

Long-Acting Octreotide Versus Placebo for Treatment of Advanced HCC: A Randomized Controlled Double-Blind Study

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Although numerous treatment modalities have been explored in patients with advanced HCC, the therapeutic options are still limited. Somatostatin has been shown to have anti-mitotic activity in endocrine as well as in a variety of nonendocrine tumors. Expression of somatostatin receptors is found in HCCs, but the efficacy of the somatostatin analogue octreotide remains controversial. Therefore, a randomized double-blind placebo-controlled multicenter trial was performed to assess the efficacy of long-acting octreotide for the treatment of advanced HCC. One hundred twenty untreated patients with histologically confirmed HCC were randomized to receive either long-acting octreotide (Sandostation LAR 30 mg) intramuscularly every 4 weeks or placebo. The study groups were comparable with respect to clinical characteristics. There was no difference in the cumulative survival. The median survival time was 4.7 months in the octreotide group compared with 5.3 months in the control group. Six-month survival rates were 41% for octreotide patients and 42% for control patients, respectively. The unadjusted relative risk for mortality in the octreotide group compared with patients in the control group was 1.11 (95% CI 0.76-1.63; $P = 0.59$). When adjusted for Okuda, CTP, and Cancer of the Liver Italian Program (CLIP) scores, the relative risk for octreotide did not change markedly and was 1.05 (95% CI 0.71-1.55; $P = 0.83$). The CLIP score seems to predict survival better than both Okuda and CTP score. **Conclusion:** The randomized controlled double-blind HECTOR trial showed no survival benefit for HCC patients treated with long-acting octreotide compared with placebo. (HEPATOLOGY 2007;45:9-15.)

HCC is one of the major malignancies worldwide. High incidence areas include Eastern Asia, Central Africa, and some countries of Western Africa.¹ Recent studies have shown an increasing incidence in developed countries as well.² Liver transplantation or resection are the only potentially curative therapies. Due

to advanced or decompensated cirrhosis, comorbidity, and multicentricity of the HCC, lesions in 70%-80% of patients are inoperable at the time of diagnosis.³ Therefore, several local ablation methods have been developed as minimally invasive strategies for HCC treatment, including transarterial chemoembolization, percutaneous ethanol injection, and radiofrequency thermal ablation.⁴ However, these therapies are not suitable for patients with advanced, large, or multicentric HCC, leaving systemic treatment as the only option. Systemic HCC therapy trials including intravenous chemotherapy or antioestrogenic drugs have been disappointing, however.⁵

In a recent study of 58 patients, Kouroumalis et al.⁶ reported significant improvement in survival in HCC patients treated with short-acting octreotide (analogue of the cyclic peptide hormone somatostatin [250 µg subcutaneously, twice daily]) compared with best supportive care (median survival 13 mo and 4 mo, respectively; $P = 0.002$). Stimulated by these results and the fact that there is no established systemic HCC treatment available, we

Abbreviations: CLIP, Cancer of the Liver Italian Program; HECTOR, *HE*patocellular *C*arcinoma: *T*reatment with *O*ctReotide.

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conducted the multicenter HECTOR (HEpatocellular Carcinoma: Treatment with OctReotide) trial. In the study by Kouroumalis et al., the need to give octreotide subcutaneously at least twice daily was associated with significant morbidity. Therefore, we used the recently introduced long-acting formula of octreotide, Sandostatin LAR, which is given once a month intramuscularly. The aim of the randomized placebo-controlled double-blind HECTOR trial was to evaluate whether treatment with long-acting octreotide improves survival of HCC patients who are not eligible for surgery or local intervention.

Patients and Methods

Patient Characteristics and Study Design. The study was performed as a multicenter randomized controlled double-blind study comparing treatment with long-acting octreotide and placebo. To be able to detect a 6-month survival improvement from 35% to 55% in a 2-sided test with a significance level of 5% and a power of 80%, we calculated a sample size of at least 108 patients. To allow a dropout rate of 10%, we decided to include 120 patients. Participants were recruited from seven centers in Germany and Switzerland (see Acknowledgment). Inclusion criteria were: previously untreated patients with histologically confirmed HCC and no indication for surgery or any local treatment. There was no age limit. Exclusion criteria were: second malignancy, any local or systemic pretreatment (i.e., chemotherapy or treatment with tamoxifen), first diagnosis of HCC >6 months before inclusion, tumor stage Okuda III (after February 2000, as declared by amendment), symptomatic cholelithiasis, contraindications for intramuscular injection, and known allergic reactions to octreotide. All participants provided written informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of University Hospital Freiburg and also the ethics committee of each participating center. The study was conducted according to the guidelines of Good Clinical Practice. One blinded interim analysis according to the alpha spending function approach of Lan-DeMets using O'Brien-Fleming type sequential boundaries with a nominal significance level of $P = 0.003$ was planned in advance after the death of 50 participants. Twenty-four months were planned as period of recruitment. After inclusion of the last patient, a follow-up period of 12 months was scheduled.

Therapeutic Procedures. Using external blockwise randomization performed centrally via fax, patients were assigned to monthly intramuscular injection with 30 mg octreotide (Sandostatin LAR; Novartis-Pharma, Nürn-

berg, Germany) or placebo. Study medication was either 30 mg octreotide dissolved in 2 mL NaCl (verum) or 2 mL NaCl (placebo). The study medication was injected by a trained study nurse or a medical doctor. Patients as well as investigators were blinded in all centers. Study medication (verum and placebo) was coded and labeled to guarantee blinding. Drug accountability procedures and reporting of all adverse events and serious adverse events was performed. Source data verification was also performed; 100% source data verification (checkup of all data) was performed for inclusion and exclusion criteria, informed consent, release and return of study medication, adverse events and serious adverse events, date of birth, and initials, and 20% source data verification (review of random samples) was performed for laboratory results and comedication. Trial monitoring following established written standard operating procedures was performed by trained monitors.

Follow-Up. The primary end point of the study was death of any cause. Secondary end points were side effects, cost, safety, compliance, and quality of life. Patients were seen on an outpatient basis every 4 weeks $\pm$ 14 days for monthly injection of study medication. In addition, patients had routine follow-up examinations at month 1, 3, and 6, and every 6 months thereafter. Routine follow-up included clinical examination, Karnofsky score determination, serum alpha-fetoprotein and HbA1c determination, abdominal ultrasonographic examination, and quality of life questionnaire (EORTC QLQ 30). Chest X-ray and abdominal CT were performed $\pm$ 14 days before treatment to assess extrahepatic metastases. After inclusion of the last patient, a follow-up period of at least 1 year was scheduled.

Statistical Analysis. Baseline data are presented as the mean $\pm$ SD for quantitative variables and as absolute and relative frequencies for qualitative variables. Prognostic relevance of treatment and clinical patient characteristics on survival was assessed via Cox's proportional hazards regression model for univariate and multivariate analysis. Survival probabilities within treatment groups were estimated via the Kaplan-Maier method. All significance tests were 2-sided, and a P value of less than 0.05 was considered statistically significant—except for the final analysis of the primary end point, for which a nominal significance level of 0.049 was used to adjust for the preplanned interim analysis. Data processing and analysis were performed using SAS software (SAS Institute, Cary, NC).

Results

One hundred twenty patients were enrolled in the study between October 1999 and February 2002 and randomly assigned to the octreotide group ($n = 61$) or the

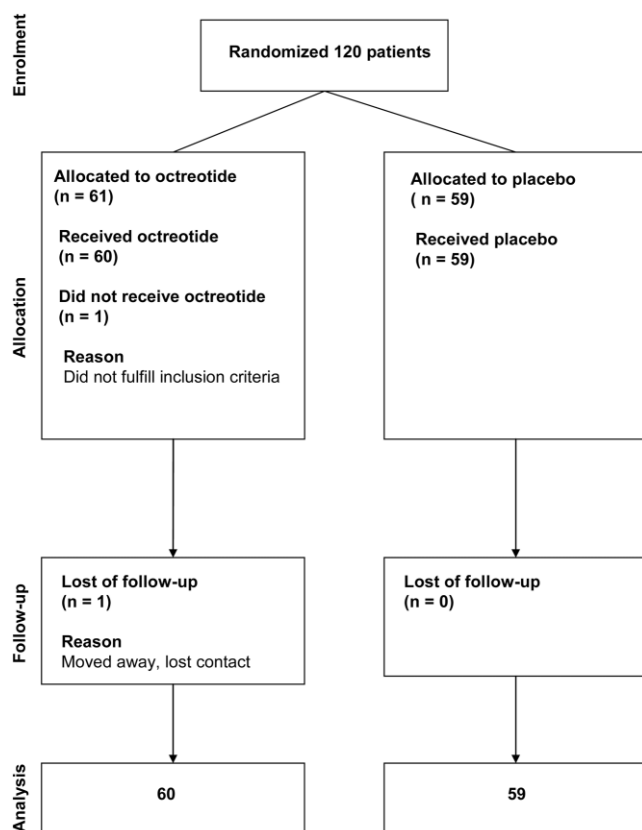


Fig. 1. Flowchart of study patients.

placebo group ($n = 59$). One patient was excluded after randomization because control of the source data revealed that the histopathological diagnosis was not HCC but liver metastasis of unknown origin. The remaining 119 patients (octreotide, $n = 60$; placebo, $n = 59$) received the allocated intervention. An intention to treat analysis was performed for 119 patients (Fig. 1). As planned in advance, a blinded interim analysis was performed after the death of 50 patients. Unblinding or untimely termination after interim analysis was not necessary. As scheduled, the follow-up period was 12 months after inclusion of the last patient. The median follow-up was $30.2 (\pm 8.6)$ months in the octreotide group and $32.5 (\pm 7.5)$ months in the placebo group.

Both groups were well balanced with respect to baseline characteristics (Table 1).

Survival. At the time of final analysis and a mean follow-up time of 32 ± 8 months, 54 patients in the octreotide group and 52 patients in the control group had died. The median survival time was 4.7 months in the octreotide group compared with 5.3 months in the control group. Six-month survival rates were 41% for patients in the octreotide group and 42% for patients in the control group (Fig. 2).

Table 1. Baseline Characteristics of Control Group and Octreotide Group

Baseline Characteristics (n = 119)	Placebo (n = 59)	Octreotide (n = 60)
Median age (yr)*	67.1 $\pm$ 8.9	65.1 $\pm$ 8.8
Karnofsky index (%)*	79.1 $\pm$ 9.87	81.0 $\pm$ 11.8
Male (%)	85	92
Diabetes mellitus (%)	37	32
Cirrhosis (%) (n = 114)	91	95
Alcohol (%)	52	55
Hepatitis B (%)	10	16
Hepatitis C (%)	16	18
Hemochromatosis (%)	6	2
Other/unknown etiology (%)	16	9
CTP class A:B:C (%)	53:37:10	53:35:12
Okuda stage I:II:III (%)	32:58:10	30:65:5
CLIP score 0/1/2/3/4-6 (%)	3/14/29/19/32	7/15/15/28/30
AFP (n = 115)		
<400 ng/mL (%)	61	49
≥ 400 ng/mL (%)	39	51
Portal vein thrombosis (n = 118)		
None (%)	56	46
Partial (%)	29	34
Complete (%)	15	20
Number of lesions (n = 118)*	2.2 $\pm$ 1.4	2.6 $\pm$ 2.0
Diameter (cm)*	7.4 $\pm$ 4.0	7.6 $\pm$ 3.5
Growth: diffuse/single/multicentric (%) (n = 118)	51/21/28	48/18/33
Histology: good/moderate/poor (%) (n = 113)	33/52/15	27/59/14
Lung metastases (%) (n = 118)	11	8

NOTE. There were no significant differences between groups. *Mean $\pm$ SD.

The unadjusted relative risk for mortality of patients in the octreotide group versus patients in the control group was 1.11 (95% CI 0.76-1.63; $P = 0.59$). When adjusted for Okuda, CTP, and Cancer of the Liver Italian Program (CLIP) score, the relative risk in the octreotide group did not change markedly and was 1.05 (95% CI 0.71-1.55; $P = 0.83$) (Table 2). Furthermore, Table 2 shows that the CLIP score is superior to both the Okuda score and CTP score in predicting survival.

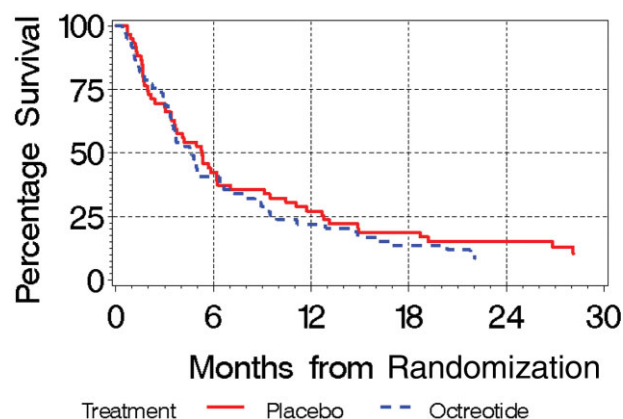
Fig. 2. Cumulative patient survival (P value not significant).

Table 2. Relative Mortality Risk

Variable	Univariate Analysis			Multivariate Analysis		
	Relative Risk	95% CI	P Value	Relative Risk	95% CI	P Value
Octreotide treatment	1.112	0.759-1.628	0.586	1.045	0.705-1.548	0.826
Okuda stage I vs. stages II + III	0.398	0.257-0.618	<0.0001	0.723	0.432-1.212	0.219
CTP class A vs. classes B + C	0.397	0.269-0.587	<0.0001	0.609	0.386-0.959	0.032
CLIP vs. next higher category	0.624	0.518-0.751	<0.0001	0.716	0.583-0.879	0.0014

Tumor Response. One lesion was identified as a target lesion and measured via ultrasonography at baseline. All other lesions or sites of disease were identified as nontarget lesions. Target lesions were measured at baseline and at months 1, 3, and 6, and every 6 months thereafter. The overall response was determined by assessing the target lesions and/or identification of progressive disease. A complete response was defined as disappearance of all lesions. A partial response was defined as $\geq 50\%$ decrease of the longest diameter of the target lesion. Stable disease was defined as decrease of $< 50\%$ or a $< 25\%$ increase and no new lesions. Progressive disease was defined as a $\geq 25\%$ increase of the longest diameter of target lesion or the appearance of one or more new lesions. Tumor regression did not occur in any patient. With respect to stable disease or progressive disease, there was no statistically significant difference between the placebo and the octreotide group.

Compliance and Side Effects. Treatment compliance was not statistically significant between groups. Compliance with treatment was 81% in the octreotide group and 82% in the placebo group, respectively (Table 3).

According to Good Clinical Practice standards, all adverse events in the study had to be reported and analyzed and were categorized as an adverse event or a serious adverse event.

Three hundred thirty adverse events were reported—169 in the placebo group and 161 in the octreotide group (Table 4). The most common side effect was diarrhea, a known side effect of octreotide. In the octreotide group, 13/60 patients suffered from diarrhea (which subsided on continuation of treatment) compared with 7/59 patients treated with placebo ($P = 0.220$ [Fisher exact test]). Hyperbilirubinemia was observed in 3 patients in both groups, respectively, and was probably due to liver failure. Sludge in the gall bladder was observed in 1 patient. Serious adverse events occurred in 25 patients in the placebo group and in 16 patients in the octreotide group. Unblinding was necessary in 1 patient because of severe hypoglycemia. Detailed analysis of the source data showed that only 3 serious adverse events were possibly related to octreotide; 1 of these patients died because of sudden bradycardia resulting in asystolia. Cardiac arrhythmia is

not a known side effect of octreotide. Because of ascites, the patient was treated with diuretics that could have caused either hypokalemia or hyperkalemia. Blood tests were not performed—neither was an autopsy performed. However, a relationship to the study medication cannot be excluded, though it is unlikely. One patient suffered from significant hyperglycemia, and another patient suffered from significant hypoglycemia after injection of octreotide. Fluctuations in blood glucose level are a known side effect of octreotide treatment. Therefore, both serious adverse events are likely to be related to octreotide. In summary, treatment with octreotide was well tolerated by most patients.

Quality of Life. Quality of life was assessed by means of the EORTC QLQ-C30 at baseline and at month 1, 3, 6, and every 3 months thereafter. We did not observe significant differences of any of the 15 subdomains at any time.

Discussion

This is the first randomized controlled trial that analyzed the effect of long-acting octreotide on HCC growth and patient survival. We observed no survival improvement in HCC patients treated with octreotide compared with placebo-treated patients (median survival 4.7 versus 5.3 mo, respectively). Furthermore, the study showed no objective tumor regression on ultrasonographic examination or serum alpha-fetoprotein reduction in patients treated with octreotide.

Kouroumalis et al.⁶ described a significant survival benefit in HCC patients treated with octreotide versus best supportive care (median survival 13 months and 4 months, respectively; $P = 0.002$). Yuen et al.⁷ performed a smaller randomized trial that was limited to patients with advanced HCC and did not find a significant survival benefit for patients treated with octreotide. This study is characterized by a high proportion of patients with advanced HCC (CLIP score > 4 : 54% in the octreotide group, 66% in the control group).⁸ The median survival in both groups was only 2 months, and the majority (21/35 patients) of the treated patients received no injection or only one injection of long-acting octreotide.⁹

Table 3. Number of Injections and Treatment Compliance (% of Optimal Dosis)

Number of Applied Injections	Placebo (n = 59)	Octreotide (n = 60)
0	0 (0%)	1 (2%)
1-3	23 (39%)	25 (42%)
4-6	16 (27%)	16 (27%)
7-35	20 (34%)	18 (30%)
% Compliance with treatment scheduled	81.8 ± 24.7	80.9 ± 29.4

Therefore, it was suggested that patients at stage D of Barcelona classification¹⁰ or patients with a CLIP score¹¹ >5 should be excluded.⁹

There are some important differences between the studies of Kouroumalis et al.,⁶ Yuen et al.,⁷ and our HECTOR trial. First, compared with earlier studies, the HECTOR trial had a lower proportion of HCC patients with advanced tumor stage (Okuda stage III: Kouroumalis et al., 52%; Yuen et al., 17.1%; HECTOR trial, 7.5%; CLIP score >4: Yuen et al., 60%; HECTOR trial, 30%). (CLIP score was not mentioned in Kouroumalis et al. study.) Furthermore, the HECTOR trial had the lowest proportion of patients with distant metastasis compared with the earlier studies (Table 1). The percentage of patients with portal vein infiltration or thrombosis, an important negative predictor of survival,¹² was slightly lower in the HECTOR trial compared with the Yuen et al. study (Yuen et al., 55%; HECTOR trial, 49%). Second, regarding liver function, which is also a strong predictor of survival, approximately 90% of our patients had a compensated liver function (CTP class A or B) which was comparable to the Yuen et al. study (95%) but

was significantly higher than that of the Kouroumalis et al. study (45%). Third, the major etiological factors were different in all 3 trials. In our study, approximately 50% of chronic liver disease was due to alcohol; in the Kouroumalis et al. study, 50% of patients had chronic HCV infection; and in the Yuen et al. study, more than 80% of patients had chronic HBV infection reflecting geographic differences. Because of the differences in the study population regarding etiology, liver function, and tumor stage, it is impossible to compare the different studies with respect to survival.

To our knowledge, the HECTOR trial is the first study investigating the efficacy of octreotide in a placebo-controlled double-blind design. In the studies by Kouroumalis et al.⁶ and Yuen et al.,⁷ the control group did not receive a placebo, and there was no blinding of patients or care providers. A study by Dimitroulopoulos et al.¹³ and a recently published study by Gill et al.¹⁴ also investigated the role of long-acting octreotide, but in these studies again the control group consisted of patients receiving no treatment. A study conducted by Samonakis et al.¹⁵ compared patients treated with long-acting somatostatin to historical control groups. A recent study by Plentz et al.¹⁶ investigated the efficacy of octreotide without a control group, and Rabe et al.¹⁷ retrospectively analyzed a cohort of 63 HCC patients treated with octreotide. However, placebo effects being observed whenever the patient and the clinician perceive a treatment as effective are often much greater than the widely accepted figure of 30% and can lead to erroneous claims of efficacy as pointed out by Eddy.¹⁸ Blinding of patients and care providers prevents performance bias and also minimizes differences in pla-

Table 4. Serious Adverse Events and Maximally Achieved Toxicity

World Health Organization Class	Placebo (n = 59)				Octreotide (n = 60)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Decreased hemoglobin	1	1		1		2		3
Bleeding			1	6			1	3
Hyperbilirubinemia		2		1		1	1	1
Elevated alkaline phosphatase	1							
Oral affection	1							
Diarrhea	4	3				10	3	
Nausea and vomiting	4				3		1	
Elevated urea or creatine	1				1		1	
Pulmonal affections	1				1	2		
Fever	1	2						
Skin affections	1					1		
Hair loss					1			
Infection				1		1	2	
Cardial				1				
Consciousness	2			1	3		1	
Constipation					1			
Pain	4	6			4	4	3	
Other	105	17			95	11		

NOTE. Classification of toxicity was determined according to World Health Organization toxicity grading criteria.²⁴

cebo responses between comparison groups. Therefore, an intervention, especially in a drug trial, should ideally be placebo-controlled as in the placebo-controlled double-blind design of our HECTOR trial. Slijkhuis et al.¹⁹ recently investigated long-acting octreotide in 24 patients in an open-label study without control group. They found a median survival of the treated patients of 5.1 months. Our findings (median survival 4.7 months in patients treated by octreotide, 5.3 months in the control group, respectively) do confirm these results. By contrast, Kouroumalis et al.⁶ found a median survival of 13 months in patients receiving octreotide versus 4 months in untreated patients. Two other small trials from Greece also found a survival benefit in patients treated with octreotide. Dimitroulopoulos et al. demonstrated a median survival of 7.8 months in the octreotide group compared to 4 months in the untreated group.¹³ Samonakis et al.¹⁵ found a median survival of 15 months in patients with advanced HCC treated with long acting octreotide as compared to a median survival of 8 months in a historical control group of untreated patients. A major limitation of these 3 Greek studies is that they did not address patient characteristics including CLIP score,¹¹ portal vein thrombosis, or presence or absence of extrahepatic disease. Therefore, an imbalance between the treatment arms cannot be excluded,¹⁹ especially if the control arm consists of a historical control group as in the study by Samonakis et al.¹⁵ or of patients unable to receive treatment as in the study by Dimitroulopoulos et al.¹³ As Slijkhuis et al.¹⁹ pointed out, patient selection is critical in any HCC treatment study. There are many prognostic variables that determine the individual natural course. This may explain the obvious discrepancy of the results.

Approximately 40% of HCCs express somatostatin receptors.²⁰ Compared with neuroendocrine tumors, the receptor density of HCCs is low, and no correlation has been found to the histological HCC subtype or grading. Furthermore, it has been found that HCC predominantly expresses somatostatin receptor subtype 2.^{20,21} Octreotide has a high affinity for somatostatin receptor subtypes 2 and 5.²² The lack of octreotide efficacy could be due to low or missing expression of somatostatin receptors in HCC. Nevertheless, we could have expected a clinical response in at least a subgroup of patients with somatostatin receptor expression if the effect was mediated via somatostatin receptors. The mechanism of the antimitotic activity of octreotide was not explored in this trial, but a direct effect seems to be unlikely. An alternative indirect mechanism could be mediated by suppression of tumor trophic hormones (e.g., insulin or insulin-like growth factor 1).²³ Our negative results, however, suggest that either

the effect of octreotide in this subset is negligible or this subgroup of patients is very small.

In the studies by Kouroumalis et al.⁶ and Samonakis et al.,¹⁵ a survival benefit from octreotide treatment could be demonstrated only after at least 6 months of treatment. In our study, 42% of patients received 1 to 3 octreotide injections and 30% received more than 7 injections (Table 3). We investigated the effect of octreotide in patients with advanced HCC and found that 80% of patients had either diffuse or multiple lesions and 54% had partial or complete portal vein thrombosis (Table 1). The clinical effectiveness of somatostatin analogues in patients with early stages of HCC who can be treated over a longer period by octreotide alone or in combination with local therapies (e.g., radiofrequency thermal ablation or percutaneous ethanol injection) has not yet been investigated.

In conclusion, our placebo-controlled randomized double-blind study showed no survival benefit for patients with advanced HCC treated with long-acting octreotide.

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