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Role of somatostatin analogs in the management of neuroendocrine tumors

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ABSTRACT

Neuroendocrine tumors are rare neoplasms. During the last two decades, somatostatin analogs, exerting their activity through both receptor binding and enzymatic inhibition mechanisms, have been a key option in the management of neuroendocrine tumors. The treatment of neuroendocrine tumors with high doses of somatostatin analogs determined high rates of tumor stabilization, but the dose-response of somatostatin analogs on symptomatic relief and stabilization of tumor growth remains unpredictable. Several studies have indicated a higher efficacy of somatostatin analogs in well-differentiated, low-grade malignancy tumors that express a high density of somatostatin receptors. Synthesis of new, more effective molecules, with different pharmacokinetic profiles, receptor affinity and binding stability, will ease the clinician's tasks and improve patient expectancies in terms of survival and quality of life. Further studies are needed to clarify mechanisms underlying the better antiproliferative effect of higher doses of somatostatin analogs and to determine the optimum dose to saturate specific receptor subtypes. **Free full text available at www.tumorionline.it**

Introduction

Neuroendocrine tumors (NETs) are rare neoplasms, with a mean incidence estimated at 1-2 new cases per 100,000 people per year[1]. The age-adjusted incidence for digestive system NETs increased 720% over the last 30 years[2]. In most cases, NETs are low-grade malignancies with a long survival, such as malignant forms with lymph node and liver metastases (15-20%). Poorly differentiated, high-grade malignancy tumors with possible lung, bone, brain and skin metastases always have an unfavorable prognosis.

According to synthesis and secretion of aspecific peptides, NETs are classified as functioning (with clinical symptoms of hormonal excess, about 20% of cases) and nonfunctioning (without clinical symptoms). Atypical signs and symptoms can help to identify NETs, i.e., flushing and chronic refractory diarrhea which occur in carcinoid syndrome, diabetes and necrolytic migratory erythema which result from glucagonoma, and erosive gastritis with diarrhea from gastrinoma.

An early anatomic classification of NETs was based on their embryological origin (foregut, midgut and hindgut). A recent pathologic review classified NETs in tumors and carcinoma according to their malignancy grade, combining traditional morphological criteria (like istotype and grading) to histochemical parameters (like biological activity, angioinvasivity, mitotic and cell proliferation index), which are crucial for a correct prognosis[3].

In relation to disease status and variable biological behaviors, diagnostic procedures and therapy may be different. For advanced NETs, surgery can be combined with conventional chemotherapy, whereas biological therapy (hormone therapy and immunomodulating agents) can be effective in low-grade malignancy forms.

Among the latter therapies, somatostatin analogs (SSAs) have demonstrated their value in NET treatment regimens. Furthermore, to decisively stimulate the interest of

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clinicians in a not well known neoplastic disease, SSAs often allow modification of the therapeutic approach, with a balance between the aggressive approach of the surgeon and the watchful waiting approach of the oncologist and endocrinologist, resulting in an improvement in quality of life.

Somatostatin analogs

Of the many hundreds of SSAs synthesized, noteworthy are octreotide (SMS 201-995) and lanreotide (BIM 23014), as well as octastatine or vapreotide (RC-160), which was used in a Scandinavian experimental trial[4]. In the two last decades, the role of SSAs has undergone a number of transformations, contributing to better understand the specific properties of these molecules.

In the meantime, new therapeutic opportunities have been developed through pharmacological studies, and prognostic aspects have been clarified by pivotal immuno-histochemical studies. For a better understanding of the strategic role played by SSAs in the management of NETs, it is necessary to highlight the following aspects.

The therapeutic space for SSAs cannot be considered exclusive as a complete antineoplastic option. Since one molecule entirely satisfying the therapeutic needs of patients with NETs does not exist, the ideal spirit with which we have to approach the treatment of these tumors is the integration with more molecules, such as chemotherapeutic and immunomodulating agents in association with surgery.

For a long time, the clear division between benign and malignant forms prevented the correct classification of a number of intermediate forms. Today, the observation of several factors expressed by the neoplastic cell can be of great help for a better definition of the prognosis within a wide range of therapeutic options, with SSAs playing a prominent role.

The different embryological origin of NETs (ecto/endodermic) determines different natural histories of the disease and, sometimes, a different response to the therapy.

The prognosis strongly depends on the clinician's cultural approach. For instance, surgeons are trained to consider exploratory methods even in advanced disease. Surgical tumor debulking is an option that does not significantly modify life expectancy but considerably improves the quality of life[5], mainly in patients with symptomatic low-grade NETs. Cytoreductive surgery has a role in moderating the use adjuvant therapies for residual tumor.

Pharmacological profile

In addition to their recognized suppressive effects on secretory symptoms, SSAs induce an antiproliferative effect through two different mechanisms – 1) a direct action, mediated by somatostatin receptors (SSTRs) expressed by tumor cells (with antimitotic and apoptotic effects), and 2) indirect actions, independent of the receptors, which include inhibition of growth-promoting hormone and growth factor secretion and antiangiogenic and immunomodulating activity[6]. The inhibition of mitosis is mediated by the interaction with $SSTR_2$ and $SSTR_5$ subtypes and results in blocking cell division[7]. The induction of apoptosis (programmed cell death) seems to be due to two different actions: interaction with $SSTR_3$[8] and inhibition of insulin-like growth factor 1[9] with a 70% correlation for biochemical response and disease stabilization[10,11].

The antiproliferative actions of SSAs are also based on an antiangiogenic effect mediated by inhibition of both vascular endothelial growth factor[12] and tyrosine kinase[6]. Finally, antitumor effects due to changes in the activity of components of the immunocompetent system, such as natural killer cells, have been reported during SSA treatment[6,13].

In the past decade, several studies have been performed with the aim of verifying the antiproliferative effect of SSAs. Stabilization of disease was obtained in 40-63% of cases. A wider variability (0-31%) was reported for partial responses, with higher rates for high dosages (6000 µg/day) of octreotide, thus supporting a dose-response relationship[14-22] (Table 1). Similar results were obtained with high doses of lanreotide and for RC-160[4,11,23-33] (Table 2).

In the last years, the study that has probably given definitive confirmation of the ability of long-acting SSAs to control tumor growth is the PROMID trial, the first randomized, double-blind, placebo-controlled, multicentre, phase IIIb study of octreotide LAR (Long-Acting Release) in patients with locally inoperable or metastatic

Table 1 - Antiproliferative activity of octreotide (50-6000 µg/day)

Author(s)	Year	No. cases	PR (%)	SD (%)	PD (%)
Gorden[15]	1989	94	13	63	24
Kvols *et al*[21]	1989	66	17	–	–
Eriksson *et al*[20]	1990	14	28.5 (16-21 mo)	–	–
Öberg *et al*[22]	1991	22	9	–	–
Arnold *et al*[16]	1992	68	4.4	50	45
Anthony *et al*[14]	1993	13	31	15	54
Saltz *et al*[18]	1993	34	0	50 (0-27 mo)	–
Arnold *et al*[17]	1994	47	0	40	–
di Bartolomeo *et al*[19]	1996	58	3	43 (>6 mo)	–
Total		416	11.7	43.5	41

PR, partial response; SD, stable disease; PD, progressive disease.

Table 2 - Somatostatin analogs: objective response (882 patients)

Dose	Octreotide 50-6000 µg/d	Lanreotide 2250-15000 µg/d	Lanreotide 10 10 mg × 3/mo	Lanreotide 30 30 mg × 2/mo	Lanreotide 30 30 mg × 3/mo	RC-160 1.5 mg (CI)
PR	0-31%	14.1%	–	6.9%	–	–
SD	40-63%	47%	90%	45%	77.7%	68%
PD	24-54%	52.4%	–	39.1%	–	24%
No. cases	416	62	10	341	18	35

PR, partial response; SD, stable disease; PD, progressive disease; CI, continuous infusion.

midgut NETs. A total of 85 treatment-naïve patients was randomized to receive either octreotide LAR 30 mg/month or placebo for 18 months, until tumor progression or death. Median time to progression in the octreotide LAR group and the placebo group was 14.3 and 6 months, respectively. After 6 months of treatment, stable disease was seen in 64% and 37.2% of patients treated with octreotide and with placebo, respectively. Nearly two-thirds of patients treated with the analog achieved stable disease at 6 months. With the study, octreotide LAR showed a more favorable response than placebo, and it should be considered the standard cure in patients with metastatic well-differentiated midgut NETs[34].

Frequently occurring neuroendocrine tumors and somatostatin analogs

Octreotide treatment of gut NETs improved biochemical indexes in 90% of cases with gastrinoma[35] and reached a complete objective response in two studies[36,37]. In 90% of patients with benign insulinoma, octreotide therapy did not achieve an objective response; hormone secretion was poor and clinically important hypoglycemia was observed[38]. In VIPomas, octreotide was efficient in the control of watery diarrhea in 56% of patients, whereas biochemical indexes were improved in 60%[35,39]. Furthermore, two studies showed that the drug induced a reduction in metastatic tumor size[40,41]. In the glucagonoma syndrome, octreotide obtained glycemic control in 10-90% of patients[42], the control of necrolytic migratory erythema in 55-90% of cases[43,44], and the control of diarrhea in 70% of cases[45]. The control of symptoms in malignant carcinoid syndrome, with dosages between 150 and 750 µg/day, was obtained in 77% of cases for diarrhea and in 87% for flushing[46]. Biochemical control, in terms of 5-hydroxyindoleacetic acid levels, was obtained in 70-87% of cases with dosages of 50 to 200 mg/day[22]. In the same study, 28% of assessable patients showed objective tumor response[22]. Mean survival was more than 3 years, superior to that observed with chemotherapy[22].

Infrequent neuroendocrine tumors and somatostatin analogs

In a patient with metastatic growth factor-releasing hormone tumor, treatment with octreotide (2000 µg/day) gave a complete response on secondary localizations and a partial response >50% on the primary localization, which were stable for more than 6 years[47]. The conventional treatment of advanced pheochromocytoma resulted in a survival >5 years in 45% of cases. A case report on the administration of octreotide (600 µg/day) in a patient describes good control of pain, blood pressure and catecholamine release, but the objective control of the disease was poor[48]. In a patient with a metastatic paraganglioma, treatment with octreotide (500 µg/day) had beneficial effects, reducing meta-iodobenzylguanidine uptake, with an improvement in Karnofsky index, digestive function and biological parameters[49]. The therapeutic benefits obtained with octreotide in the treatment of advanced medullary carcinoma of the thyroid are poor, except a good control of diarrhea. In Merkel cell carcinoma, chemotherapy guarantees a 3-year survival in 55% of cases. In a patient suffering from metastatic Merkel cell carcinoma, treatment with octreotide (1000 µg/day) determined the immediate disappearance of metastasis and a complete remission of disease after 10 months, which was stable for 3 years[50]. The combination of octreotide (1500 µg/day) and prednisone produced a complete clinical response in a patient with a malignant thymoma and pure red-cell aplasia. The patient remained in complete remission for more than 2 years without surgical intervention[51].

Dosage and limitations of treatment with somatostatin analogs

The dose of SSAs influences the history of the disease and, in particular, symptom control, tumor stabilization, and, in a few cases, tumor objective response[4,14,30]. Several studies have demonstrated that SSTRs are expressed mainly in cells of well-differentiated tumors with a low-grade of malignancy, that some advanced tu-

mors can lose part of the five distinct receptor subtypes ($SSTR_{1-5}$)[52,53], and that subtypes of somatostatin receptor can assemble as functional homo- and heterodimers[54]. In principle, non-functioning tumors and an in vivo low density of membrane-bound SSTRs (OctreoScan®) thus represent the main limitations for the treatment of NETs with SSAs. Usually, the in vivo absence of receptors is seen in poorly differentiated tumors with an unfavorable prognostic index, where a treatment with SSAs is not recommended. However, the apparent absence/low-density of receptors may be due the expression of other SSTR subtypes ($SSTR_1$, $SSTR_3$, $SSTR_4$) not evidenced by OctreoScan®. In these cases, SSA treatment in patients with functioning tumors could guarantee an effective symptom control, as described in a paper in 4% of cases[55].

Long-acting somatostatin analogs

The introduction of SSAs in an LAR formulation (octreotide LAR 10, 20, 30 mg; lanreotide 30, 60, 90 mg, Autogel® 60, 90, 120 mg) eased their use and improved patient compliance. In the case of octreotide, for instance, the switch allowed a change from 90 subcutaneous administrations/month to one or two intramuscular administrations every 28 days. The different clearance of octreotide and lanreotide, as well as the differences in the carrier microparticles, determines a different pharmacokinetic profile, which results, in the case of lanreotide, in a higher number of administrations per month. According to the characteristics of molecule and carrier, the steady state is reached in a maximum of 90 days, and often a daily rescue treatment is required for symptom control[56]. With a correct use of LAR doses, at steady state there is no evidence of tachyphylaxis (typical of subcutaneous administration). In fact, these formulations allow a constant receptor saturation and avoid desaturation, resulting in less drug efficacy over time.

Receptor desensitization could be due to the selection of SSTR-negative cell clones rather than to internalization and receptor down-regulation[57,58]. Another hypothesis, yet to be proved, could involve new SSTR subtypes unable to keep a stable binding with the SSAs. Finally, it should be pointed out that SSAs, in addition to a natural affinity for some SSTR subtypes, may have a different binding stability, with a higher clearance as for lanreotide[59,60]. For this reason, two recent studies evaluated the possibility of alternating lanreotide and octreotide. At present, results are controversial and further investigations are needed[61,62]. Affinity for the cellular receptor and binding stability are the key points for SSAs to be investigated in future studies.

Treatment with high doses of SSAs in progressive metastatic NETs has been evaluated in a number of studies[2,32,63-66]. In a personal research, the high rate of disease stabilization (66.6%) confirmed that SSAs have a better response in well-differentiated tumors with a low grade of malignancy, a low proliferation index and an in vivo high receptor-specific density. The control of functioning disease (for chronic refractory diarrhea only) was obtained in more than 90% of cases, with an improvement in quality of life[62].

New somatostatin analogs

New possibilities to regulate cellular hormonal sensitivity with higher receptor affinity are now under evaluation. The studies deal with subtype-selective agonists of the SSTR, somatostatin peptidomimetics[67], receptor homo/heterodimerization[54] and hybrid molecules[68]. In this evolving picture, SOM-230 (pasireotide) – a cyclohexapeptide analog developed to treat acromegalic tumors, Cushing's syndrome and NETs – was introduced. SOM-230 binds with a high affinity to four out of the five SSTR subtypes, with IC_{50} for $SSTR_5$ >$SSTR_2$ >$SSTR_3$ >$SSTR_1$. The affinity for $SSTR_4$ is less than 100 nM. Compared to octreotide, SOM-230 has a receptor affinity 30, 5, 40 and 2.5 times higher for $SSTR_1$, $SSTR_3$, $SSTR_5$, and $SSTR_2$, respectively. The high affinity for $SSTR_5$ is the basis for the enhanced effect in lowering insulin-like growth factor 1 plasma levels, whereas the antiproliferative and proapoptotic effects are based on the inhibition of $SSTR_5$ and $SSTR_3$. The latter subtype may also have a role in immunological responses, because human peripheral B- and T-lymphocytes exclusively express $SSTR_3$.

SOM-230, which contains only six modified and unmodified amino acids instead of the 14 amino acids in somatostatin, shows a very favorable $t_{½}$ of nearly 24 h, longer than that of octreotide and lanreotide. SOM-230 inhibits the secretion of the growth hormone in human growth hormone-secreting pituitary tumors, ACTH release by corticotroph tumor cells in Cushing's syndrome, and prolactin secretion from prolactinomas and controls symptoms related to functioning NETs.

To date, despite promising premises, a real advantage for SOM-230 in comparison with currently used SSAs has not been shown[68,69].

Discussion

SSAs can guarantee an optimum control in more than 80% of functioning NETs, without major side effects. Despite experimental and clinical evidence of disease control and favorable responses, mainly in low-grade malignancy tumors, SSAs effects are often unpredictable and sometimes independent of receptor status, with a possible deficit of internalization of receptor message. Some response indexes for a strategic use of SSAs have been identified: tumors with well-differenti-

ated grading, tumors with a low proliferation index, tumors with a small number of mitosis, tumors with a low grade of malignancy, and tumors with in vivo high receptor density.

Analogously, to have a suitable pharmacological response to control tumor growth, the selection of the SSA should consider the following aspects: high selectivity for $SSTR_2$ and $SSTR_5$ and high binding stability and low clearance.

Finally, the dosage of the selected SSA should guarantee an optimum receptor saturation. Plasma levels should be at least 0.5 ng/ml for octreotide and a little higher for lanreotide. Furthermore, to avoid tachyphylaxis, a better control of hormonal symptoms and tumor could be reached. In some studies, an increase in therapeutic doses gave better antineoplastic control, probably due to a dose-response relationship and a more favorable Karnofsky index[62]. The SSA treatment of patients with non-functioning NET (metastatic or not) remains controversial, as does their use as adjuvant therapy after surgical debulking, radiofrequency ablation or tumor embolization[70].

Conclusions

To date, SSAs are a milestone for the management of NETs and the control of NET-related syndromes. In the future, new, more potent molecules – with different pharmacokinetics, receptor affinity and stability – will ease the tasks of the clinician, prolong patient life expectancy, and improve quality of life. Current *in vitro* and *in vivo* data suggest a role for high-dose SSAs in the treatment of patients with NETs, in particular in non-responders to standard dosages. However, further studies are needed to clarify mechanisms of proliferation control by high doses and to define the optimum dose to properly saturate specific SSTRs. Recently, SSAs were also associated with a small number of new targeted agents in the treatment on NETs, particularly sunitinib malate[71], mammalian target of rapamycin (mTOR) kinase inhibitor everolimus[72], and vascular endothelial growth factor ligand-binding monoclonal antibody bevacizumab[73], whose results are still being evaluated by the clinicians.

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