for response assessment. There were no objective responses. Thirteen of the sixteen (81%) (95% CI: 54%–96%) achieved stable disease as their best response. The median progression free survival was 6.0 months (95% CI 3.6 – undefined) with median Kaplan Meier potential follow-up of 7.6 (95% CI 3.9 – undefined) months. The median overall survival was 10.5 months (95% CI 7.1 – undefined) with median Kaplan Meier potential follow-up of 26.8 months (95% CI 23.9 – undefined).

Correlative studies

Circulating levels of pretreatment HGF, IGF-1, IGF-2 and IGFBP-3 were examined using univariate Cox proportional hazard models to assess if they were associated with either progression or overall survival. A half ln increase in pretreatment HGF resulted in a 1.8 fold increase in risk of death (coef=1.19, se=0.57, p=0.03). The baseline circulating levels of IGF-1, IGF-2 and IGFBP-3 were not significantly associated with these outcomes. We also looked at slopes over time in the four markers (HGF, IGF-1, IGF-2, IGFBP-3) but found no relationship with progression or survival. It should be noted that the sample size of 16 for the slope analysis limited our ability to distinguish signal from noise.

Discussion

In this phase I study, the combination of cixutumumab and sorafenib had a manageable toxicity profile with the majority of the adverse events being typical of sorafenib toxicity. Dose limiting toxicities included one episode each of hyperglycemia, hypophosphatemia, and peritonitis. The maximum tolerated dose was 400 mg orally twice daily of sorafenib and 4 mg/Kg of cixutumumab IV weekly. Despite the fact that 86% of patients had grade 3 or higher toxicity, only 1 patient discontinued study therapy due to toxicity; this may be explained by the fact that the majority of the adverse events were related to known sorafenib toxicity familiar to the treating physicians and able to managed proactively. Indeed, the sorafenib dose was reduced twice as frequently as cixutumumab in this study. We observed grade 3 hyperglycemia in 10% of patients, a toxicity that has been observed in prior studies of cixutumumab in HCC [14]. Overall, this study did not reveal new safety concerns in

comparison to the safety profile reported in large trials of HCC patients treated with sorafenib.

Evaluation of efficacy is limited by the dose escalation nature of the study and the small sample size. The median PFS and OS noted are consistent with those reported in the randomized phase 3 trial (SHARP) which compared sorafenib to placebo, which would suggest the absence of a benefit from the addition of cixutumumab. However, such conclusions are limited by the sample size, the nature of cross-study comparisons, and by the variability in the patient population. In contrast to SHARP, our study included 10% of patients with Child-Pugh score of B 7, and only 24% were white. Cixutumumab monotherapy did not manifest meaningful clinical activity as a single agent in a published phase 2 study of patients with HCC with a median survival of 8 months [14]. To date, the strategy of developing single agents to improve on outcomes for advanced HCC over those observed with sorafenib monotherapy has failed [15–17]. An alternative strategy is to combine sorafenib with other agents targeted against relevant growth pathways to enhance activity and overcome resistance. This approach has not born-fruit in the clinic as manifested in our small study and in the larger phase 3 trial comparing sorafenib and erlotinib to sorafenib alone [18]. In the case of our study, the discrepancy of the clinical observations with the preclinical data related to the role of the IGF pathway in HCC and the potential for enhanced efficacy with the dual targeting of the IGF and VEGF pathways may be partially explained by the absence of a reliable biomarker to optimize the patient population selection for IGF inhibition. Therefore, the combination of sorafenib and cixutumumab should not be developed further in an unselected patient population with HCC.

We found that pre-treatment plasma HGF level was a strong predictor of outcome. HGF is a paracrine growth factor and a potent mitogen responsible for hepatocyte proliferation [19]. HGF activates a tyrosine kinase signaling cascade after binding to the c-Met proto-oncogene receptor. In resected HCC patients, high serum HGF levels denote a poor prognosis after hepatic resection [20]. In unresectable HCC, the HGF level has variably been associated with survival time [21, 22]. Moreover, it has recently been proposed that c-Met signaling cooperates with IGFR to increase tumor invasiveness through engagement of the urokinase plasminogen activator system [23, 24]. Therefore, signaling through HGF-c-Met may mitigate against the therapeutic effects of IGF-1R inhibition. In the absence of a randomized study, we are unable to determine the prognostic versus predictive nature of the observed HGF effect in this study.

In summary, the recommended dose of cixutumumab is 4 mg/kg IV weekly when combined with standard dose sorafenib. Toxicities observed with this combination are generally consistent with those observed from sorafenib monotherapy in this population. The median PFS and OS for the combination suggest limited clinical activity in an unselected patient population. Further studies should clarify the role of plasma HGF as a prognostic marker or as a predictive marker for the efficacy of this combination.

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Table 1.

Patient Demographic and Clinical Characteristics (n = 21)

Characteristic	n (%)
Age, years	
Median (range)	61 (43–85)
Zubrod Performance Status	
0	9 (43)
1	12 (57)
Gender (Male)	17 (81)
Race/Ethnicity	
Asian	10 (48)
White	5 (24)
Hispanic	4 (19)
Black	1 (5)
Native American	1 (5)
Child Pugh Score	
A5	17 (81)
A6	2 (10)
B7	2 (10)
Primary Risk Factor	
Hepatitis B *	6 (29)
Hepatitis C *	9 (43)
Other risk factors ***	2 (10)
Unknown	4 (19)
Extent of Disease	
Macrovascular involvement (yes)	12 (57)
Extra Hepatic Metastases (yes)	4 (19)
Prior Therapy	
Transarterial Chemo Embolization (TACE)	4 (19)
Surgery	5 (24)

* Risk factors included Hepatitis B+, but may also have included alcohol.

** Risk factors included Hepatitis C+, but may also have included alcohol.

*** Other risk factors included hemochromatosis and alcohol.

Table 2.

Dose Levels and Dose Limiting Toxicities

Dose Level	Cixutumumab (mg/kg IV weekly)	Sorafenib mg PO BID	Patients Treated (n)	Patients Evaluable for DLT (n)	DLTs
1	2	400	8	5	1 (grade 3 hyperglycemia)
2	4	400	6	5	None
3	6	400	7	5	2 (grade 3 hypophosphatemia, grade 5 peritonitis)

Table 3.

Treatment-Related Adverse Events (attributed at the level of possibly or above)

Adverse Event	Any Grade*		Grade 3 and above**	
	N	%	N	%
Any	21	100	18	86
Blood and lymphatic system disorders				
Anemia	3	14	0	0
Gastrointestinal				
Colonic Perforation**	1	5	1	5
Diarrhea	13	62	4	19
Dyspepsia	3	14	0	0
Nausea	6	29	0	0
Vomiting	5	24	0	0
General Disorders				
Fatigue	12	57	2	10
Infections and Infestations				
Lung Infection	1	5	1	5
Peritoneal Infection**	1	5	1	5
Investigations				
Alanine aminotransferase	5	24	0	0
Aspartate aminotransferase	7	33	1	5
Blood bilirubin increased	4	19	0	0
Platelet count decreased	11	52	3	14
Lymphocyte count decreased	2	10	1	5
Weight loss	5	24	1	5
Metabolism and Nutrition				
Anorexia	10	48	1	5
Hyperglycemia	13	62	2	10
Hypokalemia	3	14	0	0
Hypoalbuminemia	3	14	0	0
Hyponatremia	3	14	1	5
Hypophosphatemia	7	33	1	5
Nervous system disorder				
Dysgeusia	3	14	0	0
Peripheral sensory neuropathy	4	19	0	0
Respiratory, thoracic and mediastinal disorders				
Dyspnea	3	14	0	0
Skin and Subcutaneous Tissue				
Dry Skin	6	29	0	0
Erythroderma	2	10	1	5
Palmar-plantar				
Erythrodysesthesia syndrome	5	24	2	10

Adverse Event	Any Grade [*]		Grade 3 and above ^{**}	
	N	%	N	%
Pruritus	5	24	0	0
Acneiform rash	3	14	0	0
Vascular Disorders				
Hypertension	7	33	5	24
Thromboembolic event	1	5	1	5

^{*} This table reports all grade 3 and above toxicities lower grade toxicities of the same type, and lower grade toxicities that were seen in 3 or more participants.

^{**} One patient experienced grade 4 colonic perforation and grade 5 peritoneal infection, all other toxicities in this column were grade 3.