Review article

Octreotide LAR in neuroendocrine tumours – a summary of the experience

Agnieszka Kolasińska-Ćwikła, MD, PhD

Department of Chemotherapy, Oncology Clinic, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw, Poland

Head of the Clinic: prof. Michał Tenderenda, MD, PhD

Correspondence:
Agnieszka Kolasińska-Ćwikła, MD, PhD
Department of Chemotherapy, Oncology Clinic, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warszawa
02-034 Warsaw, ul. Wawelska 15B

Received:
1.03.2017.
Accepted:
15.03.2017.

DOI: 10.5604/01.3001.0009.7412

ABSTRACT

Neuroendocrine tumours are a rare and heterogeneous group of neoplasms. Most of the patients are diagnosed with locally advanced or metastatic disease and curative surgery is rarely an option. Somatostatin analogues have been shown to control the symptoms and growth of well-differentiated metastatic neuroendocrine tumours. Octreotide LAR is one of the treatment options.

Key words: neuroendocrine tumours, somatostatin analogues, octreotide LAR

INTRODUCTION

Neuroendocrine tumours (NET) are a heterogeneous group of rare neoplasms derived from endocrine cells dispersed throughout the body, creating a diffuse endocrine system (DES), and capable of producing and secreting bioactive substances. In the years 1994–2009, incidence of neuroendocrine neoplasms (NEN) went up from 2.48 to 5.86 per 100,000 people per year [1]. NET prevalence is now estimated as 5.3 cases/100,000 persons, with the disease being diagnosed slightly more often in males (5.35 per 100,000 people per year) than in females (4.76 per 100,000 people per year) [2, 3].

70% of neuroendocrine tumours are gastro-entero-pancreatic neuroendocrine tumours/neoplasms (GEP-NET/NEN) [4]. They may be hormonally active, but most of them do not produce enough hormones and/or biogenic amines to trigger clinical symptoms. Due to the lack of characteristic symptoms, a considerable percentage of GEP-NETs are diagnosed at an advanced stage, when it is too late for a radical surgical therapy. Somatostatin (SST) receptor analogues play a major role in the treatment of unresectable and/or metastatic neuroendocrine neoplasms, as over 80% of NETs show overexpression of somatostatin receptors (SSTR) [5]. 5 receptor subtypes are distinguished, whose different configurations are to be found on various types of cancer cells, including GEP-NEN, but also neuroblastoma, medulloblastoma, meningioma, ganglioma, lymphoma, breast cancer, kidney, liver and lung cancers [6].

SOMATOSTATIN ANALOGUES

SSTRs are present on most cells of the well and moderately differentiated GEP-NETs, irrespective of their grade (G1, G2, often G3) [7]. Under physiological conditions, in the different parts of the GI tract and elsewhere, somatostatin is synthesized as a large prohormone that converts into the active 14-amino-acid form. Somatostatin acts through receptors, inhibiting the secretion of different GI and pancreatic hormones. Its short half-life amounts to 2–3 min. Hence, synthetic SST analogues, octreotide and lanreotide (as well as their long-acting forms, octreotide LAR and lanreotide autogel), whose half-life is longer, have been used to manage that group of neoplasms. Somatostatin binds equally strongly to all receptor subtypes, while its analogues show a high affinity to SSTR2 and SSTR5, moderate affinity to SSTR3, and low or no affinity to SSTR4 and SSTR1 [8].

SST analogues play a major role in the treatment of functioning neuroendocrine tumours. Significant reduction in the clinical symptoms was observed in the course of the carcinoid syndrome treated with SST analogues (both lanreotide and octreotide), with fewer episodes of diarrhoea and facial flushing reported in 60–70% and 70–80% of the GEP-NEN patients respectively. Lower tumour marker levels were observed in nearly 50% of the cases, tumour regression only in 5% of the cases, and disease stabilization in 40–80% of those on SST analogues. SST analogues are also efficacious in symptom control of pancreatic NETs. They are recommended in the perioperative period for patients with functioning tumours, believed to protect them from the carcinoid crisis and other complications. The drugs are generally well tolerated [9, 10]. Binding to specific transmembrane receptors on tumour cells, they decrease secretion of hormones and biologically active substances, thus reducing the symptoms and inhibiting disease progression. Treatment with SST analogues is currently a standard in GEP-NET patients, with short-acting preparations administered only for rapid control in life-threatening situations caused by functioning GEP-NETs [10].

ANTI-CANCER EFFECT

SST analogues demonstrate not only anti-secretory, but also anti-cancer effects. Their anti-proliferative effect was observed both *in vitro* and *in vivo* in the experimental studies carried out as early as in the 1990s [11–14]. Over the recent years, prospective randomized phase III study outcomes have been published, confirming the anti-tumour effect of both octreotide LAR (PROMID study) and lanreotide autogel (CLARINET study) [15, 16].

The anti-cancer activity of SST analogues depends on the type of cancer and on the receptor subtypes involved. It may result from a direct impact on the receptors present on cancer cell membranes, involving the anti-mitotic and apoptotic mechanisms, or from an indirect inhibition of growth factors and angiogenesis, induction of apoptosis, impact on the immune system, and in particular on the proliferation of lymphocytes and synthesis of immunoglobulins [17, 18].

Directly affecting all receptor subtypes, SST analogues induce cell cycle arrest, activating tyrosine phosphatase proteins. As a result of the activation, the intracellular signalling pathway is stimulated by cycline-dependent kinase inhibitors. Only SSTR2 and SSTR3 receptor subtypes are responsible for the stimulation of apoptosis in both normal and neoplastic cells, based on two different mechanisms: direct interaction with SSTR3 and inhibition of the insulin-like growth factor 1 (IGF1) [19].

The pro-apoptotic effect of SST analogues is of clinical significance. Eriksson et al. observed increased apoptosis in the tissue

samples collected from GEP-NET patients treated with SSAs. Additionally, it was indicated that apoptosis was correlated with biochemical response to treatment and disease stabilization in 70% of the patients [20, 21].

The indirect effect of SST analogues involves inhibition of angiogenesis and growth factors. Angiogenesis plays a significant role in tumour growth and its ability to infiltrate tissues and form metastases. Therefore, by inhibiting the angiogenesis, somatostatin and its analogues may delay tumour progression. Receptor subtypes 2 and 5 are particularly important in terms of the inhibition of growth hormone secretion by the pituitary gland, and the GH/IGF1 feedback loop. Through SSTR2 and 3, SSAs also inhibit production of growth hormone-dependent IGF1 in the liver [22, 23]. Another indirect mechanism of action is immunomodulation, i.e. impact on the immune system, and in particular on the proliferation of NK lymphocytes and synthesis of immunoglobulins. It has not yet been established whether that mechanism is of clinical significance, but it appears to be enhancing the anti-angiogenic effect of somatostatin analogues [23].

CLINICAL EXPERIENCE WITH OCTREOTIDE LAR

Initially, octreotide was mainly used for symptomatic treatment of functional GEP-NETs, even though small-size retrospective studies had indicated the anti-proliferative effect of the drug. As molecular biology developed, the anti-cancer effect of octreotide became a subject of interest for numerous researchers.

Extensive evidence of the anti-proliferative effect of octreotide LAR was provided by the first randomized, double-blinded, placebo-controlled phase III study PROMID. It was carried out in 18 German academic centres, involving 84 patients naïve to analogue treatment, with disseminated well-differentiated neuroendocrine tumours of midgut origin or of unknown origin, but possibly arising from the midgut. When enrolling patients in the trial, the dynamics of the disease was not determined, and the group of patients with well-differentiated G1 NETs amounted to just under 98%. In the treatment-naïve patients from the octreotide LAR study arm, receiving octreotide LAR dosed at 30 mg every 4 weeks, the median time to tumour progression (TTP) was 14.3 months as compared to 6 months in the placebo group, which demonstrated an aggressive course of the disease. 6 months into the treatment, disease stabilization was observed in 66.7% of the subjects on octreotide LAR, and in 37.2% of those receiving placebo. It is worth emphasising that treatment efficacy was established based on the WHO radiology assessment, which is no longer applied in oncological studies. The two-dimensional WHO measurement shows a greater percentage increase in the size of the target lesion as compared to the one-dimensional RECIST measurement, which means that assessment of the response to treatment based on the WHO criteria may indicate a shorter time to progression. Hence, it is difficult to compare results of the PROMID study with those from other trials. Still, the study demonstrated that the risk of disease progression was reduced by 66% on octreotide LAR. Importantly, the drug exhibited anti-cancer properties, irrespectively of whether the tumours were functioning (39% of the study subjects) or non-functioning (61% of the patients). While response to treatment was similar for functioning and non-functioning tumours, those patients who had undergone prior resection of the primary tumour as well as those whose hepatic metastatic mass was < 10% responded better to the anti-proliferative treatment. It should be noted, though, that liver involvement > 25% was only reported in 19% of the study subjects, i.e. 7 patients.

One can thus conclude that the PROMID study delivered proof of the anti-proliferative activity of octreotide LAR in patients with metastatic NETs of midgut origin. Those who were included in the study constituted a representative group for the population of patients affected by that type cancer. Median time to progression of 6 months in the placebo arm indicated an aggressive course of the disease in the patients enrolled in the study. The most beneficial outcome reported was tumour growth stabilization, also reflected in the extended time to disease progression [15]. In a recently published observational analysis of the survival of patients treated in the PROMID study, and followed up on until 2014, median overall survival (OS) amounted to 84.7 months. No differences in OS were reported between the actively treated subjects (84.7 months) and those from the placebo arm (83.7 months). However, it should be emphasised that 88.4% of the placebo patients (38 out of 43) were qualified for treatment with octreotide LAR 30 mg, following disease progression, which greatly impacted the final outcomes, resulting in the lack of statistical significance of the differences observed. One of the most important factors influencing median overall survival was the degree of liver involvement by cancer. Median OS was 107.6 months in the subgroup with liver involvement ≤ 10%, while in the subgroup with liver involvement >10% it was 57.5 months (HR = 2.49; 95% CI: 1.36–4.55; p = 0.002). Despite the lack of statistical significance, there was a clear trend for prolonged OS in the subgroup of patients treated with octreotide LAR, whose liver involvement was ≤ 10%. Median overall survival was not reached in the actively treated subgroup, and in the placebo subgroup it amounted to 87.2 months (HR = 0.59; 95% CI: 0.29–1.20; p = 0.142). Median survival from diagnosis to cancer-related death was not reached in the group of patients receiving

30 mg of octreotide LAR every 28 days, and in the placebo group it totalled 107.6 months (HR = 0.50; 95% CI: 0.22–1.16; p = 0.11). Another factor which was found to influence the overall survival was primary tumour resection (HR = 0.39; 108 vs. 49 months; 95% CI: 0.22–0.69; p = 0.0011). Interestingly, symptoms of carcinoid syndrome had no impact on median overall survival [24].

The PROMID study involved patients with neuroendocrine tumours of midgut origin or of unknown origin (but probably arising from the midgut), and despite the clinical practice supporting the rationale behind the administration of octreotide LAR in other locations, including the pancreatic one, there were no data regarding the efficacy of the drug in pancreatic NETs.

In 2013, a retrospective analysis was published by a German academic centre, looking into the efficacy of octreotide LAR administered every 28 days as first-line treatment in 43 patients with pancreatic NETs. The study assessed the best response to treatment based on the RECIST radiological response criteria, defined as disease control rate: stable disease (SD) + partial response (PR). Additionally, response was evaluated 12 months into the treatment based on the RECIST 1.0 radiological response criteria, and disease control rate was reported 12 months into the therapy (SD + PR). It should be noted that 80% (30) of the subjects were patients with G2 pancreatic NETs with the Ki-67 index of up to 20%, 18% (8) of them suffered from G1 NETs, and in 5 cases the Ki-67 index was not determined. 19 patients included in the analysis were diagnosed with functioning pancreatic neuroendocrine tumours (pNETs), and 24 of the subjects had non-functioning tumours, with 39 patients classified as stage 4 upon initiation of octreotide treatment, and 4 patients classified as unresectable stage 3. Median overall survival was calculated with the Kaplan–Meier method, totalling 98 months. Median time to progression (TTP) was 13 months (range: 2–51). Analysis of the differences in terms of median OS and TTP depending on the response to octreotide LAR 12 months into the treatment demonstrated a statistically significant difference between the patients who responded to treatment (SD + PR) (with median TTP of 22 months in that group) and those who progressed (PD) (with median TTP of 3 months only). Median OS for patients with stable disease or partial response amounted to 137 months as compared to 68 months for patients with progressive disease. It is worth emphasising that 19 patients received octreotide LAR dosed at 30 mg, 16 patients received octreotide dosed at 20 mg or less, and for the remaining 8 patients there is no information on the dose administered. The study did not demonstrate a statistically significant impact of the dose on time to progression. In those on octreotide LAR ≤ 20 mg, median time to progression was 6 months, and in those receiving the 30 mg dose it amounted to 15 months. Similarly, no differences were reported in median TTP between patients with functioning and non-functioning tumours or between those who had undergone primary tumour resection and those who had not. On the other hand, an important factor impacting disease control turned out to be the Ki-67 pNET proliferation index. The longest TTP (15 months) was observed in the subgroup with Ki-67 < 5%, it was 12 months in the subgroup with Ki-67 5–10%, and only 3 months in the subgroup with Ki-67 > 10%. Treatment with octreotide LAR resulted mainly in disease stabilization (25 cases), with 3 cases of partial response as assessed based on the RECIST criteria, which translated into a disease control rate of 65%. 12 months into the octreotide LAR treatment the rate was 42% [25].

In a yet another retrospective study, presented at ESMO (European Society for Medical Oncology) in 2014, results of the Italian centres were analysed with respect to the efficacy of long-acting somatostatin analogues (octreotide LAR 30 mg and lanreotide autogel 120 mg) in the treatment of well and moderately differentiated neuroendocrine tumours with Ki-67 index of up to 20%. In a group of 137 patients with disseminated GEP-NETs (including 50 subjects with pNETs), octreotide LAR 30 mg was administered every 28 days (101 subjects) or lanreotide autogel 120 mg every 28 days (35 subjects). The Ki-67 index was also determined for the study population, amounting to < 3% in 89 cases, 3–5% in 38 patients, 5–10% in 15 subjects, and over 10% in 21 of them. Treatment efficacy assessment was based on the RECIST 1.0 criteria. In 81% (112) of the patients, the treatment resulted in stable disease, and in 9% of them the outcome was partial response (PR). Median TTP for octreotide LAR and lanreotide autogel was 24.6 and 21.83 months respectively. In the subgroups of gastro-enteric NETs and pancreatic NETs median TTP was 21.73 and 24.73 months respectively. For patients with neuroendocrine tumours and Ki-67 index of < 3%, 3–5%, 5–10%, and > 10%, median TTP was 27.15; 34.77; 28.3; and 20.0 months respectively. Based on the presented data, it appears that SSAs may also be used in selected patients with Ki-67 index > 10% [26]. However, further prospective studies are required to verify the results.

In the light of the positive results of the studies on octreotide LAR in neuroendocrine tumours, and out of necessity to determine predictive factors, another retrospective study was carried out, aimed at establishing the time to radiological disease progression, and factors related to a higher efficacy of octreotide LAR therapy. The study involved 254 subjects with advanced neuroendocrine tumours, and with the presence of somatostatin receptors revealed in scintigraphy. Radiological assessment was

performed based on the RECIST 1.0 criteria. Univariate and multivariate analyses were conducted in order to determine predictive factors. The average age of the study subjects was 60.5 (±12.8), and the mean follow-up period was 42 months. The majority of the patients (n = 204) were diagnosed with small intestine tumours, 22 of them suffered from pancreatic tumours, 14 were diagnosed with lung cancer, 7 with rectal cancer, and in 7 patients the tumour was not localized. In 68% of the study participants, octreotide LAR treatment was initiated for symptom control, in 13% of them it was initiated due to radiological progression (TTRP, time to radiological progression), and in the remaining 29% of the patients, with non-functioning NETs and stable disease, the treatment was started based on the PROMID study results. Partial response was accomplished in 5% of the patients. Median TTRP for the entire population was 37 months (95% CI: 32–52 months), and it was statistically significantly shorter in the following subgroups: patients with pancreatic NETs (p = 0.001), patients with G2 tumours (p = 0.001), patients with high liver involvement (p = 0.006), and those with baseline chromogranin A (CgA) concentration over 10-fold higher than the upper limit of the reference range (p = 0.006). The average time to radiological progression was longer in patients with stable disease at baseline, amounting to 53 months. No correlation was demonstrated between disease progression and age, mesenteric metastases, desmoplasia, and prior resection of the primary lesion. On the other hand, the female gender and presence of bone metastases had some negative impact on TTRP, but the differences were not statistically significant. Authors of the study concluded that the anti-proliferative effect of octreotide LAR was longer than indicated in the earlier PROMID study. Tumours arising from the small intestine, G1 grade of differentiation, low liver involvement by cancer, low CgA concentration and stable disease at baseline were all linked to a higher response to treatment with octreotide LAR [27].

In the most recent *post-hoc* analysis of the RADIANT-2 study placebo arm, the efficacy of octreotide LAR 30 mg was assessed, following progression in patients with advanced GEP-NETs and symptoms of carcinoid syndrome. Impact of the treatment on OS and TTP was evaluated with the use of the Kaplan–Meier method. Out of the 213 patients randomised to the placebo arm, data collected from 196 patients were used for the analysis. 41 patients out of that group had not been previously treated with somatostatin analogues, whereas 155 had undergone prior analogue therapy before inclusion in the study. In the subgroup of 41 patients who had not received prior SSA treatment, centrally assessed median TTP was 13.6 months, with 22.2 months for the patients diagnosed with tumours of midgut origin (24 subjects). On the other hand, in the group of 155 patients who had undergone prior SSA treatment, median TTP was 11.1 months for the entire population, and 12 months for those with tumours of midgut origin. An additionally conducted multivariate analysis demonstrated that poorer general condition, i.e. PS (performance status) > 0, and elevated CgA concentration were factors that correlated with a shorter time to progression. Median OS in the analysed group was 35.8 months, but it was significantly longer in the subgroup of previously untreated patients (50.6 months), while in the group of patients who had received prior SSA treatment it amounted to 33.5 months. The multivariate analysis indicated that patients' general condition of PS > 0, and elevated concentrations of CgA and 5-HIAA correlated with a statistically significantly shorter overall survival. The *post-hoc* analysis of the phase III RADIANT-2 study demonstrated a significantly longer time to progression and overall survival in previously untreated patients with progressive NETs of midgut origin on octreotide LAR (median TTP of 22.2 months) than it was indicated in the PROMID study (median TTP of 14.3 months). Most probably the difference resulted from the application of different radiological response criteria to evaluate treatment efficacy (RECIST 1.0 in RADIANT-2, and WHO in PROMID) in the two studies [28].

SUMMARY

Despite the lack of prospective studies on the use of octreotide LAR in the treatment of GEP-NETs based on the RECIST 1.0 radiological response criteria, data collected in the above presented studies do confirm the earlier observations on the anti-proliferative effect of octreotide LAR in neuroendocrine tumours of pancreatic and midgut origin, and thus support the rationale behind the use of octreotide LAR in those indications. At the same time, the studies complement our knowledge on a rational use of SST analogues in the treatment of functioning and non-functioning GEP-NETs of different dynamics.

References

1. Hallet J, Law CH, Karanicolas PJ et al. Rural-urban disparities in incidence and outcomes of neuroendocrine tumors: A population-based analysis of 6271 cases. Cancer 2015; 121(4): 589-597.
2. Yao JC, Hassan M, Phan A et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063-3072.

3. Öberg K, Knigge U, Kwekkebom D et al.; On behalf of the ESMO guidelines working group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis,treatment and follow-up. Ann Oncol 2012; 23: 124-130.
4. Öberg K. Neuroendocrine gastrointestinal tumors – a condensed overview of diagnosis and treatment. Ann Oncol 1999; 10: S3-S8.
5. Baldelli R, Barnabei A, Rizza L et al. Somatostatin analogs therapy in gastroenteropancreatic neuroendocrine tumors: current aspects and new perspectives. Front Endocrinol (Lausanne) 2014;5: 7. doi: 10.3389/fendo.2014.00007.
6. Reubi JC, Waser B, Schaer JC et al. Somatostatin receptor sst1--sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype – selective ligands. Eur J Nucl Med 2001; 28:836-846.
7. Reubi JC, Mengod G, Palacios JM et al. Somatostatin receptors in human cancer: incidence, characteristics, functional correlates and clinical implications. J Steroid Biochem Mol Biol 1992; 43(1-3): 27-35.
8. Öberg K. Established clinical use of octreotide and lanreotide in oncology. Chemotherapy 2001; 47: 40-53.
9. Oberg K. Future aspects of somatostatin-receptor-mediated therapy. Neuroendocrinology 2004; 80: 57-61.
10. Oberg K, Kvols L, Caplin M. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol 2004; 15: 966-973.
11. Schally AV. Oncological applications of somatostatin analogues. Cancer Res 1988; 48: 6977-6985.
12. Scarpignato C, Pelosini I. Somatostatin analogs for cancer treatment and diagnosis: an overview. Chemotherapy 2001; 47: 1-29.
13. Weckbecker G, Raulf F, Stolz B, Bruns C. Somatostatin analogs for diagnosis and treatment of cancer. Pharmacol Ther 1993; 60: 245-264.
14. Schally AV, Nagy A. Chemotherapy targeted to cancers through tumoral hormone receptors. Trends Endocrinol Metab 2004; 15: 300-310.
15. Rinke A, Müller HH, Schade-Brittinger C et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009; 27(28): 4656-4663.
16. Caplin ME, Pavel M, Ćwikła JB et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. CLARINET. N Engl J Med 2014; 371(3): 224--233
17. Pyronnet S, Bousquet C, Najib S et al. Antitumor effects of somatostatin. Mol Cell Endocrinol 2008; 286: 230-237.
18. Reubi JC. A somatostatin analogue inhibits chondrosarcoma and insulinoma tumour growth. Acta Endocrinol (Copenh.) 1985; 109: 108-114.
19. Pollak MN, Schally AV. Mechanisms of antineoplastic action of somatostatin analogs. Proc Soc Exp Biol Med 1998; 217: 143-152.
20. Imam H, Eriksson B, Lukinius A. Induction of apoptosis in neuroendocrine tumors of the digestive system during treatment with somatostatin analogs. Acta Oncol 1997; 36: 607-614.
21. Eriksson B, Renstrup J, Imam H et al. High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. Ann Oncol 1997; 8 :1041-1044.
22. Arena S, Pattarozzi A, Corsaro A et al. Somatostatin receptor subtype-dependent regulation of nitric oxide release: involvement of different intracellular pathways. Mol Endocrinol 2005; 19, 255-267.
23. Bousquet C, Puente E, Buscail L et al. Antiproliferative effect of somatostatin and analogs. Chemotherapy 2001; 47: 30-39.
24. Rinke A, Wittenberg M, Schade-Brittinger C et al. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results of Long-Term Survival. Neuroendocrinology 2017; 104(1): 26-32.
25. Jann H, Denecke T, Koch M et al. Impact of octreotide long-acting release on tumour growth control as a first-line treatment in neuroendocrine tumours of pancreatic origin. Neuroendocrinology 2013; 98(2): 137-143.
26. Marconcini R, Ricci S, Vasile E et al. Efficacy of Somatostatine Analogs (SSA) in Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) according to ki67 index. J Clin Oncol 2014; 32(5 suppl.): abstr. 1145.
27. Toumpanakis Ch, Laskaratos F, Maragkoudakis E et al. Antiproliferative activity of octreotide LAR in advanced neuroendocrine tumors. J Clin Oncol 2014; 32(5 suppl.): abstr. 4110.
28. Strosberg JR, Yao JC, Bajetta E et al. Efficacy of octreotide long-acting repeatable in neuroendocrine tumors: RADIANT-2 placebo arm post hoc analysis. Endocr Relat Cancer. 2015; 22(6):933-40.

Conflict of interests:
None.
Financial support:
None.
Ethics:
The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.