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Treatment of neuroendocrine gastroenteropancreatic tumours with somatostatin analogues: a personal case series and review of the literature

Trattamento dei tumori neuroendocrini gastroenteropancreatici con analoghi della somatostatina: casistica personale e revisione della letteratura

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Summary

Neuroendocrine tumours (NETs) are rare neoplasms characterized by low clinical incidence (approximately 1 case/100,000/year). The most frequent sites are in the digestive tract (70%). The aim of this retrospective study is to assess objective and symptomatic responses (limited to refractory chronic diarrhoea) after somatostatin analogue treatment and to compare our case history data with that available in the literature. The Rare Hormonal Tumour Group of Cremona has, since 1990, observed 165 patients with digestive NETs. Of these, 57 (34.5%) were treated with somatostatin analogues, of whom 20 were considered eligible for this study. The patients were divided into two groups: the first group included all 20 patients, while the second group included 9 tumour cases in 7 patients already studied in the first group who, during the follow-up, received a modified dose or different molecule type or a diverse formulation of the analogue. In this study, the high rate of disease stabilization in both groups (60% and 66.6%, respectively) confirmed that somatostatin analogues guarantee better responses in NETs with low grades of malignancy. Control of chronic refractory diarrhoea also demonstrated an overall partial response (PR) in 90.9% of the cases, which corresponds with improvement in the patient's

Riassunto

I tumori neuroendocrini (NETs) sono neoplasie rare caratterizzate da una bassa incidenza (circa 1 caso/100.000/anno). La sede più frequentemente colpita è il tratto digestivo (70%). L'obiettivo di questo studio retrospettivo è di valutare la risposta obiettiva e sintomatica (limitatamente alla diarrea cronica refrattaria) dopo trattamento con analoghi della somatostatina e di confrontare i dati della nostra casistica con quelli disponibili in letteratura. Il Polo Tumori Ormonali Rari di Cremona dal 1990 ha osservato 165 pazienti affetti da NETs del tratto digestivo. Di questi, 57 (34,5%) sono stati trattati con analoghi della somatostatina di cui 20 sono stati considerati eligibili per questo studio. I pazienti sono stati suddivisi in due gruppi: nel primo gruppo sono rappresentati tutti i 20 pazienti, nel secondo gruppo sono invece inseriti 9 casi di tumore relativi a 7 pazienti già studiati nel primo gruppo ai quali, nel corso del *follow-up*, è stata modificata o la dose del farmaco, o il tipo di molecola, o la formulazione dell'analogo. In questo studio l'elevata percentuale di stabilizzazione della malattia nei due gruppi (60% e 66,6% rispettivamente) conferma il dato che gli analoghi della somatostatina garantiscono migliori risposte nei NETs a basso grado di malignità. Anche il controllo sulla diarrea cronica refrattaria ha mostrato una ri-

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quality of life. In conclusion, somatostatin analogues can play a rôle in the treatment of digestive NETs with low grades of malignancy, with good differentiation, a low cellular proliferation index and a high specific receptorial density *in vivo*. An increased dosage of the analogue appears to determine better control of the disease and of the chronic refractory diarrhoea. New opportunities may arise from the synthesis of new, more powerful and selective analogues. Eur. J. Oncol., 11 (1), 57-64, 2006

Key words: **neuroendocrine tumours, somatostatin analogues, chronic diarrhoea, quality of life**

sposta parziale complessiva (PR) nel 90,9% dei casi che coincide con un miglioramento della qualità di vita del paziente. In conclusione, gli analoghi della somatostatina possono trovare un loro posto nel trattamento dei NETs digestivi a basso grado di malignità, con buona differenziazione, un basso indice di proliferazione cellulare e un'alta specifica densità recettoriale *in vivo*. L'aumento della dose dell'analogo sembra determinare un miglior controllo della malattia e della diarrea cronica refrattaria. Nuove opportunità potranno arrivare dalla sintesi di nuovi analoghi sempre più potenti e selettivi. Eur. J. Oncol., 11 (1), 57-64, 2006

Parole chiave: **tumori neuroendocrini, analoghi della somatostatina, diarrea cronica, qualità di vita**

Introduction

Neuroendocrine tumours (NETs) are rare neoplasms with a frequent hormonal component, characterized by a low clinical incidence (almost 1 case/100,000/year)[1]. The more frequent sites are the in digestive tract (70%), and the respiratory tract (25%)[2]; followed in 5% of cases by the skin, the thyroid and the adrenal glands.

The most recent WHO NETs classification[3] totally revised the previous one, finally providing a *dynamic* classification which considers not only the classic anatomo-pathological evaluation parameters (histotype, dimensions, site of the tumour, and grading) but also introduces new immuno-histochemical parameters (cellular proliferation index, number of mitosis, angio-invasiveness) and clinical parameters (hormonal hyperfunction symptoms, presence of metastases), distinguishing well differentiated tumours and carcinomas (with low grades of malignancy) and with good prognosis, from poorly differentiated carcinomas (with high grade of malignancy) characterized by an elevated cellular proliferation index and a bad prognosis.

The increased number of cases observed in recent years justifies the growing attention given by clinicians and pathologists to the improved imaging and laboratory methods, and to the use of new molecules, also with a radio-metabolic approach, with positive benefits for survival and quality of life.

The aim of this retrospective study is to assess objective and symptomatic responses (limited to refractory chronic diarrhoea) after somatostatin analogue treatment and to compare our case history data with that available in the literature.

Patients and methods

Eligibility criteria

Patients were required to have histologically confirmed metastatic NETs. Additional eligibility requirements were: bidimensionally measurable diameters, survival expectancy more than 12 weeks, Eastern Cooperative Oncology Group performance status of less than 2, adequate bone marrow function, and hepatic and renal function. Prior pretreatments with surgery, α-interferon, chemotherapy, and chemo-embolization were allowed.

A period ranging from one week to one month was required in the case of prior treatment with α-interferon, chemotherapy, and chemo-embolization. For surgical treatment, we considered complete enucleation of the primitive lesion or palliative care treatment (biliary and/or digestive by-pass); for the metastatic sites we considered only incomplete debulking.

Pretreatment and on-treatment evaluations

Pretreatment evaluation included complete medical history, physical examination, vital signs, assessment of symptoms, and complete biochemical profile.

All patients had a baseline chest radiograph, a computed tomography scan (CT) of pertinent lesions, and a scintigraphy with ^{111}In-DTPA-D-Phe^{1}-octreotide (OctreoScan®).

Clinical examinations were scheduled at start and after 6 months and included complete physical examination, vital signs, and assessment of symptoms.

At the end of the sixth month period of somatostatin analogue treatment, the patients underwent a CT of pertinent indicator metastatic lesions, in order to highlight the objective and symptomatic responses, where present; our attention was focussed on the refractory chronic diarrhoea as, in our experience, this is the most common symptom (11%) of those characterizing the functioning forms of NETs[4]. The patient indicated a score from 0 to 10 at the beginning and after 6 months' somatostatin analogue treatment.

Treatment

The patients enrolled in this retrospective study were treated with somatostatin analogues in different therapeutic lines.

The molecules used were as follows:
– octreotide subcutis (sc) (range: 1500-2000 μg/*die*);
– octreotide LAR 20 mg (every 14 days);
– octreotide LAR 30 mg (range: from 30 mg/every 14 days, to 30 mg/every 28 days);
– lanreotide PR 60 mg (range: from 60 mg/every 14 days, to 60 mg/every 28 days);
– lanreotide Autogel 120 mg/every 28 days;
– association of octreotide LAR 30 mg/every 14 days with lanreotide PR 60 mg/every 14 days.

Response

Two response categories were assessed: objective and symptomatic. Objective responses were defined according to International Union Against Cancer criteria, and were the following: complete response (CR): complete disappearance of all known disease for a minimum of 1 month; partial response (PR): more than 50% decrease in the product of perpendicular diameters of measurable tumour lesion for at least 1 month; stable disease (SD): tumour size decrease by less than 25% or increased by less than 25%; progressive disease (PD): tumour size increased by more than 25%. Measurements were taken on the largest lesion.

Symptomatic response (limited to refractory chronic diarrhoea) was defined as follows: CR, complete relief of symptoms, and PR, a reduction of at least 50% in both the frequency and intensity of symptoms.

The response was calculated from the beginning of therapy up to 6 months.

Patient characteristics

The Rare Hormonal Tumours Group of the Azienda Ospedaliera Istituti Ospitalieri at Cremona, has studied NETs since 1990. To date it has observed 165 patients with gastroenteropancreatic NETs, 18 with carcinoid tumours, 11 with Merkel cell carcinoma, 6 with pheochromocytoma, 3 with medullary thyroid carcinoma, and over 30 cases of carcinomas with neuroendocrine differentiation of different sites (such as breast, prostate, paraganglions, soft tissue, and paranasal sinus).

Of all the digestive NETs, 57 (34.5%) were treated with somatostatin analogues, and 20 of them were considered eligible for this study. Overall patients characteristics are given in Table 1.

Thirteen patients were male and 7 female, with a mean age of 59 years (range: 20-74 years).

All patients included in the study exhibited advanced disease, and most patients showed progressive disease. Seven patients had endocrine pancreatic tumours (EPT), 5 mid-gut carcinoids, 3 primitive unknown site, and 1 gastric, colonic, rectal, duodenal and mesenteric neuroendocrine carcinoma.

In 19/20 patients the tumour was well differentiated (G_2). In 9/20 patients the cell proliferating index (ki67) was studied and in only one case (1/9) it was found to be

Table 1 - Patient characteristics

Patients enrolled	20
Female/male	7/13
Mean age/ (range)	59 (20-74)
Type of tumour	
• EPT[a]	7
• Mid-gut carcinoid	5
• Primitive unknown site	3
• Gastric carcinoid	1
• Colonic carcinoid	1
• Rectal carcinoid	1
• Duodenal net	1
• Mesenteric net	1
Well differentiated tumour	19/20
Sites of metastases	
• Liver	17
• Lymph-nodes	9
• Lung	2
Previous treatment	
• Surgery (explorative)	16 (6/16)
• Chemotherapy	9
• α-interferon	3
• Chemoembolization	1
• No treatment	1
OctreoScan® positive	16/17
Functioning disease	9/20

[a] Endocrine pancreatic tumour

more than 60%; in the other cases the value of ki67 varied in a range from less than 1% to 5%. All patients had measurable disease.

The sites of metastases were as follows: liver 17, lymph nodes 9, lung 2.

Sixteen patients had received primary surgery (6 only explorative), 9 were pretreated with chemotherapy, 3 with α-interferon, 1 with chemo-embolization, and 1 had no previous treatment. Nine out of 20 patients (45%) were symptomatic (refractory chronic diarrhoea).

Octreotide scintigraphy was positive in 16 out of 17 cases (94%, 3 patients not available).

The patients in the study were divided into two groups: the first group included all 20 patients, while the second group included 9 tumour cases in 7 patients already studied in the first group who, during the follow up, received a modified dose or different molecule type or a diverse formulation of the analogue.

The patients in the second group were as follows: 3 EPTs, 1 mid-gut carcinoid, 1 primitive unknown site, 1 duodenal, and 1 mesenteric neuroendocrine tumour. All tumours were well differentiated with ki67 below 3%. The metastases sites were: 7 liver, 2 lung, and 2 lymph nodes. Octreotide scintigraphy was positive in 6/6 patients (100%, 1 patient not available). Five patients received primary surgery (2 explorative), 4 chemotherapy, 1 α-interferon, and 1 no previous treatment. Two out of 7 patients were symptomatic (28.5%). The median age was 62 years.

Therefore, the full study considered a total of 29 cases of patients with digestive NETs treated with different somatostatin analogue molecules, with diverse formulations and dosage.

Results

In the first group we separated patients treated with octreotide sc at the dose of 1500 μg/*die* (13 patients), from patients treated with long acting analogues: octreotide LAR 30 mg/every 28 days (5 patients); lanreotide PR 60 mg/every 14 days (1 patient), and octreotide LAR 30 mg in association with lanreotide PR 60 mg/every 14 days (1 patient).

In the second group, 9 tumour cases (7 patients) were distributed in the following way: 1 patient treated with lanreotide PR 60 mg/every 28 days, 1 patient treated with octreotide LAR 20/every 14 days, 1 patient treated with octreotide sc with 2000 μg/*die*, 1 patient treated with octreotide LAR 30 mg/every 14 days, 1 patients treated with lanreotide Autogel 120 mg/every 28 days, 1 patients treated with the association of octreotide LAR 30 mg and lanreotide PR 60 mg every 14 days, and 3 patients treated with octreotide LAR 30 mg/every 28 days. These were patients for whom we adopted an increased dose of the current analogue therapy (3), or a shift from the sc formulation to LAR (4), or a different analogue type (1), or an association of the two different analogues (1).

While recognizing a different pharmacokinetic profile in the two analogues used[5] and different clearance[6], we decided to consider the second group as a whole in order to avoid impediment of recognition of statistically significant data due to data dispersion.

In both groups of patients we measured the product of perpendicular diameters of the major metastatic lesion at the start of the treatment and after 6 months. In the same way, we scored the different number of stools at the start and after 6 months of treatment with somatostatin analogues.

First group

In the first group, in 13 patients with measurable disease and treated with octreotide sc 1500 μg/*die*, 2/13 (15.3%) achieved a PR, 8/13 (61.5%) had no change (SD), and 3/13 (23%) had PD. Of 5 patients treated with octreotide LAR 30 mg/every 28 days, 4/5 (80%) had no change (SD), 1/5 (20%) had PD. In particular, one patient treated with lanreotide PR 60 mg/every 14 days had PR, while the only one treated with the association of analogues achieved CR. Overall objective response was CR 5% (1/20), PR 15% (3/20), SD 60% (12/20), and PD 20% (4/20).

In relation to control of symptoms, 8/20 (40%) had functioning tumours with refractory chronic diarrhoea. Of the 8 patients with a measurable number of stools, 5 were treated with octreotide sc, and 3 with octreotide LAR 30 mg: 4/5 (80%) treated with octreotide sc achieved a PR, and 1/5 (20%) had no change (SD), whereas 3/3 patients (100%) treated with octreotide LAR 30 mg had CR. In one patient with one carcinoid of the right colon, treated with octreotide sc, the progression of disease coincided with the appearance of diarrhoea not present at the start of the therapy. Applying the Student test a difference is encountered, albeit of low significance, in refractory chronic diarrhoea control with octreotide LAR 30 mg *vs* octreotide sc (p=0.087 *vs* p=0.163).

Second group

In the second group, among 9 cases with measurable disease, 6/9 (66.6%) had no change (SD), and 3/9 (33.3%) had PD. Regarding the control of refractory chronic diarrhoea, only 2 patients had a functioning tumour with a 100% response (Table 2).

Table 2 - Evaluation of response

	Objective		Symptomatic response	
	N.	%	N.	%
First group				
Assessable	20		8	
CR[a]	1	5	3	37.5
PR[b]	3	15	4	5.0
SD[c]	12	60	1	12.5
PD[d]	4	20		
Second group				
Assessable	9		2	
CR	-		2	100.0
PR	-		-	
SD	6	66.6	-	
PD	3	33.3	-	

[a] Complete response
[b] Partial response
[c] Stable disease
[d] Progressive disease

Discussion

Somatostatin analogues have, without doubt, written an important chapter in the treatment of neuroendocrine tumours. Not only have they stimulated clinical interest in a little known neoplastic pathology, they have also permitted, in many cases, a change in the approach to the disease, often delivering, in the case of advanced forms, an equilibrium between the interlocutory position of oncologists and the aggressive position of surgeons, producing improved patient quality of life.

Somatostatin analogues are highly effective in the control of clinical symptoms in patients with functioning NETs. Inhibition of tumour growth or even decrease in tumour size have also been reported[7-15]. With the use of octreotide, partial responses are not encouraging (0-31%), yet the observation of a high percentage of stabilization of the disease (15-63%) authorizes us to think that octreotide may modify cellular growth progress and may thus be indicated in metastatic patients with neuroendocrine tumours with a low grade of malignancy [2, 16-19].

It is also interesting to note that the best partial response rate (31%) is referable to high dose octreotide treament (1,500-6,000 μg/*die*) (Table 3).

The heterogeneity of the cases recruited in the multi-centre studies (mid-gut carcinoid, endocrine tumour of the pancreas, Merkel cell carcinoma, medullary thyroid carcinoma, pheochromocytoma), the different hormonal state (functioning/non functioning tumours), the often unknown receptorial state *in vivo*, the ample variability of the octreotide dosages (50-6,000 μg/*die*) and, finally, its use in different lines can put the objectivity of the data collated in doubt.

Lanreotide activity has been evaluated in numerous studies. With daily lanreotide doses ranging from 2,250 to 15,000 μg, and monthly lanreotide PR from 10 to 30 mg, a total of 431 patients have been treated[8, 20-33] (Table 4).

We currently observe a certain superimposition of lanreotide and octreotide, especially in symptom control and in the biological response. Significant objective

Table 3 - Antiproliferative activity of octreotide (50-6000 μg/*die*) in the scientific literature

Author	Year	Patients	PR (%)[a]	SD (%)[b]	PD (%)[c]
Gorden[7]	1989	94	13	63	24
Kvols *et al*[14]	1989	66	17	-	-
Eriksson *et al*[15]	1990	14	28.5 (16-21 months)	-	-
Öberg *et al*[13]	1991	22	9	-	-
Arnold *et al*[12]	1992	68	4.4	50	45
Anthony *et al*[8]	1993	13	31	15	54
Saltz *et al*[9]	1993	34	-	50 (0-27 months)	-
Arnold *et al*[10]	1994	47	-	40	-
Di Bartolomeo *et al*[11]	1996	58	3	43 (> 6 months)	-
Total		416	11.7	43.5	41

[a] Partial response
[b] Stable disease
[c] Progressive disease

Table 4 - Somatostatin analogues: objective responses (882 patients)

	Octreotide	Lanreotide	Lanreotide 10	Lanreotide 30	Lanreotide 30	RC-160
Dose	50-6000 μg/*die*	2250-15000 μg/*die*	10 mg x 3/month	30 mg x 2/month	30 mg x 3/month	1.5 mg (continuous infusion)
Patients	416	62	10	341	18	35
PR[a]	0-31%	14.1%	-	6.9%	-	-
SD[b]	40-63%	47%	90%	45%	77.7%	68%
PD[c]	24-54%	52.4%	-	39.1%	-	24%

[a] Partial response
[b] Stable disease
[c] Progressive disease

responses were observed with high doses of lanreotide[30] with incremented apoptosis associated with stabilization of the disease[27, 34-35]. As in the case of octreotide, lanreotide treatment determines a global improvement in the quality of life, influenced by optimal diarrhoea control and a secondary gain in night time rest[25, 26].

The introduction of lanreotide 60 to therapy has delivered an unquestionable benefit to patients in terms of compliance, with data relative to symptom control and to the disease in comparison to earlier formulations[36].

More recently, the synthesis of the Autogel® 120 preparation created a basis for a new formulation of the drug, more potent and with different pharmacokinetic characteristics[37, 38].

In our survey, the PR percentage in the first group (15%) and the SD percentages in both the first (60%) and second groups (66.6%) confirm the data in the literature. Of the 3 cases in the first group with PR, 2 were observed after 6 months' treatment with octreotide sc (1 mid-gut carcinoid tumour with low grade of malignancy treated with surgery and chemo-embolization, and 1 duodenal metastatic low grade gastrinoma treated with surgery); the response was complete (CR) after therapy with octreotide LAR 30 mg/every 28 days for both patients (the first, after 3 years of treatment, and the second after 4 years). The third PR in the first group was observed after 6 months of treatment with lanreotide PR 60 mg/every 14 days (a low grade metastatic EPT not previously treated). The only CR in this study refers to a case of metastatic mid-gut carcinoid tumour treated surgically and previously with chemotherapy, α-interferon, and association of the two analogues for 6 months. The latter two cases confirm the data in the literature where the best objective responses were observed with increased doses of somatostatin analogues, suggesting a dose-dependent function for somatostatin analogues in the treatment of NETs.

In the second group too, despite the absence of PR, we emphasise that in 3 cases SD was achieved with increased analogue dosage: 1 metastatic EPT treated with octreotide LAR 20 mg/every 14 days, 1 primitive unknown metastatic tumour treated with octreotide LAR 30 mg/every 14 days, and 1 metastatic pancreatic GRFoma treated with octreotide 2000 μg sc/*die*. In the latter case, at a dosage of 1500 μg sc/*die* an important objective control of the disease after 6 months of treatment was observed, with reduction in the diameters of the primitive lesion from 7x3 to 2.7 cm, and after 6 months treatment with 2000 μg sc/*die* from 5x3.6 to 4x3 cm. The patient continued to refuse surgical treatment, and after 8 years of chronic hormonal treatment the disease spontaneously progressed[39].

By contrast, the only patient treated with the association of analogues progressed after 6 months. But it is very important to note that this patient had been in chronic treatment with analogues since 1993: he had SD with octreotide sc (first group), and with octreotide LAR (second group) before shifting to PD, despite supplementing with other therapies, such as chemotherapy and immunotherapy.

The disease control observed in both groups confirms the rôle of OctreoScan® as an effective prognostic indicator, as our survey indicates that benefits from somatostatin analogue treatment are delivered principally in metastatic NETs with a low grade of malignancy and with elevated receptorial density *in vivo*, as also reported in the literature[2, 17]. Some new elements are provided by a recent consensus by Öberg *et al*[40], which confirms the unquestionable rôle of OctreoScan® as an indispensable method in the selection of patients for somatostatin analogue treatment. The treatment of patients with non functioning disease (also metastatic) remains controversial, as does adjuvant or precautionary therapy after surgical debulking, radio-frequency or embolization, all the more in the absence of residual disease[40].

In our study also, the elevated SD percentage in the two groups (60% and 66.6%) confirms that somatostatin

analogues deliver better responses in tumours with low grades of malignancy, represented in 95% of cases in the first group (19/20) and 100% in the second group. In our study, OctreoScan® presented a very low density of receptors in the only case with scarce cell differentiation (G_3), and with ki67 more than 60%; the patient went at once to PD before the end of the study.

In relation to symptom control, somatostatin analogue treatment showed a good control of diarrhoea as confirmed in the literature[41, 42]. Diarrhoea control thus assumes a determinant importance as it improves patients' quality of life, considered as improvement of fatigue, sleeping problems, and general health[25].

Conclusions

In conclusion, somatostatin analogues play a rôle in the treatment of NETs with a low grade of malignancy, with good differentiation, a low cellular proliferation index and OctreoScan® with high receptorial density *in vivo*.

An increased analogue dose appears to determine better control of the disease and of the chronic diarrhoea.

Hormonal symptom control, and, in particular, that of chronic diarrhoea, delivers improved quality of life in the patients studied. New opportunities may derive from SOM 230 experimentation[43], from the synthesis of new selective BIMs and of other peptidomimetic analogues still under evaluation by researchers[44]. Finally, studies in receptorial homo/heterodimerization[45] and in the synthesis of molecular hybrids[46] may produce new opportunities for better hormonal regulation and better receptorial affinity with favourable effects on treatment of NETs.

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