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Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours☆

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Abstract

A few studies have suggested an antitumour activity of somatostatin analogues in neuroendocrine tumours (NET). The aim of this study was to evaluate the antitumour efficacy of somatostatin analogues in patients with documented progressive tumours. 35 consecutive patients with documented tumour progression were treated with somatostatin analogues. Patients were classified into two groups. In Group 1, tumours were progressing rapidly (an increase of 50% or more in the lesion surface area in 3 months) and in Group 2, tumours were progressing more slowly (an increase of less than 50% in the lesion surface area in 3 months but greater than 25% in 6 months). Treatment consisted of subcutaneous (s.c.) octreotide, 100 μg thrice daily for 17 patients, intramuscular lanreotide, 30 mg/every 14 days for 11 patients and for 7 patients both somatostatin analogues were used successively during the follow-up. Primary tumour sites were the small intestine ($n=12$), pancreas ($n=13$), lungs ($n=5$), and other sites ($n=5$). 18 patients had the carcinoid syndrome with flushing and/or diarrhoea. The median duration of treatment was 7 months. Treatment was discontinued in 3 patients due to side-effects. One patient (3%) achieved a partial response and the disease was stabilised in 20 patients (57%) for a median duration of 11 months (6–48 months). Stabilisation of patients in Group 1 was significantly less frequent at 6 months than that of patients in Group 2 (4/12 and 13/17 respectively, $P<0.02$). Somatostatin analogue treatment resulted in one partial response (3%) and 20 cases of stabilisation (57%) in 35 patients with progressive NET. A slow tumour growth rate before treatment is predictive of a good response to somatostatin analogues which could be considered an option for first-line treatment.

Keywords: Neuroendocrine tumour; Carcinoid tumour; Biotherapy; Somatostatin analogue scintigraphy; Cancer

1. Introduction

Malignant neuro-endocrine tumours (NET) are rare, accounting for approximately 1% of all human tumours. Gastroenteropancreatic (GEP) NET are derived from endodermal cells with a secretory capacity that are found in practically all the organs in the human body. The main primary carcinoid tumours arise in the digestive tract (small bowel 29%, appendicular 19% and rectum 13%) and in the respiratory tract 25% [1]. GEP NET are classified into three different groups according to their embryological origin as lesions of the foregut- (upper digestive tract, duodenum, proximal jejunum, pancreas and lung), midgut- (distal jejunum, ileum and proximal colon) and hindgut- (distal colon and rectum) derived tumours [2].

Despite common morphological and immunohistochemical features, the prognosis and treatment strategy differ considerably according to the primary site, histological differentiation (poor- or well-differentiated) and stage [3–5].

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GEP NET subtypes, poorly-differentiated NET and well-differentiated pancreatic NET, are known to be chemosensitive [6–8]. However, in other well-differentiated GEP NET, the results of systemic chemotherapy are disappointing, yielding only a 30% response rate of short duration [6]. Multiple therapeutic approaches have been developed for patients with inoperable disease. They include hormonotherapy, immunotherapy, or locoregional therapy mainly targeting the liver [9–11]. However, given the heterogeneous growth pattern of these tumours, and the absence of well-established prognostic factors, the natural growth pattern of these tumours was proposed as a target for the selection of patients and the evaluation of therapeutic approaches [12]. GEP NET are characterised by the expression of somatostatin receptors [13] and by hormonal secretion which has been demonstrated to be life-threatening [14]. Somatostatin analogues have proved effective in controlling hormonal secretions in GEP NET [9,15]. With respect to anti-tumour activity, three phase II studies have pointed out frequent stabilisation with somatostatin analogue therapy in progressive GEP NET [16–18]. No factors predictive of antitumour activity were identified in these studies. In order to further define the profile of patients with NET likely to benefit from somatostatin analogue therapy, we studied 35 patients with NET, who were subclassified according to their slope of tumour growth.

2. Patients and methods

2.1. Patients

From September 1992 to February 1997, 79 patients with metastatic NET were treated with somatostatin analogues at the Institut Gustave-Roussy, Villejuif, France.

The histological diagnoses of NET were reviewed in our institution. Among these 79 patients, 28 had stable disease before treatment, 16 were on another anticancer treatment or had missing data and were not included in the study. 35 patients were classified as having progressive NET according to World Health Organization (WHO) criteria and were included in the present study. Among these 35 patients, 29 had documented progression of the tumour surface area of more than 25% over 6 months, as reviewed by an independent radiologist (the surface was defined as the sum of the products of the perpendicular diameters of measurable lesions) and in the 6 other patients, new metastases had emerged during the 6 months preceding their inclusion. The slope of the tumour growth rate (STGR) was determined in these 29 patients during the 3 months preceding treatment. The percentage increase in the tumour surface area was calculated before and after the initiation of somatostatin analogue treatment. Patients were classified into two groups. Group 1, designated 'progressing rapidly', included 12 patients with an increase of 50% or more in the tumour surface area in 3 months. Group 2, designated 'progressing slowly', comprised 17 patients with an increase in the tumour surface area of less than 50% in 3 months, but greater than 25% in 6 months.

Octreoscans (Mallinckrodt, The Netherlands) were performed in 32 patients (91%) and classified semi-quantitatively into two groups according to tumour-liver uptake. Patients with no tumour uptake or in whom tumour uptake was lower than in the non-tumorous liver were classified in the low tumour uptake group. Patients with higher tumour uptake than that found in the non-tumorous liver were classified in the high tumour uptake group. When low and high uptake were found in the same patient, the patient was classified in the high tumour uptake group. A radiologist independently reviewed the octreoscans.

The following parameters were recorded for each patient: STGR, age, sex, carcinoid syndrome, time between the diagnosis and inclusion, WHO performance status at inclusion, the number of metastatic sites (the different sites were the liver, lungs, distant lymph nodes, bones and brain), somatostatin analogue type, previous antitumour therapy, octreoscan uptake, tumour primary and tumour differentiation. Measurements of serum neurone-specific enolase (NSE), glycoprotein α-subunit (GPα), calcitonin and gastrin, as well as 24 h urinary measurement of 5-hydroxyindolacetic acid (5-HIAA) were performed in foregut-derived NET. Only NSE and 5-HIAA measurements were performed in midgut-derived NET.

2.2. Somatostatin analogue treatment

Treatment consisted in a subcutaneous (s.c.) injection of octreotide (Sandostatine®, SMS 201-995, Sandoz, Basel, Switzerland), 100 μg three times daily or an intramuscular (i.m.) injection of lanreotide (Somatuline®, Ipsen Biotech, Paris, France), 30 mg every 14 days. Doses were increased in four patients to control carcinoid symptoms (doses of octreotide attained 0.5 mg×3/days and lanreotide, 30 mg/10 days).

2.3. Evaluation of response

Bidimensional measurements of tumour lesions were performed on computer tomography (CT) scan and ultrasound images according to WHO criteria by the same radiographer. A radiologist independently reviewed the CT scans. Every 3 months, patients underwent a physical examination, measurement of hormonal tumour markers, a CT scan and ultrasound to evaluate response. Patients were considered as

responders when, at 6 months, they achieved a partial response according to WHO criteria (reduction of the tumour surface area >50%), or stabilisation for at least 6 months after the beginning of the treatment. The pre- and posttreatment STGR were compared. Biological responses were defined as a decrease of more than 50% in the level of all the tumour markers. Tumour characteristics of responders and non-responders were compared in an attempt to determine predictive factors for response to treatment.

2.4. Statistical analysis

The χ^2 test was used to compare qualitative variables. The Student's *t*-test was used to compare quantitative variables. Survival analyses were performed using the Kaplan–Meier method. A *P* value of 0.05 was considered statistically significant. The duration of response or stabilisation and overall survival was calculated from the first day of treatment with somatostatin analogues. The duration of progression-free survival was calculated from the first day of documented stabilisation or response to the day of documented progression.

Table 1
Patient characteristics

Total number	35
Median age (years) (range)	56 (22–76)
Male/female	20 (57%)/15 (43%)
Functional tumour	18 (51%)
Median time between diagnosis and inclusion (months) (range)	37 (3–155)
WHO PS at inclusion	
0	19 (54%)
1	14 (40%)
>1	2 (6%)
Number of metastatic sites	
1	16 (46%)
2	14 (40%)
3	5 (14%)
Somatostatin analogue	
Octreotide	17 (49%)
Lanreotide	11 (31%)
Both	7 (20%)
Previous antitumour treatments	
Surgery	27 (77%)
Chemotherapy	26 (74%)
Number of previous lines of chemotherapy	
0	9 (26%)
1–2	18 (51%)
3–4	8 (23%)
Octreoscan[a]	
Negative or low intensity	12 (38%)
Moderate or high intensity	20 (63%)

PS, Performance status. WHO, World Health Organization.
[a] 32 (91%) patients had an octreoscan.

3. Results

35 patients had documented disease progression and were analysed. Patient and tumour characteristics are detailed in Tables 1 and 2. The median time from the diagnosis to entry in the study was 37 months, (range 3–155 months). The performance status (PS) was 0 or 1 in 94% of cases. 77% of patients had undergone surgical debulking of tumour and 74% had received chemotherapy. Most of the primary tumours were located in the small intestine and pancreas (71%). Thirty tumours (86%) were well differentiated. 18 patients (51%) had the carcinoid syndrome. The median duration of treatment for all patients was 7 months (range 1–48 months). 17 patients were treated with octreotide alone, 11 with lanreotide alone and 7 received both somatostatin analogues successively during follow-up. The reason of switch was mostly problems of tolerance of daily s.c. injections of octreotide. Overall survival was 75% at 1 year and 58% at 2 years with a median survival of 29 months. No significant difference was observed between Groups 1 and 2 for the median survival after the begining of somatostatin analogue treatment. Treatment was discontinued in 3 patients due to side-effects (abdominal pain in 2 and diabetes in 1).

3.1. Tumour response and progression-free survival

One patient (3%) achieved a partial response for 48 months and in 20 cases (57%) stabilisation was obtained for a median duration of 10.5 months (range 6–43 months). Progression-free survival (PFS) for all 35 patients was 26% at 1 year and 11% at 2 years. PFS for the 21 patients who were stabilised following somatostatin treatment is shown in Fig. 1.

The pretreatment STGR decreased by more than 50% in 72% of patients after 3 months of somatostatin analogue treatment, and in 65% after 6 months. The mean STGR declined in both groups. In Group 1, the mean

Table 2
Site and type of the primary

Small intestine	12 (34%)
Functional tumour (carcinoid)	9
Non-functional tumour	3
Pancreas	13 (37%)
Functional tumour	3
Gastrinoma	2
Glucagonoma	1
Non-functional tumour	10
Lungs	5 (14%)
Others: colon and gall-bladder	2 (6%)
Unknown	3 (9%)
Differentiation	
Well	30 (86%)
Poor	5 (14%)

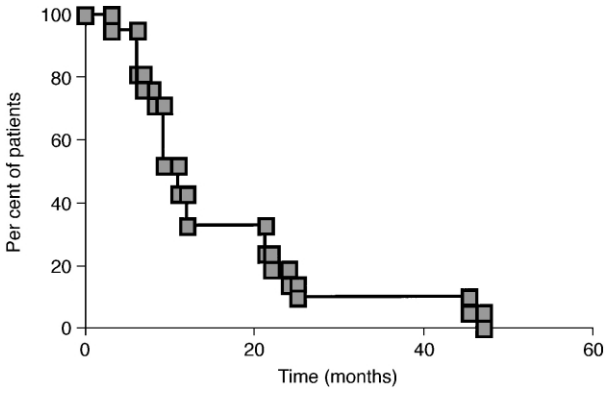

Fig. 1. Progression-free survival (PFS) of the 21 patients stabilised with somatostatin analogue.

decrease was 66% at 3 months (range: 0–98%) and 44% at 6 months (range: 0–98%). In Group 2, the mean decrease was 64% at 3 months and 59% at 6 months.

The higher dose of somatostatin analogues used in 4 patients did not enhance the antineoplastic effect. A similar percentage of tumour stabilisation was observed in patients treated with octreotide or lanreotide (10/17 for a median duration of 9 months and 6/11 for a median duration of 10.5 months, respectively). Among the 7 other patients treated successively with both somatostatin analogues, 5/7 stabilisations were observed for a median duration of 22 months.

Among the 9 patients treated with somatostatin analogues in first line therapy, 5 (56%) had a stabilisation for 11 months.

3.2. Predictive factors for response

The pretreatment STGR was the only predictive factor for response to somatostatin analogue treatment. In Group 1, disease stabilisation was achieved in only 4 (33%) patients for 6 months compared with 13 (76%) patients in Group 2 for the same duration. The difference is statistically significant ($P<0.02$).

Sex, age, previous chemotherapy, the number of metastatic sites, the WHO PS and the time from the diagnosis to study entry were not predictive of response to treatment. In the univariate analysis, a trend was noted towards a lower response rate in the absence of or for low tumour uptake on the octreoscan, the absence of the carcinoid syndrome, poorly-differentiated lesions and primary pancreatic tumours (Table 3) However, the numbers in the subgroups limit the statistical analysis.

3.3. Functional and biological response

Of the 18 patients suffering from the carcinoid syndrome, a decrease of 50% was observed in diarrhoea and flushing in 16 over a median duration of 10.5 months (range 4–55 months). A decreased of 50% in symptoms was observed in 3/4 patients for a median duration of 6 months in Group 1 (range: 5–9 months), and in 9/10 patients for a duration of 11 months (range: 4–55 months) in Group 2.

Table 3
Predictive factors of response or stabilisation

Characteristics	No. of patients	No. with growth inhibition (%)	*P*-value
Sex			
Male	20	10 (50)	0.2
Female	15	11 (73)	
Age (years)			
<60	19	11 (58)	ND
>60	16	10 (63)	
Slope of tumour growth rate			
Group 1	12	4 (33)	<0.02
Group 2	17	13 (76)	
Primary tumour site			
Small intestine	12	9 (75)	0.1
Pancreas	13	6 (46)	
Histology			
Well-differentiated	30	19 (63)	0.1
Poorly-differentiated	5	1 (20)	
Carcinoid syndrome			
Present	18	13 (72)	0.2
Absent	17	8 (47)	
Octreoscan[a]			
Negative[b] or low intensity	12	6 (50)	0.2
Moderate or high intensity	20	14 (70)	

ND, not determined.
[a] 32 patients had an octreoscan.
[b] Disease stabilisation did not occur in the 2 patients with no tumour uptake.

Biological markers were available in 23 (66%) patients: 5-HIAA was used in 18 patients. Other markers were used in specific cases: GPα ($n=5$), calcitonin ($n=2$), gastrin ($n=2$), glucagon ($n=1$) and somatostatin ($n=1$). After treatment for 3 months, marker levels decreased by 50% in 39% of patients and stabilised in 22% over a median duration of 7 months (range 4–19 months). A 50% decrease of biological markers was observed in 3/10 patients for a median duration of 6 months in Group 1 and in 6/10 patients for a median duration of 5.5 months in Group 2.

4. Discussion

In our study, somatostatin analogues arrested the growth of progressive NET in 21/35 (60%) cases for a median duration of 11 months. Moreover, two patient subgroups were distinguished based on to their tumour growth rate before somatostatin analogue treatment. Disease stabilisation was achieved in 76% of patients classified in the 'slowly progressing' group with a low pretreatment tumour growth rate. In contrast, stabilisation was achieved in only 33% of patients classified in the 'rapidly progressing' group with a high pretreatment

tumour growth rate. Interestingly, the decrease in the STGR between slowly and rapidly progressing tumours was similar in magnitude. This suggests that the somatostatin receptor pathway is not neutralised in aggressive tumours, but that its effect in rapidly progressing tumours is too weak to permit tumour stabilisation. These results are interesting for they authorise the selection of patients in whom somatostatin analogues will be beneficial. However, only one objective response was observed, which is consistent with the weak antitumour effect of somatostatin analogues.

The median duration of survival of 29 months was rather short. This could be explained by the fact that most of the patients in our study were highly pretreated and had a median time of 37 months from diagnosis to entry in the study.

Our results are consistent with previous studies that evaluated the antitumour activity of somatostatin analogues. Arnold and colleagues [16] reported the results of treatment with 200 μg of octreotide three times daily in 52 patients with progressive NET. Stabilisation was achieved in 19 (37%) patients for at least 3 months with a median duration of 18 months. The Karnofsky index was found to be the only factor predictive of response in that study. Another study [17] on 34 patients with progressive NET treated three times daily with 250 μg of octreotide, reported disease stabilisation in 50% of cases for at least 2 months with a median duration of 5 months. Neither study obtained an objective tumour response. In their study on 19 patients treated with high doses of lanreotide (750–12 000 μg/day), Eriksson and colleagues reported one major response and disease stabilisation in 70% of cases over a median duration of 12 months [18]. 9 of the patients in this study had previously been treated with standard doses of octreotide suggesting a possible benefit of dose escalation. Interestingly, the same percentage of stabilisation was observed in our study using lower doses of somatostatin analogues. Moreover, no enhanced antitumour effect was gained by administering higher doses in 4 patients. The dose–response effect is still poorly understood. O'Toole and colleagues compared the efficacy of octreotide and lanreotide for treatment of the carcinoid syndrome in 33 patients. They found that both somatostatin analogues were equally effective in controlling symptoms [19]. In our study, no difference was noted in tumour stabilisation between octreotide and lanreotide. However, no conclusion can be drawn given the small number of patients.

Variations in tumour stabilisation rates between studies could be explained by the great heterogeneity of NET patients. This justifies at least the classification of patients based on the STGR. We found no other predictive factors for treatment response probably because of the small number of patients treated in each subgroup. Although a non-significant trend was observed for some characteristics, a primary tumour of the small intestine has already been reported to be predictive of treatment response in one study [17], but not in another study on a larger series of patients [16]. In our study, a trend was observed in favour of small intestine NET. Octreoscan uptake has never been evaluated as a predictive factor for tumour response, but a previous study showed that octreoscan uptake may predict functional response to somatostatin analogues in patients with carcinoid tumours [20]. We found no relationship between the intensity of octreoscan uptake and tumour stabilisation, but such quantification is difficult. It is, however, noteworthy that no tumour stabilisation was observed in the two patients with no tumour uptake on the octreoscan.

Only one out of five poorly-differentiated NET was inhibited by somatostatin analogue therapy. Poorly-differentiated NET most often present as aggressive metastatic disease [8,21]. Furthermore, the density of somatostatin receptors expressed in these tumours is low [22]. These overall results suggest that somatostatin analogue therapy is not appropriate for poorly-differentiated NET. Other patient characteristics such as sex, age, previous treatments and the time between diagnosis and inclusion were not predictive of response, as already reported [16].

Systemic chemotherapy yields a low response rate with a short median duration in metastatic carcinoid tumours [6]. In selected patients, liver chemoembolisation seems to offer better results [11]. Somatostatin analogue therapy should nonetheless be considered as a possible first-line treatment for carcinoid tumours.

In well-differentiated islet cell carcinoma, doxorubicin- and streptozocin-containing chemotherapy yields long-term objective response rates ranging from 33 to 69% [7,23]. However, this regimen is not suitable for some patients because of doxorubicin-induced toxicity. Somatostatin analogue therapy is an option worth considering in these patients for both first- and second-line therapy.

Another potentially active biotherapy in NET is interferon (INF). INF treatment yields an 11% objective response rate and a 39% stabilisation rate in patients with carcinoid tumours, which is comparable to results obtained with somatostatin analogues but interferon is more toxic [10]. In a recent study, Faiss and colleagues suggested that combination INF–somatostatin analogue therapy yields the same response rate as INF or somatostatin analogues alone, but the duration of response is longer [24].

Future studies will have to compare somatostatin analogues to chemotherapy in NET with a slow tumour growth pattern and determine the benefit, if any, of combining somatostatin analogues with chemotherapy. Furthermore, we need to investigate the signal transduction pathways mediated by somatostatin receptors,

that govern the antineoplastic effect and the inhibition of hormonal release. The development of specific analogues targeting the receptor mediating the antiproliferative effect should enhance the antitumour efficiency of somatostatin analogue therapy considerably. Assessment of Ki-67, a proliferation marker, in histopathological section should be investigated to predict tumour growth stabilisation with somatostatin analogues treatment.

In summary, our study confirms that somatostatin analogues produce an inhibitory effect that leads to tumour stabilisation in most patients with 'slowly progressing' NET. Determining the pretreatment STGR is a useful yardstick for selecting patients likely to benefit from somatostatin analogue therapy. NET differentiation, the primary tumour site, the carcinoid syndrome and the intensity of octreoscan uptake are potential predictive factors for response to somatostatin analogue therapy that merit further investigation in a larger series.

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