

Biologic Study of the Effects of Octreotide-LAR on Growth Hormone in Unresectable and Metastatic Hepatocellular Carcinoma

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Abstract: Background: Animal models suggest that growth hormone participates in hepatocarcinogenesis. **Objective:** To correlate the effect of octreotide long-acting release (LAR) on insulin-like growth factor-I (IGF-I) and -II (IGF-II) with response and survival in patients with unresectable and metastatic hepatocellular carcinoma. **Methods:** We conducted a phase II, single-institution trial of octreotide-LAR (30 mg intramuscularly every 4 weeks) in 15 patients while monitoring serum IGF-I and -II levels. **Results:** Patients (median CLIP score 2, Okuda stage II, and ECOG performance status 1) were treated for a median of 2.0 cycles. No responses occurred. Median overall survival was 116 days (range, 27–937 days) and median progression-free survival was 60 days (range, 27–444 days). One patient had prolonged stable disease (16 months). There were no grade 4 and four grade 3 toxicities: abdominal cramping, elevated creatinine, diarrhea, and dyspnea. Median serum IGF-I decreased from baseline (42.2 ng/mL; range, 14.2–109 ng/mL) to day 29 (27.9 ng/mL; range, 5.7–71.1 ng/mL), and median serum IGF-II decreased from baseline (25,000 ng/mL; range, 12,400–93,600 ng/mL) to day 29 (18,400 ng/mL; range, 4,061–79,400 ng/mL; 2-sided $P < .006$ and $P < .04$, respectively; Wilcoxon signed rank test). This suppression did not correlate with clinical activity. Baseline serum IGF-I > 30 ng/mL was associated with greater progression-free survival and overall survival ($P = .0005$ and $P = .0173$, respectively; 2-sided log-rank test). **Conclusions:** Octreotide-LAR lowered serum IGF-I and -II levels; however, this lowering did not correlate with clinical activity. There were no responses, and progression-free survival and overall survival were similar to historical patients not on treatment. Baseline serum IGF-I predicted prognosis.

Hepatocellular carcinoma (HCC) ranks globally near the top in cancer incidence and cancer-related deaths.¹⁻³ The incidence of HCC is increasing in the United States, mainly due to a rise in hepatitis C infection.^{4,5} Liver transplantation is the best means of cure for HCC, although most presentations are late, precluding this approach. The median survival of advanced HCC is measured in months.

The resistance of advanced HCC to systemic and local therapies is reflected by the National Comprehensive Cancer Network's recommendation that patients with unresectable disease, those who decline surgery, or those who are not candidates for resection or transplantation be considered for entry into frontline investigational trials.⁶

The hypothesis that growth hormone (GH) participates in the pathogenesis of HCC has existed since at least the 1950s. Richardson and colleagues demonstrated that normal, but not hypophysectomized, rats fed the hepatocarcinogen 3'-methyl-4-dimethylaminoazobenzene developed hepatomas^{7,8}; moreover, this protection was lost when hypophysectomized rats were administered GH.^{8,9} Orian and coworkers showed a high rate of hepatoma formation in a murine model that expressed a metallothionein-ovine growth hormone fusion gene but not in nontransgenic littermates.¹⁰ Thereafter, Snibson and associates reported an increased incidence of HCC in GH-overexpressing transgenic mice.¹¹ Conversely, GH-deficient models demonstrate resistance to hepatocarcinogenesis. For instance, mice with the *lit* mutation in the GH-releasing-hormone receptor gene have isolated GH deficiency and a dramatically lower rate of developing HCC when treated with carcinogen.¹² Overall, these experiments suggest that overexpression of GH may increase the risk of developing HCC in these animals.

There are limited data exploring the relationship of GH and HCC in humans. However, an association between GH activity and carcinoma is postulated, particularly among patients with acromegaly. Females with acromegaly experience an increased incidence of breast carcinoma¹³⁻¹⁶ and colon carcinoma.¹⁷ Furthermore, cancer is the third most common cause of death among patients with acromegaly, accounting for 15% of deaths.¹⁸ Orme and associates reported excess cancer mortality in acromegalic patients whose posttreatment GH levels remained elevated compared with normal posttreatment-level controls.¹⁹

Octreotide is a somatostatin analog with potent suppression of GH release^{20,21} used in the treatment of acromegaly.^{22,23} Octreotide long-acting release (octreotide-LAR) is more amenable to in vivo testing than the short-acting form of this drug.²⁴ HCC cells express somatostatin receptors²⁵⁻²⁹ and octreotide has shown activity in HCC in vitro and in vivo via inhibition of angiogenesis^{30,31} and induction of apoptosis.^{25,32} Randomized clinical trials exploring the use of octreotide in the treatment of advanced HCC have produced conflicting results. Kouroumalis and coauthors showed that in 58 patients assigned to octreotide or best supportive care on a randomized basis, octreotide provided a superior median survival of 13.0 versus 4.0 months ($P=.002$).³³ Yuen and coworkers, however, failed to demonstrate a survival ben-

efit for octreotide-LAR over best supportive care.³⁴ Similarly, Becker and colleagues showed no survival benefit for octreotide-LAR in a randomized, placebo-controlled, double-blind trial of 121 patients with untreated HCC.³⁵ Two nonrandomized trials that selected patients for treatment with octreotide-LAR only if their tumors were positive for the somatostatin receptor on scintigraphy also demonstrated inconsistent results. Dimitroulopoulos and associates reported a superior median survival in 15 patients with baseline tumor uptake on scintigraphy with indium-111-labeled octreotide compared with 13 scintigraphy-negative controls (31 vs 16 weeks; $P=.037$).³⁶ Lersch and coauthors, however, failed to show a survival advantage in scintigraphy-positive patients compared to scintigraphy-negative controls.³⁷ More recently, a prospective study by Slijkhuis and coworkers of octreotide-LAR in 24 patients with unresectable HCC found a median survival of only 5.1 months.³⁸ These conflicting reports may be due to the small numbers of patients enrolled or to the fact that patients in different countries tend to have different etiologies of HCC. Octreotide may be more helpful in tumors related to hepatitis C versus hepatitis B or less helpful in alcohol-induced cirrhosis.

In order to further examine the role of octreotide in patients with HCC and to determine if insulin-like growth factor (IGF), a surrogate marker of GH, is a potential prognostic indicator, we conducted a phase II trial of octreotide-LAR in patients with unresectable and metastatic HCC. We hypothesized, given the preclinical data, that suppression of GH would accompany response to octreotide-LAR. The primary endpoint of this study was to characterize the effects of octreotide-LAR on serum IGF-I. Secondary endpoints were to assess the toxicity of octreotide-LAR as well as the overall survival (OS) of these patients.

Patients and Methods

Patient Enrollment

Eligible patients were at least 18 years of age, with an estimated life expectancy of at least 3 months, and had histologically confirmed unresectable or metastatic HCC measurable by conventional methods using RECIST (Response Evaluation Criteria in Solid Tumors Group) criteria,³⁹ an Eastern Cooperative Oncology Group performance status (ECOG-PS) of at least 2, and adequate major organ function at baseline (creatinine ≤ 2.0 mg/dL, blood urea nitrogen [BUN] ≤ 40 mg/dL, granulocyte count $\geq 1,500/\mu\text{L}$, platelet count $\geq 50,000/\mu\text{L}$, and total bilirubin ≤ 3.0 mg/dL). Exclusion criteria included chemotherapy or chemoembolization within 4 weeks of enrollment; extrahepatic disease expected to be life-threatening within 3 months, such as brain or symptomatic lung

metastases; active, life-threatening secondary malignancy; and inability to understand the investigational nature of the study and give informed consent. The Institutional Review Board of the University of Wisconsin-Madison approved this study, and written informed consent was obtained from every enrolled patient.

Baseline evaluation, occurring no more than 14 days prior to registration, included physical examination; assessment of ECOG-PS; complete blood count; platelet count; prothrombin time (PT); international normalized ratio (INR); BUN; creatinine; glucose; total bilirubin (TB); alkaline phosphatase (ALP); aspartate transaminase (AST); serum alpha-fetoprotein (AFP); IGF-I, IGF-II, and GH levels; and albumin; and urine pregnancy testing for women of childbearing potential. Core needle biopsy was required prior to enrollment.

Octreotide Formulation

Octreotide-LAR depot (Novartis) is a synthetic octapeptide consisting of octreotide acetate microencapsulated by a biodegradable polymer, poly(DL-lactide-co-glycolide)D-(+) glucose. The ratio of polymer to peptide is approximately 20:1 (w/w). Mannitol (17% w/w) was added to remove solvents, augment injectability of the microspheres, and establish isotonicity.

Patient Treatment and Follow-up

Hypersensitivity to octreotide was assessed with a subcutaneous 100 mg dose of its short-acting formulation. If uneventful, 30 mg of octreotide-LAR was given intramuscularly within 4 days and was repeated 2 and 4 weeks later and monthly thereafter.

While on treatment, complete blood and platelet counts were assessed every 4 weeks; BUN, creatinine, glucose, TB, ALP, AST, albumin, AFP, PT, and INR were measured at 2 and 4 weeks and every 4 weeks thereafter. Patients on treatment were examined 1 month after initiation of treatment and then every 4 weeks. Patients not on treatment were followed every 3 months by phone or office visit to assess survival. Serum IGF-I, IGF-II, and GH were drawn at 2 weeks, at 1 month, then every 2 months until 11 months from first treatment. Blood to assess IGF-I and -II levels was not drawn at any particular time of day.

Tumor Assessment

Measurable disease was defined at baseline (≤ 4 weeks prior to initial therapy) as at least one lesion that could be accurately measured in at least one dimension as at least 20 mm with conventional techniques or as at least 10 mm with spiral computed tomography scan. Response was assessed using RECIST by comparison of baseline imaging to scans performed every 2 months after first treat-

ment. Responders or those with stable disease continued treatment until progression, intolerance, or withdrawn consent occurred.

Toxicity

Toxicities due to therapy had to resolve to grade 1 or less (as per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0) prior to administration of subsequent doses. Patients for whom this resolution did not occur within 28 days of their last dose were removed from treatment. Dose modifications were not made for toxicity.

Statistical Considerations

Following from the hypothesis that GH affects the treatment of HCC, the primary endpoint of this trial was decrease in serum IGF-I. A sample size of 25 would give an 80% power using a 1-sided paired t test with a significance level of 0.05 to detect an anticipated 25% decrease in serum IGF-I levels from baseline to posttreatment, assuming a standard deviation of 50%. Secondary endpoints included toxicity, response rate, and survival. Enrollment was suspended after 15 patients because of a lack of clinical efficacy.

Results

Baseline Patient Characteristics

The baseline characteristics of the 15 patients enrolled on this study from December 2002 through October 2004 are shown in Table 1. Accrual was suspended after these patients were enrolled because of lack of response. The median age was 59 years (range, 50–76 years), 80% were male, 80% were white, 80% had an ECOG-PS of 1, and for only 2 patients (13%) was HCC a confirmed second malignancy. Prior to enrollment, 27% had received systemic chemotherapy for HCC. Six patients (45%) had not undergone prior systemic or localized therapy for HCC. The remaining 9 patients had undergone local therapies including resection, chemoembolization, cryotherapy, and radiofrequency ablation. In addition, 1 patient had palliative radiotherapy to a radial metastasis. Eight patients (53%) had confirmed viral hepatitis, predominately type C (6 patients). Seven patients (47%) had a history of heavy and prolonged alcohol consumption. Most patients (73%) had biopsy-proven cirrhosis and a majority of patients (60%) had Child-Pugh class A^{40,41} liver disease.

Baseline Tumor Characteristics

Table 2 displays baseline tumor characteristics for the enrolled patients. The most common hepatic tumor pat-

Table 1. Baseline Characteristics of 15 Enrolled Patients

Characteristic		Characteristic	
Age, years		Cirrhosis status, n	
• Median	59	• Yes	11
• Range	50–76	• No	4
Sex, n		Child-Pugh Class, n	
• Male	12	• A	9
• Female	3	• B	6
ECOG performance status, n		• C	0
• 0	2	Prior cancer therapy, n	
• 1	12	• Chemotherapy (distinct patients)	4
• 2	1	– Doxorubicin	1
Race, n		– Cisplatin	1
• Asian	1	– Investigational (bortezomib)	1
• Caucasian	13	– Thalidomide, mitoxantrone, 5-FU/LV	1
• Hispanic	1	• Resection	4
Hepatitis status, n		• Radiofrequency ablation	1
• Hepatitis B	1	• Cryotherapy	3
• Hepatitis C	6	• Chemoembolization	3
• Hepatitis B and C	1	• Radiation (bone lesions)	1
• Neither B nor C	6	• None	6
• Unknown	1	Prior malignancies, n	
Other etiologic factors, n		• None	13
• Heavy alcohol history	7	• Basal cell carcinoma	1
• Unknown	3	• Prostate carcinoma	1

ECOG=Eastern Cooperative Oncology Group; 5-FU=5-fluorouracil; LV= leucovorin

tern was multilobar (60%), and nearly all patients (93%) had metastatic HCC. Histologically, 33% of tumors were well differentiated, 33% were moderately differentiated, 13% were poorly differentiated, and 20% did not have the degree of differentiation specified by the pathologist. The most common sites of extrahepatic metastasis were lymph node (n=11), lung (n=5), soft tissue (n=4), adrenal gland (n=2), invading diaphragm (n=1), and bone (n=1). The median CLIP (Cancer of the Liver Italian Program) score⁴² was 2 (range, 0–4). Most patients (8/15) had Okuda⁴³ stage II liver disease. Nearly 33% (4/15) of patients had portal vein thrombosis at baseline.

Treatment and Toxicity

Fifteen patients were treated with octreotide-LAR for a median of 2.0 cycles (range, 0.5–16 cycles; total 55 cycles). Adverse events, regardless of attribution to study drug,

are summarized in Table 3. Treatment was well tolerated and most adverse events were mild. Three patients experienced a total of four grade 3 adverse events: abdominal cramping, elevated creatinine, diarrhea, and dyspnea; only abdominal cramping and diarrhea were deemed secondary to octreotide-LAR. The main reasons for treatment discontinuation were progressive disease (n=14) and toxicity (n=1). Adverse events prompting removal from treatment but most likely unrelated to study drug were grade 3 creatinine elevation (n=1) and death (n=3). Treatment was delayed for 1 patient due to a high TB level.

Response Assessment and Survival

No complete or partial responses occurred and thus the trial was stopped after 15 patients were enrolled. As of April 2006, 3 of 15 patients were alive and median OS was 116 days (range, 27–937 days; Figure 1). Median pro-

Table 2. Baseline Tumor Characteristics for 15 Enrolled Patients

Parameter	n
Tumor dimensions	
• Solitary ≤5 cm	1
• Solitary >5 cm	0
• Multifocal, ≤3 nodules each ≤3 cm	0
• Multifocal, unilobar, >3 cm	5
• Multilobar	9
Unresectable	1
Metastatic	14
Histologic differentiation	
• Well	5
• Moderate	5
• Poorly	2
• Not specified	3
Extrahepatic disease	
• Lung	5
• Bone	1
• Adrenal gland	2
• Lymph node	11
• Soft tissue	4
• Invading diaphragm	1
CLIP score	
• 0	1
• 1	3
• 2	4
• 3	5
• 4	1
• 5	0
Okuda stage	
• I	7
• II	8
• III	0
Portal vein thrombosis	4
Baseline AFP	ng/mL
• Median	294
• Range	2–24,1430

AFP=alpha-fetoprotein; CLIP=Cancer of the Liver Italian Program.

Table 3. All Adverse Events Observed in 15 Patients With Unresectable and Metastatic Hepatocellular Carcinoma Treated With 30 mg of Octreotide-LAR Every 4 Weeks Over 55 Cycles

Adverse Events	Grade			
	1	2	3	4
Abdominal cramping	5	1	1	
Alopecia	1			
Anorexia	3	1		
Biliary stasis	1			
Chills/rigors	1			
Constipation	2			
Cough		1	1	
Creatinine elevated			1	
Depression		1		
Diarrhea	2		1	
Dyspnea			1	
Early satiety	1			
Edema	1	1		
Fatigue		3	2	
Foot pain	1			
Headache			1	
Lightheadedness		2		
Nausea	1	2		
Urinary frequency	1			
Vomiting		1		

gression-free survival (PFS) was 60 days (range, 27–444 days). One patient had stable disease lasting 16 months. Two additional patients had stable disease lasting 5 and 7 months each. Three patients died while on study due to progressive disease unrelated to treatment.

Biochemical Response

Figure 2 shows the IGF-I levels for 13 patients for whom data were available at baseline and cycle 2, day 1. At baseline, the median IGF-I level was 42.2 ng/mL (range, 14.2–109 ng/mL). A significant decrease to a median of 27.9 ng/mL (range, 5.7–71.1 ng/mL) was observed on cycle 2, day 1 (2-sided $P < .006$, Wilcoxon signed rank test). Figure 3 shows data for 10 patients who had IGF-II levels drawn both at baseline and on cycle 2, day 1. The median baseline IGF-II level was 25,000 ng/mL (range,

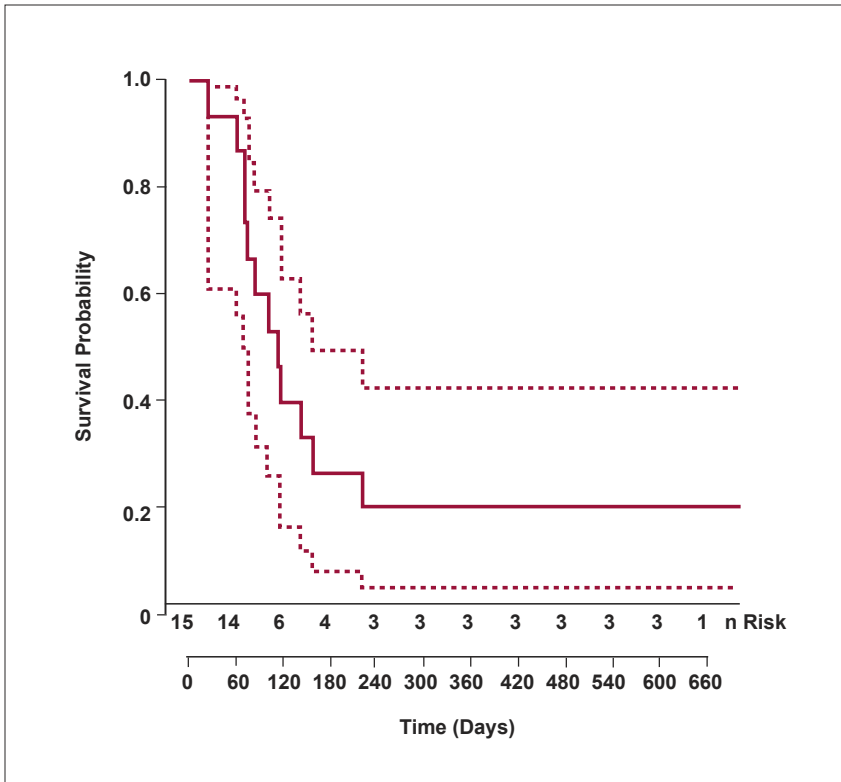


Figure 1. Kaplan-Meier plot of overall survival for 15 patients with unresectable and metastatic hepatocellular carcinoma treated with 30 mg of octreotide-LAR every 4 weeks. The dashed lines show the 95% confidence interval bounds.

nRisk= number at risk.

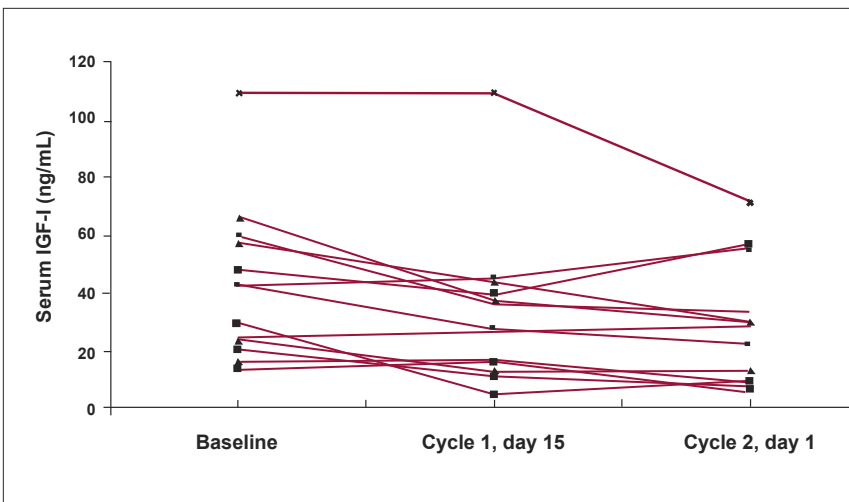


Figure 2. Serum IGF-I levels drawn at baseline and days 15 and 29 of cycle 1 for 13 patients with data available at these time points.

IGF=insulin-like growth factor.

12,400–93,600 ng/mL) and decreased to a median of 18,400 ng/mL (range, 4,061–79,400 ng/mL) on cycle 2, day 1 (2-sided $P < .04$; Wilcoxon signed rank test). Circulating levels of IGF-I and -II were highly correlated for the 10 patients for whom data were available for both growth factors, both at baseline and on cycle 2, day 1 (Spearman $\rho = 0.87$ and 0.92 , respectively; $P < .01$). Overall, there was

no relationship between decreases in IGF-I or -II and clinical response. Figures 4 and 5 demonstrate the serum IGF-I and -II levels, respectively, over 11 cycles for the patient with prolonged stable disease for 16 cycles. In this case, a persistent reduction in IGF-I levels was observed, but with an apparent increase in IGF-II level on cycle 1, day 15, relative to baseline.

Figure 3. Serum IGF-II levels drawn at baseline and days 15 and 29 of cycle 1 for 10 patients with data available at these time points.

IGF=insulin-like growth factor.

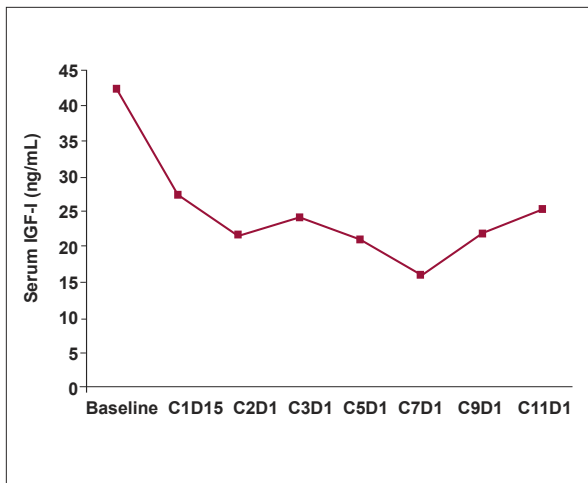
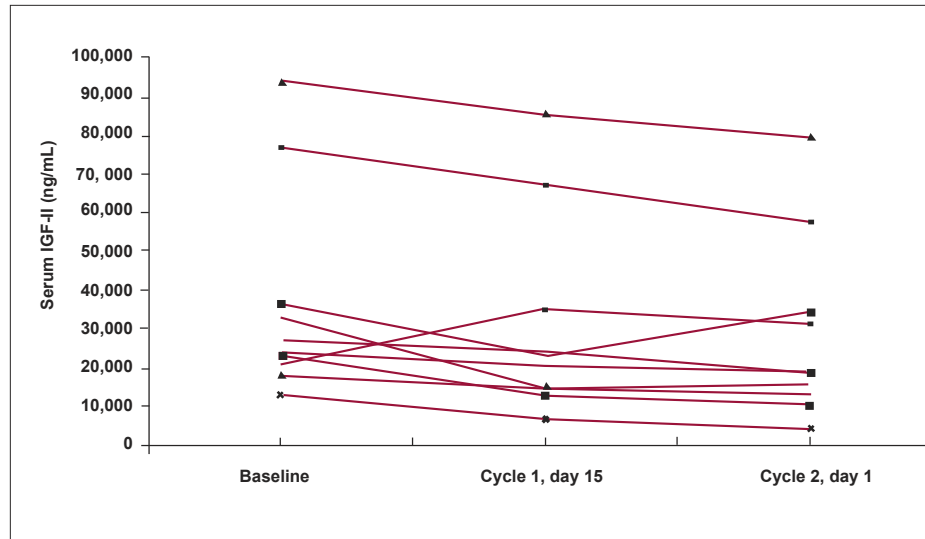


Figure 4. Serum IGF-I level over 11 cycles of treatment with octreotide-LAR in a patient with stable disease over 16 cycles. C=cycle; D=day; IGF=insulin-like growth factor.

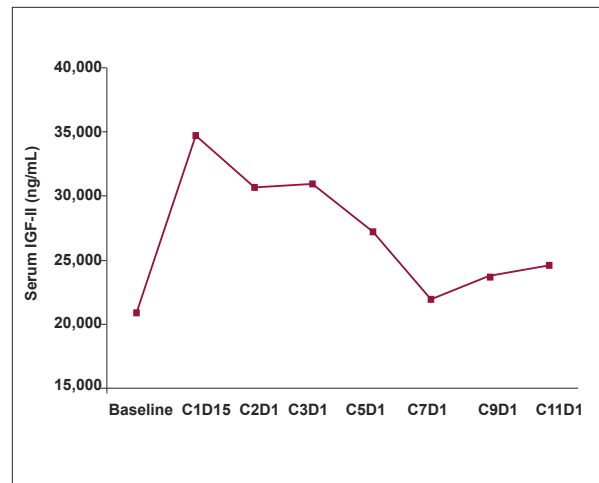


Figure 5. Serum IGF-II level over 11 cycles of treatment with octreotide-LAR in a patient with stable disease over 16 cycles. C=cycle; D=day; IGF=insulin-like growth factor.

There was a significant association between serum IGF-I levels drawn at baseline and PFS and OS ($P=.0005$ and $P=.0173$, respectively; 2-sided log-rank test). Specifically, the median PFS in patients with low baseline serum IGF-I levels (<30 ng/mL, the median value for the 15 patients for whom baseline IGF-I data were available) was 30 days (range, 27–61 days), whereas the median PFS in patients with high baseline serum IGF-I levels (≥ 30 ng/mL) was 116 days (range, 37–444 days). The median OS in patients with low baseline serum IGF-I levels (<30 ng/mL) was 82 days (range, 27–159 days),

whereas the median OS in patients with high baseline serum IGF-I levels (≥ 30 ng/mL) was 222 days (range, 71–937+ days). Figure 6 shows the Kaplan-Meier curves for OS for patients with low versus high baseline serum IGF-I values. There was no significant association between serum IGF-II levels and PFS or OS.

Median baseline AFP was 294 ng/mL (range, 2–241,000 ng/mL), and patients' AFP levels paralleled progression in 12 of 14 patients from whom baseline and later values were obtained.

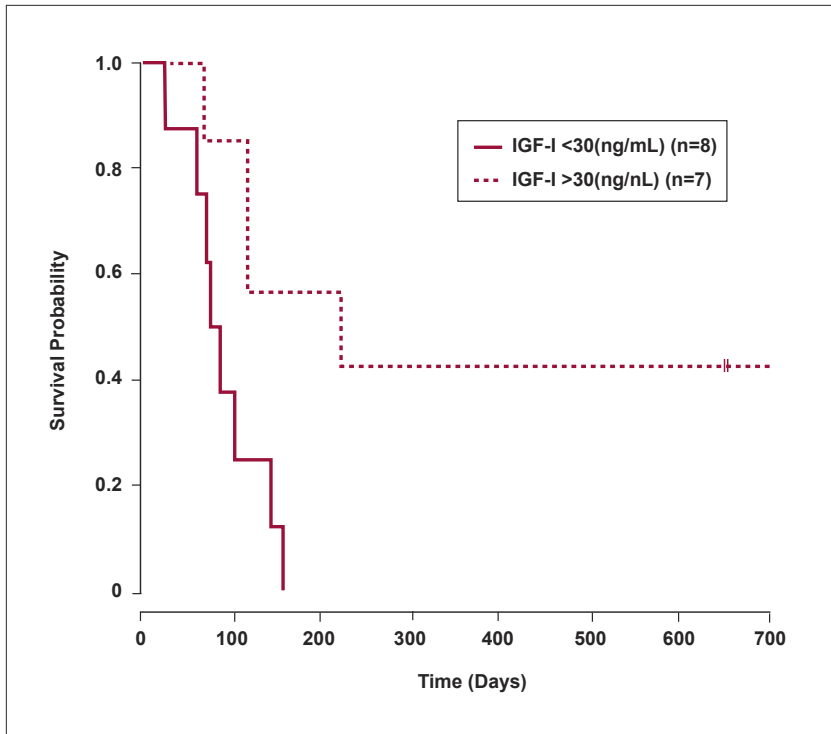


Figure 6. Kaplan-Meier curves for overall survival for patients with low (<30 ng/mL) versus high (>30 ng/mL) baseline serum IGF-I values.

IGF=insulin-like growth factor.

Discussion

A handful of clinical trials have been conducted examining the activity of octreotide in the treatment of HCC, although studies with similar designs have shown conflicting results. There are two important differences between the randomized trials by Kouroumalis³³ and Yuen.³⁴ First, Yuen and colleagues enrolled patients with disease predominately related to hepatitis B virus (HBV) infection (80% vs 21%), whereas Kouroumalis and colleagues enrolled patients with disease predominately related to hepatitis C virus (HCV) infection (2.8 vs 54%). Although patients with HCV have a higher incidence of HCC,⁴⁴ patients with HBV-associated HCC have a worse prognosis⁴⁵⁻⁴⁶ and more aggressive disease,⁴⁷ suggesting that differences in etiology may have an impact on the observed results. The second difference between the two trials is the number of patients randomized to the treatment arm not receiving therapy. In the Yuen trial, 37.1% (13/35) of patients assigned to octreotide-LAR did not receive therapy, in contrast to 14.3% (4/28) enrolled on the Kouroumalis trial. This difference may have affected survival in the Yuen trial; however, early deaths in the control arm are not reported, hampering conclusions. In addition, efficacy inequalities may be at least in part attributable to differences in short- versus long-acting octreotide. Furthermore, a recently published random-

ized, placebo-controlled study by Becker and associates showed no survival benefit for octreotide in untreated HCC.³⁵ Nonrandomized trials by Dimitroulopoulos and colleagues³⁶ and Lersch and colleagues,³⁷ which similarly preselected patients for treatment if their tumors were positive on scintigraphy, produced contradictory results. The inconsistent results for the use of octreotide in HCC and the relative dearth of effective treatments for this disease as a whole remind researchers of our incomplete understanding of its pathogenesis.

To our knowledge, this clinical trial is the first to evaluate the suppression of IGF-I as a primary endpoint during use of octreotide-LAR in the treatment of HCC. The present study failed to demonstrate the clinical activity of octreotide-LAR for 15 patients with unresectable and metastatic HCC, prompting early closure of the trial. As expected, lowering of IGF-I and IGF-II serum levels occurred with treatment; however, this suppression did not correlate with clinical activity as hypothesized. One patient experienced stable disease for 16 cycles and is alive 937 days since study entry at the time of writing.

Our finding of a lack of a survival benefit and progressive disease occurring during suppression of IGF-I on octreotide is similar to the observations of Treiber and coauthors,⁴⁸ who measured biomarkers, including serum IGF-I, at baseline and during treatment with octreotide. Additionally, these investigators correlated an elevated

baseline serum IGF-I level (as well as a low baseline serum vascular endothelial growth factor A level) with better prognosis (ie, PFS and OS). In contrast to our study, Treiber and coauthors performed biomarker analysis on data pooled from patients receiving either octreotide alone or octreotide and rofecoxib, although there was no difference in biomarkers and PFS/OS between groups. We also observed that our patients who had higher serum IGF-I levels at baseline had a longer PFS and OS. It would be interesting to know whether patients with HCC in a placebo arm with higher serum IGF-I levels would show similar results. However, taken together, these data are hypothesis-generating in that they strengthen the suggestion that IGF-I may play a role in the pathogenesis of HCC and that further research is required to completely understand this role.

Preclinical data suggest that GH plays a role in the development of HCC⁷⁻¹² and that octreotide has activity in this cancer.^{24,29-31} As in prior research in treating acromegaly with octreotide, we demonstrated that octreotide reduces levels of IGF,^{49,50} a clinical surrogate of GH. Why, then, were no responses seen here?

There are several possible explanations for why we did not see a response with octreotide. First, if GH plays a role in HCC, perhaps it is either not as critical as hypothesized—this dose and schedule of octreotide did not reduce GH secretion sufficiently to modulate HCC growth in these patients—or octreotide does play an important role but treatment with this agent triggers compensatory mechanisms not studied in this trial, which overcome GH suppression and ensure tumor survival. Secondly, *in vitro*^{51,52} and *in vivo*⁵³ models suggest that angiogenesis, one probable target of octreotide,^{30,31} is an important process for HCC survival. We know that hypoxia subsequent to chemoembolization of HCC⁵⁴ can stimulate angiogenesis,^{55,56} which may, in part, be a cause for treatment failures involving systemic, nonablative therapies such as octreotide. A third possible explanation for lack of efficacy with octreotide-LAR is that GH may aid in initiation of hepatocarcinogenesis but does not, in humans, drive propagation or metastasis, accounting for its lack of efficacy in a patient population already afflicted with this disease. Fourth, somatostatin receptor status may help justify treatment failures and successes.^{33,38,57} In this study, somatostatin receptor analysis was not required for enrollment nor was it studied. Fifth, it is also possible that suppression of GH causes growth arrest and subsequent stable disease; therefore, partial response may not be the most important endpoint for such a therapy. Sixth, given the complexity of HCC and the generally mild side effect profile of octreotide, perhaps octreotide would have greater efficacy in combination with an active agent with multiple targets such as sorafenib (Nexavar,

Bayer/Onyx).⁵⁸ Lastly, accrual to this study was limited and the study lacked power so we are unable to conclude that a lack of efficacy translates into inactivity of octreotide-LAR in this cancer or that GH does not play a role in the pathogenesis of HCC. At the outset, the design and correlative investigations of this trial were not built to answer these questions.

There are examples reported within trials^{38,59} and case reports⁶⁰⁻⁶² of responses and prolonged stabilization of disease with octreotide in HCC. In our trial, 1 patient had stable disease for 16 cycles. Did this patient benefit from octreotide-LAR or does he have slow-moving, nonaggressive HCC that would have taken the same path whether or not he was treated with this drug? These cases urge clinicians to conceptualize each individual's HCC as a distinct but related cancer, each with its own genotype that determines its repertoire of malignant survival skills. Reports involving cDNA microarray analysis⁶³⁻⁶⁶ and proteome analysis^{67,68} and their role in defining prognosis in HCC add insight in this sense and are critical steps in shedding light on what we should be targeting.

Advanced HCC has a poor prognosis given its resistance to local and systemic therapies. This trial did not demonstrate a survival benefit or radiographic response despite suppression of IGF-I and -II with octreotide-LAR in patients with unresectable and metastatic HCC. More research is required regarding initiation, propagation, and metastasis of HCC to understand the variables that make some, but not other, patients' HCC more sensitive to octreotide and to elucidate novel approaches to treating cases that are not responsive to this agent.

Acknowledgments

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