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Current status and future directions of Targeted Peptide Receptor Radionuclide PET Imaging and Therapy of GEP-NETs

Theranostics in GEP-NETs

Neil Grey, Michael Silosky, Christopher H Lieu, Bennett B. Chin

Abstract

Theranostics is the highly targeted molecular imaging and therapy of tumors. Targeted peptide receptor radionuclide therapy (PRRT) has taken the lead in demonstrating the safety and effectiveness of this molecular approach to treating cancers. Metastatic, well-differentiated gastroenteropancreatic neuroendocrine tumors may be most effectively imaged and treated with DOTATATE ligands. We review the current practice, safety, advantages, and limitations of DOTATATE based theranostics. Finally, we briefly describe the exciting new areas of development and future directions of GEP-NET theranostics.

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Core Tip: We review the current accepted practices of imaging and therapy for gastroenteropancreatic neuroendocrine tumors and we additionally summarize future directions of each.

INTRODUCTION

Neuroendocrine tumors (NETs) are a relatively rare and heterogeneous group of tumors arising from neuroendocrine cells throughout the body, which can cause a variety of symptoms based on the location and cell type. Midgut NETs are the most common, with the small bowel being the most frequent site of the primary lesion (1, 2). Although the incidence is relatively low, the majority are slow-growing, well-differentiated tumors which effectively contributes to a high prevalence. Improved clinical, laboratory, and imaging detection also likely contribute to an apparent

increasing prevalence. NETs are often detected incidentally or after they metastasize and cause clinical symptoms either from their hormonal release and/or from mass effect.

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) comprise the majority of NETs (over 75%), with lung NETs comprising an additional approximately 15% (1). GEP-NETs are characterized according to the WHO 2010 classification system based on the Ki-67 index, a widely used marker of cell proliferation. In this classification, GEP-NETs are scored as G1 (Ki-67 <2%), G2 (Ki-76 = 3-20%), or G3 (Ki-67 >20%), with G1 and G2 classified as well-differentiated tumors, and G3 tumors classified as poorly differentiated/de-differentiated carcinomas. Further stratification of G3 tumors can be assigned into well-differentiated (Ki-67 20-50%) and poorly differentiated carcinomas (Ki-67 >50%). This classification system, as well as the proposed subdivision of G3 tumors, has prognostic utility and helps direct appropriate diagnostic imaging and therapy.

The majority of well differentiated GEP-NETs (>90%) express the G-coupled protein somatostatin receptors (SSTR) (3-5). The WHO classification typically correlates with SSTR expression with well-differentiated tumors (G1 and G2) highly expressing SSTRs, and poorly differentiated tumors (G3) having lower SSTR expression. Diagnostic imaging and targeted radionuclide therapy take advantage of tumor SSTR expression by utilizing radiopharmaceuticals that bind to the same ligand. This elegant duality is emblematic of the expanding field of "theranostics", a portmanteau of therapy and diagnostics.

In this paper, we review the current approaches to the diagnosis and treatment of GEP-NETs. We focus primarily on DOTATATE (^{68}Ga DOTATATE and ^{64}Cu DOTATATE) PET / CT imaging and ^{177}Lu DOTATATE peptide receptor radionuclide therapy (PRRT), and conclude with future directions of GEP-NET theranostics.

BACKGROUND

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imaging and targeted radionuclide therapy take advantage of tumor SSTR expression by utilizing radiopharmaceuticals that bind to the same ligand. This elegant duality is emblematic of the expanding field of "theranostics", a portmanteau of therapy and diagnostics.

In this paper, we review the current approaches to the diagnosis and treatment of GEP-NETs. We focus primarily on DOTATATE (^{68}Ga DOTATATE and ^{64}Cu DOTATATE) PET / CT imaging and ^{177}Lu DOTATATE peptide receptor radionuclide therapy (PRRT), and conclude with future directions of GEP-NET theranostics.

DOTATATE PET IMAGING

Somatostatin is an endogenously produced peptide hormone that binds to various SSTRs. In humans, there are 5 subtypes (6), with GEP-NETs predominantly expressing SSTR-2 both in the primary tumor and in their metastases (7).

The currently approved nuclear medicine DOTATATE PET imaging agents used to bind SSTR-2 are composed of three functional parts: the radioactive PET imaging component (^{68}Ga or ^{64}Cu), 2) the PET radiometal chelator and linker, DOTA (tetraazacyclododecanetetraacetic acid), and 3) the peptide binding part, TATE (tyrosine-3-octreotate (8). The earlier imaging agents used to visualize GEP-NETs was a single photon octreotide-based agent, [^{123}I-Tyr^3]octreotide (4), followed by ^{111}In pentetreotide (Octreoscan, Mallinkcrodt) (9). ^{111}In pentetreotide remained the mainstay of GEP-NET imaging until the approval of the PET imaging agents. Both ^{68}Ga DOTATATE and the closely related ^{68}Ga DOTATOC have received approvals in Europe and the US (10, 11), as has the more recently approved ^{64}Cu DOTATATE. Because of the extremely high binding affinity of ^{68}Ga DOTATATE to SSTR-2 (approximately 100 times greater than ^{111}In-pentetreotide) (12), the superior imaging characteristics of PET compared to SPECT, and the lower radiation delivered, DOTATATE PET imaging is

now recommended in all cases over ^{111}In-pentetreotide (13), including use in both adults and children (14).

Indications

The appropriate use criteria for SSTR imaging in cases of known or suspected well-differentiated NETs with [68]Ga- and ^{64}Cu DOTATATE PET / CT imaging and ^{177}Lu DOTATATE peptide receptor radionuclide have been recently summarized (13).   These include the following nine indications: 1) initial staging after the histologic diagnosis of NET; 2) evaluation of an unknown primary; 3) evaluation of a mass suggestive of NET not amenable to endoscopic or percutaneous biopsy; 4) staging of NET before planned surgery; 5) monitoring of NET seen predominantly on SSTR PET; 6) evaluation of patients with biochemical evidence and symptoms of a NET; 7) evaluation of patients with biochemical evidence of a NET without evidence on conventional imaging or a prior histologic diagnosis; 8) restaging at time of clinical or laboratory progression without progression on conventional imaging; and 9) new indeterminate lesion on conventional imaging with unclear progression (13).

In addition to its primary use in GEP-NETs, ^{68}Ga DOTATATE PET has been used to image other SSTR positive tumors such as paragangliomas, pheochromocytomas, neuroblastomas, meningiomas, medullary thyroid cancers, Merkel cell carcinomas, small cell carcinomas, esthesioneuroblastomas, and tumor-induced oncogenic osteomalacia (8).

Technique

[68]Ga DOTATATE is readily compounded from generator eluted ^{68}Ga and a sterile vial kit (15). Before intravenous administration, there is little patient preparation except for good hydration and frequent voiding to minimize radiation dose to the kidneys. An uptake phase between radiotracer administration and PET imaging is typically

approximately 60 minutes, similar to ^{18}F fluorodeoxyglucose (FDG) PET. This allows time for tumor uptake and for background washout clearance *via* the kidneys, which is analogous to the procedure used in FDG PET. Patients are typically imaged from the mid-thigh to the skull. In cases where tumor is known or suspected outside of this field of view, or in cases of unknown primary, longer imaging times may be needed to include the extremities. Intravenous contrast is not essential for accurate interpretation in most cases, but it can be helpful in some clinical settings. Additional procedural details are listed in the European Association of Nuclear Medicine (EANM) guidelines (14).

Many patients with GEP-NETs will be on short- or long-acting somatostatin analogue (SSA) therapy which could interfere with ^{68}Ga DOTATATE PET uptake due to competitive binding. Temporary discontinuation of short-acting SSAs is recommended for 24-48 h, and long-acting SSAs should be avoided for approximately 4-6 wk (8, 16). Long-acting release (LAR) SSAs are administered on 4 wk cycles, allowing ^{68}Ga DOTATATE imaging to be scheduled for the end of the monthly cycle prior to redosing. Regardless of the specific approach, subsequent ^{68}Ga DOTATATE scans are preferably performed with the exact timing between SSA injections.

Normal Biodistribution
The normal biodistribution of ^{68}Ga DOTATATE differs in several aspects compared to the most commonly used radiotracer, ^{18}F FDG. For both ^{68}Ga DOTATATE and ^{18}F FDG, the genitourinary tract is the normal route of excretion for unbound radiotracer, and thus high radiotracer activity can be seen in the kidneys, ureters, and bladder. In ^{68}Ga DOTATATE, the spleen has the highest normal activity, followed by the adrenal glands (17). Unlike FDG, the pituitary is the only part of the central nervous system with high physiologic uptake. Salivary glands and the thyroid can have moderate uptake. Activity in the pancreas is variable and occasionally focal in the head and uncinate process (18). Variable but typically lower-level diffuse uptake is seen in the small and large bowel

(8). Physiologic uptake in the liver can be quite variable (19), and uptake can be low in the spleen and liver if total body tumor burden is high ("sink effect") (20). [68]Ga DOTATATE uptake is otherwise low throughout the muscles, adipose tissue, and bone.

Dosimetry

The recommended dose for ^{68}Ga DOTATATE is 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 mCi). The organ with the highest dose delivered is the spleen due to its high uptake. The whole body radiation effective dose equivalent (EDE) from ^{68}Ga DOTATATE PET is 2-3 mSv (21, 22), which is approximately only 10% of the 26 mSv received from a typical dose (222MBq or 6 mCi) of ^{111}In pentetreotide. Despite the addition of an EDE of 1-9 mSv from the CT component, which is needed for attenuation correction and anatomic localization, the total dose of ^{68}Ga DOTATATE PET / CT (3-12 mSv) remains significantly lower than that of ^{111}In pentetreotide.

Imaging Performance

Due to the very high affinity of ^{68}Ga DOTATATE for SSTR-2, target lesions typically show extremely high uptake. With deficient (i.e., very low) background radiotracer uptake throughout most of the body including the thorax, head and neck, bone marrow, muscle, and brain (except the pituitary), the tumor to background ratio can be exceptionally high. In a large prospective study of GEP-NETs comparing accuracy of ^{68}Ga DOTATATE, conventional imaging (CT and MRI), and ^{111}In pentetreotide, ^{68}Ga DOTATATE showed clear superiority in lesion detectability with a mean tumor SUV max values of over 65 (23). **Figure 1** shows an example of normal intense uptake in the spleen and adrenals and moderate ^{68}Ga DOTATATE uptake in the liver. Small liver lesions can also be visualized despite relatively high liver background activity. Extremely high radiotracer activity can be seen in larger lesions, as shown in **Figure 2**.

False positives are uncommon and do not typically present a diagnostic dilemma. The most common causes of false positives are inflammation or infection due to leukocytes and macrophages expressing SSTR-2 (24). For example, inflammatory prostatitis is relatively common and can show intense focal uptake within the prostate (25). Other potential causes of false positive can arise from osteoblastic activity (26), such as in degenerative changes, fractures, fibrous dysplasia, vertebral hemangiomas, and epiphyses in pediatric patients (27, 28).

False negative results may be due to loss of receptor expression. GEP-NETs that dedifferentiate and subsequently lose SSTR-expression may show lower ^{68}Ga DOTATATE avidity. Another cause of false negatives, as seen in PET imaging, may arise from small lesions below PET resolution. In our experience, however, the highly avid ^{68}Ga DOTATATE uptake in well differentiated GEP-NETs is commonly adequate to overcome the limitations of partial volume effect. If tumor uptake is sufficiently high, it can also overcome the detrimental effects of a relatively low administered dose and other physical limitations of ^{68}Ga compared to [18]F (29-32). Small lesions can be readily visualized in phantom and patient clinical studies if the background activity is low. The non-contrast portion of the CT frequently does not reveal hepatic lesions; however, hepatic GEP-NETs as small 5 mm may be visualized despite high normal background liver activity (30).

Role in Evaluation and Value in Management
[68]Ga DOTATATE is an excellent study for evaluating GEP-NETs and demonstrates very high sensitivity and specificity of 93% and 95%, respectively (33). Its superior performance in detecting GEP-NETs compared to ^{111}In pentetreotide and CT or MR is well established (23). This can result in a significant change in clinical management in up to a third of patients even when compared to ^{111}In pentetreotide (34-37). [68]Ga DOTATATE has also shown increasing utility in detecting lesions not seen on other modalities. It can confirm suspicion of GEP-NET found on other modalities, determine

the true extent of tumor, stage disease, identify otherwise occult tumors such as thoracic ACTH-secreting carcinoids, and guide treatment options. It may be used to confirm a clinical or biochemical suspicion of GEP-NET, identify the primary lesion in known metastatic disease, determine resectability, exclude greater extent of disease prior to resection, and importantly, identify candidates for hormonal therapy or PRRT (8).

^{64}Cu DOTATATE

The primary practical advantage of ^{64}Cu DOTATATE is its longer physical half-life (^{64}Cu $t_{1/2}$=12.7 h). This allows for more flexibility in production, shipment to distant locations, and flexibility in the timing of PET imaging. ^{68}Ga DOTATATE (^{68}Ga $t_{1/2}$=68 minutes) is typically produced at a site close to the PET imaging center due to the short physical half-life. ^{64}Cu DOTATATE allows flexibility for delayed imaging three hours after injection with no significant difference in lesion detectability (38). Compared to the DOTATOC ligand, the ^{64}Cu DOTATATE showed slightly higher lesion detectability than ^{68}Ga DOTATOC (39). Other differences between ^{64}Cu compared to ^{68}Ga do not appear to have a large clinical impact on lesion detectability. ^{64}Cu compared to ^{68}Ga has a disadvantage in a lower percentage of positrons emitted per decay (17.5% *vs* 88.9%). However, ^{64}Cu has the physical advantage of shorter mean positron range prior to annihilation (0.7 mm *vs* 3.5 mm) which can improve spatial resolution (40). Data are emerging to support quantitative imaging of ^{64}Cu DOTATATE which correlates with prognosis (41, 42). Finally, pre-clinical studies of new investigational agents, such as ^{55}Co DOTATATE, show the potential for further improvements in tumor uptake and image contrast when compared to currently approved agents (43).

Role of FDG-PET
FDG is a glucose analogue that enters cells through glucose transporters, undergoes phosphorylation, and then remains trapped within the cell as FDG-6-phosphate. This

imaging metric of glycolysis is frequently upregulated in many cancers, and generally associated with more aggressive, rapidly growing malignancies.

Well differentiated GEP-NETs, however, are typically slower growing, have lower mitotic rates, and have lower rates of proliferation including lower Ki-67 indices. The WHO classification of GEP-NETs relies on the Ki-67 index which reflects cellular proliferation. As GEP-NETs become more dedifferentiated, they tend to lose SSTRs expression and decrease in ^{68}Ga DOTATATE avidity. These often exhibit a more aggressive and faster growing phenotype with increasing proliferation (Ki-67) and increasing glycolytic activity. Clinically, when a known GEP-NET tumor increases in size, yet decreases in ^{68}Ga DOTATATE avidity, an FDG-PET can be useful in identifying tumor which may be exhibiting this dedifferentiating phenotype ("flip-flop" effect), and warrant consideration of a change in therapy. Patients with NETs demonstrating FDG avid disease are at a 10 fold increased risk of death (44). Other studies have shown similar findings with (45, 46).

FDG PET may also be useful in identifying heterogeneity of tumors by directing biopsy of tumors suspicious for a more aggressive or higher-grade histology. When both ^{68}Ga DOTATATE PET-CT and FDG PET-CT are performed, the differential imaging features may assist in prognosis and guide therapy options. FDG PET can therefore be complementary and aid in management decisions in which tumor dedifferentiation is suspected. An example of an FDG positive hepatic metastasis is shown in **Figure 3**.

THERAPY

Treatment Options

Partial or complete surgical resection of GEP-NET is the preferred approach when possible (47). Hormone therapy is another mainstay of GEP-NET treatment. Short- or long-acting SSAs bind to SSRTs and inhibit or slow tumor growth while simultaneously helping with hormone secretion related symptoms. Additional treatment options may

include the mTOR inhibitors, VEGF inhibitors, chemotherapy, radiation, and liver metastases directed embolization therapies (48). More recently, [7] ^{177}Lu DOTATATE peptide receptor radionuclide therapy (PRRT) has been established as a safe and effective treatment of metastatic GEP-NETs.

Peptide Receptor Radionuclide Therapy (PRRT)

PRRT is the logical extension of SSTR imaging into the treatment realm and comprises the therapy component of theranostics. The imaging radionuclide (^{68}Ga or ^{64}Cu) is replaced with a beta emitter ^{177}Lu which deposits lethal radiation precisely to the SSTR-2 positive cells, providing targeted radiotherapy to tumors. The resultant ^{177}Lu DOTATATE radionuclide delivers local radiation specifically to tumor visualized on ^{68}Ga DOTATATE imaging. ^{177}Lu is primarily a beta emitter with a mean range of 2 mm in tissue, and a small fraction is gamma radiation (6.6% at 113-keV and 11% at 208-keV). This results in a relatively low exposure to individuals surrounding the patient, allowing therapies to be performed as an outpatient. The relatively long half-life of 6.7 days (160 h) delivers sustained radiotherapy for a prolonged period; however, this requires extended precautions to avoid exposure from urinary contamination. ^{177}Lu DOTATATE (Lutathera) was approved by the EMA in 2017 and by the FDA in January 2018 (48).

Patient Selection

^{177}Lu DOTATATE was approved specifically for treatment of SSTR-positive GEP-NETs that have progressed on SSA therapy(48). The most appropriate patients for therapy are based upon guidelines developed by the NETTER-1 trial (49). There are multiple considerations for patient selection for PRRT; however, patients with progressive metastatic low and intermediate grade GEP-NETs typically have highly positive SSTR scans and are most likely to benefit.

Technique

The standard protocol for ^{177}Lu DOTATATE therapy is based upon the NETTER-1 trial (49). Patients are prescribed four doses of 7.4 GBq (200 mCi) eight weeks apart for a cumulative dose of 29.6 GBq (800 mCi). At least 30 minutes prior to therapy administration, an amino acid infusion is started for renal protection and lasts four hours. The two amino acids required for renal protection are arginine and lysine. Although other formulations of different amino acids exist, they do not provide any additional benefit and can cause significant nausea and vomiting.

Based on the typical dose of 7.4 GBq of ^{177}Lu DOTATATE, the exposure rate at 1 m is 2 mR/h and decreases by 50% within 24 h (48). If the patient is able to abide by standard radiation safety precautions, this can be performed as an outpatient. Precautions include bathroom hygiene, similar to radioiodine treatments, and appropriate distancing from others, specifically children and pregnant women, for approximately 3 days after therapy. Individualized safety instructions may be prepared by a radiation safety officer or radiation physicist, depending on the institution, and reviewed with the patient during the consent process.

Efficacy
[177]Lu DOTATATE therapy in GEP-NETs has demonstrated efficacy in many studies over several years. The most notable large prospective randomized trial is the NETTER-1 trial (49). This prospective randomized trial in adults with biopsy-proven low- and intermediate grade (G1 or G2, i.e., Ki-67 Level $\leq$20%) GEP-NETs evaluated subjects treated with ^{177}Lu DOTATATE and SSA compared to a control group on high dose SSA alone. Inclusion criteria were metastatic disease or locally advanced and inoperable disease which was progressing on SSA (49).

The primary endpoint of the study was progression free survival (PFS) with secondary endpoints of objective response rate (ORR), overall survival (OS), safety, and the side-

effect profile. Patients were judged to have failed treatment if there was tumor progression based on follow up imaging by CT or MRI according to RECIST 1.1 criteria (50).

Patients in the treatment arm experienced significantly better PFS at 20 mo of 65.2% (95%CI, 50.0-76.8) compared to 10.8% (95%CI, 3.5-23.0) in the control group. In other words, in the treatment group there was a 79% lower risk of disease progression or death and a 60% lower risk of death alone. The secondary endpoint of ORR was 18% in the treatment group and 3% in the control group. As noted in the NETTER-1 study, multiple large randomized trials with other systemic therapies, such as SSAs alone or in combination with other non-radionuclides, showed response rates of only 5% or less (51-54). Median overall survival could not be calculated yet at the conclusion of NETTER-1, but there was a trend towards longer overall survival in the treatment group. An example of a patient with partial response to ^{177}Lu DOTATATE is shown in **Figure 4**.

Adverse Side Effects and Overall Safety
In NETTER-1, transient WHO Grade 3 and 4 hematologic toxicity (thrombocytopenia 2%; lymphopenia 9%; neutropenia 1%) and no renal toxicity were reported after 14 mo of follow up (49). Rare but serious side effects including acute leukemia and myelodysplastic syndrome have been reported, occurring in <1% and <1-2% of patients, respectively (48, 49, 55). Other studies have similarly shown limited side effects with ^{177}Lu DOTATATE therapy (55, 56).

Common mild side effects (Grade 1 or 2) include nausea (59%) and vomiting (47%) (49); however, this has been primarily attributed to the specific amino acid infusion. Use of the simpler arginine and lysine infusion appears to have much lower incidence and

severity of side effects. Fatigue (40%), decreased appetite (18%), headache (16%), and alopecia (11%) were significantly higher in the ^{177}Lu DOTATATE treatment group (49). Although relatively frequent, abdominal pain (26%), and diarrhea (29%) were not statistically different compared to the control group. An uncommon side effect of treatment is hormone crisis, which in one study of 504 patients happened in only 6 (or 1.2%) and can be adequately managed in a brief hospital stay with complete recovery (55).

FUTURE DIRECTIONS

While ^{68}Ga- and ^{177}Lu DOTATATE have shown remarkable efficacy in imaging and treatment of GEP-NETs, many additional imaging and treatment options are currently under investigation. A comprehensive review is not possible in the context of the rapidly evolving landscape of theranostics. A few representative clinical trials are briefly mentioned to provide a perspective of the breadth of ongoing investigations.

Current Clinical Trials

Extending PRRT into higher grade GEP-NETs is an active area of investigation. The COMPOSE trial compares well-differentiated higher grade (G2 or G3, Ki-67 index between 10-55%) GEP-NETs treated with ^{177}Lu Edotreotide (DOTATOC) compared to best standard of care chemotherapy regimens (57). The COMPETE trial similarly evaluates advanced GEP-NETs for safety and efficacy of ^{177}Lu DOTATOC compared to Everolimus (58). The NETTER-2 trial investigates higher proliferation index tumors (G2 or G3) as first line therapy with ^{177}Lu DOTATATE therapy and SSA compared to high dose SSR therapy alone (59).

^{177}Lu DOTATATE Retreatment

While ^{177}Lu DOTATATE is now given as a four dose regimen, additional doses have been administered on an investigational basis. If a patient shows continued improvement in tumor burden and symptoms throughout the ^{177}Lu DOTATATE

treatment course established by NETTER-1, (four cycles, 8 wk apart), they may benefit from continued treatment with additional doses of ^{177}Lu DOTATATE. A meta-analysis suggests that ^{177}Lu DOTATATE re-treatment in patients with advanced GEP-NETs is well tolerated with a safety profile similar to initial PRRT (60). This provides an additional treatment strategy potentially to improve PFS, OS, and disease related survival.

Alternative PRRT Agents

Either systemic or arterially-delivered PRRT with ^{90}Y DOTATATE or -DOTATOC is an approach that is under further investigation. ^{90}Y is beta emitter with a higher energy and longer mean free path in soft tissue than ^{177}Lu. This theoretically favors treatment of larger tumors where high intratumor pressure limits blood flow and radiotracer delivery. However, a variety of factors mediate tumor killing including bystander effect (61). A major limiting drawback of ^{90}Y is its greater toxic effects to surrounding tissues and bone marrow (62). Renal dose is also higher than ^{177}Lu which poses a higher risk of nephrotoxicity (63). Arterially-administered ^{90}Y DOTATATE is more focally directed but is operator intensive and requires a prolonged procedure typically performed in the interventional radiology suite.

Novel Imaging and Treatment Agents
Antagonists

In contrast to the established SSTR agonists (e.g., DOTATATE), somatostatin antagonists are currently being investigated for imaging and therapy of GEP-NETs. Agonist-ligand complexes are internalized into the cell and entrapped, which is believed to generate higher contrast imaging and prolonged tumor targeted therapy. Antagonists were developed to evaluate the functions of receptors (64) are typically not internalized, but this may be overcome by binding to a higher number of receptor sites than agonists (65). The SSTR-2 antagonist JR11 has shown uptake in renal cell cancers, most breast cancers, non-Hodgkin lymphomas, and medullary thyroid cancers with

binding comparable to NET targeting with SSTR-2 agonists(66). This study also showed peritumoral vessels, lymphocytes, nerves, mucosa, or stroma were more strongly labeled with the antagonist than with the agonist. Antagonists, therefore, may show higher binding leading to improved detection and more avid tumor binding in targeted radiotherapy. [68]Ga NODAGA-LM3, ^{68}Ga DOTA-LM3, and ^{68}Ga NODAGA-JR11 (OPS202) are three of the agents showing early promise(67-70) with clinical trials underway(71). Similar to DOTATATE, therapeutic radionuclides can be attached to these antagonists for PRRT(72, 73).

Alpha emitters

PRRT for GEP-NETs is currently performed primarily by beta emitters (^{177}Lu and ^{90}Y), but targeted alpha therapy (TAT) is potentially much more effective (74, 75). Alpha particles travel a much shorter distance in tissue, typically on the order of only a few cell diameters, and deliver a dramatically higher damaging radiation effect to cells compared to beta emitters. In contrast to beta emission, which results primarily in single breaks in DNA, highly energetic alpha particles result in clusters of double stranded DNA breaks which are irreparable and highly lethal (74). Alpha particles also generate more ionization events and an immunogenic cell death which could generate an immunostimulatory environment and promote an abscopal effect (75). The dual effect of higher tumor cell death and limited radiation to non-target tissues increases the lethality to tumor cells and decreases the off-target adverse side effects.

The primary systemic alpha emitter under investigation is [225]Ac which can be stably bound to DOTATATE or DOTATOC (75). Early studies have shown promising results (76, 77) with avoidance of severe renal and hematologic toxicity (78). In the future, this could be given as an initial treatment strategy, in sequence with ^{177}Lu DOTATATE, or as a salvage therapy for patients progressing on ^{177}Lu PRRT.

Additional Therapies or Combination Therapies

Beyond radionuclides, there are other drugs and regimens being developed for treatment of GEP-NETs. These therapies may provide additional benefits to PRRT, particularly if they can be used to sensitize tumors to PRRT or be sequenced in such a way to deliver synergistic lethality. Alternative methods of administration may also allow higher local dose PRRT *via* intra-arterial rather than systemic delivery (79, 80). PRRT could also be used in a neoadjuvant fashion prior to surgery to make some patients operative candidates and increase the chances of curative resection (55). The sorting out of the milieu of therapies, their timing, and indications will require ongoing research.

CONCLUSION

Currently, the most sensitive and accurate established method to image well-differentiated GEP-NETs is with DOTATATE PET imaging. Due to the favorable uptake properties and biodistribution, targeted PRRT with ^{177}Lu DOTATATE has been established as best standard of care for patients with progressive, metastatic, or unresectable well-differentiated SSTR positive GEP-NETs. ^{177}Lu DOTATATE is well tolerated with a very mild toxicity profile and rare serious adverse events. Ongoing investigations are continuing to expand in both imaging and therapy applications for DOTATATE and novel ligand theranostics for GEP-NETs.

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