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Review Article

^{177}Lu-DOTATATE Radionuclide Therapy: Current Status and Trends

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Abstract

The relevance of developing effective methods for the treatment of neuroendocrine tumors is associated with an increase in the incidence of this type of cancer worldwide. The article presents a review of the literature on the accumulated international experience in peptide receptor radionuclide therapy in neuroendocrine tumors and meningiomas. International practical recommendations on the rational selection of patients for therapy with ^{177}Lu-DOTATATE are outlined, taking into account the principles of personalized medicine, indications and contraindications for this type of treatment. Considering that the Russian Federation is the largest country in terms of the number of registered patients with neuroendocrine tumors, the introduction of this method of treatment as a second- and third-line therapy will allow such patients to receive an additional effective treatment option, which will increase the time without progression in these patients and will significantly improve their quality of life.

Keywords: Neuroendocrine Tumors (NETs); Radionuclide Therapy; Oncologist

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms originating from neuroendocrine cells of the embryonic gut that have biologically active properties. Neuroendocrine cells have certain secretory characteristics which leads to the development of syndromes of overproduction of regulatory peptides. The appearance of NETs may be associated with the presence of hereditary syndromes of multiple neuroendocrine neoplasias. Over the past 30 years there has been a significant increase in the incidence of NETs of all localizations (this fact is most likely associated with an improvement in their detection including due to the progress of imaging methods). About 7,350 patients with NETs are registered annually in Russia [1].

The most common localizations of NETs are the gastrointestinal tract and pancreas, approximately 30% of NETs occurs in the bronchopulmonary system. About 40% of NETs of the digestive system are functional, i.e. secrete hormonally active substances that cause typical symptoms [2]. According to the US SEER (Surveillance, Epidemiology, and End Results) registry up to 50% of patients already have regional or distant metastases at the time of diagnosis [3].

The variety of forms and localizations of NETs has led to the creation of several classifications. Each classification is based on a specific feature of NETs (e.g., classification by localization, origin, and grade).

The clinical presentation of NETs is diverse: the symptoms are associated with the localization of the tumor and its functional activity, for example, the production of biologically active

substances. Non-functioning tumors can be asymptomatic for a long time. The classic symptoms of functioning NETs include diarrhea, hot flashes, flushing of the skin and in rare cases, bronchospasm. The frequency of hot flashes varies from several times a day to 1–3 or more attacks per hour.

When the tumor is resectable, surgical treatment in the form of R0 resection is considered the preferred treatment for NETs. In patients with well-differentiated NETs, and if surgical treatment is not possible, biotherapy with somatostatin analogues is indicated [1]. In case of progression of liver metastases, chemoembolization or radioembolization is often used. In recent years, a number of targeted drugs for systemic therapy and chemotherapy have been developed and approved for the treatment of metastatic or unresectable NETs. The treatment and follow-up plan for patients with NETs is quite individual and should be discussed by a multidisciplinary council (oncologist, surgeon, nuclear radiologists).

Meningiomas grow from the cells of the meninges and usually adjoin the bone structures of the skull, often infiltrating them [4]. Most often meningiomas are localized in the region of the parietal, frontal and temporal bones of the skull, parasagittally, in the falciform process and sinuses (falx meningiomas). Basal meningiomas often originate from the wings of the sphenoid bone, tubercle of the sella turcica, olfactory fossa and parasellar structures. A distinctive feature of basal meningiomas is the lesion of the cranial nerves and vessels of the base of the brain. This is due to the involvement of adjacent structures, nerves and vessels in the tumor process [5]. Benign meningiomas often have a homogeneous structure, while malignant ones are characterized by the presence of calcifications, hemorrhages, necrosis and cysts. In malignant meningiomas peritumoral edema may be present. A characteristic feature is their expansive growth and pronounced mass effect [6].

Development of radionuclide imaging of NETs and meningiomas

One of the main features of NETs pathogenesis is the overexpression of somatostatin receptors (SSR) on the cell surface. Somatostatin is a neuropeptide which consists of 14 amino acids. A strictly defined amino acid sequence in the structure of somatostatin and its analogues provides specific binding to somatostatin receptors located on the surface of NETs cells.

In total, 5 subtypes of somatostatin receptors are noted. Five types of somatostatin receptors were first described by J. C. Reubi., *et al.* in 1987 [7]. Each subtype is associated with a specific cellular regulation. For example, the secretory activity of endocrine cells is regulated by SSR-2 and SSR-5, the angiogenesis is regulated by SSR-1 and apoptosis is associated with the expression of SSR-3 [1]. This feature allows for the use of radioactively labeled somatostatin analogues for imaging and therapy of NETs. The first study of a radiolabeled peptide in humans was published in 1989 by E. P. Krenning., *et al*. [8]. It was an Iodine-123 labeled somatostatin analogue. Subsequently, a radiopharmaceutical (RPh) with Indium-111 ^{111}In-Octreotide was developed. ^{111}In-Octreotide scintigraphy has long been the gold standard for diagnosing NETs [9].

With advances in technology, such as positron emission tomography (PET/CT), and the advent of Gallium-68 (^{68}Ga) labeled somatostatin analogues (DOTATOC, DOTANOC and DOTATATE), more accurate diagnosis has become possible due to the higher resolution of PET/CT and better contrast resolution of radiopharmaceuticals developed for PET diagnostics [10]. The sensitivity of the PET/CT method with DOTA-conjugates exceeds 90% according to the medical reports [11]. Moreover, the advent of another somatostatin analogue labeled with Technetium-99 (^{99m}Tc) (Tektrotyd) significantly increased the sensitivity of SPECT/CT in diagnosing NETs [12]. The use of Tektrotyd may be an alternative to PET/CT method in cases of limited availability. An important advantage of radionuclide imaging using SSR markers is the fact that the assessment of the NETs receptor status allows determining indications for radionuclide treatment. At the same time, the Krenning score for visual assessment of the NETs receptor status (1–4) is used to select candidates for therapy [13].

Regardless of the degree of malignancy, meningiomas have a high level of SSR expression, especially of the subtype 2 [14,15], due to which they are well visualized on PET using DOTATOC, DOTANOC, and DOTATATE markers labeled with the ^{68}Ga isotope. Due to the high affinity of these RPh to SSR and the high degree of SSR expression in meningiomas, PET with SSR markers allows detecting relatively small meningiomas foci and allows determining tumor boundaries more accurately than the conventional radiography (CT, MRI). The use of the ^{68}Ga-DOTATATE marker may be preferable compared

to the DOTATOC and DOTANOC markers in the diagnostics of meningiomas due to the higher accumulation of SSR in the tumor tissue [16]. PET/CT with SSR markers improves the detection of meningiomas and has advantages over contrast-enhanced MRI in the detection of parafalcine tumors and meningiomas of the skull base [17]. A recently published prospective study in 21 patients with meningiomas demonstrated a higher sensitivity of preoperative PET with SSR markers compared to MRI for detection of tumor tissue (90% vs. 79%, p = 0.049) with comparable specificity and positive predictive value of both methods (for both De Novo and recurrent tumors). Data were obtained from histological analysis of 115 tissue samples [18].

In recent years, several medical reports confirming the value of PET/CT with SSR markers for radiotherapy planning in meningiomas have been published. The method turned out to be especially informative in case of infiltration of the bone structures at the base of the skull and multifocal meningiomas [19,20]. This approach makes it possible to reduce the radiotherapy toxicity and increase its effectiveness by reducing the amount of radiation and focusing more precisely on the tumor tissue [21,22].

^{177}Lu-DOTATATE therapy: accumulated experience and development trends

The basic theranostic principle involves the sequential labelling of the tumorotropic vector (in case of NETs these are somatostatin analogues): first, it is labelled by a diagnostic radionuclide for PET or SPECT, and then it is labelled by a therapeutic RPh. Carrying out the first diagnostic stage makes it possible to predict how the therapeutic RPh will be distributed and calculate its optimal dose [1].

Currently, there are several theranostic pairs for the diagnosis and treatment of NETs. The PRRT (Peptide Receptor Radionuclide Therapy) technique has been developed at the University Hospital of Rotterdam since 1985 [23]. The high expression of SSR in neuroendocrine tumors and the low level in healthy tissue made it possible to develop RPh for effective targeted radionuclide therapy (RNT). Initially, the radionuclide Yttrium-90 (^{90}Y) was used to label the SSR. Favorable physical properties of ^{90}Y, such as the beta spectrum and sufficient penetration depth (up to 11 mm), provide a good effect in the treatment of space-occupying lesions. A significant disadvantage of ^{90}Y is the absence of gamma rays, which makes it impossible to register scintigrams and dosimetric control.

^{177}Lu-DOTATATE is the second-generation drug. It consists of DOTATATE, a man-made (synthetic) form of the natural somatostatin hormone, and the radioactive element Lutetium-177. Second-generation RPhs (^{177}Lu-DOTATOC/TATE/NOC), which like the ones of the first generation are agonists of SSR, have important advantages over the latter. In particular, due to the presence of two gamma lines (113 and 208 KeV), it became possible to carry out scintigraphic control within the therapy and obtain data on the RPhs concentration in target organs and tumor foci which allows to calculate dosimetric parameters. A significant advantage of ^{177}Lu-labeled SSR-tropic ligands is their lower nephrotoxicity. Thus, a retrospective analysis of the side effects of the therapy in two different, comparable groups of patients showed a significantly lower increase in creatinine after the treatment with ^{177}Lu-DOTATATE (mean 3.8%/year) compared to the group of patients treated with ^{90}Y-DOTATOC (mean 7.3%/year) [24]. Therefore, the use of RPhs labeled with ^{177}Lu gave a new impetus to the development of peptide radioreceptor therapy.

The NETTER 1 trial

The NETTER 1 multicentre clinical trial was the first randomized, prospective, phase 3 trial in patients with small bowel NETs. This work demonstrated a high efficiency of the therapy with ^{177}Lu-DOTATATE and gave impetus to the wide clinical dissemination of the method [25]. The study included 230 patients with inoperable well-differentiated NETs of the small intestine (G1-2), who had progression of the tumor process. A prerequisite for the therapy was an increased expression of SSR, proven on a scintigram or PET/CT. In the group of patients treated with PRRT with ^{177}Lu-DOTATATE (n = 115), 13 deaths were observed, in the group treated with "cold" sandostatin (n = 115) — 22 deaths. Both progression-free survival and overall survival were significantly higher in the ^{177}Lu-DOTATATE-treated group. At the same time, PRRT reduced the risk of tumor progression or death by 79%.

Preliminary results from the NETTER 1 trial led to the approval of ^{177}Lu-DOTATATE (Lutathera®) for clinical use in the USA and Europe.

The recently published final results of NETTER 1 (after long-term follow-up of patients) showed that the median 5-year overall survival in the ^{177}Lu-DOTATATE-treated group was 48 months and was higher than in the control group [26]. The difference of 11.7 months was considered clinically significant, but did not reach the threshold of statistical significance (HR = 0.84; log-rank P = 0.30). The authors note that this result is most likely due to the fact that 36% of the control group patients received radioligand therapy (primarily ^{177}Lu-DOTATATE) during the observation period.

ERASMUS I/II study

In Erasmus Medical Center, the University Hospital of Rotterdam, where the PRRT method was developed and pioneered, a single-centre, open-label phase 1-2 study (ERASMUS I/II) was conducted. The efficacy of ^{177}Lu-DOTATATE was evaluated according to RECIST criteria in a subgroup (n = 360) of 1,214 patients included in the study. At the same time, patients with well-differentiated neuroendocrine tumors of the lung, pancreas, and intestines were included in the study. The course of therapy consisted of 4 intravenous injections of ^{177}Lu-DOTATATE at a dose of 7.4 GBq with an interval of 6–13 weeks. The positive response to therapy (ORR) was 16% (n = 58), including 3 complete responses (CR) in this subgroup of 360 patients [27].

The NETTER 2 trial

The aim of the NETTER 2 randomized phase 3 trial is to determine whether Lutathera (^{177}Lu-DOTATATE) in combination with long-acting octreotide products can prolong progression-free survival in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs), which have relatively high proliferation rate (G2 and G3). At the same time, two types of systemic therapy are compared as first-line therapy: Lutathera (^{177}Lu-DOTATATE) + Octreotide-Depo and monotherapy with high-dose Octreotide-Depo (60 mg). The study includes both patients not previously treated with somatostatin analogues and patients treated with somatostatin analogues in the absence of progression. Preliminary data should be published in December 2023.

Review of indications for 177Lu-DOTATATE therapy considering international guidelines. «In-label» indications

At the end of 2017 ^{177}Lu-DOTATATE (Lutathera by Advanced Accelerator Applications — AAA, Novartis) was approved for clinical use by the European Medicines Agency (EMA). In 2018, the drug was licensed by the US Food and Drug Administration (FDA) [28]. Indications for Lutathera therapy were formulated as follows: «to treat GEP-NETs that cannot be removed by surgery, have spread to other parts of the body or are not responding to treatment. The drug is intended only for GEP-NETs, on the surface of cells of which there are somatostatin receptors».

It is noteworthy that Lutathera was approved not only for the treatment of tumors of the small intestine, but also for NETs in other parts of the gastrointestinal tract. This is because the experts took into account both results of the NETTER 1 phase 3 trial and less evidence-based data obtained in the ERASMUS phase 1 and 2 studies. The extended approval of Lutathera drug is also explained by its status as an “orphan drug” for the treatment of rare tumors. However, further developments in the field of chemotherapy and targeted therapy for NETs have led to a review of the role of ^{177}Lu-DOTATATE treatment and to a more differentiated approach to the treatment of various forms of NETs, depending on their localization, proliferative activity and previous therapy.

^{177}Lu-DOTATATE remains the standard treatment for unresectable/metastatic well-differentiated NETs of the small intestine that have progressed on therapy with somatostatin analogues (G1-2, Ki67 < 10%). However, the latest 2020 ESMO (European Society for Medical Oncology) guidelines for NETs with a higher proliferation index (Ki67 > 10%) recommend second-line therapy with the mTOR inhibitor everolimus, and ^{177}Lu-DOTATATE is considered as a third-line therapy [29].

For well-differentiated (G1) pancreatic NETs, in case of their progression on therapy with somatostatin analogues, chemotherapy (streptozocin/5-FU capecitabine, sunitinib) is recommended as a first-line therapy, and treatment with ^{177}Lu-DOTATATE is considered as a second-line therapy.

For pancreatic G2-NETs, therapy with somatostatin analogues was found to be ineffective, so chemotherapy (streptozocin/5-FU capecitabine, sunitinib) is recommended as a first-line therapy, and treatment with ^{177}Lu-DOTATATE is recommended as a second-line therapy.

For poorly differentiated (G3) pancreatic NETs with Ki67 > 10%, a combination of everolimus and sunitinib is recommended as a

second-line therapy, and ^{177}Lu-DOTATATE is recommended as a third-line therapy.

«Off-label» indications

^{177}Lu-DOTATATE targeted radionuclide therapy is used to treat a wide range of tumor diseases in case of widespread metastasis or local progress that is not responding to local or systemic therapy. An indispensable condition for carrying out the therapy with ^{177}Lu-DOTATATE is a high level of expression of somatostatin receptors in tumor foci. In addition to GEP-NETs, ^{177}Lu-DOTATATE has been successfully used to treat the following tumors: metastatic lung carcinoid, unresectable or metastatic paragangliomas and pheochromocytomas, metastatic medullary thyroid cancer resistant to systemic therapy, thymus and thymoma NETs, unresectable progressive meningiomas if radiotherapy is not possible, neuroblastoma.

Thus, recommendations for the rational selection of patients for therapy with ^{177}Lu-DOTATATE taking into account the principles of personalized medicine include the following indications. First, histologically confirmed G1-G2 GEP-NETs as a second-line therapy; G3 as a third-line therapy («in-label» indications, according to current ESMO guidelines). Secondly, the "off-label" indications presented above. It should be remembered that since PRRT with ^{177}Lu-DOTATATE in these cases has the status of an experimental therapy, its use must be justified in each individual case. Generally, PRRT can be started if standard therapies have been exhausted or are at high risk of complications. An individual decision on assigning a patient the radionuclide therapy with ^{177}Lu-DOTATATE should be made by an oncological council with the participation of specialists in the field of nuclear medicine and radiation oncology, gastroenterologists, surgeons, oncologists, radiologists, pathologists, taking into account the possibility of standard and/or alternative methods (surgical treatment, chemotherapy, targeted therapy, radiation therapy, chemo- or radioembolization of liver metastases). Depending on the oncopathology, it is possible to involve specialists from other disciplines.

Finally, one more indication for ^{177}Lu-DOTATATE therapy is when PET/CT with ^{68}Ga-DOTATATE or SPECT/CT with SSR markers reveals increased expression of SSR in metastases/tumor foci. In this case all foci are assessed visually according to the Krenning score: Grade 1 — the intensity of radiopharmaceutical accumulation in the tumor focus is less than in the liver parenchyma, Grade 2 — the intensity of radiopharmaceutical accumulation in the tumor focus is equal to the accumulation in the liver parenchyma, Grade 3 — the intensity of radiopharmaceutical accumulation in the tumor focus is more than in the liver parenchyma, Grade 4 — the intensity of radiopharmaceutical accumulation in the tumor focus is more than in the parenchyma of the spleen or kidneys [30]. In the joint recommendations of the International Atomic Energy Agency (IAEA), the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) published in 2013, experts consider scintigraphy with the ^{111}In-Pentreotid marker or immunohistochemical evidence of the presence of SSR-positive metastases to be sufficient [31]. According to experts, these recommendations can be considered outdated. If PET/CT with ^{68}Ga-DOTATATE is not possible, at least a SPECT/CT scan should be performed (in addition to routine scintigraphy), preferably with a ^{99m}Tc-Tektrotyd marker. The results of immunohistochemical studies are insufficient, since they show the expression of SSR in one focus and cannot assess the prevalence of metastasis, and also cannot rule out the presence of metastases with low affinity for SSR.

Absolute contraindications for therapy with ^{177}Lu-DOTATATE include unsatisfactory patient performance status (ECOG > 2, Karnofsky index < 60%), severe mental disorders, pregnancy. Relative contraindications include severe renal failure (GFR < 30 mL/min), severe myelosuppression (WBC count of less than 3.0 x 10^9/L, neutrophil count of less than 1.0x10^9/L, platelet count of less than 75.0 x 10^9/L), the presence of metastases requiring preliminary local therapy, for example, surgical stabilization of the spine or radiation therapy; fecal incontinence. Typical side effects of the therapy are mild nausea and vomiting (up to 20% of patients), weakness (25% of patients, especially in the first 4 weeks after the therapy), dry mouth (up to 20% of patients), nephrotoxicity (25% of patients), grade 3 or 4 hematotoxicity (10% of patients).

It should be noted that in case of "in-label" indications therapy for legal reasons should be carried out with Lutathera®. In case of "off-label" indications or deviations from the permitted conditions of «in-label» use, it is possible to conduct experimental PRRT with ^{177}Lu-DOTATATE synthesized in our own laboratory.

Conclusion

The relevance of the development of effective methods for the treatment of NETs is associated with an increase in the incidence of this type of tumor worldwide. The targeted radionuclide therapy with [177]Lu-DOTATATE for the treatment of locally advanced and disseminated NETs as a second-line and third-line therapy will increase the time without progression in these patients and will significantly improve their quality of life. The standardization of the therapy will make it possible to conduct numerous original scientific studies and introduce them into wide clinical practice in the Russian Federation.

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