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Radioligand therapy — personalized treatment for patients with neuroendocrine tumors

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ABSTRACT

Over the past 2 decades, radioligand therapy (RLT), previously referred to as peptide receptor radionuclide therapy, has been proven to be an effective and safe therapeutic option in patients with advanced, unresectable, often progressive, well-differentiated neuroendocrine tumors. The NETTER-1 study, the only randomized phase-III trial to date, established RLT with 177Lu-DOTATATE as the "gold standard" in the treatment of metastatic or locally advanced tumors, which are unresectable, well-differentiated with somatostatin receptor (SSTR) expression, and progressive neuroendocrine tumors.

Key words: neuroendocrine tumours (NET), radioligand therapy (RLT), peptide receptor radionuclide therapy (PRRT), somatostatin receptor overexpression

Introduction

In the era of personalized medicine, new targets localized on the surface of neuroendocrine tumors have been used for radioligand therapy (RLT).

During the last 2 decades RLT, previously described as peptide receptor radionuclide therapy (PRRT), has proved to be an effective and safe therapeutic option in patients with advanced, unresectable, often progressing, well-differentiated (NET neuroendocrine [NET]) tumors [1–6].

This form of molecularly directed therapy, or RLT/PRRT, is based on the use of a synthetic somatostatin analogues (SSA) linked by a so-called linker-chelator (the most currently used substance is DOTA) with an appropriate radioactive isotope (radioisotope). This therapy can be used in patients with well-differentiated neuroendocrine tumors, which are characterized by overexpression of the somatostatin receptor (SSTR). The therapy aims to provide permanent binding of the prepared complex of the radioisotope and somatostatin analog with the receptor on the surface of the tumor cell and irradiate it with high-energy electrons originating from beta decay within the atomic nucleus. The binding of the analog complex and the radioisotope with the membrane receptor does not have to be associated with the internalization of the formed ligand-receptor complex to the interior of the cell as just the permanent binding of the radiopharmaceutical to the receptor causes irradiation of the tumor cell and additionally of neighboring cells [1, 4–6]. The range of this corpuscular irradiation is, at most, several millimeters. This distance is sufficient for damaging many tumor cells, with practically minor damage to tissues adjacent to the tumor. Additionally, this type of therapy is currently characterized by low, manageable adverse effects and toxicity.

The success of this therapy and its position in the current algorithm of treating well-differentiated neuroendocrine neoplasms (NEN) depend on the selection

of patients, appropriate imaging markers qualifying for RLT, and an appropriate structural, functional, and clinical evaluation of the response to treatment [1, 7].

The synthetic somatostatin receptor ligand (SRL) labeled with high doses of the Indium-111 radioisotope was the first radiopharmaceutical that was used in NET therapy. The high activities of 111In-DTPA-Octreotide used during therapy yielded encouraging results in the control of the symptoms of well-differentiated secreting NET. However, objective responses were rare, and hematological adverse effects were also observed [8].

Next new analogs labeled with β-emitting radionuclides were introduced: Yttrium-90 (^{90}Y) and Lutetium-177 (^{177}Lu). During the next 15 years in many retrospective and prospective phase I, II studies using both radiopharmaceuticals and various types of synthetic SRL, disease control rate (DCR) at the level of 68–94% was observed in patients with various types of neuroendocrine tumors, as well as significant prolongation of overall survival (OS) and progression-free survival (PFS,) [6, 9–11]. Biochemical and clinical responses were also observed in the form of decreased symptoms of hormone hyperactivity and improved quality of life [12].

Data concerning PRRT safety are also encouraging for the use of this form of therapy [6, 13–15]. The most common acute adverse effects are nausea and vomiting, mainly associated with amino acid infusions (AA), which are supposed to protect against RLT nephrotoxicity. Among other adverse effects, the following should be mentioned: fatigue, general malaise, sporadic stomach pains, and transitory lymphopenia, which are generally mild, self-limiting, and reversible. Breakthrough carcinoid syndrome during therapy in the case of hormonally active NET originating most commonly from the midgut is a very rare complication. Nephrotoxicity is a late adverse effect of PRRT mainly when ^{90}Y is used. Based on long-term observation of patients participating in the NETTER-1 trial, the frequency of occurrence of strong nephrotoxicity in patients treated with ^{177}Lu-DOTATE was low (5%) and similar to that observed in the control group (4%). Comparable changes in creatinine clearance in a defined time in both studied groups suggest that there is no detrimental, long-term effect of ^{177}Lu-DOTATE on kidney function in patients in the arm with RLT [16].

Hematological toxicity, such as acute lymphoblastic leukemia (ALL) or myelodysplastic syndrome (MDS), was observed in less than 5% of patients who received PRRT [13, 14].

Preliminary phase I and II clinical trials on using RLT in various types of NET were successful. However, only the NETTER-1 trial published in 2017 established PRRT using ^{177}Lu-DOTATATE as a standard of care in treating patients with metastatic or locally advanced well-differentiated progressing NEN with the expression of the somatostatin receptor [15].

The basis of radioligand therapy — RTL/PRRT

As mentioned above, RLT/PRRT using radioisotope labeled somatostatin analogs (SSTA) is a reasonable option in treating unresectable and/or metastatic well/moderately differentiated NET [1–7]. The main aim of this therapy is to provide a high dose of corpuscular beta radiation, and currently in the phase of clinical trials, also radionuclides with alpha decay, to tumor cells and to obtain the effect of a cross-fire directed at nearby cells. Due to this phe nomenon, the therapy additionally encompasses cells with a low expression of the SST receptor or its absence in the case of a heterogeneous distribution of the receptor on the NET surface. Because of the range of this irradiation, the total dose absorbed by normal tissues surrounding the tumor is significantly decreased. In the case of the currently commonly used lutetium (^{177}Lu), the majority of the electrons derived from radioactive decay have a range below 1 mm.

Synthetic somatostatin analogs labeled with a radioisotope are used by their systemic administration in fractionated doses and sequential cycles (generally 4) every 6 to 9 weeks [1–7]. The potential risk of damage to the kidney and bone marrow limits the cumulative dose of radioactivity that can be administered to the patient [12].

Generally, the response to treatment is associated with the initial very high accumulation of the radiopharmaceutical in somatostatin receptor imaging (SRI) performed by single-photon emission computed tomography (SPECT/CT) using, for example, ^{99m}Tc HYNICTOC or by PET/CT employing analogs of the SST receptor labeled with ^{68}Ga DOTATATE/DOTATOC [1, 2]. The effectiveness of the therapy is associated with the high affinity of the used radiopharmaceuticals for somatostatin receptors mainly of subtype 2 (sst2) and moderate affinity for subtype 5 (sst5) and other SSTR subtypes. The response also depends on the tumor mass, the biology of its cells with a potentially high index of resistance, and the high absorbed dose of energy deposited inside neoplastic cells with high SSTR expression [4, 5, 8].

The next factor affecting the effectiveness of therapy is the choice of the type of radionuclide. Each of the β emitters currently used in therapy — ^{177}Lu and ^{90}Y, has its advantages. In particular ^{90}Y electrons have high energy (Emax 2.27 MeV, penetration range R_{max} 11 mm, halflife $T_{1/2}$ 64 hours) and are characterized by a higher range of penetration within the tumor, which leads to greater irradiation of larger lesions with a heterogeneous accumulation of the radiopharmaceutical. The cross-fire phenomenon also occurs.

The shorter half-life of ^{90}Y contributes to decreasing its toxicity in respect to sensitive organs such as bone marrow and kidneys. In turn, ^{177}Lu has lower energy

and thus the range of beta irradiation, which allows better deposition of energy in the case of smaller tumors. An advantage of ^{177}Lu is also its lower toxicity for bone marrow and kidneys in comparison to [90]Y [2, 12, 13].

Prognostic and predictive factors of RLT

In the context of RLT, the degree of differentiation of the tumor cells described as G1 or G2 on the basis of the proliferation index Ki-67 (MIB1 antibody), is the strongest prognostic factor in patients with gastro-entero-
-pancreatic NET (GEP-NET). Data from various studies indicate that in patients with NET G1 and low G2 (Ki-67 from 3 to 10%), significantly better results of treatment are obtained in the form of an increased median PFS and OS in comparison with patients with NET G2 with higher Ki-67 ≥ 10% and on NET G3 with Ki-67 > 20%. This is one of the main factors affecting international recommendations concerning the treatment of neuroendocrine tumors, for example, of the European Association of Nuclear Medicine (EANM), European Neuroendocrine Tumor Society (ENETS), or North American Neuroendocrine Tumors Society (NANETS) [1, 7, 17, 18].

Even though the Ki-67 index is most commonly used for NEN classification, it is burdened by a sampling error as there are differences in Ki-67 within the whole tumor and/or its metastases. The next factor affecting the effectiveness of treatment is the localization of the primary GEP-NET lesion. Radiological responses to treatment, according to the classification of Response Evaluation Criteria in Solid Tumors (RECIST) are more frequent in the case of pancreatic NET in comparison with other localizations, but with a shorter time of duration. The disease recurrence is also faster in patients with hormonally active, symptomatic NET in comparison with NET without secretory activity [5, 6, 9–11, 14, 17–19].

The results of some studies indicate that the degree of liver burden by the tumor and the patient's performance status (PS), according to WHO (World Health Organization) or ECOG (Eastern Cooperative Oncology Group), and rapid clinical improvement directly after treatment are independent prognostic factors of overall survival (OS) and predictive ones for the effectiveness of RLT (PRRT) [2, 6, 9–11].

SSTR-2 overexpression (based on the intensity of radiopharmaceutical accumulation 3 and 4 according to Krenning's qualitative scale) appears to be directly associated with the RLT result. Radiopharmaceuticals attaching with high specificity to an appropriate transmembrane receptor may be used when there are specific clinical, radiological, or molecular indicators that justify their use. Up to now, the Krenning scale is used as a reference point in selecting patients for PRRT [1, 17, 18].

Natural development of the NET and gradual dedifferentiation of tumor cells with the acquisition of loss of overexpression of the receptor subtype SST 2 and the further heterogeneity and variability of receptors on tumor cells, which leads to the concept of "target heterogeneity", is increasingly emphasized. This molecular development of tumor cells affects not only therapeutic decisions, but also the results of target therapy [20]. As tumors distinguish, different cell populations appear in them with the expression of other receptor systems and overexpression of the glucose transporter receptor (GLUT). A positive result of FDG PET (fluoro-
-deoxyglucose positron emission tomography) in well-
-differentiated NET of an intermediate or high grade identifies the heterogeneous components of the disease and additionally is a poor prognostic and predictive factor of the response to RLT [7, 14, 21]. The NET-PET scale proposed by Chan et al. [22] has made the NET FDG- and ^{68}Ga-PET-positive characterization objective, but it is still missing prospective validation, especially from the point of view of prognostic value. Metabolic parameters, such as the standard uptake value SUV_{max} or SUV_{mean}, the metabolic tumor volume (MTV), and total lesion glycolysis (TLG) did not provide any coherent results from the point of view of predictive factors [23].

A significant group of patients with neuroendocrine tumors do not respond to treatment despite the high expression of SSTR, low Ki-67, low burden of tumor lesions to the liver, and lack of FDG uptake in PET analysis. Graf et al. [24] proposed that among all known significant clinical and pathological parameters the "quality" of SSTR expression, evaluated visually in SRI analysis (imaging of somatostatin receptors) on the basis of MIP images (maximal intensity of projection), should be the criterion for qualifying patients for RLT treatment. However, this proposal still does not take into consideration the differentiated expression of SSTR in the tumors [1, 6, 7, 9, 11, 22–24]. The short range of lutetium-177 (^{177}Lu) irradiation may lead to the lack of irradiation of a tumor with a large volume and low or heterogeneous SSTR expression. Data encompassing patients with a disease with heterogeneous SST receptor activity indicate that the 28-month median PFS for NET G1 and NET G2 was shorter than for patients with homogeneous SSTR expression. The "quality" of SSTR expression has, thus, provided another independent parameter allowing us to foresee the response to PRRT [24].

The effect of the tumor microenvironment on the effectiveness of therapy should also be stressed. Tumor cells change their reactions to drugs through interactions with their environment. The role of the tumor microenvironment (TME) in tumor progression and the effectiveness of various drugs has recently attracted a lot of attention. The tumor microenviron-

ment is the earliest determinant of ligand binding and if many factors in the TME, such as the immunological response, hypoxia factors, etc. do not favor the activity of the receptor-radioligand complex, further action is difficult, which affects the therapeutic efficacy. When TME is favorable, the further course of radioligand action is determined by physical and chemical factors such as the biological $T_{1/2}$ and the receptor density. This is a dynamic process in time that explains the phenomenon of the differentiated response to RLT despite the currently used criteria and guidelines based on the appropriate selection of patients. Besides the above-mentioned factors, the effectiveness and toxicity of radioligands are also time dependent. The response to RLT, in general, does not depend on the dose, is non-linear, and delayed, especially in midgut type tumors, and sometimes the objective response to treatment can only be seen a year or even 2 years after the last cycle of radioligand treatment. During successive cycles of treatment, genetic changes, and selection of dedifferentiated clones of tumor cells affect the degree of expression of selected molecular targets, which is directly translated to the effectiveness of therapy [25].

Theranostics is the concept of selecting patients for targeted RLT based on the imaging phenotype in the generally concomitant functional diagnostic analysis. However, the appearance of heterogeneity in receptor expression in different stages of tumor progression is an inevitable challenge for the future [23–26].

RLT/PRRT effectiveness

During the last two decades, RLT/PRRT using ^{90}Y and ^{177}Lu DOTA SSTA has proved to be an effective therapy for patients with advanced, unresectable, and progressing NEN in respect to radiological and marker responses, in mitigation of clinical symptoms, and improvement of the quality of life evaluated by standard questionnaires of the European Organisation for Research and Treatment of Cancer (EORTC QLQ C-30 and GI NET21) [10–12, 15].

Currently, most clinical trials concerning RLT/PRRT focus on [177]Lu [DOTA0.Tyr3] (DOTATATE). The radiopharmaceutical is composed of the radioisotope lutetium-177, which is a medium-energetic β-emitter with the maximum energy of 0.5 MeV and maximum tissue penetration of 1–2 mm. Its half-life is 6.7 days. [177]Lu also emits low energy radiation with an energy of 208 and 113 keV making up 10% and 6% of the emitted radiation, which makes possible scintigraphic imaging and calculating precise internal dosimetry using the same therapeutic compound [1, 6–9, 12, 14, 15].

The capture of radioactivity, expressed as the percentage of administered ^{177}Lu-DOTATATE activity was comparable with the use of ^{177}Lu DOTATOC in organs such as the kidneys, spleen, and liver, but was three to four times higher in 4 out of 5 tumor lesions [13]. Therefore, ^{177}Lu-DOTATATE has a potential advantage due to higher absorbed doses, which may be attained in most neoplasms without increasing the accumulated doses in critical organs, which could potentially limit the therapy [13, 26, 27].

The first elaboration about the use of ^{177}Lu DOTATATE was published by Kwekkeboom et al. [28] in 2003. The trial encompassed 35 patients with GEP-NETs. In the patients, dose acceleration was used from 3.7 GBq, 5.55 GBq to 7.4 GBq, ^{177}Lu DOTATATE to the final cumulative dose of 22.2–29.6 GBq, obtaining partial and complete responses in 38% (according to WHO response criteria). No serious adverse effects were observed in the studied group [28]. In the next study, the same group of scientists analyzed the response to ^{177}Lu-DO- TATATE depending on the type of tumor in 310 patients [6]. Patients were treated up to planned cumulative activity 22.2–29.6 GBq. The general objective response rate (ORR) was 46%. The result of this study indicated a significant effect of PRRT on survival with a median OS of over 48 months and median PFS of 33 months [6]. Direct comparison with data from the literature concerning similar groups of patients indicated a significant 40–72-month benefit for survival in persons treated with PRRT [29].

The results of the next prospective phase I/II trial encompassing 51 patients with advanced unresectable mainly GEP-NET were published by Bodei et al. [9]. The aim was to evaluate the effectiveness and toxicity of therapy using ^{177}Lu-DOTATATE. Patients were divided into 2 groups, receiving escalated activities from 3.7 to 5.18 GBq and from 5.18 to 7.4 GBq, with cumulated activity up to 29 GBq, based on dosimetry. Partial (PR) and complete (CRO) responses were observed in 15 patients (32.6%). Median PFS was 36 months, and the percentage of 36-month overall survival — 68%. Patients who did not respond to treatment and patients with the massive occupation of the liver had poorer survival rates [9].

Even though the data do not come from solid, prospective phase-III trials, this significant difference in survival with a high probability reflects the true effect of RLT/PRRT as a very effective therapeutic method in advanced unresectable NET [2, 6, 28, 29]. A significant breakthrough in using RLT were the results of the NET-TER-1 study with randomization [177]Lu- DOTATATE vs. Octreotide LAR in large doses of 60 mg i.m. given every 28 days to patients with unresectable progressing neuroendocrine tumors derived from the midgut after progression on SSA analogs [15].

In this phase-III trial, the effectiveness and safety of using [177]Lu- DOTATATE was evaluated in 229 pa-

tients with advanced well-differentiated G1 and G2, progressing neuroendocrine tumors derived from the midgut after progression on SSA analogs (Somatostatin Analogs). Altogether 111 patients received ^{177}Lu-DOTATATE in a dose of 7.4 GBq administered every 8 weeks in the form of four intravenous infusions with the continuation of treatment with SSA analogs (octreotide LAR 30 mg given intramuscularly between administration of PRRT). On the other hand, the control group of 110 patients received 60 mg octreotide LAR intramuscularly every 4 weeks (dose not compliant with registration indications). The primary endpoint was PFS, and the secondary endpoints were ORR, OS, safety, and the profile of adverse effects. The results indicated a significantly higher — 20-month PPS index of 65.2% (95% CI, 50.0–76.8) in the group receiving ^{177}Lu-DOTATATE in comparison with 10.8% (95% CI, 3.5–23.0) in the control group. In this trial, ORR was found to be 18% in the group receiving ^{177}Lu-DOTATATE in comparison with 3% in the control group (p < 0.001). These data translated to the significant lengthening of median PFS in the group treated with ^{177}Lu-DOTATATE — 28.4 months compared to 8.5 months in the group receiving octreotide LAR. The hazard ratio was 0.21 (95% CI 0.14–0.33), which was associated with a 79 percent reduction of the relative risk of progression in the group treated with radioisotope therapy. Moreover, permanent therapeutic benefits associated with ^{177}Lu-DOTATATE administration were observed regardless of stratification and prognostic factors, including the following: level of radiopharmaceutical uptake in scintigraphy, tumor grade, age, sex, and concentration of tumor markers. The most common adverse effects in patients treated with ^{177}Lu-DOTATATE were nausea (59%) and vomiting (47%), which, in over 65% of cases, were ascribed to the amino acids given before treatment. The frequency of grade 3 or 4 adverse effects was similar in both groups; however, hematological events occurred only in the PRRT treated group. Lymphopenia, thrombocytopenia, and anemia at grade 3/4 occurred in 9%, 2%, and 1% patients, respectively. Two patients treated with ^{177}Lu-DOTATATE (1.8%) developed MDS, but there was no evidence of kidney toxicity in the observed period (the median time of observation was 14 months) [15].

In the first update of data from 2018 concerning OS and PFS in the population of the NETTER-1 trial, median OS in the arm with octreotide 60 mg *i.m.* every 28 days was 27.4 months, whereas in the arm with ^{177}Lu-DOTATATE, it had still not been reached. The hazard ratio (HR) for PFS was unchanged in relation to the HR presented in the original publication [30].

The final results of the NETTER-1 trial were presented at the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncol-ogy (ESMO) in 2021 and were published in November in *Lancet Oncology*. The median observation time was over 6.3 years. The final OS analysis (secondary endpoint) in the ITT (intention to treat) population did not attain statistical significance between the tested group (RLT/PRRT) and the control group (Octreotide 60 mg) HR = 0.84; 95% CI 0.60–1.17. This finding could have been affected by the high percentage (36%) of patients in the control arm who received RLT/PRRT after progression (crossover). Median OS was 48 months in the study arm and 36.3 months in the control arm. Annual indices of overall survival up to 5 years in group receiving ^{177}Lu-DOTATATE in comparison with the control group were: 1 year, 91.0% (95% CI 84.0–95.1) *vs.* 79.7%(70.8–86.1); 2 years, 76.0% (66.7–83.0) compared with 62.7% (52.6–71.2); 3 years, 61.4% (51.4–69.9) *vs.* 50.1% (40.0–59.4); 4 years, 49.5% (39.5–58.6) *vs.* 41.8% (31.8–51.4); 5 years, 37.1% (27.8–46.4) compared with 35.4% (25–7–45–2). In two patients treated with ^{177}Lu-DOTATATE (1.8%), MDS developed, which is in agreement with earlier reports. During long-term observation, no new MDS or ALL cases were observed. No new signals concerning safety appeared during long-term observation [16].

The analysis of the quality of life in the NETTER-1 trial was published separately. QOL (quality of life) results were evaluated by QLQ C-30 and G.I. NET-21 questionnaires. The patients filled in the questionnaires at the beginning of the trial and then every 12 weeks until disease progression. The primary endpoint was time-to-QOL deterioration (TTD) which was counted if the QOL of the patient decreased by ≥ 10 points. The QOL result was significantly better in the arm with ^{177}Lu-DOTATATE compared with patients in the arm with octreotide, who were given high doses, in respect to the general state of health (HR= 0.41; p < 0.001), physical functioning (HR = 0.52; p < 0.015), diarrhea (HR = 0.47; p = 0.011), and fatigue (HR = 0.62; p = 0.03). The ^{177}Lu-DOTATATE arm did not yield poorer results for any of the parameters [31].

Moreover, in the publication by Strosberg in the *Journal of Nuclear Medicine* in March 2021, an analysis of the diaries of symptoms of patients from the NETTER-1 trial was presented. These data indicate that besides improvement of PFS and prolonging TTD in respect to the quality of life, [177]LuDOTATATE treatment is also associated with a statistically significant alleviation of the symptoms, which gives the patients measurable benefits compared with octreotide LAR in the nonstandard dose of 60 mg *i.m.* [32]. A significant decrease was observed in the number of days when patients suffered from stomach pain, diarrhea, and facial flushing associated with carcinoid symptoms. The alleviation of these typical symptoms is particularly important for patients with progressing midgut NET and reflects

the general benefit of using ^{177}Lu-DOTATATE in this population of patients [32].

During the ESMO 2019 Congress, results were presented of the analysis of the correlation between an objective radiological response and PFS, evaluating the dependence between the dynamics of the size of "targeted" lesions and the effectiveness of treatment evaluated as an increase in median PFS in patients treated in the NETTER-1 trial. In the case of patients treated with nonstandard doses of octreotide 60 mg, based on the analysis of Cox regression, a 9-percent reduction in the risk of progression was obtained for each increase of the fraction with a decrease in the size of the lesion — HR = 0.914; 95% CI 0.86–0.97; p = 0.0034. Among patients treated with ^{177}Lu DOTATATE no association was shown between the decrease in the size of the lesions and prolongation of median PFS, HR = 1.01; 95% CI 0.98–1.03; p = 0.624, suggesting that therapy with ^{177}Lu-DOTATATE affects PFS prolongation even when no radiological response is observed during treatment [33]. This analysis provides key information on the evaluation of the effectiveness of PRRT treatment, which should not be exclusively based on the percentage of radiological responses based on the RECIST classification.

It is worth noting that despite the recommendation concerning the use of RLT/PRRT in neuroendocrine tumors of the GI tract, no prospective phase-III clinical trials have been performed concerning the use of RLT/PRRT in neuroendocrine tumors derived from the pancreas (panNET). Moreover, the NETTER-1 trial (the largest trial using RLT/PRRT) did not encompass patients with panNET. There are, however, data, both prospective and retrospective, indicating the justification for using RLT/PRRT in panNET. The joint analysis of these trials indicated a median for disease control of 83% (range from 50% to 94%), and median ORR — 58% (13–73%). Median PFS was 25–34 months, and median OS was 42–71 months [6, 29, 34–37].

During the ASCO 2021 Congress, data were presented from a retrospective registry of patients with unresectable or metastatic well-differentiated, SSTR-positive, progressing neuroendocrine tumors of the pancreas panNET, treated with ^{177}Lu-DOTATATE in Great Britain, France, and Spain (NETTER-R). The analysis encompassed patients, who received ≥ 1 administration of ^{177}Lu-DOTATATE. The primary endpoint was PFS. Secondary endpoints included OS, safety, and response to treatment. This registry included data from 110 patients. The effectiveness of therapy was evaluated in 63 patients according to RECIST v1.1 criteria. Median PFS was 24.8 months (95% CI 17.5–34.5), and ORR — 40.3% (95% CI 28.1–53.6); all responses were partial. The index of response, including radiological, clinical, metabolic, and marker evaluation, which could be estimated in 100 patients, was 54.0% (95% CI

43.7–64.0), including 2 patients with CR (Complet Response). During the time of observation, whose median was 24.5 months (2.0–123.4), median OS attained was 41.4 months (95% CI 28.6–50.2). In 71.8% (n = 79/110) patients at least one treatment-emergent adverse event (TEAE) occurred. The most common ones were nausea (28.2%) and fatigue (22.7%). Anemia and grade 3 lymphopenia occurred in 1 (0.9%) and 4 (3.6%) patients, respectively. Treatment-related adverse effects concerning the kidneys occurred in 6 patients (5.5%; grade 1: n = 1, grade 2: n = 2, grade 3: n = 3). During the period of observation, no ALL nor MDS were observed.

The presented data concerning everyday clinical practice led to the conclusion that therapy with ^{177}Lu-DOTATATE for pan-NET is well tolerated, and the safety profile s in agreement with the results of NETTER-1. In the limited time of observation, OS and PFS were favorable compared with cohorts of patients with panNET progression treated with other systemic drugs [38].

RLT/PRRT in NET G3

With the new classification of neuroendocrine tumors from 2017 and 2019, particular attention was paid to the possibility of utilizing RLT in patients with NET G3 tumors, in whom in 60–70% of cases the primary lesion is in the pancreas. The biology of this group of tumors is not completely understood, and effective therapies are being sought.

The published data concerning RLT in NET G3 in a group of about 280 patients in four retrospective trials with the number of patients in the range of 28–149 with Ki-67 > 20% indicate that PRRT should also be considered for this indication [40–43]. General results have shown indices of disease control in the range 30–80%, PFS 9–23 months, and OS 19–53 months. The results were significantly better in patients with Ki-67 < 55% compared with patients with higher Ki-67 values [9, 41–43]. RLT can be considered in patients with NET G3, but careful selection of patients is necessary, and further prospective studies are required to further determine prognostic and predictive factors in this group of patients. The NETTER-2 trial including patients with NET derived from the pancreas has started recently aiming to solve this problem (NCT03972488).

Combined RLT + chemotherapy treatment

According to the newest tendencies in oncology, experiments using RLT/PRRT are concentrated on combined therapies which allow more effective treatment of patients with NEN with SSA receptor overex-

pression. Moreover, multimodal therapies frequently are characterized by a balanced toxicity profile. So far, few studies have been performed evaluating the effect of therapies combined with PRRT. Chemotherapy in low doses may have a radiosensitizing effect by increasing DNA lesions, inhibiting DNA repair, stopping the proliferation of cells, reoxygenation of tumor cells, synchronization of the cell cycle, or apoptosis. The most frequently used substances in treatment combined with PRRT are capecitabine, temozolomide, and 5-fluorouracil (5-FU) [43].

The first report on combined treatment was from Rotterdam, where radiosensitizing capecitabine was used with ^{177}Lu-DOTATATE. In this study, the safety of four cycles of PPRT [7.4 GBq (^{177}Lu) Lu-Octreotate] combined with capecitabine (1650 mg/m^2 daily for 2 weeks) was evaluated. Among seven patients included in the study, one grade 3 anemia and one grade 3 thrombocytopenia were observed. No other serious adverse effects were observed [44].

A phase-II trial using combined chemotherapy and PRRT was conducted by an Australian group. In the preliminary study ^{177}Lu DOTATATE (7.8 GBq in each cycle) was used with capecitabine in the case of progressing, disseminated NEN. Encouraging results were obtained in respect to treatment response: 24% objective responses, 70% stable disease (SD), and in only 6% progressive disease (PD) was observed. Median PFS and median OS were not attained with the median observation of 16 months (range 5–33 months). Survival after 1 year and 2 years was 91% (95% CI 75–98%) and 88% (95% CI 71–96%) respectively [45]

The next study by the same group yielded even better results using a combination of standard activity and a protocol encompassing, on the average, four administrations of ^{177}Lu DOTATATE (7.8 GBq in each cycle) and chemotherapy with capecitabine and temozolomide in treating advanced NET. In about 3% of patients, grade 3 nausea occurred, and in about 6% grade 3 neutropenia. About 53–70% of patients had ORR to the treatment. The percentage of CR was relatively high at 13–15% [46]. Patients attained a median PFS of 48 months, and median OS after median observation of 33 months was not reached [46]. It is worth pointing out that the response indices were higher in patients with gastric-pancreatic NET than in patients with primary enteric-NETs; CR 18% *vs.* 13%, PR 64% *vs.* 13%, SD 12% *vs.* 67% [46].

In a similar study, Nicolini et al. [47] with combined therapy PRRT plus capecitabine in 37 selected patients with SSR-positive and FDG-positive GEP-NET and (Ki-67% < 55%), median PFS was 31 months, and median OS after median observation of 38 months was not reached. The most common symptoms of toxicity G3/G4 were neutropenia (11%), fatigue (5%), and diarrhea (5%). According to RECIST 1.1, a response was obtained in 30% of patients, and stabilization in 55%.

Pioneering work from Poland using combined therapy for patients with advanced forms of GEP-NET was presented by Kolasińska-Ćwikła et al. [48] at the European Neuroendocrine Tumor Society (ENETS) Congress in 2021. In a single-arm intervention trial of combined PRRT + CAPTEM treatment, 21 patients were included (NCT04194125). In 14 patients (67%) PR was attained, and the rest (33%) had SD. Control of the disease during the clinical observation was found in 16 (76%) patients. Objective responses were noted in 12 (86%) patients with panNET, the range of the best response in reducing target lesions was 32–88%, and in the remaining 2 patients SD was observed. In 4 patients who attained PR (RECIST) surgical excision of the primary tumor was performed. During the observation, disease progression occurred in 4 persons, whereas in the remaining patients PR or SD was maintained [48]. This treatment caused a low percentage of serious adverse grade 3 and 4 effects. During therapy, transitional lymphopenia occurred in most patients which normalized during the clinical observation [49]. In the recent update of PFS of this trail indicated that median PFS for all subjects including (95%CI) was 32.0 months (23.0–n.r.), for subjects with pancreatic NET 28.0 months (26.0–n.r.), and those with midgut = 32.0 months (19.0–n.r.) [50].

Conclusions

Radioligand therapy (RLT), previous PRRT with the use of radioisotope-labeled synthetic somatostatin analogs bring benefits in the reduction of symptoms and potentially prolong overall survival in patients with unresectable, advanced, and progressing GEP-NET. RLT is a reasonable treatment option for patients with neuroendocrine tumors showing overexpression of somatostatin receptors. The NETTER-1 clinical trial, the first phase-III clinical trial in the group of patients with neuroendocrine tumors derived from the midgut after progression on SSA analogs showed that treatment with ^{177}Lu-DOTATATE has significant clinical effects and statistically changes median PFS (HR = 0.18; 95% CI 0.11–0.29; p < 0.0001), as well as clinically increases median OS by 11.7 months compared with long-acting high dose octreotide (60 mg i.m.). Data from various treatment centers using RLT/PRRT of patients with neuroendocrine tumors with other localizations of the primary lesion also provide evidence justifying this type of treatment.

Moreover, this treatment is safe with acceptable toxicity and has a favorable effect on the quality of life. Numerous prospective trials are being conducted to show the effectiveness of RLT treatment in patients

with NET with other localizations than the midgut. Prognostic and predictive factors of response to this type of treatment are being sought.

Intensive research is ongoing on combined therapies using RLT and chemotherapy to improve effectiveness. Other variants of treatment using RLT/PRRT are also the subject of interest of researchers, as well as using alpha, instead of beta, radiation to improve RLT effectiveness.

Conflict of interest

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