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Treatment of advanced hepatocellular carcinoma with long-acting octreotide: A phase III multicentre, randomised, double blind placebo-controlled study

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ABSTRACT

Background: A previous study reported a significant survival benefit for octreotide compared with no treatment in patients with advanced hepatocellular carcinoma (HCC). This was investigated further in this multicentre study.

Patients and methods: Two hundred and seventy two patients with HCC who were ineligible for curative treatments or had relapsed following potentially curative therapies were randomised to receive long-acting octreotide, 30 mg as an intramuscular injection once every 4 weeks for up to 2 years, or placebo.

Results: At the time of the final analysis, median overall survival (OS) was 6.53 months (95% confidence interval [CI], 4.8–8.3) for octreotide versus 7.03 months (95% CI, 5.43–8.53) for placebo ($p = 0.34$). Progression-free survival ($p = 0.26$) also did not differ significantly between the two treatment groups. No objective responses were achieved in the octreotide group but 33% of patients achieved disease stabilisation for a mean time of 5.5 months (95% CI, 1.1–9.9). The median time until definitive global health score deterioration (according to QLQ-C30) was 2.3 months (95% CI, 1.4–3.7) in the octreotide and 4 months (95% CI, 2.2–5.7) in the placebo group ($p = 0.09$). There were four objective responses in the placebo group. Octreotide was well tolerated; seven patients reported severe adverse events possibly related to octreotide and there were no cases of haematoma or cholecystitis.

Conclusions: In patients with advanced HCC, octreotide has a favourable safety profile but does not improve OS and could have a negative impact on quality of life.

1. Background

Primary liver cancer is the fifth most common cancer and the third most common cause of cancer-related deaths in the world.[1] Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer.[2] It is particularly widespread in Asia and Africa where the prevalence of chronic hepatitis B infection is high,[3] but there has been a substantial increase in the incidence of HCC in developed countries during the past three decades.[4] This is related to the improvement of other complications of cirrhosis, to the current peak of Hepatitis C virus (HCV)-induced HCC, to new aetiologies such as obesity and diabetes and to immigration from countries of high prevalence of viral infection. HCC is now responsible for approximately 6000 deaths per year in France, according to a recent study.[5]

Most patients with HCC present with advanced disease for which there is no curative treatment. Until recently, systemic treatment remained the only option for most of these patients, but results to date have been generally disappointing.[6] Fortunately, sorafenib, a targeted oral multikinase inhibitor, has demonstrated a significant survival advantage over placebo in a phase III study,[7] and is now considered as the reference standard for systemic therapy of HCC patients.

However, in 2001, when the study reported here was initiated, no systemic therapy was considered to be effective for patients with HCC, and evaluating new possibilities in large clinical trials was strongly encouraged.[8] One systemic treatment that has been investigated in a number of studies is octreotide, an analogue of the cyclic peptide hormone, somatostatin. Somatostatin is an inhibitory hormone that suppresses the release of various other hormones and has shown regulatory or suppressive effects against various tumours.[9,10] Somatostatin is believed to act *via* somatostatin receptors expressed on responsive tumours. In particular, octreotide has a high affinity to somatostatin receptors subtypes 2 and 5.[10] Although the expression of somatostatin receptors in HCC has not been studied extensively, the results of two studies suggest that 40–50% of HCC cases express or overexpress somatostatin receptors.[11,12] This suggests that octreotide may be active against HCC.

The randomised clinical phase III trial reported here was designed to investigate the efficacy of octreotide in advanced HCC. The main aim of the study was to determine whether treatment with long-acting octreotide could prolong overall survival (OS) in patients ineligible for curative treatments. Octreotide was administered as a long-acting formulation, in contrast to the short-acting formulation used in an earlier study, which required twice-daily administration. By reducing the number of injections required, the long-acting formulation could be expected to improve quality of life and reduce the cost of treatment; important benefits if the treatment was shown to be effective.

2. Methods

2.1. *Patients and study design*

Two French cooperative groups, the Fédération Francophone de Cancérologie Digestive (FFCD) and the Association Nationale des Gastroentérologues Hospitaliers (ANGH), performed this multicentre placebo-controlled, phase III study in which patients were recruited from 79 centres in France. Patients were required to have a diagnosis of HCC which was either histologically or cytogenetically confirmed, or based on the presence of the following three criteria: (1) presence of cirrhosis and a tumour with a measurable mass of at least 3 cm in diameter, (2) having a picture consistent with the diagnosis of HCC as determined by two contrast enhanced imaging techniques (ultrasonography and/or computed-tomography scan

and/or MRI), and (3) a serum alpha-fetoprotein (AFP) level of $\geqslant$500 μg/l. In addition, patients were required to be at least 18 years of age; be ineligible for curative treatments (transplantation, surgery, percutaneous ablation or chemoembolisation), or to have relapsed following potentially curative therapy; have a Cancer Liver Italian Program (CLIP) score of 0–3[14]; and measurable disease. Exclusion criteria included: the presence of hyperglycaemia ($\geqslant$2.5 g/l) or hypoglycaemia; life-threatening extra-hepatic disease; pregnancy; serum creatinine level of >120 μmol/l; decreased prothrombin time (<50%); low platelet counts (<50,000/μl); tumour not assessable by medical imageries; symptomatic cholelithiasis.

After checking eligibility criteria, patients were registered at the FFCD data centre. They were then centrally randomised (by computer) 1:1 to receive octreotide (study arm) or placebo (control arm). A minimisation technique was used with stratification according to: institution; CLIP (0 versus 1 versus 2–3); portal hypertension severity; presence or absence of previous oesophageal or gastric haemorrhage; and the presence or absence of oesophageal varice grade $\geqslant$2.

The protocol was reviewed and approved by the Ethics Review Committee of Région Picardie, France (16th May 2002). All patients provided written informed consent and the study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and Good Clinical Practice guidelines. Patients as well as investigators were blinded in all centres. Trial monitoring using written operating procedures was performed by a trained clinical research assistant from the FFCD. Furthermore queries source data verification was also performed on site; 100% source data verification (checkup of all data) was performed for inclusion and exclusion criteria, informed consent, study medication, adverse events, serious adverse events and for primary and secondary endpoints.

2.2. Treatment

Octreotide (Sandostatin LAR, Novartis Pharma, Nürnberg, Germany) was administered as an intramuscular injection at a dose of 30 mg, given once every 4 weeks. Each dose of octreotide was dissolved in 2 ml sodium chloride (NaCl). Patients in the placebo group received injections of 2 ml NaCl once per month. Study treatment or placebo was delivered according to randomisation for 2 years or until death or early stopping (due to a serious adverse event (AE) or patient refusal). If at any time during the trial intramuscular injection was contraindicated, treatment was temporally stopped until prothrombin time and/or platelets counts recovered. Injections were administered by a trained study nurse. Study medication was coded and labelled by Novartis Pharma to preserve blinding.

Best supportive care and appropriate management of the liver disease as usually practised in the individual centres were continued. During the trial no other anti-tumour treatments were permitted. If required, corticosteroid medication (up to 20 mg/d) was permitted to prevent development of decompensated diabetes mellitus.

2.3. Assessments

Prior to randomisation (within 2 weeks), age, weight, diagnosis, history and aetiology of cirrhosis were recorded for each patient. In addition, a clinical examination was performed and World Health Organization (WHO) performance status was determined, while patients also completed the EORTC QLQ-C30 quality of life (QoL) assessment. Blood samples were collected for assessment of laboratory parameters including prothrombin time and AFP levels. Child-Pugh and CLIP stage were determined. Liver morphology and tumour staging were assessed either by abdominal computed-tomography scan or abdominal MRI and thoracic fluoroscopy ($\leqslant$1 months), and from this information tumour size was determined according to response evaluation criteria in solid tumours (RECIST) criteria.[15] Permeability of the portal vein was checked on contrast-enhanced techniques and an endoscopic examination of the upper gastrointestinal tract was required within 3 months of randomisation.

During the study, patients were evaluated every 4 weeks for 2 years or until treatment was stopped and then every 12 weeks until death. This assessment included a clinical examination, and assessment of quality of life and laboratory parameters. Thoracic and abdominal computer tomography (CT) scans were performed at weeks 12 and 24 to assess objective responses. For patients with evidence of an objective response (partial or complete), a further CT scan was performed 4–8 weeks after the initial scan to confirm the response. During these evaluations digestive bleeding and hepato-renal syndromes were recorded if present. Toxicity data and AEs were systematically recorded during treatment. Those potentially related to octreotide treatment are reported. Those probably due to tumoural progression or underlying cirrhosis are not.

2.4. Statistical analysis

All analyses were performed according to a strict intent-to-treat principle (all included patients whatever treatment received and eligibility criteria). Analysis of primary endpoint was also done in per-protocol population defined as all eligible patients receiving at least one dose of treatment or placebo.

The study was powered to detect an improvement in median OS from 7.7 months with placebo to 12 months with octreotide treatment, with a type I error (bilateral) alpha of 0.05 and a power of 90%. To achieve this, it was required to observe 221 deaths. The study therefore aimed to enrol 270 patients over 3 years (allowing for a dropout rate of 5%) with at least 1 year of follow-up for the last included patient.

The primary endpoint was OS, calculated from the date of randomisation until death from any cause or censored at the last follow-up. Secondary endpoints included: progression-free survival, defined as the time interval between randomisation and progression or death; quality of life; objective tumour response; and safety. Time until definitive Global health score deterioration was defined as the time interval between randomisation and the first occurrence of a $\geqslant$5 point decrease in QLQ-C30 score without a $\geqslant$5 point improvement in QoL score or any further available QoL data. It was censored at the last follow-up in cases of no score deterioration.

The Kaplan–Meier method was used to estimate survival. Log-rank and stratified log-rank tests (according to randomisation stratification criteria) were used to assess differences

between arms. A univariate Cox model was used to calculate the hazard ratio (HR) with a 95% CI. A multivariate Cox model was applied to calculate the treatment HR independently of the stratification criteria and the main clinical factors at inclusion not included in CLIP score. Interaction between stratification criteria and treatment were tested and, if significant, subgroup analyses were performed. The chi square or Fisher's exact test was used to compare the incidence of AEs and to compare incidence of any grade AEs between treatment groups amongst patients receiving at least one dose of treatment or placebo.

An interim analysis was planned when 150 deaths had been observed in order to estimate median OS in each arm (without statistical comparison) and to determine whether an increase in sample size might be required. This interim analysis was performed in January 2004 and the independent data monitoring committee (composed of two hepatologists and one biostatistician) recommended not increasing the sample size.

All statistical analyses were performed using Stata V 10 at a 5% level of significance.

3. Results

3.1. *Patients*

A total of 272 patients were recruited between July 2002 and October 2003, and were randomised to receive octreotide ($n = 135$) or placebo ($n = 137$). In the placebo and octreotide groups, 55 (40%) and 65 (48%) patients were included from centres enrolling less than five patients, respectively. As shown in Fig. 1, 32 (24%) patients in the octreotide group and 40 (29%) patients in the placebo group did not meet the eligibility criteria. The data cut off for final analysis was per-

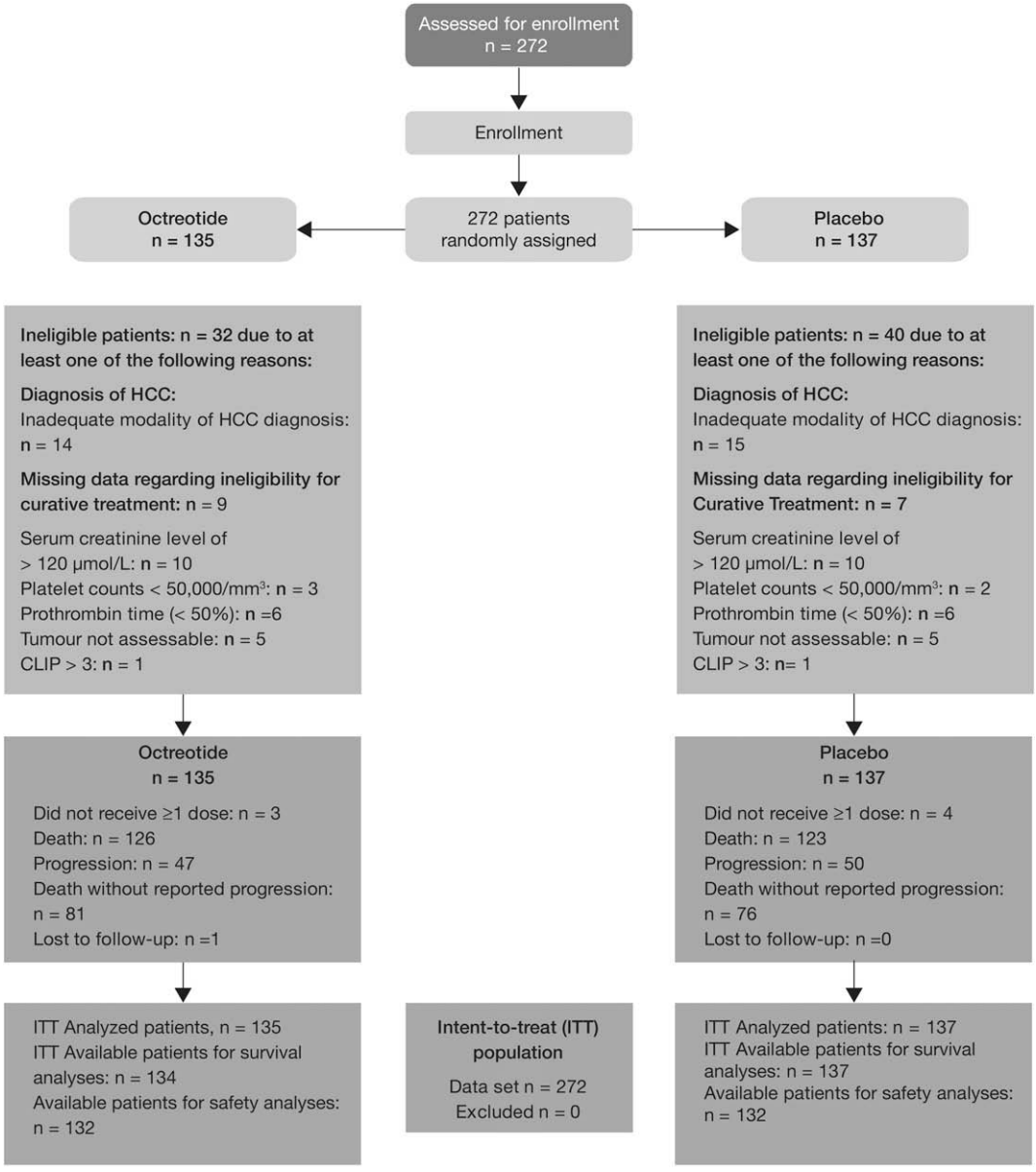

Fig. 1 – Flow chart showing patient disposition.

formed in October 2005. Median follow-up was 31 months in the octreotide arm and 30 months in the placebo arm.

Baseline characteristics were similar between the two treatment groups and are summarised in Table 1. Most (75%) of the patients were male and the median age was 70 years [range, 39–88 years]. Cirrhosis was present in 79% of patients and was alcohol-related in 75% of patients. A quarter (25%) of the patients had a CLIP score of 3 while 38% had a CLIP score of 2. Most patients (79%) had a good performance status (World Health Organization [WHO] score 0–1). Metastases were present in a fifth (21%) of patients and 22% had portal thrombosis. A quarter (25%) of patients had oesophageal varice grade $\geqslant 2$, while 7% had had previous oesophageal or gastrointestinal bleeding, and 35% had elevated AFP levels ($\geqslant 500$ μg/l).

3.2. *Treatment and safety*

The median number of injections received was 5 (0–25) for the octreotide group and 6 (0–27) for the placebo group. The median duration of treatment was 4 months (0–26) for the octreotide group and 5 months (0–23) for the placebo group. Octreotide was generally well tolerated. Approximately two-thirds of patients in both treatment groups experienced at least one AE that was possibly related to treatment, and approximately a quarter (24% for octreotide and 29% for placebo) experienced at least one severe (grade 3/4) AE (Table 2).

The most frequently reported treatment-related AEs are summarised in Table 2. Diarrhoea was the most frequently reported treatment-related AE, occurring in 40% of the octreotide group and 26% of the placebo group, but only one patient in each treatment group experienced severe diarrhoea. The other AEs reported in more than 10% of patients in either group were: nausea, reported in 19% of the octreotide group and 29% of the placebo group; heartburn, which occurred in 10% of the octreotide group and 13% of the placebo group; hyperglycaemia, reported by 33% of the octreotide group and 28% of the placebo group; and injection-site reaction, reported in 17% of the octreotide group and 15% of the placebo group. Nine patients (7%) in the octreotide group and 7 (5%) in the placebo group experienced severe hyperglycaemia, and one patient in the octreotide group experienced a severe injection-site reaction. In addition, one patient in the octreotide group suffered a stroke. There were no significant differences between the two groups in the incidence of treatment-related AEs, except for diarrhoea, and there were no cases of haematoma due to needle puncture or cholecystitis.

Detailed analysis of the source data showed that only seven patients (5.2%) experienced serious AEs that were possibly related to octreotide. One patient (0.7% of those treated with octreotide) died due to sudden stroke. For this patient, imaging (CT scan and MRI realised in the 2 d following stroke) results were normal, even in an a posteriori review by radiologists and neurological and cardiovascular risk factors were absent. In addition, no potential causal underlying brain disease was found at autopsy. Unfortunately, this unexpected death could not be adequately explained despite the post-mortem examination procedure.

Four patients (2.9%) suffered from glycoregulation disorders (hyperglycaemia, $n = 2$; hypoglycaemia, $n = 2$), while 2 pa-

Table 1 – Patients baseline characteristics.

	Octreotide, $n = 135$	Placebo, $n = 137$
Patients enrolled from centres including, %		
<5 pts	48	40
$\geqslant 5$ pts	52	60
Men, %	81	69
Mean age, (SD), years	65 (9)	69 (9)
Cirrhosis present, %	79	77
Alcohol-related cirrhosis, %	77	74
Child-Pugh score, %		
A	67	67
B	24	23
C	1	1
CLIP score, %		
0	6	7
1	28	25
2–3	65	67
4	1	1
WHO performance status 0–1, %	79	80
Portal thrombosis, %	21	23
Metastases present, %	22	21
αFP $\geqslant$ 500 μg/l, %	30	43
Previous oesophageal or gastric haemorrhage, %	8	6
Presence of oesophageal varice grade $\geqslant$ 2, %	28	23
Mean serum creatinine level, μmol/l (SD)	80.9 (22.8)	82.3 (23.0)
Patients received prior therapy, %	31	28

Table 2 – Incidence (%) of the most frequently reported adverse events during treatment with octreotide or placebo among patients receiving at least one dose of treatment.

	Octreotide, $n = 135$	Placebo, $n = 137$	p
Patients receiving at least one dose of treatment, n	132	133	
Patients reporting ⩾ 1 adverse event, n (%)			
• No	38 (28.79)	35 (26.32)	0.926
• Yes	88 (66.67)	92 (69.17)	
• Unknown	6 (4.55)	6 (4.51)	
Incidence of most frequently reported AE (any grade), n (%)			
– Diarrhoea	53 (40)	35 (26)	**0.046**
– Nausea	25 (19)	39 (29)	0.132
– Heartburn	13 (10)	17 (13)	0.692
– Hyperglycaemia	44 (33)	37 (28)	0.466
– Injection-site reaction	23 (17)	20 (15)	0.918
Patients reporting ⩾ 1 grade 3/4 adverse event, n (%)			
• No	94 (71.21)	88 (66.17)	0.966
• Yes	32 (24.24)	39 (29.32)	
• Unknown	6 (4.55)	6 (4.51)	
Incidence of most frequently reported severe AE (grade 3/4), n (%)			
– Diarrhoea	1 (0.76)	1 (0.75)	0.892
– Nausea	0 (0.00)	0 (0.00)	0.596
– Heartburn	0 (0.00)	0 (0.00)	0.596
– Hyperglycaemia	9 (6.82)	7 (5.26)	0.702
– Injection-site reaction	1 (1)	0 (0.00)	0.892
– Other toxicities	24 (18)	36 (26)	0.892

tients (1.5%) suffered from severe digestive tract disorders (diarrhoea, $n = 1$; vomiting with dehydration, $n = 1$).

3.3. *Survival and tumour responses*

3.3.1. *Overall survival*

At the time of the final analysis, 126 patients had died in the octreotide group and 123 in the placebo group. Median OS was 6.53 months (95% CI, 4.8–8.3) for the octreotide group and 7.03 months (95% CI, 5.43–8.53) for the placebo group. The difference between treatment groups was not statistically significant (log-rank $p = 0.34$, stratified log-rank $p = 0.52$) (Fig. 2). OS at 6, 12 and 24 months was similar for the two treatment groups: 6 months: 56% (octreotide) versus 53% (placebo); 12 months: 28% (octreotide) versus 30% (placebo); 24 months: 8% (octreotide) versus 14% (placebo).

After adjusting for stratification criteria and significant univariate clinical characteristics at baseline (not included in CLIP staging system), multivariate Cox analyses confirmed that treatment had no significant impact on OS (Table 3). In contrast, CLIP > 1, WHO PS 1, WHO PS 2/3, presence of oedema and presence of metastases were independently associ-

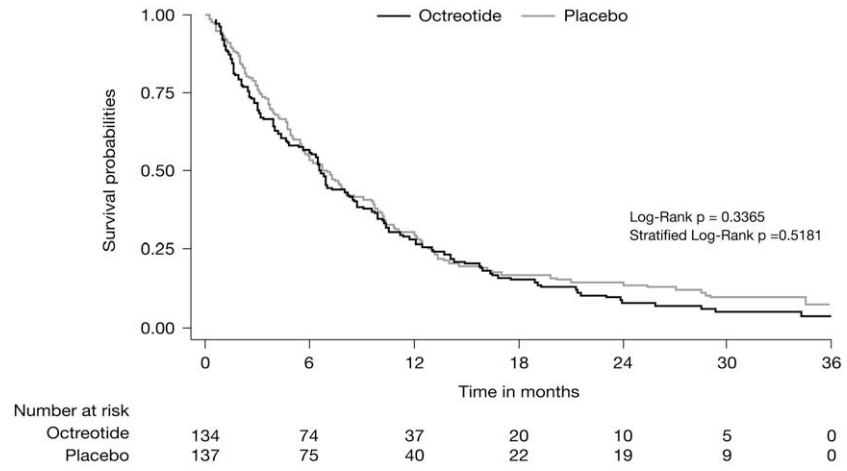

Fig. 2 – Overall survival according to treatment arm (intent-to-treat population, $n = 271$) Kaplan–Meier estimate (one was lost to follow-up).

Table 3 – Univariate and multivariate Cox analyses of overall survival (intent-to-treat population).

	$n = 261$					
	Univariate COx			Multivariate Cox		
	HR	IC 95%	*p*	HR	IC 95%	*p*
Treatment						
Octreotide	1			1		
Placebo	0.88	0.69–1.14	0.338	0.90	0.70–1.17	0.440
Centre						
<5 pts included pts	1			1		
⩾5 pts included pts	0.93	0.72–1.19	0.543	1.17	0.89–1.54	0.260
CLIP						
0	1			1		
1	1.96	1.06–3.64	⩽0.033	1.80	0.96–3.37	0.068
>1	3.28	1.82–5.93	0.001	3.26	1.77–6.00	0.000
Previous haemorrhage						
No	1			1		
Yes	0.80	0.49–1.31	0.382	0.86	0.51–1.45	0.564
Previous varice						
No	1			1		
Yes	1.17	0.88–1.55	0.268	1.07	0.79–1.45	0.674
WHO PS						
0	1			1		
1	1.43	1.10–1.92	0.017	1.44	1.06–1.94	0.018
2/3	2.00	1.40–2.85	0.000	1.73	1.18–2.53	0.005
Ascite						
No	1					
Yes	1.84	1.32–2.56	0.000			
Jaundice						
No	1			1		
Yes	1.42	1.12–1.79	0.004	1.14	0.89–1.47	0.292
Oedema						
No	1			1		
Yes	1.59	1.33–1.89	0.000	1.43	1.19–1.72	0.000
Hepatomegaly						
No	1					
Yes	1.13	0.99–1.28	0.074			
Encephalopathy						
No	1					
Yes	6.40	1.55–26.44	0.010			
Digestive haemorrhage						
No	1					
Yes	0.91	0.68–1.22	0.541			
Portal thrombosis						
No	1					
Yes	1.76	1.23–2.50	0.002			
AFP						
< 500	1					
⩾ 500	1.36	1.04–1.83	0.027			
Cirrhosis						
No	1					
Yes	1.33	0.96–1.84	0.085			
Child-Pugh						
A	1					
B/C	2.05	1.53–2.74	0.000			
Metastases						
No	1			1		
Yes	1.21	1.04–1.40	0.012	1.28	1.10–1.50	0.002

Table 3 – *continued*

	$n = 261$					
	Univariate COx			Multivariate Cox		
	HR	IC 95%	p	HR	IC 95%	p
Number of localisations						
Uninodular	1					
Multinodular/diffuse	1.25	0.93–1.68	0.131			
				Log likelihood = −1107.8184		

ated with risk of death (Table 3). Interaction tests between stratification criteria and treatment showed no significant interaction.

Respectively 100 patients in the octreotide group (96 deaths) and 96 in the placebo group (86 deaths) were included in the per-protocol population analysis of OS. Median OS was 6.50 months (95% CI, 4.4–8.3) for the octreotide group and 6.77 months (95% CI, 5.40–8.00) for the placebo group. The difference between treatment groups was not statistically significant (log-rank $p = 0.34$, stratified log-rank $p = 0.32$).

3.3.2. *Progression-free survival*

At the time of the final analysis, disease progression or death had occurred in 128 patients (95%) in the octreotide group compared with 126 (92%) in the placebo group. Median progression-free survival was 3.37 months (95% CI, 3.03–4.13) for the octreotide group and 3.93 months (95% CI, 31.13–4.09) for the placebo group. The difference between treatment groups was not statistically significant (log-rank $p = 0.2626$, stratified log-rank $p = 0.5616$) (Fig. 3).

3.3.3. *Tumour response*

During the course of the study, four objective responses were observed in the placebo group – one complete response and three partial responses. The complete response lasted for 3.4 months. There were no objective responses achieved in the octreotide group, although 33% of patients achieved stable disease.

3.3.4. *Quality of life*

The median time until definitive global health score deterioration (according to QLQ-C30) was 2.3 months (95% CI, 1.4–3.7) in the octreotide group and 4 months (95% CI, 2.2–5.7) in the placebo group. The difference between treatment groups approached statistical significance (log-rank $p = 0.09$, stratified log-rank $p = 0.033$).

4. Discussion

This is the third and largest randomised placebo-controlled study of the efficacy and safety of octreotide in the treatment of patients with advanced HCC.

After the publication of the preliminary study by Kouroumalis and colleagues,[13] two randomised placebo-controlled studies were published. In a randomised controlled trial involving 70 patients, Yuen and colleagues[16] reported no survival benefit compared with placebo for long-acting octreotide (1.9 versus 2 months). In a European randomised controlled trial involving 120 patients, Becker and colleagues[17] also reported no survival benefit for long-acting octreotide compared with placebo (4.7 versus 5.3 months).

In general, the results of our study confirm those of the previous two placebo randomised studies,[16,17] reporting that long-acting octreotide is well tolerated but does not prolong OS or progression-free survival, nor does it induce objective responses. In our study, the median OS was 6.7 months with octreotide, and was somewhat longer than that reported by

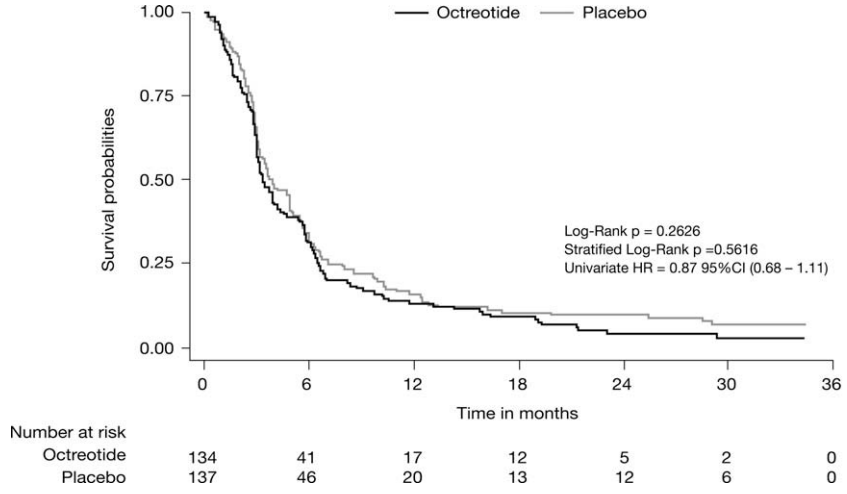

Fig. 3 – Progression-free survival according to treatment arm (intent-to-treat population, $n = 271$), Kaplan–Meier estimate.

Becker et al. (4.7 months) and Yuen et al. (1.9 months). This may well reflect differences in the patient populations regarding aetiology (mainly of viral origin in the Chinese study) and severity of liver disease. In our study, a third of patients achieved disease stability during treatment with octreotide but no patients achieved objective responses. Similar results were shown in the other two randomised studies. Furthermore our study highlights that quality of life using time until definitive deterioration of global health score could have been altered by octreotide. It is a surprising result since we have performed a double blind randomisation and PFS as well as tolerance did not differ between arms. Nevermind in cirrhotic patients with cancer, this impairment of quality of life may be a consequence of the natural history of cirrhosis or of tumour progression or of treatment-related toxicities. While it reinforces results of absence of octreotide efficacy in health outcomes we are currently investigating the longitudinal quality of life to explain more precisely this treatment impact.

These results are in contrast to those reported from an earlier study that showed a significant survival benefit for octreotide versus no treatment (OS: 13 versus 4 months, $p = 0.002$).[13] This study involved a smaller patient population ($n = 58$) and there was no administration of placebo in the patients of the control group. Thus the results may be less reliable and could reflect differences between the two treatment groups.

Two other non-randomised studies have also reported suggested survival benefits for octreotide compared with control groups. Dimitroulopoulos et al.[18] reported a median OS of 7.7 months for treatment with octreotide (given three times daily for the first 6 weeks followed by a monthly administration of the long-acting formulation) compared with 4 months for patients who were unable to receive treatment ($p = 0.037$). However, the fact that patients in the control group were unable to receive treatment suggests that the difference in OS may reflect differences in the patient populations rather than the effect of treatment with octreotide. The other study to report a survival benefit for octreotide compared OS for 32 patients with inoperable HCC who received octreotide with that of a historical control group of 27 untreated patients.[19] Median OS for the octreotide group was 15 months compared with 8 months for the historical control group. As in our study, no patients achieved objective responses, but the tumour remained stable or regressed in 40% of patients. Again, the difference in survival between the two groups in this study may well have reflected differences in the two patient populations rather than the effects of octreotide.

The results from all studies suggest that octreotide is generally well tolerated. In the three randomised studies that reported on AEs (our study, the German study[17] and the Greek study[13]), the most commonly reported AE was mild diarrhoea, a known side effect of octreotide. This was reported in 40% of patients in our study and the Greek study, and in 27% in the German study. The other clinically significant adverse effect was fluctuations in glucose control, another known side effect of octreotide. In our study, a third of patients experienced hyperglycaemia, which was severe in 7% of patients. However, the incidence of hyperglycaemia was only slightly lower in the placebo group (any grade, 28%; severe, 5%).

The results reported from the three randomised placebo-controlled studies, which have involved 462 patients in total, suggest that octreotide does not improve OS in patients with advanced HCC. However, some authors believe it is possible that octreotide may benefit a subgroup of patients whose tumours express high levels of the somatostatin receptor. This hypothesis is supported by the results of a study that assessed the level of receptor expression in patients with HCC and then randomised those with high levels of expression to receive octreotide or placebo.[12] In this subgroup, median OS was significantly higher in patients receiving octreotide (45 versus 27 weeks), and survival in the placebo group was similar to that in patients with low receptor levels (who did not receive octreotide). Moreover, a recent study revealed that 35% of the HCC had an increased 111IN-pentetreotide uptake at scintigraphy.[20] This could warrant further investigation, in this specific subgroup, given the favourable safety profile of octreotide.

Four objective responses (2.9%) were observed in the placebo group – one complete response and three partial responses, as assessed according to RECIST criteria.[15] This phenomenon is somewhat surprising but in fact was already described in the literature. Objective responses were documented in randomised trials evaluating chemoembolisation, sorafenib or long-acting octreotide in 7.6%, 1% and 12.5% of the patients in the placebo or control group patients, respectively.[7,16,21] So, it could be considered as a common, but a rare, phenomenon. Two explanations might be advanced: in one hand, some cases of spontaneous regression of large HCC has been reported in the literature yet,[22] and in the other hand it is now considered that classical RECIST criteria are somewhat inadequate for response assessment in patients with HCC.[6]

Recently a significant OS benefit for the targeted therapy, sorafenib, was reported in patients with inoperable HCC.[7] The therapeutic benefit of sorafenib has been demonstrated in a large double blind placebo-controlled phase III study (SHARP trial) which reported an improvement in OS for sorafenib over placebo ($p = 0.0006$); median OS was 10.7 months versus 7.9 months.[7] These results prompted the FDA and EMEA to approve sorafenib for treatment of HCC. Thus, this targeted therapy has become the new standard systemic treatment for patients with HCC.

However, in the SHARP trial, the incidence of severe diarrhoea was greater in the sorafenib group than in the placebo group (11% versus 2%), as was the incidence of severe hand–foot skin reaction (8% versus 1%), an AE that can seriously impact the quality of life of patients. Octreotide is not associated with hand-foot skin reaction and has a much lower incidence of severe diarrhoea than sorafenib. Thus, it could be appropriate to draw a randomised trial in patients whose tumours express high levels of the somatostatin receptor in the aim of identifying a subgroup of patients who could benefit from octreotide. If so, these patients under treatment might retain a better quality of life during their final months. Moreover one could speculate on possible benefits of combining sorafenib with octreotide. Preliminary results suggesting the feasibility of this combination were recently reported.[23]

5. Conclusions

The results of this large, randomised, double blind placebo-controlled study confirm the results of two other large randomised placebo-controlled studies and suggest that octreotide does not prolong OS in patients with HCC.

Conflict of interest statement

None declared.

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