Phase 2 Study of Cetuximab in Patients With Advanced Hepatocellular Carcinoma

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BACKGROUND. Epidermal growth factor receptor (EGFR) and ligand expression is frequently seen in hepatocellular carcinoma (HCC). A phase 2 study was performed with cetuximab, a chimeric monoclonal antibody that binds specifically to EGFR, in patients with advanced HCC.

METHODS. Eligibility criteria included unresectable or metastatic measurable HCC, an Eastern Cooperative Oncology Group performance status $\leq$2, Cancer of the Liver Italian Program (CLIP) score $\leq$3, and adequate organ functions. The initial dose of cetuximab was 400 mg/m^2 given intravenously followed by weekly intravenous infusions at 250 mg/m^2. Each cycle was defined as 6 consecutive weekly treatments. EGFR expression was assayed by immunohistochemistry and trough serum concentrations of cetuximab were determined during the first cycle.

RESULTS. Thirty patients were enrolled and assessable for efficacy and toxicity. No responses were seen. Five patients had stable disease (median time, 4.2 months; range, 2.8–4.2 months). The median overall survival was 9.6 months (95% confidence interval [CI], 4.3–12.1 months) and the median progression-free survival (PFS) was 1.4 months (95% CI, 1.2–2.6 months). The treatment was generally well tolerated. No treatment-related grade 4–5 toxicities occurred. Grade 3 (according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [version 3.0]) aspartate aminotransferase, hypomagnesemia, and fever without neutropenia were noted in 1 patient (3.3%) each. On Week 6 of Cycle 1, arithmetic mean serum cetuximab concentrations for patients with Child-Turcotte-Pugh (CTP) A and CTP B disease were 47.6 mcg/mL and 66.9 mcg/mL, respectively.

CONCLUSIONS. Although cetuximab could be safely administered with tolerable toxicity profiles, it demonstrated no antitumor activity in HCC in this phase 2 study. Cetuximab trough concentrations were not notably altered in patients with mild to moderate hepatic dysfunction. ***Cancer*** **2007;110:581–9.** © *2007 American Cancer Society.*

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Worldwide, hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related death.[1] In the U.S., 18,510 new cancers of the liver and intrahepatic bile duct are expected to be diagnosed in 2006, with an estimated 16,200 deaths.[2] Unresectable or metastatic HCC carries a poor prognosis and systemic therapy with cytotoxic agents provides marginal benefit.[3,4]

Increasing evidence has highlighted the importance of epidermal growth factor receptor/human epidermal growth factor receptor-1 (EGFR/HER-1) and its ligands EGF and transforming growth factor-

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alpha (TGF-α) in hepatocarcinogenesis. The expression of several EGF family members, specifically EGF, TGF-α, and heparin binding-epidermal growth factor, as well as the EGFR, has been described in several HCC cell lines and in tissue.[5–11] Recent data from 2 clinical trials have demonstrated the safety and modest efficacy of erlotinib, an oral EGFR tyrosine kinase inhibitor, in advanced HCC.[12,13] In the study by Philip et al.,[12] 3 of 38 patients (9%) achieved partial responses and 12 of 38 patients (32%) were free of disease progression at 6 months. In another preliminary report by Thomas et al.,[13] 8 of 25 patients (32%) achieved progression-free survival (PFS) at 4 months.

Cetuximab (IMC-C225, ERBITUX) is a chimeric immunoglobulin (Ig) G1 monoclonal antibody that binds specifically to the EGFR on both normal and tumor cells. Cetuximab blocks the binding of EGF or TGF-α to EGFR on the cell surface and inhibits ligand-induced receptor phosphorylation.[14] Many studies have demonstrated that cetuximab treatment alone effectively inhibits proliferation of EGFR-positive tumor cells in vitro and tumor growth in xenograft models.[14–16] Several clinical studies have demonstrated its activity as a single agent or in combination with chemotherapeutic agents in refractory colorectal cancer, head and neck cancer, and others.[17–19] Cetuximab could inhibit the growth of HepG2 HCC cells in a time-dependent and dose-dependent manner.[20] Cetuximab may mediate its antitumor activity through its effects on many important downstream signaling pathways including apoptosis, cell cycle control, and angiogenesis.[21,22]

The poor treatment outcome of systemic chemotherapy in HCC, the increased expression of EGFR in HCC, the preliminary encouraging results with erlotinib in HCC, and the in vitro growth inhibition of HCC cells by cetuximab prompted us to perform the current phase 2 study to examine the efficacy and tolerability of cetuximab in unresectable or metastatic HCC.

MATERIALS AND METHODS

Patient Selection

The protocol for this clinical trial was reviewed and approved by the Institutional Review Board at Dana-Farber/Harvard Cancer Center. All patients were required to provide written informed consent before study participation according to institutional and federal guidelines. Eligibility criteria included histologically proven and measurable locally advanced, recurrent, or metastatic HCC and no more than 2 prior systemic chemotherapy regimens. Prior chemoembolization therapy was permitted if performed more than 4 weeks before study entry and measurable disease was present outside of the prior chemoembolization field. Patients who had received prior treatments were required to have documented progressive disease before study entry. Patients were also required to be at least 18 years of age; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; Cancer of the Liver Italian Program (CLIP) score ≤ 3[23]; and adequate hepatic, renal, and bone marrow functions (serum bilirubin ≤ 3.0 mg/dL, aspartate transaminase ≤ 7 times the institutional upper limit of normal, serum creatinine ≤ 2.0 mg/dL, absolute neutrophil count [ANC] $\geq 1.0 \times 10^9$/L, and a platelet count of $\geq 75 \times 10^9$/L). Patients were required to have tumor tissue available for assessment of EGFR status by immunohistochemistry (IHC) on diagnostic tissue. Exclusion criteria included a concurrent malignancy; significant medical comorbidities; clinically significant cardiovascular disease including uncontrolled hypertension, myocardial infarction, and unstable angina; major surgery within 28 days before the initiation of study treatment; pregnancy or lactation; prior treatment with cetuximab or other therapy that specifically and directly targets the EGF pathway; prior allergic reaction to chimerized or murine monoclonal antibody therapy; known central nervous system metastases; or an inability to give written informed consent.

Treatment Protocol

The initial dose of cetuximab was 400 mg/m^2 administered intravenously over 120 minutes, followed by weekly infusions at 250 mg/m^2 intravenously over 60 minutes. Each cycle consisted of 6 weekly treatments. All patients were premedicated with diphenhydramine hydrochloride at a dose of 50 mg (or an equivalent antihistamine) intravenously 30 to 60 minutes before treatment.

Before study entry, all patients provided a complete medical history and underwent a physical examination, including an assessment of ECOG performance status, weight, height, and concurrent nonmalignant disease and therapy. Laboratory studies included a complete blood count, differential count, platelet count, biochemistry (sodium, potassium, chloride, bicarbonate, glucose, uric acid, lactate dehydrogenase, albumin, magnesium, and calcium), hepatic and renal function tests, and alpha-fetoprotein (AFP). Required radiologic studies included a chest and abdominopelvic computed tomography (CT) scan or magnetic resonance imaging (MRI) scan. Serum hepatitis B and C serology were also determined before treatment. A pregnancy test was

obtained from all women of childbearing potential within 7 days before the initiation of therapy.

During treatment, patients were monitored weekly during the first cycle and once every 2 weeks for the subsequent cycles for a brief history, physical examination, assessment of ECOG performance status and toxicity, and laboratory evaluation. AFP was performed before the beginning of each cycle. CT or MRI scans were performed at the end of each cycle. Response and disease progression were evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.[24] Treatment was continued until 1 of the following criteria was met: disease progression per RECIST criteria, unacceptable toxicity, patient refusal, or the need to delay therapy more than 3 weeks.

Toxicity Evaluation and Dose Modification

Toxicity was evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) and cetuximab dose modifications were performed as specified in the protocol. If the patient experienced a mild or moderate (grade 1 or 2) infusion reaction, the infusion rate was permanently slowed by 50%. Cetuximab was immediately and permanently discontinued in patients who experienced severe (grade 3 or 4) infusion reactions. If a patient experienced severe acneiform rash (grade 3), cetuximab treatment adjustments were made according to the following scheme: for the first occurrence, cetuximab was withheld for up to 2 weeks and resumed at the same dosage when the rash decreased to $\leq$grade 2; for the second occurrence, cetuximab was withheld for up to 2 weeks and resumed at 200 mg/m^2 when the rash decreased to $\leq$grade 2; if there was no improvement in the rash while withholding the treatment within 2 weeks, cetuximab was discontinued. Rash was treated with topical and/or oral antibiotics. For all other grade 3/4 nonhematologic treatment-related toxicities, cetuximab was resumed when the toxicities resolved to $\leq$grade 2.

Immunohistochemistry of EGFR

Paraffin-embedded tissue blocks were obtained at the time of tissue biopsy and assessment of EGFR status by IHC was performed as described previously.[25] EGFR expression was recorded as negative (0), weakly positive (1+), positive (2+), or strongly positive (3+). Results were interpreted as blinded from patients' identity and clinical outcomes data.

Pharmacokinetic Study

One venous blood sample (approximately 5 mL) was collected for pharmacokinetic (PK) evaluation of trough (Cmin) serum cetuximab concentrations at 00:00 (predose) immediately before the start of the infusion of cetuximab, beginning with the second dose of cetuximab, and was continued for 5 weekly doses (Weeks 2-6) in Cycle 1. Serum cetuximab concentrations were determined using a validated enzyme-linked immunosorbent assay by PPD (Richmond, Va). Recombinant human EGFR (full-length receptor; ImClone Systems, Somerville, NJ) was used as the capture reagent. Bound cetuximab was detected using a peroxidase-conjugated, rabbit anti-human, IgG Fcγ fragment specific antibody and TMB-peroxide substrate. Serum was diluted at least 1000-fold with buffer (phosphate-buffered saline containing 1% bovine serum albumin [BSA] and 0.05% Tween-20). The range of quantitation (at 1:1000 dilution) was 1.0 to 32.0 μg/mL. Linearity of dilution was validated to a total dilution of 100,000-fold, which extended the upper limit of quantitation to 3200 μg/mL. From prestudy validation the within-assay and between-assay precision (%CV) was within 8.5% and 9.2%, respectively. The accuracy (percent of nominal) was within 6.3%. Summary statistics were derived from all measurable, observed individual Cmin values at each study week using Microsoft Excel 2002.

Statistical Analysis

The primary endpoint of this phase 2 study was PFS. The planned accrual was for 30 evaluable patients. If the lower 80% confidence bound estimate for the proportion of patients alive with no disease progression by 3 months exceeded 0.50 the regimen would be considered for further investigation. The lower 80% confidence bound would exceed 0.50 if 18 or more of 30 patients were alive with no progression at 3 months. If the true rate of PFS at 3 months was 0.7 (a median PFS of 5.8 months), the probability of observing $\geq$18 patients with no disease progression at 3 months would be 90%. If the true rate of PFS at 3 months was $\leq$0.50, this probability would be $\leq$18%. The secondary endpoints were to define toxicity profiles, response rate, and overall survival. Overall survival was defined as time from study entry until death from any cause. Overall survival and PFS were calculated using the Kaplan-Meier method, and confidence limits for survival estimates were calculated using the Greenwood formula. All categories of toxicity and complications of the treatment were recorded.

TABLE 1
Patient Characteristics

Characteristic	Value	Range	%
No. of patients	30		
Sex			
Male	23		77
Female	7		23
Median age, y	58	33–82	
Median ECOG performance status	0	0–2	
Median CLIP score	2	0–3	
CTP A	18		60
CTP B	12		40
Prior treatments			
Systemic chemotherapy	7		23
Surgical resection	3		10
Chemoembolization	3		10
Radiofrequency ablation	1		3
Baseline hepatitis serologies			
Hepatitis C antibody positive	8		27
Hepatitis B surface antigen positive	8		27
Baseline clinical features			
Chronic liver disease	14		47
Median baseline laboratory values			
Alkaline phosphatase, U/L	159	79–748	
AST, U/L	77	25–187	
Total bilirubin, mg/dL	0.7	0.3–2.9	
AFP, ng/mL	233.9	3.5–93,330	

ECOG indicates Eastern Cooperative Oncology Group; CLIP, Cancer of the Liver Italian Program; CTP, Child-Turcotte-Pugh; AFP, α-fetoprotein.

RESULTS

Patient Characteristics

Between February 2005 and October 2005, 30 patients with unresectable or metastatic HCC were entered into this trial. No patients had fibrolamellar or hepatocholangiocarcinoma histology. All patients were evaluable for toxicity and response. Baseline patient characteristics are summarized in Table 1 There were 23 men (77%) and 7 women (23%), with a median age of 58 years (range, 33–82 years). Median ECOG performance status for the population was 0 (range, 0–2). The median CLIP score was 2 (range, 0–3), and of these 2, 9, 14, and 5 patients had CLIP scores of 0, 1, 2, and 3, respectively. Eighteen patients had Child-Turcotte-Pugh (CTP) A disease and 12 had CTP B disease. Fifteen patients (50%) had extrahepatic metastasis. Seven patients (23%) had received 1 previous systemic therapy. Twenty-five patients (83%) had an elevated AFP level at the time of entry.

Clinical Efficacy

Among all patients, 45 cycles of treatments were administered. A median of 1 cycle was administered to each patient (range, 1–3). The median dosage of cetuximab received per patient was 250 mg/m^2 Twenty-four patients (80%) withdrew from therapy due to disease progression, 1 patient (3%) withdrew as a result of nontreatment-related toxicity, and 5 patients (17%) withdrew consent during treatment. All patients came off study and 20 patients had died at the time of last follow-up. The median follow-up time was 7.4 months (range, 1–14.6 months).

No patient achieved a complete response (CR) or partial response (PR). Five patients (17%) had stable disease (SD) as their best response with a median duration of 4.2 months (range, 2.8–4.2 months). The response or progression was based on RECIST criteria and not on AFP levels. No patients were taken off study based on rising AFP levels alone. However, of the 25 patients who had baseline elevated AFP levels, 5 patients had decreased AFP levels and 2 patients had a >50% decrease in AFP levels.

The median overall survival time was 9.6 months (95% confidence interval [CI], 4.3–12.1 months) and median PFS time was 1.4 months (95% CI, 1.2–2.6 months) (Fig. 1A and 1B); the PFS rate at 3 months and 6 months was 23% and 3%, respectively.

Toxicity

Data on toxicity for all 30 patients are provided in Table 2 The toxicities recorded represent the maximum grade toxicity observed for a given patient for the entire course of therapy. Cetuximab was generally well tolerated. There were no treatment-related deaths or discontinuations. No patients required a dose reduction. Nine patients had cetuximab withheld during treatment. Nine patients received fewer than 6 doses of cetuximab and 8 of them had progressive disease before the 6 doses were completed.

No grade 4 treatment-related toxicity was noted in this study. No infusion reactions were observed. Grade 3 AST, hypomagnesemia, and fever without neutropenia were seen in 1 patient (3.3%) each. Twenty-five patients (83.3%) had grade 1-2 skin rash; however, no patients developed grade 3 rash. The incidence of toxicity was similar in patients with normal and impaired hepatic function (data not shown).

EGFR Expression

In this study, patients were required to have tissue blocks available for EGFR testing but not for initiation of therapy. Of the 30 patients enrolled in the study, 22 patients had adequate tissue blocks available for IHC testing for EGFR. The rest of the patients had inadequate tissue materials on further examination for EGFR testing. Of the 22 patients with evaluable blocks, 18 (82%) tested positive (10 patients with 3+ and 4 patients with 2+ positive)

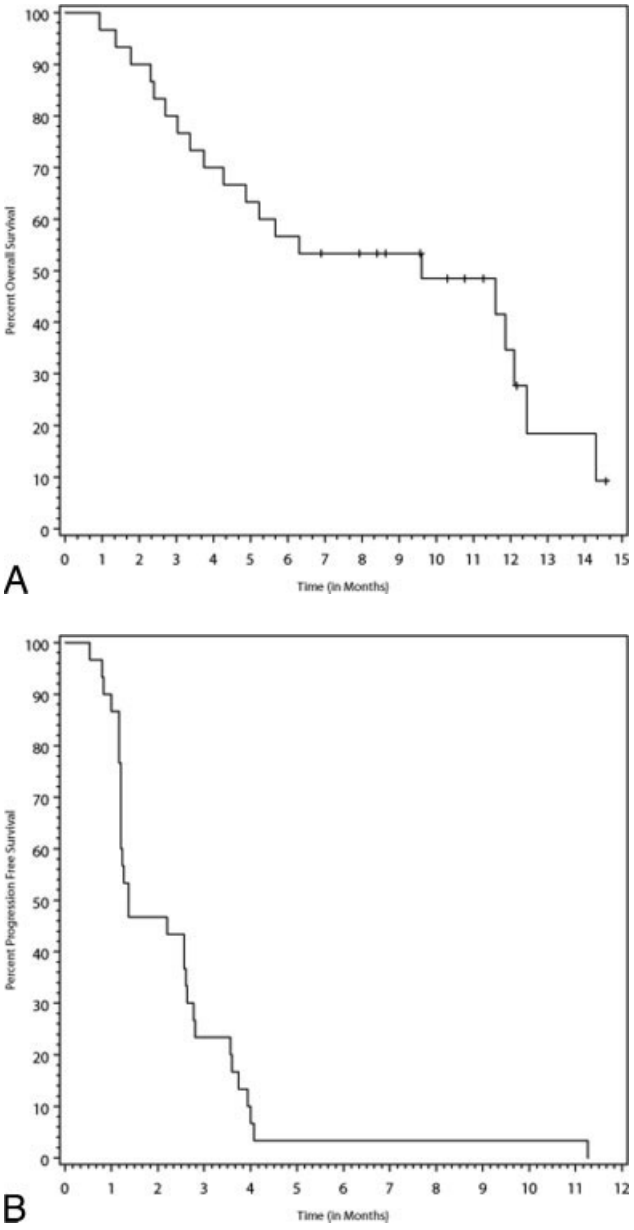

FIGURE 1. (A) Kaplan-Meier estimation of overall survival. (B) Kaplan-Meier estimation of progression-free survival.

and 4 patients (18%) tested negative for EGFR. No correlation between EGFR expression and clinical efficacy was observed (data not shown).

Pharmacokinetics Study

Trough (Cmin) serum cetuximab concentrations were determined from blood samples obtained just before dosing on Weeks 2, 3, 4, 5, and 6 in Cycle 1. Subjects were divided into the following groups: l) CTP A and CTP B; 2) baseline serum bilirubin values equal or less than the upper limit of normal for the subject's study site (normal) and values greater than the upper limit of normal (elevated).

TABLE 2
Treatment-Related Toxicities

	Grade 1–2		Grade 3	
Toxicity	**No. of patients**	**%**	**No. of patients**	**%**
Acneiform rash	25	83.3	–	
Fatigue	14	46.7	–	
Hypomagnesemia	8	26.7	1	3.3
Nausea	6	20	–	
Dry skin	5	16.7	–	
Leukopenia	4	13.3	–	
Anorexia	4	13.3	–	
Diarrhea	4	13.3	–	
Anemia	4	13.3	–	
AST	3	10	1	3.3
Vomiting	3	10	–	
Lymphopenia	3	10	–	
ALT	3	10	–	
Hypoalbuminemia	3	10	–	
Pruritus	3	10	–	
Thrombocytopenia	2	6.7	–	
Alkaline phosphatasealign	2	6.7	–	
Edema	2	6.7	–	
Cough	2	6.7	–	
Mucositis	2	6.7	–	
Infection w/out neutropenia	2	6.7	–	
Fever	–		1	3.3

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.

Figure 2A shows the mean (SD) cetuximab trough concentrations versus time for subjects classified as CTP A and CTP B. The total number of subjects with measurable concentrations, and the subjects from that total for whom there were 5, 4, 3, 2, or 1 week(s) of measurable trough samples available were 17 (11, 2, 2, 1, and 1) and 11 (8, 2, 1, 0, and 0) for CTP A and CTP B subjects, respectively. On Week 6 (the time of maximum observed exposure), for the CTP A (n = 11) and CTP B (n = 10) groups, respectively, arithmetic mean serum concentrations were 47.6 mcg/mL and 66.9 mcg/mL, geometric mean concentrations were 40.9 mcg/mL and 57.7 mcg/mL, standard deviations were 26.7 and 32.8, coefficients of variation (percent) were 56.1 and 49.0, median concentrations were 40.9 mcg/mL and 72.2 mcg/mL, minimum concentrations were 11.0 mcg/mL and 19.3 mcg/mL, and maximum concentrations were 107.0 mcg/mL and 122.0 mcg/mL.

Figure 2B shows the mean (SD) cetuximab trough concentrations vs time for subjects with normal or elevated baseline bilirubin values. The total number of subjects with measurable concentrations, and the subjects from that total for whom there were

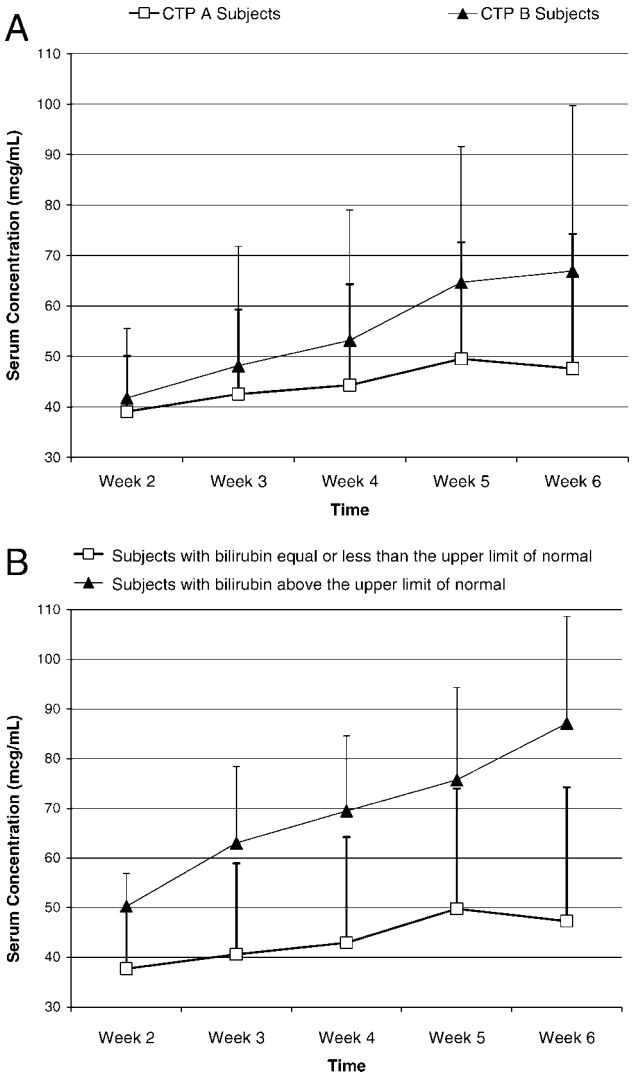

FIGURE 2. (A) Arithmetic mean (SD) cetuximab trough concentrations versus time based on Child-Turcotte-Pugh (CTP) classification. Subjects were divided into 2 groups: those with CTP A disease and those with CTP B disease. (B) Arithmetic mean (SD) cetuximab trough concentrations versus time (by study week during Cycle 1) based on serum bilirubin levels.

5, 4, 3, 2, or 1 week(s) of measurable trough samples available were 23 (14, 4, 3, 1, and 1) and 5 (5, 0, 0, 0, and 0) for normal and elevated subjects, respectively. On Week 6 (the time of maximum observed exposure), for the normal (n = 16) and elevated (n = 5) groups, respectively, arithmetic mean serum concentrations were 47.3 mcg/mL and 87.1 mcg/mL, geometric mean concentrations were 40.3 mcg/mL and 85.2 mcg/mL, standard deviations were 26.9 and 21.6, coefficients of variation (percent) were 56.9 and 24.8, median concentrations were 37.7 mcg/mL and 83.0 mcg/mL, minimum concentrations were 11.0 mcg/mL and 69.0 mcg/mL, and maximum concentrations were 107.0 mcg/mL and 122.0 mcg/mL.

TABLE 3
Treatments After Progression on Cetuximab

Additional therapy	No. of patients	Type of therapy (No. of patients)
No	13	–
Yes	14	Gemcitabine/oxaliplatin/bevacizumab (5)
		Phase I studies (4)
		Chemoembolization (3)
		Capecitabine (3)
		Sorafenib (2)
		5-FU/leucovorin (1)
		Paclitaxel/bevacizumab (1)
		Doxorubicin (1)
		Gemcitabine/oxaliplatin (1)
		Doxorubicin /thalidomide (1)
		Bevacizumab (1)
		Erlotinib (1)
		Gemcitabine/cisplatin/bevacizumab (1)
		Sunitinib (1)
Unknown	3	-

5-FU indicates 5-fluorouracil.

Treatments After Progression on Cetuximab

Due to the short PFS observed, we examined the subsequent treatment regimens these patients received upon progression on cetuximab. Fourteen patients received subsequent treatments, as detailed in Table 3 Some patients received >1 regimen after developing disease progression while receiving cetuximab. Five patients were treated on a combination regimen of gemcitabine, oxaliplatin, and bevacizumab based on our earlier phase 2 experience[26] and 3 patients had disease control for >4 months. In addition, 3 patients had stable disease for >4 months on phase 1 studies or other empiric therapies.

DISCUSSION

The prognosis for locally advanced and metastatic HCC is dismal, with a median survival of <8 months and the development of an effective systemic therapy for HCC remains a major challenge. We postulated that cetuximab, a monoclonal antibody that can bind EGFR and block ligand binding to EGFR, might have direct anti-HCC activity. Unfortunately, our results demonstrated lack of antitumor activity of cetuximab in this population. In this study, no responses were observed and 80% of patients received only 1 cycle of treatment due to rapid progression of disease. The median PFS was only 1.4 months.

Cetuximab proved to be well tolerated in our study. No grade 4 treatment-related toxicity occurred

TABLE 4
Summary of Recent Phase II Studies With EGFR Inhibitors in HCC

Study	Regimen	No. of patients	RR (%)	Median PFS/TTP, mo	PFS at 4 or 6 mo (%)	Median survival, mo
Philip et al., 2005[12]	Erlotinib	38	9	3.2	32 (6 m)	13
Thomas et al., 2005[13]	Erlotinib	25	0	2.2	32 (4 m)	6.2
Ramanathan et al., 2006[30]	Lapatinib	30	5	2.3	NR	6.2
Current study	Cetuximab	30	0	1.36	3 (6 m)	9.6

EGFR indicates epidermal growth factor receptor; HCC, hepatocellular carcinoma; RR, response rate; PFS, progression-free survival; TTP, time to tumor progression; NR, not reported.

and grade 3 toxicity was noted in only 3 patients. Interestingly, although 25 patients (83.3%) had grade 1-2 skin rash, no patients developed grade 3 rash. This is likely due to the close observation and aggressive early intervention of rash management. In addition, the short duration of cetuximab treatment most patients received might be another contributing factor.

Although cetuximab has not been reported to undergo hepatic metabolism, the possibility of large pharmacokinetic perturbations due to hepatic dysfunction could be possible, such as via altered apparent volume of distribution as a result of fluid shifts. To screen for macroscopic changes in cetuximab pharmacokinetics, trough drug concentrations values were collected. The trough is the least variable point in the dosing interval because it is obtained immediately predose when there has been maximal time for redistribution. Trough values are routinely used for the purpose of therapeutic drug monitoring as a method to screen for large and, therefore, potentially clinically relevant, pharmacokinetic differences. The intent of the current study was to screen for such large deviations and thereby determine whether further study is warranted, rather than to conduct a definitive study of a moderately impaired hepatic versus a control population powered to discriminate statistical relevance.

In earlier studies, after administration of an initial dose of 400 mg/m^2 and subsequent weekly doses of 250 mg/m^2 in patients, trough concentrations were reported to approximate steady-state conditions by the third weekly infusion, with arithmetic mean trough concentrations across studies ranging from 41 mcg/mL to 85 mcg/mL.[27] A population pharmacokinetic analysis was also performed that explored the potential effects of hepatic function as a covariate. No impact on the pharmacokinetics of cetuximab was found.[27] In the present study, there appeared to be a trend toward modestly higher trough serum concentrations and delayed achievement of steady-state conditions in patients with mild to moderate hepatic impairment. However, arithmetic mean trough values between groups were generally close to or within 1 SD of each other. It is interesting to note that the arithmetic mean trough concentrations for patients with hepatic impairment over the 6-week period studied were similar to those reported earlier in other patient populations. Therefore, the results of this study emphasize the general importance of careful monitoring, but do not support a need for routine cetuximab dosing modifications in patients who have mild to moderate hepatic impairment. In addition, the results indicate that a larger and more definitive investigation of the influence of moderate hepatic disease on cetuximab pharmacokinetics is not likely to be clinically useful. We also failed to observe any correlation between serum trough concentrations of cetuximab and the incidence of skin rash and other toxicities.

Multiple strategies to target EGFR signaling pathways have been developed and 2 classes of anti-EGFR agents have established clinical activity in cancer: monoclonal antibodies that competitively inhibit extracellular endogenous ligand binding and small molecules that inhibit the intracellular TK domain.[28,29] The relative benefit of EGFR inhibition by tyrosine kinase inhibitors as compared with monoclonal antibodies varies in different malignancies. Table 4 summarizes the current clinical trials of EGFR inhibitors in HCC. To our knowledge, the current study is the first to use the EGFR-directed monoclonal antibody in advanced HCC. In contrast to 2 previous reports with erlotinib,[12,13] cetuximab failed to demonstrate any antitumor activity against HCC in this study. We did observe an AFP decrease in 5 patients, with 2 patients having greater than a 50% decrease after cetuximab treatment. However, given the short duration on treatment and the transient nature of AFP decrease in these patients, it is difficult to assess the significance of AFP decrease in our study. Further studies are needed to define the AFP response and to assess if AFP decrease correlates with improved clinical outcome in HCC patients on treatment. Lapatinib, a selective dual inhibitor of both EGFR and HER-2/NEU tyrosine kinases, also

demonstrated modest activity in HCC in a preliminary report.[30] Evidence from other tumor types suggests that different classes of EGFR inhibitors may have different antitumor activity. Although both EGFR-tyrosine kinase inhibitors and EGFR-directed monoclonal antibodies appear to have single-agent activity in advanced nonsmall-cell lung cancer,[31–34] single-agent activity in metastatic colorectal cancer appears largely restricted to antibody therapy.[17,18] The lack of activity of cetuximab in HCC in the current study raises additional unanswered questions regarding the role of EGFR inhibition in HCC. Do other monoclonal antibodies against EGFR have any potential activity in advanced HCC? Does combined EGFR blockade with both cetuximab or other monoclonal antibodies and EGFR tyrosine kinase inhibitors have additive or synergistic antitumor activity in HCC? Does cetuximab have improved efficacy when combined with chemotherapy? It is worth noting that EGFR exon 18-21 mutations have not been identified in HCC.[35] Although dose escalation of cetuximab based on rash has been explored in other tumor types, the aggressive nature of HCC and the lack of any activity of cetuximab seen in our study would make this strategy difficult. Therefore, the definitive benefits of any EGFR inhibitors in HCC and the optimal combination, if any, require further studies. As an initial attempt to test the optimized cetuximab based treatment regimens in vitro, Huether et al.[20] demonstrated that cetuximab inhibited growth of p53 wild-type HepG2 HCC cells in a time- and dose-dependent manner. In this study, cetuximab treatment resulted in cell cycle arrest in the G1/G0 phase. Combining cetuximab with erlotinib or doxorubicin resulted in synergistic antiproliferative effects in these HCC cells.

We observed very short PFS (1.4 months) and relatively long overall survival (9.6 months) in our study. Although we could not fully interpret this discrepancy, 2 potential reasons might account for this. First, some of the patients on study may have relatively indolent disease. This is reflected by the fact that 47% of patients received additional treatments upon progression on cetuximab. Second, some of these patients may have received clinical benefits from additional treatment upon progression on cetuximab. In our study, 6 patients had disease control for more than 4 months from additional lines of therapy. Our study also reflects the limitation and controversy over the use of primary endpoints in HCC phase 2 study design. Although overall survival should be considered the primary endpoint in phase 3 studies, it may be less informative in small phase 2 studies due to the heterogeneity of the disease and patient selection bias. Using response criteria suffers from the inherent difficulty of consistently imaging HCC lesions and the variable pattern of HCC growth. In addition, molecularly targeted agents like cetuximab may be cytostatic instead of cytotoxic. PFS has the advantage of assessing overall tumor-modifying effects of a particular agent/regimen and may be most informative in HCC phase 2 studies. Unfortunately, PFS is dependant on using RECIST criteria to evaluate progression and, as outlined above, this is often problematic for HCC due to the difficulties in obtaining directly comparable images. To demonstrate the disease-modifying effects of cytostatic agents, it would be desirable to know the natural history of the study cohort and documented disease progression before study entry. In our study only 7 patients had prior systemic therapy, making it difficult to assess if cetuximab truly has tumor-modifying effects. Future HCC trials should consider the use of a randomized phase 2 design to assess the potential disease-modifying effects of investigational agents.

In conclusion, the results of the current study demonstrated a lack of antitumor activity of cetuximab in patients with advanced HCC in this phase 2 study. Cetuximab could be safely administered with tolerable safety profiles in this population. Cetuximab trough concentrations were not found to be notably altered in patients with mild to moderate hepatic dysfunction. Given the preclinical data for cetuximab activity and preliminary efficacy of other anti-EGFR agents against HCC, further studies are warranted to assess the role of cetuximab when combined with other targeted agents or chemotherapy in advanced HCC.

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