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Anti-proliferative effect of somatostatin analogues in gastroenteropancreatic neuroendocrine tumours

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ABSTRACT

Gastroenteropancreatic neuroendocrine tumours (GEP NET) belong to a heterogeneous group of rare tumours. Most NETs of the gastrointestinal tract are non-functioning and therefore are diagnosed at an advanced stage, which impedes radical surgery. Overexpression of somatostatin receptors (SSTR) can be found in most GEP-NETs.

Somatostatin analogues play a major role in therapy of hormonally active NETs. These agents also have an anti-proliferative effect, interacting directly with membrane receptors on tumour cells or by indirect inhibition of growth factors, angiogenesis, induction of apoptosis, or their effect on the immune system. The anti-proliferative effect of octreotide LAR was demonstrated in the phase III randomised study PROMID, which included 84 treatment-naive patients with disseminated well differentiated NETs of midgut or unknown origin. The anti-tumour effect of octreotide LAR was observed irrespective of tumour functional status. Additionally, a retrospective study was presented at the ASCO meeting in 2014, showing a therapeutic effect of octreotide LAR of even longer duration than in the PROMID study. Authors of the report identified also favourable predictive factors for octreotide LAR therapy. The anti-proliferative effect of lanreotide Autogel® was demonstrated in the CLARINET study, which included 204 patients with non-functioning GEP-NETs, differentiation grade of G1 or G2, proliferation index Ki-67 up to 10%, locally inoperable, or metastasised. Results of the study showed decreased relative risk of disease progression by 53% in patients with GEP-NETs located in the pancreas, midgut, or of unknown origin.

Key words: neuroendocrine tumours, somatostatin analogues, octreotide LAR, lanreotide Autogel®

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Introduction

Neuroendocrine tumours (NET) belong to a heterogeneous group of rare tumours of endocrine cells dispersed throughout the body, forming the so-called diffuse endocrine system (DES). These tumours are capable of synthesising and secreting bioactive substances. The NET group is dominated by gastroenteropancreatic neuroendocrine tumours/neoplasms (GEP-NET/NEN) [1].

Most NETs of the gastrointestinal tract are diagnosed at an advanced stage, which impedes radical surgery. Somatostatin receptor analogues (SSTA) play a major role in the management of non-resectable and/or disseminated tumours because almost 80% of those overexpress somatostatin receptors (SSTR) [2].

Five types of SSTR were identified, and these are expressed in various configurations on tumour cells. Overexpression of SSTR2 was found in neuroendocrine tumours originating from bronchi, stomach, and intestines as well as in schwannoma, medulloblastoma, meningioma, neuroblastoma, lymphoma, breast cancer, kidney cancer, liver cancer, and lung cancer cells. Sarcoma and prostatic cancer cells express mostly SSTR1, often in coincidence with SSTR5. Non-functioning pituitary tumours are characterised by expression of SSTR3, whereas gastrointestinal neuroendocrine tumours, pheochromocytoma, and meningioma demonstrate expression of SSTR1 and variegated positivity for SSTR2 or SSTR5 [3]. Distribution and intensity of respective SSTR subtype expression in tumours vary markedly between publications, and to a certain extent

depend on the applied detection method. Different SSTR subtypes may fuse on the cell membrane to form a homo- or heterodimer, thus creating a new receptor of different characteristics [4].

A study of 81 functioning or non-functioning NETs demonstrated expression of SSTR subtype 1, 2, 3, and 5 in most of them, whereas subtype 4 was identified in only single tumours [5]. Somatostatin receptors can be found in most well or moderately differentiated GEP-NETs. Expression of some SSTR subtypes may decrease in the course of the disease, whereas in others it may be preserved [6].

Somatostatin (SST) is a cyclic peptide, synthesised as a large molecule prohormone (preprosomatostatin) in various parts of the gastrointestinal tract or other organs. Prohormone is processed to a 28-aminoacid-long peptide (prosomatostatin), and then to 14-aminoacid-long somatostatin. The latter exerts its effect via dedicated receptors, inhibiting secretion of gastrointestinal or pancreatic hormones. The half-life of SST in blood is very short (1–3 minutes), therefore, synthetic forms of longer duration are commonly used in oncology, namely octreotide and lanreotide as well as their depot forms [octreotide long-acting release (LAR) and lanreotide Autogel®]. Other synthetic analogues, pasireotide and vapreotide, are mainly used by endocrinologists and gastroenterologists. Somatostatin binds equally strongly to all receptor subtypes but its analogues octreotide and lanreotide have a high affinity to SSTR2 and SSTR5, moderately strong affinity to SSTR3, and bind very weakly (if ever) to SSTR4 and SSTR1. Pasireotide binds strongly to SSTR1, -2, -3, and -5, and vapreotide to SSTR2, -3, and -5 but has a moderate affinity to SSTR4 [7].

Somatostatin analogues play a major role in the therapy of functioning NETs. Improvement of carcinoid syndrome was observed under SSTA treatment of GEP NETs, with fewer diarrhoeas in 60–70% of patients, and lesser rash in 70–80% subjects. Decreased synthesis of biologically active substances was found in almost 50% of cases and tumour regression in only 5%, but control of tumour growth could be achieved in 40–80% of patients. Somatostatin analogues are also effective in symptom control of pancreatic NETs, and indicated perioperatively in functioning tumours, protecting the patient from exacerbation of tumour-related symptoms. Synthetic SST analogues are generally well tolerated, with rare occurrence of adverse events [8, 9].

Binding of SST analogues to specific transmembrane receptors in tumour cells decreases secretion of hormones and biologically active substances, which reduces symptoms but also inhibits disease progression. Treatment with SST analogues is currently a standard in patients with GEP-NETs, with administration of short-acting agents for rapid control of life-threatening symptoms caused by functioning tumours [9].

Anti-tumour effect

Given the widespread SSTR expression in various tumours, studies on the interaction of SST and its analogues with tumour cells were initiated. The anti-tumour effect of SSTA was observed both *in vitro* and *in vivo* as early as in the 1990s [10–13]. Small prospective or retrospective clinical studies gave similar results [14]. Recent studies with control groups suggest that SSTA may have both cytostatic and cytotoxic effects in some tumours. The anti-tumour effect of SSTA varies in different tumour types and receptor subtypes. This effect may be due to direct interaction with membrane receptors on tumour cells, activation of proapoptotic cascade and anti-mitotic mechanisms, or by indirect inhibition of growth factors, angiogenesis, or the influence on the immune system, in particular on lymphocyte proliferation or immunoglobulin synthesis. An indirect effect of SSTA was observed in an experimental model using a chondrosarcoma cell line, which did not express SSTR [15].

Ligand binding to SSTR leads to cell cycle arrest by activation of tyrosine kinase, which in turn initiates intracellular signalling pathways, and activates cyclin-dependent kinase inhibitors. Subtypes 2 and 3 of SSTR seem to be the main mediators of apoptosis in both normal and tumour cells. This effect can be explained by two mechanisms: direct interaction with SSTR3 and indirect action by inhibiting insulin-like growth factor 1 (IGF1) [16]. Induction of apoptosis occurs due to activation of external signalling pathways, leading to loss of receptor expression, by TP53-dependent mitochondrial pathway related to SSTR3 activation or by TP53-independent SSTR2 activation. Interaction with SSTR1 and SSTR2 decreases cell migratory/invasive capacities by inhibiting phosphoinositide 3-kinase (PIK3) and/or mitogen-activated protein kinases (MAPK) for platelet-derived growth factor (PDGF) as well as by activating integrin receptors [17, 18]. Another mode of action was proposed recently, with G-protein independent inhibition of PI3K upon ligand interaction with SSTR2 [19]. These mechanisms inactivate the mammalian target of rapamycin (mTOR) signalling pathway and thus inhibit transcription and translation. An important anti-proliferative effect of SSTA involves restoration of the functional gap junctions between adjacent cells, necessary for intercellular signalling [20].

The proapoptotic effect of somatostatin analogues has shown clinical benefits. Eriksson et al. observed increased apoptosis in tissue samples from GEP-NET in patients treated with high doses of SSTA. Additionally, biochemical response and disease stabilisation was observed in 12 out of 18 subjects, but there was no correlation between apoptosis and decrease of tumour size [21, 22].

The indirect action of SSTA is related to inhibition of angiogenesis and counteracting the effect of growth

factors. Angiogenesis is crucial for tumour growth, invasion, and metastatic potential; therefore, decreased tissue vascularisation upon administration of SST and its analogues may inhibit tumour progression. Subtypes 2 and 5 of SSTR play a role in inhibiting growth hormone (GH) secretion from the pituitary gland and the effect on the GH/IGF1 feedback loop. By interaction with SSTR2 and SSTR3 somatostatin analogues also inhibit GH-dependent liver synthesis of IGF1. This occurs due to activation of tyrosine phosphatase, dephosphorylation of protein transducing signals from cell membrane to nucleus and phosphorylation of signal transducer and activator of transcription 5B protein (STAT5B), which in turn inhibits transcription of *IGF1* gene [23]. Moreover, overexpression of SSTR2 on tumour cells causes increased expression of thrombospondin 1 (TSP1), a potential anti-angiogenic factor in pancreatic tumours. Thrombospondin counteracts the proangiogenic effect of vascular endothelial growth factor (VEGF) [24]. Tumour growth and metastases may also be indirectly inhibited by suppression of endothelial proliferation and monocyte migration, with both cell types producing normally proangiogenic factors. This effect is mediated by ligand interaction with SSTR subtypes 2, 3, and 5, present on endothelial cells, which leads to inhibition of nitric oxide synthase, MAPK3 (ERK1) and MAPK1 (ERK2) [25, 26].

Somatostatin analogues also have an immunomodulatory effect, regulating mainly NK-cell proliferation and immunoglobulin synthesis. It was not definitively stated if this phenomenon is of clinical importance, but it seems to have an adjuvant effect to the anti-angiogenic action of SSTA [27].

Clinical studies

Analogues of SST were initially used for symptomatic treatment of functional GEP-NETs, although both retrospective and prospective studies in small patient groups had revealed the anti-tumour effect of these agents.

Proof of anti-proliferative effect of SSTA came from the phase III randomised placebo-controlled double blind study PROMID, involving 84 treatment-naive patients with disseminated well-differentiated NETs of midgut or unknown origin (possibly also arising from midgut). Patients received 30 mg of octreotide LAR every four weeks. Median time to progression (TTP) was 14.3 months in study group as compared to six months in the placebo group. Stable disease was noted after six months of treatment in 67% of patients treated with octreotide LAR, and in 37% subjects receiving placebo. Relative risk of disease progression decreased by 66% on treatment. Interestingly, the anti-tumour effect of octreotide was independent of tumour functional status. One of the secondary end-points of the study was overall survival (OS). Seven octreotide-treated patients and nine subjects receiving placebo died during the study. Treatment reduced, therefore, relative risk of death by 19%, but the difference was not statistically significant. The most common adverse effects of treatment included gastrointestinal symptoms (transient diarrhoea and abdominal pain, most often of mild to moderate intensity), cholelithiasis (asymptomatic in many patients), and local reactions at the infusion site (pain, nodule, or induration). To sum up, the PROMID study demonstrated the anti-proliferative effect of octreotide LAR in patients with disseminated NETs of midgut origin. Patients included in the study were representative for the overall population with this diagnosis. The most beneficial effect was stabilisation of tumour growth, which contributed to longer time to progression. Similar effects were observed irrespective of tumour functional status. A more pronounced effect was observed in patients after prior resection of primary tumour and in patients in whom metastatic tumour burden was < 10% of the liver volume [28]. Updated results were presented during the 2013 ASCO meeting, with a non-significant trend towards better prognosis on octreotide LAR treatment, especially in subjects with liver metastatic burden < 10% of organ volume. The lack of significance may be related to the fact that most persons from the placebo arm received octreotide LAR when tumour progression was documented [29].

Given the beneficial effects of octreotide LAR study in NETs, a retrospective study was performed in order to identify predictive factors. The aim of the study was to analyse the time to radiological progression of the disease (TTRP) and potential markers of better response to octreotide LAR. The study included 254 patients with advanced-stage NET and SSTR expression confirmed by scintigraphy. Radiological assessment was performed using the RECIST criteria. Both univariate and multivariate analyses were performed in order to identify predictive factors. Mean patient age was 60.5 ± 12.8 years, and mean follow-up time was 42 months. Most patients (204 persons) had tumours in the small intestine, 22 patients were diagnosed with pancreatic tumours, 14 had lung tumours, 7 persons had rectal tumours, and in 7 subjects the primary tumour location was unknown. Treatment with octreotide LAR was initiated because of symptomatic disease in 68% of patients, due to radiological progression in 13% of persons, and following publication of the PROMID study results in 29% of subjects with non-functioning NETs and stable disease. Partial response was observed in 5% of patients. Median time to radiological progression was 37 months in the entire study population [95% confidence interval (CI): 32–52 months], with significantly worse outcome in

pancreatic NETs, G2 tumours, patients with massive liver metastases, or in patients with initial chromogranin A (CgA) level of more than ten-fold the upper normal limit. In patients with initially stable disease the mean time to radiological progression was 53 months. There was no correlation between TTRP and patient age, mesenteric metastases, desmoplasia, or prior resection of primary tumour. Female sex and the presence of skeletal metastases had a negative but a non-significant impact on TTRP. The authors concluded that the duration of the anti-proliferative effect of octreotide LAR was longer than in the PROMID study. Better response to treatment was observed in patients with tumours of the small intestine, G1 differentiation grade, small liver metastatic burden, low CgA level, or with stable disease upon onset of therapy [30].

Another study demonstrating the anti-proliferative effect of somatostatin analogues was a multicentre double-blind randomised placebo-controlled study CLARINET, involving 204 patients with non-functioning gastroenteropancreatic neuroendocrine tumours (GEP-NET) of G1 or G2 differentiation grade, proliferation index Ki-67 of 10%, locally unresectable, or metastasised. Lanreotide Autogel® contributed to a significant decrease of relative risk of disease progression by 53%. This effect was noted in patients with non-functioning G1 or G2 NETs (Ki-67 < 10%) of midgut, unknown, or pancreatic origin, irrespective of liver metastatic burden (≤ 25% or > 25%). Overall survival did not differ significantly between the groups, which was probably related to the fact that upon disease progression the patients from the placebo arm were switched to lanreotide. Treatment was well tolerated, and patients' quality of life was not compromised. The most common adverse effects included diarrhoea, reported by 26% of patients treated with lanreotide and in 9% of persons in the placebo group [31].

The above-presented data confirm previous observations of the anti-proliferative effect of SSTA, which are capable of inhibiting tumour growth and stabilise the disease. These results suggest also a beneficial effect in treatment of both hormonally active and non-functioning GEP-NETs.

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