Radiopeptides Analogues of Somatostatin Used for the Treatment of Neuroendocrine Tumors – Literature Review

Fagner Santos do Carmo, Marta de Souza Albernaz and Ralph Santos-Oliveira*

Laboratory of Nanoradiopharmaceuticals, Rio de Janeiro, Brazil

Abstract: The use of somatostatin analogues is growing each year, especially for tumor imaging and treatment. In this scenario the numbers of radionuclides and the perspective of new one are quite promising. In this review we approach the possibilities and give an overview of the trends and possibilities in this area.

Keywords: Radiopharmaceuticals, peptides, endocrinology, neuroendocrine tumors.

INTRODUCTION

Neuroendocrine tumors (NETs) comprise a range of malignancies with a great increasing in incidence and prevalence in the last few years [1]. Is considered a rare tumor but most of this percepetion is due to its low increase time and small size [2-4].

In the last two decades this type of tumor has received special attention in exploratory studies in order to be better defined, biologically classified appropriately and enable the construction of new methods and strategies to combat [5]. Current data shows that there was a striking increase in the incidence from 1.09 per 100,000 in 1973 to 5.25 per 100,000 in the year 2004, representing an increase of over 400 % within 29 years [6].

Neuroendocrine tumors occur sporadically as part of a family of syndromes, some showing aggressive behavior, characterized as highly malignant, having mostly slow growth [7]. The epidemiology of most aggressive type, carcinoid, are well studied and show the occurrence of tumors throughout the gastrointestinal tract and ileum (31%), rectum (21%), appendix (17%), colorectal (12%), stomach (6%) and small intestine (duodenum and jejunum, 4% and 3%, respectively) [8].

The absence of biologically active hormone produced by GEP NETs always refer to a delayed diagnosis of the disease usually detected when there are symptoms arising from the effect of the mass and metastasis, especially liver [9].

A study conducted by Hausto *et al*. (2005) in U.S revealed that from 1993 to 2004 were reported a total of 2,030 cases. The BP-NETs are the most frequent neoplasms registered. Conformity assessment of the main symptoms of carcinoid tumor show the occurrence, simultaneously or not, of flushing and diarrhea. The natural history of patients with NETs, based on the presentation of vague abdominal symptoms in comings and goings of doctors who provide primary care, and referral to the gastroenterologist diagnosed with syndrome of irritable bowel (SIB). The persistence of these symptoms usually takes to over 9-years. In the end, the lack of a correct diagnosis, make the tumor progressing to metastases and death of the patient [10, 11].

SOMATOSTATIN RECEPTOR EXPRESSED IN NEUROENDOCRINE TUMORS

Somatostatin (SST) is a small cycle multifunctional peptide synthesized in endocrine cells and present on other cells and organs [12]. First isolated in 1973 by Brazeau *et al*., its function is linked to inhibition of the release of growth hormone and subsequently identified an inhibitory effect on general release of endocrine hormone inhibition of pancreatic exocrine secretion, gastrointestinal motility and decreasing of neurotransmitter function [13, 14].

The expression of somatostatin receptor expressed in neuroendocrine tumor, was discovered in 1987 by Reubi *et al*. using autoradiography with somatostatin labeled with radioactive iodine [15]. Papotti *et al*. (2002) investigated the expression of somatostatin receptor subtypes and found that other tumors also express this hormone, but the common subtypes expressed was 1, 2, 3 and 5, and rarely subtype 4, in the carcinoid tumors the most expressed somatostatin receptors was the subtype 2 and have been related to treatment with somatostatin analogues [16, 17].

Neuroendocrine tumors such as pituitary tumor, pancreatic islet cell, carcinoid, pheochromocytoma,

*Address correspondence to this author at the Laboratory of Nanoradiopharmaceuticals, Rio de Janeiro, Brazil; Tel/Fax: 552121733964; E-mail: roliveira@ien.gov.br

ISSN: 1927-7210 / E-ISSN: 1927-7229/14

paraganglioma, medullary thyroid carcinoma and small cell lung express dense presence of sst receptors, predominantly type 2, but other types can coexist [18, 19]. Nervous system tumors including meningioma, neuroblastoma, medulloblastoma also often express high density of these receptors. However, tumors originating from neural or endocrine cells, such as lymphoma, breast cancer, renal cell cancer, hepatocellular cancer, prostate cancer, gastric cancer and sarcomas, may also express somatostatin [20].

The specificity of somatostatin receptors has been tested by scintigraphy thereof, having as parameter the state of the receptors *in vitro* [21]. Scintigraphy *in vivo* does not establish standards of homogeneous or heterogeneous distribution within the sst receptors, only possible to quantify accurately and *in vitro* autoradiography [22].

Studies shows that patients who have high expression of sst when treated with 177Lu - or 90Y - DOTATOC DOTATATE showed better survival time [23, 24].

SOMATOSTATIN ANALOGUE

In 1978 was discussed the use of natural somatostatin for the treatment of patients with carcinoid tumor to reduce the symptoms [25]. Studies from Frank *et al*. (1999) and Fjällskog *et al*. (2002) showed a combination therapy for the potential treatment of symptoms and tumor growth [26, 27]. The breakthrough in the use of sst receptor for imaging and therapy was made using radiolabel octapeptide octreotide [28]. The somatostatin analogs may be labeled with radioactive isotopes and their distribution after intravenous administration can be captured by a gamma camera. The natural somatostatin is infeasible for use with radionuclides, because it has an extremely short half-life, about 2 minutes [29].

The peptides that showed successful results fighting neuroendocrine tumors by binding to receptors were the somatostatin analogues [28]. The duration of the therapy is equal to SST analogs half-life, normally 4-6 weeks [30, 31]. Controlled trials have shown that somatostatin analogs are more effective than placebo in controlling tumor growth and metastasis [32].

RADIOPEPTIDES USED TO COMBAT THE NETs

In the treatment of NETs surgical proceedings of the primary tumor normally satisfy most of benign tumors. However malignant tumors, shows metastases and require a more specific treatment [33]. In this case the use of radiopharmaceutical therapy is quite recommended. The success of this therapy is related to the amount of radioligand that may be internalized [34, 35]. Patients indicated peptide receptor radionuclide therapy are those who suffer from well-differentiated neuroendocrine carcinoma or moderately differentiated NET defined as grade 1 or 2 according to the classification of the World Health Organization [36].

Due the features of 177-Lu and 90-Y, both β emitters, the most stable compound is macrocyclic 1,4,7,10 - tetraazacyclododecane -N, N', N'', N'''- tetraacetic acid, or simply DOTA. This reaction results in 90-Y - DOTATOC, 90-Y - SMT -487), 90-Y - DOTA - lanreotide, and (177 Lu - DOTATATE) [37, 38].

Is important to notice that octapeptide cycles are more resistant to peptidases and have half-lives and biological activity longer than natural somatostatin [39]. For clinical purpose the octreotide and octapeptide are the most important one. They are conjugated with chelators and labeled with different rdionuclides [40, 41].

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)

Different options are possible for cancer treatment using peptides due to the ability to bind to different receptors and part of several biochemical pathways. Today, representing a major tool in diagnosis and therapy as drugs against tumor cells, derived peptide and peptide hormone therapy agents radionuclides (receptor radionuclide therapy), as been shown to be a versatile medicine [42].

The peptide receptor radionuclide therapy (TRRP) combines somatostatin analogue (e.g. octreotide) and radioactive substance (radionuclide, e.g. 90-Y) to form a highly specialized molecule, called radiolabeled somatostatin analogue or radiopeptide [43, 44].

Clinical studies have shown significant efficacy in combating tumor with somatostatin receptors. So dense cancers that express receptors amount of this peptide peculiarly subtypes sst2, are the most suitable for PRRT [45-47].

PRRT with 111In [DTPA0] - octreotide (Octreoscan®)

Although initially been dedicated to the diagnosis [111 - DTPA0] octreotide was the first radiolabeled

somatostatin analogue used for PRRT and one of the most used methods in the investigation of NETs tumors [28, 48].

The PRRT using [111 In - DTPA0] octreotide is favorable, because in addition to gamma radiation also emits Auger electrons that allows internal conversion facilitating the reaction in tissues [34, 49]. The success of this therapy related to the radioligand concentration in the tumor cells, depending on the rate of internalization, degradation and recycling of ligands and receptors [50]. Furthermore, it was discovered by Slooter *et al*. (1999) that metastatic tumors also show suitable results [51-54].

PRRT with (90Y-DOTA0, Tyr3) - octreotide [90Y-DOTATOC; OctreoTher®]

90Y is a β emitter with electron energy limit of 2.3 MeV and midrange tissue of 12 mm. The [Tyr3]-octreotide has a higher affinity for sst2 [55, 56]. However, the effects of radionuclide therapy are variable and tumor size-depending [57, 58].

PRRT with [90Y-DOTA0, Tyr3] - OCTREOTATE

Has recently been studied using 90Y connected to [DOTA0, Tyr3] - OCTREOTATE (90Y-OCTREOTATE), but the therapeutic guidelines are variable and evolutionary response has not been clearly delineated [30, 59].

PRRT with [90 Y-DOTA 0] - Lanreotide

Although lanreotide has been used in the treatment of PEG-nets, their affinity is higher for somatostatin receptor 3 and 4 [60].

PRRT with [177 Lu-DOTA0-Tyr3] OCTREOTATE (177 Lu-DOTATATE) and [177 Lu-DOTA0, Tyr3] octreotide (177 Lu-DOTATOC)

The somatostatin analogue [DTPA0, Tyr3]-OCTREOTATE differs from [DTPA0, Tyr3]-octreotide by the presence of only a C - terminal treoninol which is substituted by threonine and comparatively the [DTPA0, Tyr3] OCTREOTATE shows to be a better binding to somatostatin receptor [61-63].

TOXICITY

The short-term side effects caused by PRRT include mild nausea, vomiting and abdominal pain, but only occurred in a minority of patients [64]. In addition, at rare level cases of kidney failure and the occurrence of leukemia or myelodysplastic syndrome has been observed [65].

PERSPECTIVE

Treatment with radiolabeled analogs of sst is a therapeutic modality that grows progressively fighting inoperable or metastatic neuroendocrine tumors, especially GEP tumors. The requirement for the successful treatment includes the demonstration of the high tumor uptake and non-hematological and biochemical function. Even if there is no exact dosage absorbed, treatment with radiolabeled analogs of sst, 111In, 90Y e177Lu correspond satisfactorily to symptomatic improvement and the delimitation of the side effects, related mainly related renal function. Results obtained with [90Y - DOTA0, Tyr3]- octreotide and [177Lu - DOTA0, Tyr3]- OCTREOTATE exhibited substantial regression of the tumor, whereas the combination of these two Radiopeptides may be more effective than one of them alone. We emphasize that the safety of therapy with both methods is comparable [66, 67].

Many analogs of somatostatin receptors have been described with radiolabeled for diagnostic purposes. These proved to be an excellent tool for the clinical management of patients with NET. The diagnosis has become easier and the information is possible therapeutic decision making satisfactory. When radiolabeled with beta -emitting isotopes such as 90 Y and 177 Lu, the same peptides have been used successfully to the base of radiotherapy (PPRT) with few severe adverse effects, significant tumor response rates and progression free survival. This field is rapidly growing and better, new peptide agonists and antagonists have been described and quickly tested in clinical trials [68].

The percentages recorded tumor remission after treatment with receptor radionuclide therapy varies according to the doses and dosing schedules of different Radiopeptides (some studies use dose - escalation schemes, while others use fixed doses) [69]. The diversity of the patient and tumor characteristics determine the outcome of treatment, as the amount of absorption, the estimated total tumor load and the extent of metastatic involvement may play an important role in determining the outcome of the treatment [30].

The two main advantages of the peptides to target receptors are that they can be assigned to essentially duplicate the critical region of the natural receptor

ligand (thus achieving high specificity), and they are relatively small, therefore, can very quickly locate the focus. These advantages are significant for diagnostic imaging, leading to a high sensitivity and specificity and effective therapeutic agents that can achieve with high doses of radiation to the tumor [70].

The PRRT with the use of radiolabeled somatostatin analogs is a promising treatment for patients with neuroendocrine tumors with somatostatin receptor positive, showing the advantage of achieving a small tumors and metastatic networks typically difficult to detect [71].

The radiolabeled somatostatin analogs generally comprise three main parts: A cyclic octapeptide (e.g., octreotide), a chelating agent (e.g. DTPA or DOTA), and a radioactive element (90Y or 177Lu). These Radiopeptides are injected into the patient systemically and will bind to carcinoid tumor cells that have receptors. Once connected, these Radiopeptides emit radiation and kill tumor cells [42].

The 177Lu and 90Y radionuclide is suitable for treating this type of therapy. The 177Lu has a half -life longer, an emission spectrum that allows dosimetry studies and therapy, and is suitable for small tumors. In contrast, 90Y emits particles with longer lengths and higher energies, being preferred to 177Lu for patients who have large tumors, poorly vascularized, or tumors with heterogeneous receptor distribution. However, high doses absorbed by the tumor when patients undergo radionuclide therapy also provides high absorption in the tissue adjacent or around small tumors. Tumors can be adjacent to healthy tissue and critical organs are exposed absorption rates [72].

The PRRT proves to be relatively safe for the kidneys at doses around 25-27 Gy, with an acceptable toxicity, both hematologic and kidney. The strategic management positively charged amino acid such as lysine or arginine competitively inhibit the phenomenon. However, the loss of renal function may occur months after the end of treatment and severe renal toxicity is more common in patients with associated risk factors, as long a history of diabetes or hypertension [71].

The PRRT an alternative treatment is effective and safe for the treatment of neuroendocrine tumors sst-positive. Currently, the maximum tolerated dose is defined by the dose in critical organs, kidney and bone marrow. Probably the dose may be increased in the future, with the introduction of new protective agents and different treatment regimens and radionuclides. There is no definition of the peptide and most suitable radionuclide for the treatment of neuroendocrine tumors. In the case of the radionuclide, in particular, there is emerging evidence that a combination of nuclides with different physical characteristics can be more effective. At first, the treatment target has a number of clear advantages over systemic treatments nonspecific [73].

Further studies to improve the target PRRT include multireceptor with attempts to "overcharge" the expression of sst in tumors and the use of radiosensitizers [66]. Studies have been conducted in a wide variety of Radiopeptides that have already shown its effectiveness in clinical practice or appear to have a great potential to be useful in the future and shown several promising ligands with significant potential to make a real difference in fighting and treating patients with tumor disease are being developed. However, the promotion of the development of numerous agents radiopeptídicos clash in the absence infrastructure to make access easier [70].

Stresses the combination therapy radiolabeled somatostatin analogues as an approach to maximizing the expected positive effects and minimize the toxicity of sst receptor radionuclide therapy [40]. The treatment with PRRT demonstrates a real impact on patient survival [71].

The PRRT can be extended to many other types of tumors, including breast, prostate, intestine, pancreas, and brain tumors, which recently have been shown to express receptors for several other peptides such as gastrin releasing peptide, neurotensin, substance P, glucagon -like peptide 1 -, neuropeptide Y, and corticotropin-releasing factor receptors. A wide range of radiolabeled peptides are being developed for clinical use, improved somatostatin analogs or analogs CCK2, and newly designed bombesin, neurotensin, substance P, neuropeptide Y and peptide - type glucagon - 1. These analogs offer promise for the future PRRT [22].

Bodei (2009) list a great number of new peptides that could be used for receptor radionuclide therapy [68].

REFERENCE

[1] Rashid A, Evans DB. 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. http://dx.doi.org/10.1200/JCO.2007.15.4377

[2] Gibril F, Jensen RT. Diagnostic uses of radiolabelled somatostatin receptor analogues in gastroenteropancreatic endocrine tumours. Dig Liver Dis 2004; 36(suppl 1): S106-S120. http://dx.doi.org/10.1016/j.dld.2003.11.024

[3] Vogelstein B, Kinzler KE. Cancer genes and the pathways they control. Nat Med 2004; 10(8): 789-799. http://dx.doi.org/10.1038/nm1087

[4] Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1995; 1(1): 27-31. http://dx.doi.org/10.1038/nm0195-27

[5] Rindi G, Capella C, Solcia E. Introduction to a revised clinic pathological classification of neuroendocrine tumors of the gastroenteropancreatic tract. Q J Nucl Med 2000; 44(1): 13-21.

[6] Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, *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. http://dx.doi.org/10.1200/JCO.2007.15.4377

[7] Kaltsas G, Mukherjee JJ, Plowman PN, Grossman AB. The role of chemotherapy in the nonsurgical management of malignant neuroendocrine tumours. Clin Endocrinol (Oxf) 2001; 55(5): 575-87. http://dx.doi.org/10.1046/j.1365-2265.2001.01396.x

[8] Modlin IM, Zikusoka M, Kidd M, Latich I, Eick G, Romanyshyn J. The history and epidemiology of neuroendocrine tumors. In: Caplin M, Kvols L, eds. Handbook of Neuroendocrine Tumors. 1st ed. Bristol, UK: BioScientifica 2006; pp. 7-37.

[9] Ramage JK, Davies AH, Ardill J, Bax N, Caplin M, Grossman A, *et al*. UKNETwork for Neuroendocrine Tumours: Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. GUT 2005; 54(SUPPL 4): IV1-16. http://dx.doi.org/10.1136/gut.2004.053314

[10] Hauso O, Gustafsson BI, Kidd M, Waldum HL, Drozdov I, Chan AKC, Modlin IM. Neuroendocrine tumor epidemiology. Contrasting Norway and North America. Cancer 2008; 113: 10.

[11] Mamikunian G, Vinik A, O'Dorisio TM, Woltering EA, Liang VWG. Neuroendocrine Tumors. A Comprehensive Guide to Diagnosis and Management. 4th ed. Inter Science Institute 2009.

[12] Patel YC. General aspects of the biology and function of somatostatin. In Well C, Muller EE, Eds. Basic and Clinical Aspects of Neurosciences. Berlin: Springer-Verlag 1992; pp. 1-6.

[13] Brazeau P, Vale W, Burgus R, Ling N, Butcher M, Rivier J, Guillemin R. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 1973; 179: 77-9. http://dx.doi.org/10.1126/science.179.4068.77

[14] Reichlin S. Somatostatin I and II. N Engl J Med 1983; 309: 1495-501, 1556-63. http://dx.doi.org/10.1056/NEJM198312153092406

[15] Reubi JC, Hacki WH, Lamberts SW. Hormone producing gastrointestinal tumors contain a high density of somatostatin receptors. J Clin Endocrinol Metab 1987; 65: 1127-34. http://dx.doi.org/10.1210/jcem-65-6-1127

[16] Papotti M, Bongiovanni M, Volante M, Allia E, Landolfi S, Helhoe L, *et al*. Expression of somatostatin receptor types 1-5 in 81 cases of gastrointestinal and pancreatic endocrine-tumors. A correlative immunohistochemical and reverse-transcriptase polymerase chain reaction analysis. Virchows Archiv 2002; 440: 461-75. http://dx.doi.org/10.1007/s00428-002-0609-x

[17] Janson ET, Stridsberg M, GobL A, Westlin JE, Öberg K. Determination of somatostatin receptor subtype 2 in carcinoid tumors by immunohistochemical investigation with somatostatin receptor subtype 2 antibodies. Cancer Res 1998; 58: 2375-8.

[18] Reubi JC. Regulatory peptide receptors as molecular targets for cancer diagnosis and therapy. Q J Nucl Med 1997; 41: 63-70.

[19] Reubi JC, Waser B, Schaer JC, Laissue JA. 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. http://dx.doi.org/10.1007/s002590100541

[20] Kwekkeboom DJ, Kam BL, Martijn van Essen, Teunissen JJM, van Eijck CHJ, Valkema R, *et al*. Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocr Relat Cancer 2010; 17: R53-R73. http://dx.doi.org/10.1677/ERC-09-0078

[21] Krenning EP, Kwekkeboom DJ, Pauwels S, Kvols LK, Reubi JC. Somatostatin Receptor Scintigraphy. New York, NY: Raven Press 1995; pp. 1-50.

[22] Reubi JC, Mäcke HR, Krenning EP. Candidates for peptide receptor radiotherapy today and in the future. J Nucl Med 2005; 46(Suppl. 1): 67-75.

[23] Kwekkeboom DJ, De Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, *et al*. Treatment with the radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3] octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008; 26: 2124-30. http://dx.doi.org/10.1200/JCO.2007.15.2553

[24] Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, *et al*. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol 2011; 29: 2416-23. http://dx.doi.org/10.1200/JCO.2010.33.7873

[25] Thulin L, Samnegård H, Tydén G, Long DH, Efendic S. Efficacy of somatostatin in a patient with a carcinoid syndrome. Lancet 1978; 2: 43. http://dx.doi.org/10.1016/S0140-6736(78)91348-X

[26] Frank M, Klose KJ, Wied M, Ishaque N, Schade-Brittinger C, Arnold R. Combination therapy with octreotide and alpha-interferon: Effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors. Am J Gastroenterol 1999; 94: 1381-7.

[27] Fjällskog ML, Sundin A, Westlin JE, Öberg K, Janson ET, Eriksson B. Treatment of malignant endocrine pancreatic tumors with a combination of alpha-interferon and somatostatin analogs. Med Oncol 2002; 19: 35-42. http://dx.doi.org/10.1385/MO:19:1:35

[28] Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY, *et al*. Somatostatin receptor scintigraphy with [^{111}In-DTPAd-Phe1]- and [^{123}I-Tyr^{3}]- octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med 1993; 20: 716-731. http://dx.doi.org/10.1007/BF00181765

[29] Scarpignato C, Pelosini I. Somatostatin analogs for cancer treatment and diagnosis: an overview. Chemotherapy 2001; 47(Suppl. 2): 1-29. http://dx.doi.org/10.1159/000049157

[30] Sundin A, Vullierme MP, Kaltsas G, Plöckinger U. Mallorca Consensus Conferenceparticipants; European Neuroendocrine Tumor Society. ENETS Consensus ENETS. Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological examinations. Neuroendocrinology 2009; 90: 167-83. http://dx.doi.org/10.1159/000184855

[31] Bombardieri E, Ambrosini V, Aktolun C, Baum RP, Bishof-Delaloye A, Del Vecchio S, *et al.* Oncology Committee of the EANM. ^{111}In-Pentetreotide scintigraphy: procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging 2010; 37(7): 1441-8. http://dx.doi.org/10.1007/s00259-010-1473-6

[32] Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, *et al.* PROMID Study Group. Placebo controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours: a report from the PROMID Study Group. J Clin Oncol 2009; 27: 4656-63. http://dx.doi.org/10.1200/JCO.2009.22.8510

[33] Oberg K, Astrup L, Eriksson B, Falkmer SE, Falkmer UG, Gustafsen J, *et al*. Guidelines for the management of gastroenteropancreatic neuroendocrine tumours (including bronchopulmonary and thymic neoplasms). Acta Oncol 2004; 43(7): 617-25. http://dx.doi.org/10.1080/02841860410018575

[34] Krenning EP, De Jong M, Kooij PP, Breeman WA, Bakker WH, De Herder WW, *et al*. Radiolabelled somatostatin analogue(s) for peptide receptor scintigraphy and radionuclide therapy. Ann Oncol 1999; 10(2): 23-29. http://dx.doi.org/10.1023/A:1027396313397

[35] Wiseman GA, Kvols LK. Therapy of neuroendocrine tumors with radiolabeled MIBG and somatostatin analogues. Semin Nucl Med 1995; 25(3): 272-8. http://dx.doi.org/10.1016/S0001-2998(95)80016-6

[36] Maecke HR, Reubi JC. Somatostatin receptors as targets for nuclear medicine imaging and radionuclide treatment. J Nucl Med 2011; 52: 841-4. http://dx.doi.org/10.2967/jnumed.110.084236

[37] De Jong M, Bakker WH, Breeman WA, Bernard BF, Hofland LJ, Visser TJ, *et al*. Pre-clinical comparison of [DTPAo,Try3] octreotide and [DTPA0, D-PhelTry3] as carriers somatostatin receptor-targeted scintigraphy and radionuclide therapy. Int J Cancer 1998; 75: 406-411. http://dx.doi.org/10.1002/(SICI)1097-0215(19980130)75:3<406::AID-IJC14>3.0.CO;2-6

[38] Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr Rev 2003; 24: 389-427. http://dx.doi.org/10.1210/er.2002-0007

[39] Oberg K. Future aspects of somatostatin- receptor- mediated therapy. Neuroendocrinology 2004; 80: 57-61. http://dx.doi.org/10.1159/000080743

[40] Ambrosini A, Fani M, Fanti S, Forrer F, Maecke HR. Radiopeptide imaging and therapy in Europe. J Nucl Med 2011; 52(12) (Suppl).

[41] Heppeler A, Froidevaux S, Eberle AN, Maecke HR. Receptor targeting for tumor localisation and therapy with radiopeptides. Curr Med Chem 2000; 7: 971-994. http://dx.doi.org/10.2174/0929867003374516

[42] Thundimadathil J. Cancer Treatment Using Peptides: Current Therapies and Future Prospects. J Amino Acids 2012; Article ID 967347, 13 pages.

[43] Grozinsky-Glasberg S, Shimon I, Korbonits M, Grossman AB. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. Endocr Relat Cancer 2008; 15(3): 701-720. http://dx.doi.org/10.1677/ERC-07-0288

[44] Nicolas G, Giovacchini G, MÜller-Brand J, Forrer F. Targeted radiotherapy with radiolabeled somatostatinanalogs. Endocrinol Metab Clin North Am 2011; 40(1): 187-204. http://dx.doi.org/10.1016/j.ecl.2010.12.006

[45] Kwekkeboom DJ, Bakker WH, Kam BL, Teunissen JJ, Kooij PP, de Herder WW, *et al*. Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [(177)Lu-DOTA(0),Tyr(3)] octreotate. Eur J Nucl Med Mol Imaging 2003; 30: 417-422. http://dx.doi.org/10.1007/s00259-002-1050-8

[46] Paganelli G, Zoboli S, Cremonesi M, Bodei L, Ferrari M, Grana C, *et al*. Receptor-mediated radiotherapy with 90Y-DOTA-D-Phe1-Tyr3-octreotide. Eur J Nucl Med 2001; 28: 426-434. http://dx.doi.org/10.1007/s002590100490

[47] Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin: evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer 1991; 68: 227-232. http://dx.doi.org/10.1002/1097-0142(19910715)68:2<227::AID-CNCR2820680202>3.0.CO;2-I

[48] Krenning EP, Kooij PP, Pauwels S, Breeman WA, Postema PT, De Harder WW, *et al*. Somatostatin receptor: Scintigraphy and radionuclide therapy. Digestion 1996; 57(S1): 57-61. http://dx.doi.org/10.1159/000201398

[49] Kwekkeboom DJ, Krenning EP, de Jong M. Peptidereceptor imaging and therapy. J Nucl Med 2000; 41: 1704-1713.

[50] Schwartz AL, Fridovich SE, Lodish HF. Kinetics of internalization and recycling of the asialoglycoprotein receptor in a hepatoma cell line. J Biol Chem 1982; 257: 4230-4237.

[51] Slooter GD, Breeman WA, Marquet RL, Krenning EP, van Eijck CH. Antiproliferative effect of radiolabelled octretide in metastases model in rat liver. Int J Cancer 1999; 81: 767-771. http://dx.doi.org/10.1002/(SICI)1097-0215(19990531)81:5<767::AID-IJC17>3.0.CO;2-T

[52] McCarthy KE, Woltering EA, Anthony LB. In situ radiotherapy with ^{111}In pentetreotide: state of the art and perspectives. Q J Nucl Med 2000; 44: 88-95.

[53] Meyers MO, Anthony LB, McCarthy KE, Drouant G, Maloney TJ, *et al*. High-dose indium ^{111}In pentetreotide radiotherapy foe metastatic atypical carcinoid tumor. South Med J 2000; 93: 809-811.

[54] Martin RF, Bradley TR, Hodgson GS. Cytotoxicity of a ^{125}I-labeled DNA-binding compound that induces double-stranded DNA breaks. Cancer Res 1979; 39: 3244-3247.

[55] De Jong M, Bakker WH, Krenning EP, Breeman WA, van der Pluijm ME, Bernard BF, *et al*. Yttrium-90 and indium-111 labelling, receptor binding and biodistribution of [DOTA^0,D-Phe1,Tyr^3] octreotide, a promising somatostatin analogue for radionuclide therapy. Eur J Nucl Med 1997; 24*:* 368-371. http://dx.doi.org/10.1007/s002590050064

[56] Kwekkeboom DJ, Kooij PP, Bakker WH, Macke HR, Krenning EP. Comparison of 111In-DOTA-Tyr3-octreotide and 111In-DTPA-octreotide in the same patients: biodistribution, kinetics, organ and tumor uptake. J Nucl Med 1999; 40: 762-767.

[57] O'Donoghue JA, Bardies M, Wheldon TE. Relationships between tumor size and curability for uniformly targeted therapy with beta-emitting radionuclides. J Nucl Med 1995; 36*:* 1902-1909.

[58] De Jong M, Breeman WA, Bernard BF, Bakker WH, Visser TJ, Kooij PP, *et al*. Tumor response after [(90)YDOTA(0), Tyr(3)] octreotide radionuclide therapy in a transplantable rat tumor model is dependent on tumor size. J Nucl Med 2001; 42: 1841-1846.

[59] Baum RP, Söldner J, Schmücking M, Niesen A. Intravenous and intra-arterial peptide receptor radionuclide therapy (PRRT) usingY-90 -DOTA-Tyr 3 -octreotate (Y-90-DOTATATE) in patients with metastatic neuroendocrine tumors (abstract). Eur J Nucl Med 2004; 31(suppl 2): S238.

[60] Virgolini I, Britton K, Buscombe J, Moncayo R, Paganelli G, Riva P. In- and Y-DOTA-lanreotide: results and implications of the MAURITIUS trial. Semin Nucl Med 2002; 32: 148-155. http://dx.doi.org/10.1053/snuc.2002.31565

[61] De Jong M, Breeman WA, Bakker WH, Kooij PP, Bernard BF, Hofland LJ, *et al*. Comparison of (111) In-labeled somatostatin analogues for tumor scintigraphy and radionuclide therapy. Cancer Res 1998; 58(3): 437-41.

[62] Reubi JC, Schär JC, Waser B, Wenger S, Heppeler A, Schmitt JS, Mäcke HR. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med 2000; 27: 273-282. http://dx.doi.org/10.1007/s002590050034

[63] Esser JP, Krenning EP, Teunissen JJ, Kooij PP, van Gameren AL, Bakker WH, Kwekkeboom DJ. Comparison of [(177) Lu-DOTA (0), Tyr (3)] octreotate and [(177) Lu-DOTA (0),Tyr (3)] octreotide: which peptide is preferable for PRRT? Eur J Nucl Med Mol Imaging 2006; 33: 1346-1351. http://dx.doi.org/10.1007/s00259-006-0172-9

[64] Waldherr C, Pless M, Mäcke HR, Haldemann A, Müller-Brand J. The clinical value of [90Y-DOTA]-D-Phe1-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. Ann Oncol 2001; 12: 941-5. http://dx.doi.org/10.1023/A:1011160913619

[65] Kwekkeboom DJ, Teunissen JJ, Bakker WH, Kooij PP, de Herder WW, Feelders RA, *et al*. Radiolabeled somatostatin analog [177Lu-DOTA0, Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol 2005; 23: 2754-62. http://dx.doi.org/10.1200/JCO.2005.08.066

[66] Kaltsas GA, Papadogias D, Makras P, Grossman AB. Treatment of advanced neuroendocrine tumours with radiolabelled somatostatin analogues. Endocr Relat Cancer 2005; 12: 683-699. http://dx.doi.org/10.1677/erc.1.01116

[67] Kunikowska J, Królicki L, Hubalewska-Dydejczyk A, Mikołajczak R, Sowa-Staszczak A, Pawlak D. Clinical results of radionuclide therapy of neuroendocrine tumours with 90Y-DOTATATE and tandem90Y/177Lu- DOTATATE: which is a better therapy option? Eur J Nucl Med Mol Imaging 2011; 38: 1788-1797. http://dx.doi.org/10.1007/s00259-011-1833-x

[68] Bodei L. Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues. J Endocrinol Invest 2009; ISBN: 978-90-367-3769-2.

[69] Anthony LB, Woltering EA, Espanan GD, Cronin MD, Maloney TJ, McCarthy KE. Indium-111- pentetreotide prolongs survival in gastroenteropancreatic malignancies. Semin Nucl Med 2002; 32(2): 123-32. http://dx.doi.org/10.1053/snuc.2002.31769

[70] Graham MM, Menda Y. Radiopeptide Imaging and Therapy in the United States. J Nucl Med 2011; 52: 56S-63S. http://dx.doi.org/10.2967/jnumed.110.085746

[71] Bodei L, Pepe G, Paganelli G. Peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumors with somatostatin analogues. Eur Rev Med Pharmacol Sci 2010; 14: 347-351.

[72] Kam BL, Teunissen JJM, Krenning EP, de Herder WW, Khan S, van Vliet EI, Kwekkeboom DJ. Lutetium-labelled peptides for therapy of neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2012; 39(Suppl 1): S103-S112. http://dx.doi.org/10.1007/s00259-011-2039-y

[73] Forrer F, Valkema R, Kwekkeboom DJ, de Jong M, Krenning EP. Peptide receptor radionuclide therapy. Best Pract Res Clin Endocrinol Metab 2007; 21(1): 111-129. http://dx.doi.org/10.1016/j.beem.2007.01.007

Received on 21-11-2013 Accepted on 31-01-2014 Published on 12-02-2014

http://dx.doi.org/10.6000/1927-7229.2014.03.01.8