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Original article

Octreotide acetate long-acting release in patients with metastatic neuroendocrine tumors pretreated with lanreotide

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Summary

Background: In the present study we investigated the efficacy and tolerability of i.m. octreotide acetate (octreotide LAR) in patients with metastatic neuroendocrine tumors (NETs) previously treated and failed on i.m. lanreotide.

Patients and methods: Fifteen patients (8 females, 7 males, median age 67 years, range 28–81 years) with metastatic NETs (8 endocrine pancreatic tumors, 7 midgut carcinoids) were enrolled in the study. All patients were in progressive disease (objective: 11 patients, symptomatic: 10 patients, biochemical: 11 patients) after treatment with slow release lanreotide, 30 mg every 14 days for a median time of 8 months (range 3–19 months). All patients had measurable disease; 12 patients had elevated serum and/or urine markers and 11 were symptomatic. Octreotide scintigraphy was positive in 13 of 15 patients. Octreotide LAR was administered as i.m. injection at the dose of 20 mg every four weeks until disease progression.

Results: An objective partial response (PR) was documented in one patient (7%), no change (NC) in six (40%), and progressive disease (PD) in eight patients (53%). The PR was observed in one patient with non-functioning endocrine pancreatic tumor with progressive liver and lymph node metastases after 16 months of i.m. lanreotide therapy. The median duration of disease stabilization was 7.5 months (range 6–12+ months). The overall biochemical response rate was 41%, including CRs (33%) and PRs (8%); biochemical responses were observed in carcinoids as well as in endocrine pancreatic tumors; the median duration of response was 5 months for CRs and 7.5 months for PRs. The overall symptomatic response rate was 82%. The median duration of response for diarrhoea, abdominal pain, or both was 6.5 months (range 3–12+ months). Improvement in performance status (PS) was obtained in 5 of 11 patients with PS of 1 at study entry.

Median duration of octreotide LAR treatment was seven months (range 3–12+ months). No serious adverse events were reported; mild side effects were reported in 26% of patients.

Conclusions: Octreotide LAR 20 mg shows significant efficacy in terms of objective response rate (PR + SD), biochemical and symptomatic control in patients with metastatic NETs of the GEP system pretreated and progressing on slow release lanreotide.

Key words: depot lanreotide, neuroendocrine tumors, octreotide LAR

Introduction

Somatostatin analogues are commonly used to obtain a symptomatic control in neuroendocrine tumors (NETs), however inhibition of tumor growth and occasionally objective responses are also reported. These effects occur as a result of inhibition of hormone secretion, antagonism with growth factors, or direct antiproliferative effects on tumor cells mediated by specific membrane receptors [1]; so far five subtypes have been cloned and characterized [2–4]. Somatostatin receptors (sstrs) are found in 80%–90% of NETs with autoradiography [5] and octreotide scintigraphy [6]. The analogues presently available for clinical use (octreotide and lanreotide) bind to sstrs 2 and 5, and, at higher doses, also to sstr3 [7], which has been shown to promote apoptosis [8].

Symptomatic and/or biochemical response rates from 40% to 70% and objective response rates of 7%, respectively, have been reported with depot lanreotide 30 mg i.m. every two weeks [9–12].

Slow-release octreotide acetate (octreotide LAR) administered every 28 days was at least as effective as subcutaneous (s.c.) octreotide in suppressing growth hormone and insulin-like growth factor-1 (IGF-1) in patients with acromegaly [13 16].

In patients with carcinoid syndrome octreotide LAR given at different doses has shown comparable efficacy and tolerability to the s.c. octreotide formulation, and 20 mg was recommended as the starting dose [17]. So far, no study has evaluated the level of cross-resistance between the depot formulations of lanreotide and octreotide.

The present phase II study was conducted to investigate the efficacy and tolerability of octreotide LAR in patients with gastroenteropancreatic NETs in progression after lanreotide depot.

Patients and methods

Patients aged > 18 years with histologically confirmed metastatic NETs and disease progression (objective, biochemical and/or symptomatic)

Table 1. Patient characteristics.

Number of patients	15
Sex	
Female	8
Male	7
Age	
Median	67
Range	28–81
ECOG PS	
0	4
1	11
Type of tumor	
Carcinoid	7
EPT	8
Duration of disease (months)	
Median	34
Range	6–84
Prior treatments	
Surgery	15
S.C.Octreotide	3
Chemotherapy	1
Liver alcoholisation	3
Depot lanreotide	15
Duration of lanreotide therapy (months)	
Median	8
Range	3–19
Sites of metastases	
Liver	15
Lymph nodes	2
Peritoneum	3
Symptoms	12/15
Diarrhoea	11
Abdominal pain	6

on depot formulation of lanreotide were eligible for enrollment. Prior therapy with interferon-α (IFN-α), s.c. octreotide, chemoembolization, liver metastases alcoholisation, and chemotherapy was allowed. Additional eligibility requirements were: bidimensionally measurable disease, survival expectancy > 12 weeks, ECOG performance status (PS) ≤2, adequate bone marrow (WBC count >3500/μl, and platelet count > 100,000/μl), hepatic (serum total bilirubin level <1.5 mg/dl), and renal functions (serum creatinine concentration <2.0 mg/dl). Before study entry the patients were evaluated with chest radiograph, computed tomography (CT) scan of evaluable lesions, ultrasonography (US) of the gallbladder, and octreotide scintigraphy with ^{111}In-DTPA-D-Phe^1-octreotide. Imaging studies were repeated every three months to assess objective response.

The following tumor markers were measured in all patients before and every four weeks during treatment: neuronal specific enolase (NSE), pancreatic polypeptide (PP), α-subunit of human chorionic gonadotropin (α-HCG), and plasma IGF-1; additional markers included plasma cromogranin-A (p-CgA), serotonin (p-5-HT) and 24-hour urinary 5-hydroxy-indoleacetic acid (u-5-IHAA) in carcinoid tumors, p-CgA in endocrine pancreatic tumors (EPTs), and serum gastrin in gastrinomas. Mean concentrations of tumor markers, as well as the number and intensity of bowel movements and severity of abdominal pain (graded on a four point scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe) were evaluated after one, three, and six months of therapy and compared to baseline values. Objective responses were defined according to standard criteria.

The duration of responses were calculated from the first documentation of response to disease progression. The time to progression was calculated from the first dose of octreotide LAR to the first evidence of disease progression (symptomatic, biochemical or objective).

Octreotide LAR (Sandostatina LAR, Novartis Pharma) was administered as i.m. injections at the dose of 20 mg every four weeks until disease progression.

The study was approved by the institutional ethical committee.

Table 2. Response to treatment.

	Objective, *n* (%)	Biochemical, *n* (%)	Symptomatic, *n* (%)
Evaluable	15	12	12
CR	–	4 (33)	8 (67)
PR	1 (7)	1 (8)	1 (8)
SD	6 (40)	4 (33)	3 (25)
PD	8 (53)	3 (26)	–

Results

After giving informed consent, 15 patients with progressive metastatic NETs who had experienced a prior response or disease stabilization with lanreotide entered into the study. Patient characteristics are shown in Table 1. Twelve patients had elevated tumor markers (p-CgA = 11 patients, u-5-IHAA and 5-HT = 3 patients; NSE = 5 patients; gastrin = 2 patients; calcitonin = 3 patients; multiple markers = 10 patients). Serum PP and α-HCG concentrations, as well as plasma IGF-1 values were normal in all patients.

In the patients presenting with diarrhoea and abdominal pain, the median number of daily bowel movements was five (range 4–8) and the median intensity scores for diarrhoea and abdominal pain were 1 (range 1–2) and 2 (range 2–3), respectively. Octreotide scintigraphy was positive in 13 of 15 patients (86%). Response to treatment is summarized in Table 2. The PR was observed in a patient with nonfunctioning EPT with liver and lymph node metastases who had been pretreated with s.c. octreotide and i.m. lanreotide for a period of 5 months and 16 months, respectively. The reduction in tumor size was documented at both metastatic sites after 6 months of octreotide LAR therapy and is still lasting after 10 months of treatment.

The median duration of disease stabilization was 7.5 months (range 6–12+ months). In the 12 patients who were assessable for biochemical response, 11 of patients had elevated p-CgA, of whom 1 patient (9 %) achieved a CR, 2 patients (18%) a PR, 5 patients (46%) had NC, and 3 patient (27%) experienced PD. Of the three patients who were assessable for u-5-IHAA and 5-HT, one patient achieved a CR for both markers, and one patient had a PR for 5-HT. Two patients with gastrinomas were assessable for serum gastrin: one CR and one PR were observed. Five patients had elevated NSE, and one CR was reported. The overall biochemical response rate was 41% with a median duration of 5 months for CRs, 7.5 months for PR, and 6.5 months for SD patients.

Mean serum concentrations of p-CgA and u-5-IHAA in carcinoid tumors at different times during treatment are reported in Figure 1.

Among the 12 patients evaluable for symptomatic response, the overall response rate was 75% (Table 2). Median duration of symptomatic response was 6.5 months (range 3+–12+ months).

The mean numbers of weekly stools at 1, 3, 6 months

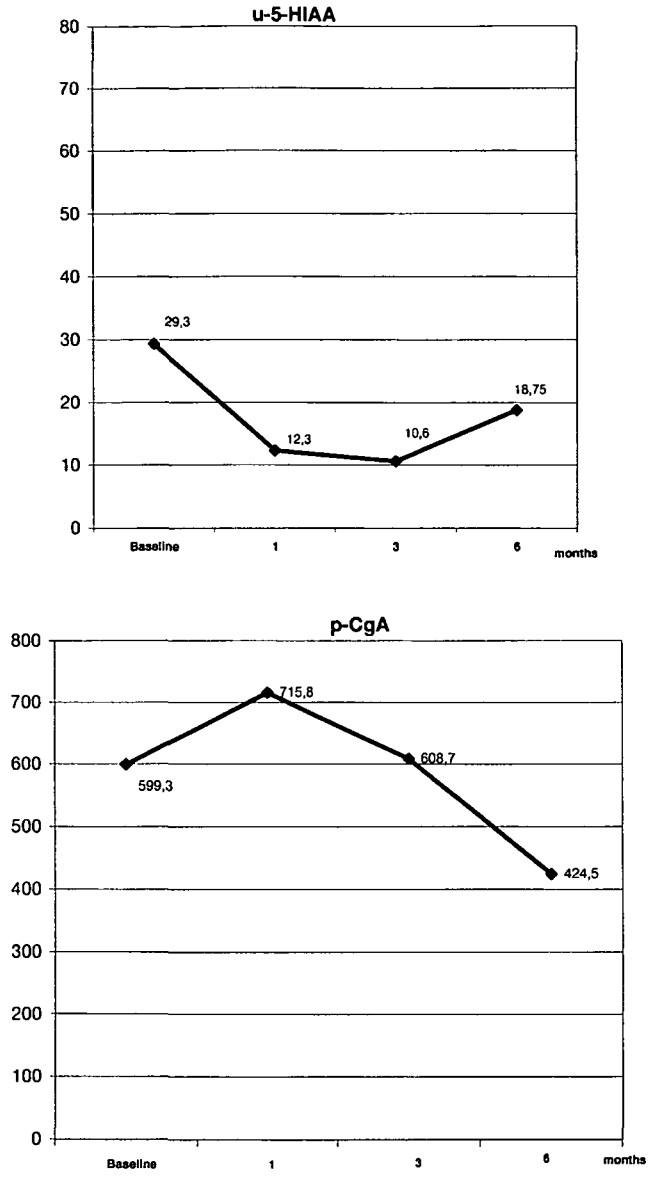

Figure 1. Mean concentrations of u-5-HIAA and p-CgA in patients with carcinoids at baseline, 1, 3, and 6 months during octreotide LAR therapy.

and at last observation compared to baseline decreased from 37 (range 28–56) to 15 (range 7–30), 10.8 (range 7–28), 8.2 (range 7–14), and 12.5 (range 7–30), respectively. A decrease of at least 50% in the number of bowel movements was seen in 6 of 11 (54%) patients at 1 month, in 8 of 11 (73%) at three months, in 8 of 11 (73%) at six months, and in 1 of 11 (9%) at 12 months. Diarrhoea completely resolved in 5 of 11 patients (45%) at 1 month, in 6 of 11 (55%) at 3 months, and in 6 of 11 (55%) at 6 months.

Abdominal pain completely resolved in three of six (50%), four of six (67%), and three of five (60%) patients at one, three, and six months, respectively. PS improvement from 1 to 0 was observed in five patients (45%) for a median period of seven months (range 4–12 months). Overall a clinical benefit, evaluated as objective, biochemical or symptomatic response was obtained in 9 of 15 (60%) patients (Table 2).

There were no serious drug-related adverse events.

Median duration of octreotide LAR treatment was seven months (range 3–12+ months).

So far 8 patients have stopped the treatment for progression (8 patients objective alone, 4 patients objective and biochemical).

Discussion

Somatostatin analogues have been used in the last years for the control of symptoms in patients with carcinoid syndrome and other functioning NETs; inhibition of tumor growth or even decrease in tumor size have also been reported [18, 19]. However, the s.c. formulation requires multiple daily injections to mantain therapeutic levels, therefore the availability of long-acting formulations which can be administered every two to four weeks represents a major advance.

Several studies have shown that depot lanreotide is active and well tolerated in patients with carcinoid tumors [9–12]; moreover, octreotide LAR given at different doses is effective in patients with carcinoid syndrome responsive to s.c. octreotide [17].

In the present study we have shown that octreotide LAR at the dose of 20 mg every four weeks is active in patients with progressive disease after treatment with depot lanreotide. The activity of octreotide LAR was documented in terms of objective responses, biochemical and symptomatic control.

The lack of cross resistance between depot lanreotide and octreotide LAR might occur as the result of a more efficient occupancy of somatostatin receptors due to differences in the pharmacokinetic profiles of the two drugs. Both octreotide and lanreotide bind with high affinity to sstr-2 and sstr-5, and with a moderate affinity to sstr-3; the biochemical and the antiproliferative effects of these analogues are mediated by sstr-2. After a single i.m. injection of octreotide LAR, the serum concentration reaches an initial peak within one hour, followed by a decrease to an undetectable level for two to seven days; thereafter, octreotide concentrations increase to a dose-dependent stable plateau that is mantained for about three to four weeks and never decrease to subtherapeutic concentrations as long as octreotide LAR is injected every four weeks [13].

In contrast, although the serum concentration/time curve of depot lanreotide is biphasic as that of octreotide LAR, the plateau phase of lanreotide is shorter (7–10 days) [20], and this might occasionally produce subtherapeutic concentrations when the drug is injected every 14 days.

In our study we have neither shortened the intervals between the injections nor have we increased the dose of lanreotide. Therefore we cannot exclude tachyphylaxis, the development of a tolerance, as a possible reason for tumor progression. Further studies are needed to explore this possibility, it is however clear from our data that octreotide LAR can produce tumor and sympto-

matic control in patients with advanced NETs previously treated with depot lanreotide. These results may expand the clinical use of somatostatin analogues.

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