

Octreotide in the treatment of inoperable hepatocellular carcinoma

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SUMMARY

Background & Aims: The progression and therapy of hepatocellular carcinoma (HCC) may be influenced by somatostatin-receptors in HCC cells. This has offered the rationale for evaluating the therapeutic usefulness of octreotide in patients with HCC. The aim of this study was to assess the clinical and biochemical impact of octreotide administration in patients with HCC.

Method: Thirty patients with HCC, who were unsuitable for surgery, ethanol injection or transarterial embolization were divided into two groups (A and B) according to the presence or not of cirrhosis. All patients received 500µg octreotide subcutaneously twice daily indefinitely.

Results: Mean survival time was 5±1.3 months in group A and 8.3±0.96 months in group B, with significant differences between the two groups (log rank test, p=0.03). Cirrhotic patients with Okuda I+II stage had a longer survival time in comparison to patients with Okuda III stage (log rank test, p=0.04). Moreover, octreotide administration stopped gradual elevation of α-fetoprotein (AFP) levels.

Conclusions: Octreotide seems to improve the survival time in non-cirrhotic patients with HCC and especially in patients with Okuda II stage with no elevation of AFP, offering acceptable quality of life, safety and tolerance.

INTRODUCTION

Tumours of the liver are encountered frequently in clinical practice and this varies according to geographic region and age group. Hepatocellular carcinoma (HCC)

is one of the most common malignancies worldwide.¹ It ranks as the seventh most common cancer in men and the ninth in women. The estimated worldwide incidence is 1 million per year, with mortality of more than 250.000 per year.² In Greece, the annual death rate has been estimated to be 10-23 per 100.000 population per year.³

Therapeutic decisions must take into account tumour stage and functional liver reserve, because most HCCs develop in cirrhotic livers. Resection and transplantation, as well as ethanol injection for small tumours, are the only potentially curative treatment possibilities. Unfortunately, only a small proportion of patients diagnosed with HCC have resectable tumours, therefore more than 80% of patients are inoperable.⁴

For those individuals with localized but unresectable HCC, local ablative therapies may be used like percutaneous ethanol injection therapy, and chemoembolization. The use of chemotherapy, either systemic or administered locally, is of limited value in HCC. Single drug systemic chemotherapy has no effect on HCC, while some combinations appear to cause a partial response.⁵ Moreover, estrogen and androgen receptors have been found to varying degrees in the tumour itself and the surrounding parenchyma,⁶ but studies on treatment with tamoxifen cyproterone acetate, ketoconazole and flutamide showed no significant effect on tumour growth or survival.^{7,8}

Octreotide is a synthetic octapeptide that has a biologic profile similar to endogenous somatostatin. Clinical trials of octreotide for the treatment of liver tumours are limited and mostly uncontrolled. This drug has been used as palliative treatment of metastatic carcinoids of the liver and it seems to have a beneficial effect on symptomatic and biochemical response of endocrine tumours.^{9,10} Furthermore, recent studies show that somatostatin receptors are frequently expressed in human HCC cells.¹⁶

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The aim of this study was to evaluate the clinical and biochemical efficacy of octreotide in the treatment of HCC.

PATIENTS AND METHODS

Between 1997 and 1999, thirty patients (M=22, F=8, mean age =63, range =53-74 years) with HCC were evaluated and considered eligible for the trial.

The inclusion criteria were hepatocellular carcinoma confirmed by liver biopsy and/or increased levels of AFP. Ultrasonography and dynamic computed tomography established the tumour stage. Moreover, the study included patients with HCC who had not been previously treated and who were not suitable for surgical resection, liver transplantation, and percutaneous ethanol injection or transarterial embolization.

Exclusion criteria were: decompensated liver disease (ie: gastrointestinal bleeding, ascites, encephalopathy), diabetes mellitus, allergic reaction to octreotide or extra hepatic metastases.

The degree of hepatic dysfunction was graded according to the criteria of Child-Pough and all patients were classified according to Okuda staging.¹¹

The thirty patients satisfying the entry requirements were divided into two groups (group A and group B) according to the presence or not of cirrhosis. All patients received 500 µg of octreotide subcutaneously twice daily.

During the trial all patients were monitored at least every month in the outpatient clinic by means of clinical examination and biochemistry. In addition to conventional clinical and biochemical parameters, recorded data included the classification of patients according to the Child-Pough and Okuda score.

The appearance of symptoms or side effects caused by octreotide administration was screened at each visit. The criteria used to define the efficacy of octreotide were: improvement in biochemical tests, AFP concentration values, survival time and quality of life status. The duration of the study was seventeenth months, whether the patients had died or were alive at the end of this period.

The baseline characteristics of patients are expressed as mean, median and range. Qualitative variables were compared by means of the Fisher's exact test. Survival was plotted using the Kaplan-Meier method and the Log-Rank test was used to assess differences in outcome between the two groups.

RESULTS

Twenty patients with cirrhosis were included in group A and 10 patients without cirrhosis in group B. Table 1 shows the baseline characteristics of the patients.

The side effects during octreotide treatment were minor and the drug was well tolerated. Only four patients dropped out of the study. Three (group A:1 and group B:2) developed mild diarrhea, abdominal pain, bloating and vomiting during the first month of treatment. Another patient, in group B dropped out voluntarily.

In only 2 patients from group A and two from group B, did the concentration of AFP decrease markedly compared to the initial value. Figure 1 shows the logarithm values of AFP before and at the end of therapy for each patient. No significant differences were observed (Fisher's exact test, p=0.51).

The mean survival time was 5.1 ± 1.3 , range: 1-17 months for the cirrhotic patients and 8.3 ± 0.86 , range: 2-10 months for the non-cirrhotic patients. At the end of the trial twenty-one patients had died (16 patients from group A and 5 patients from group B). The causes of death are shown in table 2. Five patients were alive at the end of the trial (group A: 3 and group B: 2).

The survival time difference between the two groups

Table 1. Baseline Characteristics of HCC Patients

	Group A Cirrhosis (n=20)	Group B no cirrhosis (n=10)
Age(ys)	62(52-74)	64(53-71)
Sex(M/F)	17/3	5/5
<i>Etiology of HCC</i>		
Hepatitis B	11	5
Hepatitis C	2	3
Hepatitis B+C	4	1
Alcohol	3	2
<i>AFP</i>		
<100ng/ml	8	4
>100ng/ml	12	6
<i>Child-Pugh's</i>		
A	7	-
B	5	-
C	8	-
<i>Okuda stage</i>		
I+II	16	9
III	4	1

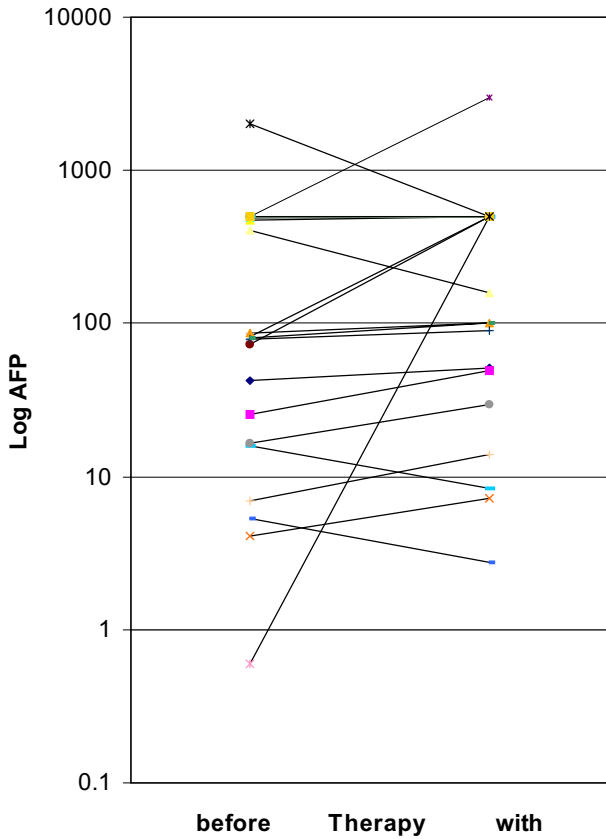


Figure 1. AFP concentration in all patients

Table 2. Causes of death

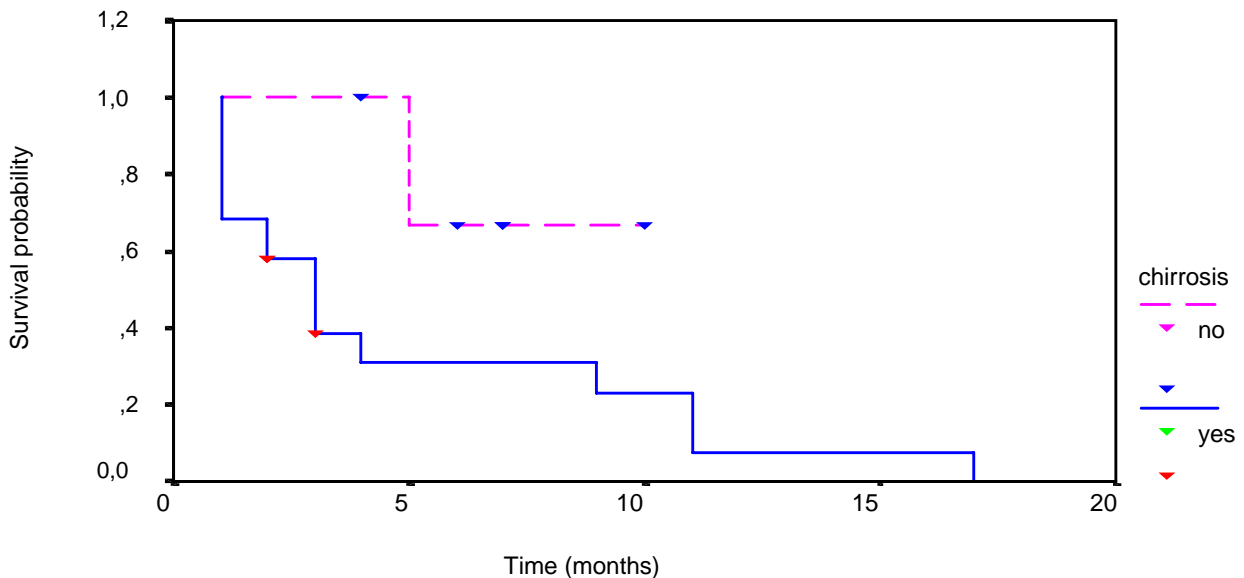
Cause of death	Group A	Group B
	cirrhosis	no cirrhosis
Tumour progression (%)	9(56)	4(80)
Hepatic failure (%)	3(19)	-
Gastrointestinal bleeding (%)	4(25)	1 (20)
Total	16(100)	5(100)

was statistically significant: group A: 5.1 ± 1.3 months (95% confidence interval=2.6-7.6) and group B: 8.3 ± 0.96 months (95% confidence interval=6.5-10.2)} (log rank test= 4.58, $p=0.0323$,) (Figure 2). Also, the Kaplan Meier analysis showed differences in mortality rates between the patients divided in two groups according to Okuda stage (Okuda I+ II and Okuda III) (log rank test= 4.23, $p=0.0398$) (Figure 3).

Table 3 shows the mean survival time in months of patients in this study, according to Okuda stage, compared to patients with HCC without treatment.¹²

DISCUSSION

Somatostatin is a hormone, which has been tested with efficacy for the treatment of hormone producing



Non Cirrhosis ($n=7$): Mean survival time : 8.3 ± 0.96 months (95% CI: 6.45-10.2)
 Cirrhosis ($n=19$): Mean survival time: 5.1 ± 1.3 months (95% CI: 2.6-7.6)

Figure 2. Probability of survival in cirrhotic (—) vs non-cirrhotic patients (- - -)

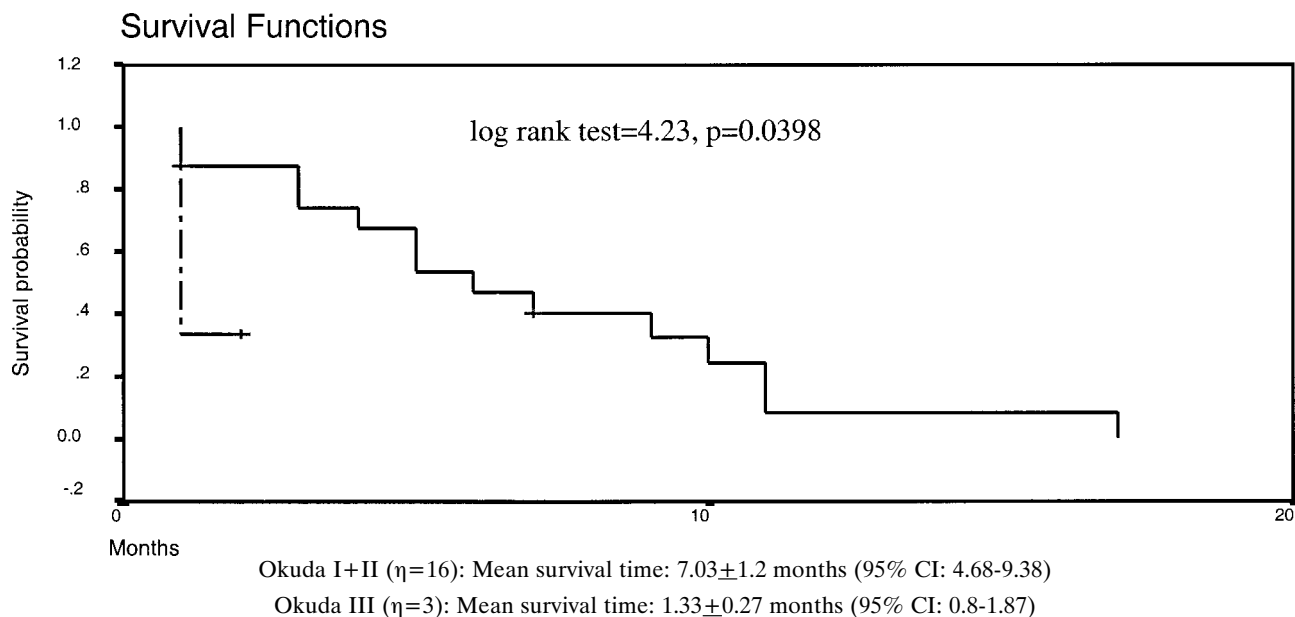


Figure 3. Probability of survival in Okuda I+II (—) vs Okuda III patients (---)

Table 3. Comparison of Mean Survival Time of Treated vs Untreated Patients

Okuda's stage	no therapy	octreotide therapy
I	8.3*	6.36
II	2*	8.73
III	0.7*	1.67

*Okuda *et al.* Natural history of hepatocellular carcinoma and prognosis in relation to treatment. *Cancer* 1985; 56:918-928

tumours, and it seems to have beneficial effects on the symptomatic and biochemical response of these tumours. Octreotide is a synthetic cyclic octapeptide that shares four essential amino acids with somatostatin. Its half-life is longer than that of somatostatin and may be as long as 4 hours in patients with cirrhosis.¹³

Schindel *et al* demonstrated in rats that octreotide can significantly inhibit the growth of residual intrahepatic or subcutaneous hepatomas, enhanced by partial hepatectomy.¹⁴ Moreover, a study from Crete showed that patients with HCC treated with octreotide, had prolonged survival compared with untreated patients.¹⁵ In that study fifty patients, most of them with Okuda stage II and III tumours, were randomized to receive either no treatment or subcutaneous octreotide 250 μ g twice daily. Treated patients had a significantly increased median survival (13 months) compared to controls (4 months) and a significantly increased cumulative survival rate at 6 and

12 months (75 vs 37% and 56 vs 13% respectively).

In our study we also investigated the efficacy of octreotide in the treatment of advanced HCC. The patients were divided according to the presence or not of cirrhosis. The results showed that there was a significantly increased mean survival time of non-cirrhotic compared to cirrhotic patients (8.3 vs 5.1 months). However, the mean survival time of all 30 treated patients in our study was 6.2 months compared to the 13 months of the previous greek study, although the octreotide was administered at a double daily dose. Nevertheless, the mean survival time of our patients, according to Okuda stage, compared with untreated patients in the Okuda study,¹² was more favourable, especially in patients with Okuda II stage (8.73 months vs 2 months).

The exact molecular and pathophysiological mechanism for the successful treatment of HCC with octreotide is unknown. Octreotide probably acts on the somatostatin receptors located in HCC.¹⁶ Several human tumours overexpress receptors for small regulatory peptides,¹⁷ an observation which has led to a number of clinical applications in diagnosis and treatment of these tumours.^{18,19} As mentioned above somatostatin receptors are expressed by most neuroendocrine tumours and the use of somatostatin is well proved in their treatment.²⁰

Recently five receptors of somatostatin have been

cloned. They belong to the family of G-protein-coupled receptors. In vitro studies have shown that octreotide presents high affinity binding to SSTR-2, SSTR-3 and SSTR-5 receptors.²¹⁻²³

Somatostatin receptors are not expressed in the normal human hepatocytes, in contrast to the HCC hepatocyte, where these receptors are frequently expressed, with the SSTR-2 subtype being predominant.¹⁵ Octreotide probably interacts with these receptors, which have a negative effect on cell growth.

Apart from the probable action of octreotide on the somatostatin receptors, it has been reported that octreotide is effective in inhibiting tumour growth in a variety of experimental models. Davies *et al* demonstrated that blockade of the reticuloendothelial system resulted in increased tumour growth, while octreotide increased the activity of the reticuloendothelial system.²⁴ These results were confirmed later by the same group in a new study.²⁵ Furthermore, recent reports of experimental models suggest that, apart from stimulating the reticuloendothelial system, octreotide might have other mechanisms of action in its anti-tumour effect, such as indirect action through the inhibition of hormonal trophic factors²⁶ or a direct antiproliferative effect through receptor-mediated growth inhibition and reduction in tumour blood flow,²⁷ possibilities that have not been adequately explored.

In a recent study Yuen *et al* failed to show any benefit in survival or tumour regression in patients receiving long acting octreotide.²⁸ On the other hand, Samonakis *et al* found that treated patients had median survival of 15 months compared to 8 months of the control group.²⁹ The relative risk of death of the untreated patients was 2.7 compared to the treated. This discrepancy could be explained by the fact that the patients of the former trial had significantly shorter survival compared to that of the literature, due to very advanced disease. Many patients received only one injection of octreotide so they could not take advantage of its action, since about 6 months' duration of treatment is probably needed to show any effect.³⁰

In conclusion, based on these results, it seems that octreotide administration could, perhaps, be a promising clinical application for the long-term treatment of patients with advanced HCC. Octreotide improves survival, especially in non-cirrhotic patients or in cirrhotic patients with low Okuda stage, offering safety and well-being. In future studies it will be important to identify somatostatin receptors in HCC hepatocytes in order to select patients for treatment with a higher possibility of benefit.

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