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NENs: FROM DIAGNOSIS TO THERAPY – A THERAGNOSTIC APPROACH: PART II

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Abstract

Diagnostics and therapy in neuroendocrine tumors (NETs) has been heavily influenced by nuclear medicine progresses, both from a diagnostic and therapeutic perspective. The introduction of somatostatin-based peptides, labeled to radionuclides (constituting radiopharmaceuticals), such as the current golden standard 68Ga-DOTA-SSAs (SomatoStatin Analogues), has revolutionized the approach to these neoplasms. That is not all: these radiopharmaceuticals have been employed also into a therapeutic context, realizing the so-called PRRT (peptide receptor radionuclide therapy), allowing NENs to be integrated into a comprehensive theragnostic approach, making advantage of the knowledge based on receptor overexpression of neuroendocrine tumors, in particular SSTRs (somatostatin receptors).

PRRT is mainly focused on the utilization of 90Y- and 177Lu-based peptides, but in this case another important factor is needed: the internalization process, a pivotal phenomenon that allows the efficacy of the therapy, thanks to the intracellular collection of radioisotopes: in this way, they are able to damage internal structures of neoplastic cells.

Keywords: *Neuroendocrine tumors, somatostatin receptors, peptides, radiopharmaceuticals, theragnostics, PRRT.*

CONVENTIONAL THERAPY OF NENs: AN OVERVIEW

Like almost every other neoplastic disease, surgery represents the most radical approach in therapy. In NENs, like other silent growing tumors, this could be not feasible, and this represents the majority of cases. (1) Often patients present an advanced/metastatic condition at first diagnosis, so a radical surgical approach is simply not possible. (2)

Nowadays, therapeutic options (3) available for NENs are different (4), here is an overview:

a) Cytoreductive surgery: a surgical approach that has the only goal to physically reduce the dimensions of the tumor, if feasible;

b) SSAs: these drugs act as somatostatin analogues and they are utilized to control the symptoms related to the secretion of hormones related to the tumor (especially if it is a so-called Functioning NEN, determining an endocrine syndrome due to hypersecretion of specific hormones in blood stream); additionally, it allows to control also (within a certain margin) tumor growth;

c) Chemotherapy: drugs like capecitabine and temozolomide represent a common combined therapeutic regimen (abbreviated in CAPTEM); alternatively, platinum-based chemotherapy is also an option;

d) Everolimus and sunitinib: new drugs included in the conception of "molecular targeted therapy";

e) Locoregional ablative therapies:
   - Radiofrequency ablation
   - Selective hepatic transcatheter arterial embolization
   - Chemoembolization
   - Selective internal radiotherapy
   - Laser-induced thermotherapy

Among all of aforementioned solution, nowadays the best option in the therapy of advanced/metastatic NENs is represented by PRRT (Peptide Receptor Radionuclides Therapy) (5): the most important advantages of this approach are various:

- it is a treatment with a highly targeted nature;
- it has an excellent tolerability with minimal toxicity profile (making possible to use them also in patient with bad performance status, within a certain limit, because one of the most relevant side effects is renal toxicity); (6)
- finally, it has a highly convenient treatment scheduling, especially if compared to chemotherapy cycles, in fact PRRT is completed in few discrete 1-day cycles at 10-12 weeks interval, not excessively weighing on the patient's routine, cutting down also the cost of management of patients themselves in healthcare structures. (7-9)

SSAs AS THERAPEUTIC STRATEGY: MECHANISM OF ACTION AND CLINICAL APPLICATION

In the field of NETs, the discovery of the key role of SSTRs made a revolution both in diagnosis and in therapeutic approach: it was thought that a great application of these new knowledges would have been represented by artificial peptides that could bind to SSTRs like native somatostatin. (10) But, why not using the simple somatostatin itself, maybe synthetizing it artificially? Well, the answer is simple as that: it is not suitable for medical usage (neither diagnostic nor therapy). The reason is mainly linked to its lifetime, due to the high susceptibility to circulating enzymes ready to degrade it; in fact, it has been measured a half-time of about 1-3 minutes, certainly not enough for a large distribution in the organism. (11)

So, how to resolve the problem? The answer was found in SSAs, or "SomatoStatin Analogues", that is to say peptides that can bind SSTRs, miming the

physiological activity of native somatostatin. In this way, the peptide is able to function as a "carrier" if bound to other molecules, like bifunctional chelators and radionuclides, fulfilling a diagnostic or therapeutic purpose. (12)

The first SSA ever realized was *octreotide* (better known as Sandostatin®, largely used with OctreoScan® imaging), that shows a high affinity to SSTR-2, but an inferior one to SSTR-3 and SSTR-5. Its main application is in OctreoScan® (dated back in 1980s), a medical nuclear imaging technique based on ^{111}In-pentetreotide, largely involved in PNETs imaging. The radiopharmaceutical is obtained labelling ^{111}In to the peptide using a chelator called "DTPA", realizing a molecule named ^{111}In-diethylene triamine pentaacetic acid (DTPA)-octreotide: as aforementioned, it is usually abbreviated in ^{111}In-pentetreotide. (13)

During last decades, other SSAs have been developed, with better and better results, receptor affinity and SSTR subtypes binding capacity and specificity. Examples are represented by *lanreotide* and *vapreotide*, but one of the most innovating and interesting concepts are "pansomatostatins", or, in other word, SSAs capable of binding all five subtypes of SSTR subtypes: *pasireotide* is the forefather of this new SSA conception, showing selective affinity for SSTR-1, SSTR-2, SSTR-3 and SSTR-5. (14-17)

SSAs, traditionally, have been used in clinical practice to treat and control secretory symptoms in NEN patients, such as flushing and diarrhea (typical conditions of metastatic conditions), because they are able to inhibit the release of hormones produced by the neuroendocrine neoplasia, like serotonin, gastrin, VIP (Vasoactive Intestinal Peptide) and other ones, as well as metabolites. (18) Nonetheless, recent studies enlightened the capability of inhibiting tumor growth: going more in-depth, SSAs interact with molecular pathways implied in tumor cell proliferation/apoptosis (as a direct effect of the drug) and angiogenesis (this time, it is both a direct and indirect consequence). (19)

One of the most important SSA effects is the anti-proliferation ability: this makes them a valid drug to control tumor stabilization. This mechanism is made possible by the interaction with SSTR-2 and SSTR-5, whereas the induction of apoptosis is controlled by SSTR-3. (20)

So, SSAs can act as a drug in themselves; in this case, they are commonly identified as "*cold SSAs*", but they find another important application: in fact, they have been studied with the purpose to use them as components of radiopharmaceuticals, labelling them to radionuclides, so they can "transport" the latter and mediate the bond with their targeted receptor. (21) In this way, SSAs allow the internalization and the accumulation of radionuclides inside neoplastic cells, realizing the so called "*PRRT*", or "Peptide Receptor Radionuclide Therapy". (22) As a consequence, a previous nuclear investigation is mandatory in order to confirm SSTRs expression by the neoplasm: in case of a positive outcome, the patient is eligible to start the treatment with cold somatostatin analogues and PRRT. (23-26)

The administration of cold SSAs (octreotide and lanreotide) is distinguished basing on the duration of the formulation, so two different formulations are available:

a. Octreotide: available as an immediate-releasing subcutaneous injection (also known as "sandostatin/octreotide short acting") or, alternatively, as long-acting repeatable formulation (known as LAR Depot, where "depot" generally refers to long-acting drug administrations; the drug is administered through an intramuscular intragluteal injection, once every month, guaranteeing a constant release into the blood stream for a certain period of time).
b. Lanreotide: available in two different alternatives, specifically a "sustained release" formulation administered by an intramuscular injection (once every 10-14 days) and an "extended release"

formulation, administered once a month (this is a "depot" solution, guaranteeing long-acting release of the drug for a much longer period of time than the previous solution).

PRRT (Peptide Receptor Radionuclides Therapy)

The nature of nuclear medicine (NM) is strictly connected to its capability of collecting functional and biological data, allowing to outline a complete account of a certain lesion. (27-36) In particular, thanks to the utilization of radiopharmaceuticals based on peptides, the investigation is able to detect the presence of specific receptors on the membrane surface of target cells: this means that when the patient provides a positive result at the diagnostic technique, it can be affirmed the neoplastic cells express the specific receptor. (37-40)

As previously explained, a radiopharmaceutical is composed by a ligand (the binding molecule that interacts with a certain receptor, giving it the specificity needed to target neoplastic cells), a bifunctional chelator and a radionuclide. Regarding the latter, it can be different depending on the purpose the drug is made for: if the isotope is capable of emitting β^+ or γ radiations, it is perfect for diagnostic techniques, whereas α and β^- emitting radionuclides provide a completely different kind of phenomenon, able to irreversibly damage a cell, inducing its death. (41)

In synthesis, it is possible to fine tune the radiopharmaceutical's composition to make it perfectly suitable for a diagnostic or a therapeutic act: the latter situation represents **PRRT**, or Peptide Receptor Radionuclide Therapy, differing from the previous diagnostic approach only modifying the radionuclide (in the majority of cases). (42)

The fundamental conception of this approach lies in the specific targeting behavior of the radiopharmaceuticals: being composed by a binding molecule that is able to interact only with a specific receptor, the drug can act as a carrier that transports the radionuclide towards the neoplastic cells; at this point, once the interaction takes place, the drug-receptor complex is activated and another pivotal phenomenon takes place: the internalization of the complex itself. This event allows the accumulation of radiation-emitting (α or β^-) isotopes inside the neoplastic cells, guaranteeing the structural damage towards cellular organelles. (43) In contrast to a diagnostic application of radiopharmaceuticals, the internalization phenomenon is far more important in PRRT. (44) The reason is quite simple: while in diagnostics the purpose is to only localize the neoplastic cells, a simple bond, even letting the drug to interact with its receptor only outside the cell (remaining on its surface) is sufficient in order to obtain positioning data; the scenario totally changes when it is supposed to kill the cell, since the accumulation of a satisfying amount of radiations is needed to make it happen, so internalization covers a pivotal role in this operation's success. (45)

A clarification is mandatory, at this point: to candidate a patient to PRRT treatment, it is absolutely needed a previous investigation with nuclear imaging based on radiopharmaceuticals, in order to demonstrate the expression on the neoplastic cells' surface of the targeted receptor themselves; so, the feasibility of PRRT is confirmed, because the interaction between the drug and the receptor is guaranteed. This kind of information is also necessary to utilize cold SSAs in the patient, in order to control signs and symptoms due to the neoplasia (such as controlling tumor growth and, also, hormone hypersecretion). (46)

Not only the internalization process, but also neoplastic differentiation becomes a crucial element: the higher the grading, the higher the probability of receptor expression loss. In this context, knowing the tumor grading is a key element for the success of the therapy, because high-graded tumors tend to express lesser receptor (low receptor density), together to an increased glycolytic activity (higher and more intense metabolic activity, due to a greater mitotic index, confirmed by higher Ki67 levels). These elements have been studied in correlation to PRRT efficacy,

demonstrating a poor outcome, whereas chemotherapy showed far better results. (47)

The highly integrated roles of diagnostic and therapeutic procedures, thanks to radiopharmaceuticals, gives reason to call this a *theragnostic* approach, representing the high interesting and promising versatility of NM in NENs' field, even enlightening that further application are being studied, with stimulating findings. (48)

PRRT IN NENs

As aforementioned, the theragnostic approach in NENs, nowadays, is pivotal in the management of this kind of patients. Only subjects who showed an *in vivo* uptake of the radiopharmaceutical during diagnostic nuclear investigation are suitable for this therapeutic strategy; otherwise, it would be completely useless, since the drug could not interact with its target. (49)

Once the patient is judged suitable for the PRRT, the next step is to correctly choose the radiopharmaceutical's composition in order to act as a therapeutic instrument.

How this goal can be reached? Nowadays, the answer consists in the simple substitution of the isotope, changing it with a α or β^- emitting one, capable of damage the cell. Several approaches are adoptable: it is possible to administer the drug via an intravenous or locoregional injection and we will later discuss them in-depth.

Another possible therapeutic strategy is represented by the combination of different treatment: the combined approach consists, simply, in the contemporaneous employment of different radiolabeled peptides or even PRRT and immunotherapy, chemotherapy and/or radiotherapy. (50)

INTRAVENOUS TREATMENT

While the main diagnostic radionuclide is ^{68}Ga (positron-emitting) coupled to DOTA-peptides, the latter radiotracers find application also in PRRT, but it is not a good isotope in therapeutic field: being mainly a positron emitter, it provides an insufficient amount of energy to appropriately damage the target cell. For this reason, other elements have been studied: current radionuclide of choice are ^{90}Y and ^{177}Lu. All these radiopharmaceuticals are administered *via* in intravenous injection.

A question could arise spontaneously: how a radionuclide is defined as "appropriate" for therapeutic context? (51)

The reason lies into its physical properties: firstly, the type of radiations, because the therapeutic activity can be explicated only by α and β^- emitters; secondarily, but strictly correlated, the particle range and tissue penetration, or in other words the capability of the radiation to define "a spatial area of action" within explicate its toxic activity (a too small one implies a lower efficacy of its action, while an excessive large one could be potentially counter-productive and dangerous). (52)

Let's propose some examples in order to clarify the latter point: thanks to its historical employment in nuclear medicine and in NENs in particular, ^{111}In-peptides (i.e. OctreoScan® or OCT) have been employed with higher dose, in order to cause a therapeutic effect in already demonstrated SSTRs-expressing neoplasms. The result was very unsatisfactory due to the small particle range of this radionuclide (meaning it showed also a low tissue penetration) and its low Linear Energy Transfer (LET).

Later, the two aforementioned isotopes were proposed: coupled to DOTA-peptides (that represent also a better choice in terms of SSTRs' affinity, as previously discussed), ^{90}Y and ^{177}Lu are β^- emitting radionuclides, showing a higher energy and longer particle ranges (even exceeding the diameter of the tumor cell itself), resulting, in conclusion, in far greater performance in comparison to ^{111}In-peptides. (53)

Currently, the theragnostic approaches is the following: first thing first, the recruitment, in other words the patient is firstly studied through ^{68}Ga-DOTA-TOC PET/CT, then the patient is considered

eligible for PRRT only in case of a positive and satisfactory result, especially in terms of receptor expression and tumor uptake of the tracers, more precisely when SUV_{max} >5 in addition to a preserved renal function (radiopeptides have frequently a renal excretion); in case of the lack of PET, a SRS can be performed in substitution, despite its limits (still today it is considered as an efficient instrument in follow-up and assessment of patient's therapeutic response). (54)

PRRT is performed with ^{90}Y or ^{177}Lu labelled to DOTA-peptides: ^{90}Y-DOTA-TOC and ^{177}Lu-DOTA-TATE are the most studied and used radiopharmaceuticals. At this purpose, several groups studied the latter drugs, especially in Europe: the main centers that are worth mentioning are in Rotterdam, Milan, Basel, Innsbrück/Vienna, Bad Berka, defining strong evidence in this field, because significant group of patients were followed in these studies. (55)

^{90}Y-DOTA-TOC and ^{177}Lu-DOTA-TATE are not lacking downsides, especially related to their intravenous administration: both cause a relatively risky **myelotoxicity**, but the main problem is represented by the impact on **renal function**. Due to the tendence to accumulate inside renal parenchyma, the radiopharmaceutical can cause an even significant GFR decrease, making renal function monitoring more than essential. In contrast, the administration of positively charged amino acids to the patient has provided great results in the prevention of renal failure/damage, because they are able to reduce the parenchymal absorbed dose of radiations. Thanks to these measures, the registered outcomes are great: PRRT with ^{177}Lu-DOTA-TATE has provided a therapeutic response in up to 30 months, in addition to self-assessed increase of both life quality and several years overall survival (from the diagnosis), as Taieb et al. exposed in their study, in 2015. (56)

This kind of approach has provided, so, extremely stimulating results especially in patients with unresectable/metastatic conditions, even if it is not a risked hypothesis then, in the future, with the further fine tuning of these techniques drugs, this procedure could become the first therapeutic choice even in patient with lower-staged conditions, as we will later discuss better when speaking about future perspective and new alternatives. (57)

LOCOREGIONAL TREATMENT

Another PRRT approach is represented by a far more precise and targeted injection of radiopharmaceuticals, allowing two main advantages: the application of a more focused irradiation in addition to a lower incidence of side effects, especially regarding bone marrow and kidneys.

The main situation this procedure would be appliable could be an unresectable tumor, which would be down staged thanks to the toxic effect of the PRRT, even making possible a subsequently surgical intervention, far improving the prognosis of the patient. (58)

At this purpose several studies can be mentioned, that provided stimulating results in this field.

Kratochwil et al. (59) employed ^{68}Ga-DOTA-TOC PET/CT administered via intra-arterial injection (through the hepatic artery) to target liver metastases: they demonstrated a 3.75-fold higher SUV_{max} in comparison to the intravenous administration of the same drug, in the same patient. These results show how these alternative techniques can provide far better outcomes in comparison to selective internal radiation therapy or trans-arterial chemoembolization.

In another study, Limouris et al. (60) studied OctreoScan® (^{111}In-DTPA-octreotide) as PRRT agent in selective intra-arterial hepatic infusion in inoperable patients presenting liver metastases: they displayed very promising results, in particular 47% of cases a partial response, 18% stability of disease and, finally, only one case even showed a complete response to the treatment. Additionally, they reported also an estimated median survival time of 3 years, objectively a great result in this context.

MacStay et al. led a study on ^{90}Y-DOTA-lanreotide, using the same technique adopted by Limouris' group, reaching an overall response rate of 79%. (61)

Even given these results, the aforementioned compounds appear as not optimal choices in locoregional PRRT approach, because other ^{90}Y- and ^{177}Lu-labelled SSAs have shown better performance, especially when considering ^{90}Y-labelled microspheres with intra-arterial infusion in NETs' liver metastases.

Even if more studies are needed, there are the premises that locoregional PRRT could provide better outcomes in comparison to local chemotherapy (a therapy limited to the tumor penetration, because of the necessity of interacting with specific molecular pathways of the neoplastic cell), while peptide therapy can count on β^- particles, that are radiations with a high penetration power, even reaching sites 5-10 mm distant from the point of penetration. (56)

COMBINED TREATMENTS

PRRT alone is very successful, but the idea of combining it to other therapeutic strategies seems to be a smart idea. There are several conceptions of "combined" treatments related to PRRT. Here there is an overview of current and future applications:

- **Administration of two radiopharmaceutical contemporaneously**

This approach seems to improve therapeutic results, thanks to the combined effect of two different drugs: in fact, administering both ^{90}Y- and ^{177}Lu-labelled SSAs might improve the results.

The group of Iowa studied the advantages of dual administration of ^{131}I-MIBG and ^{90}Y-DOTA-TOC, finding also more useful the fine regulation of mutual doses: in this particular scenario, they suggested to be more effective the administration of a ^{90}Y-DOTA-TOC dose 2-3 times higher than the ^{131}I-MIBG one.

- **New multimodal conceptions and targeted therapy combination**

Thanks to progresses made in the knowledge of genomics and proteomics, today new therapeutic strategies are thought for neuroendocrine tumors. PRRT could be intercalated into a tailored and pathway-specific therapeutic strategy basing on biological background of the neoplasia itself, taking advantages of tumor expression and other functional characteristics that can be enlightened by nuclear medicine procedures, especially when combined to other contribution coming from pathology knowledge of the disease.

PRRT, as aforementioned, could also be associated to immunotherapy, radiotherapy or chemotherapy, allowing better and better therapeutic response, depending on the performance status of the patient and his capability of treatment tolerance, virtually prospecting new and future targeted therapy protocols, with obvious need of more studies to support this possibility.

Further findings are showing also the expression of RTKs (Receptors of Tyrosine Kinase) on NETs' membrane surface, leading to the possible employment of tyrosine kinase inhibitors, like sunitinib.

Other targets could be tumor neovessels, so angiogenesis inhibitors could cover a significant role in therapy, like bevacizumab and more recent analogue drugs, even in combination with other cytotoxic pharmaceuticals.

In conclusion, another option could be inhibitors of mTOR (mammal Target Of Rapamycin), such as everolimus, again in association to other cytotoxic agents.

PROMISING NEW PEPTIDE CANDIDATES FOR PRRT: FUTURE PERSPECTIVE AND NEW ALTERNATIVES

SOMATOSTATIN ANALOGUES

As previously explained, SSAs (Somatostatin Agonists) are peptides mimicking somatostatin's

action that are used in combination with a bifunctional chelator and a radionuclide in order to compose a radiopharmaceutical. This drug can be used as in PRRT, but in addition to the radionuclide itself, also other SSAs can be used as alternatives to DOTA-TOC/TATE; in particular, SSAs that represent valid alternative for future application in the therapeutic field are DOTA-NOC, KE88 and LTT-SS28.

While DOTA-NOC is already quite widely used both in diagnostic and in therapeutic contexts, last two peptides are stimulating options, as future perspectives.

The new trend, today, is represented by so-called "***pansomatostatins***" (the prefix "pan-", in ancient Greek, means "all; of everything; involving all members") , in other words SSAs capable of binding a wider range of SSTR, to be more precise these molecules can bind with high affinity all five receptor subtypes. The rationale they are based on is simple: with such a binding affinity, the probability of interaction with the targeted receptor significantly increases; this characteristic could be use not only in therapy, but also in diagnostics, allowing a far better sensitivity performance of the radiotracer, potentially never seen before. (62)

KE88 is usually labelled to ^{90}Y through DOTA (the chelator), constituting **^{90}Y-KE88**, also known as ^{90}Y-DOTA-cyclo(D-diaminobutyric acid-Arg–Phe–Phe-D-Trp–Lys–Thr–Phe). Ginj et al. (21) studied this radiopharmaceutical, concluding that, surprisingly, its SSTR-2 depending internalization was very low, whereas tumors that high-expressed SSTR-3 showed a high and persistent uptake (these tests were performed on mice). So, the internalization capability of these analogues was not so satisfactory, especially because their worst performance was showed in relation to internalization mediated by SSTR-2, that, let's remember, is the most frequent overexpressed SSTR subtype in neuroendocrine neoplasms (positive to SSTRs); in contrast, SSTR-3 high-expressing tumors can highly internalize it, but the downside is these ones are not so frequent as SSTR-2 overexpressing ones.

This leaves a still open match in development of an appropriate pansomatostatin able to be deeply eligible for a complete theragnostic path, from diagnosis to therapy, potentially becoming the first choice in PRRT of P-NETs. (63)

Native somatostatin itself has been evaluated in order to design efficient pansomatostatins-like analogues, as Maina et al did in 2014. For this purpose, the somatostatin mimic **[DOTA]-LTT-SS28** was involved into the study, labelled to **^{111}In** (realizing ^{111}In-[DOTA]-LTT-SS28), displaying promising results even if other fine adjustments are needed in its chemical structure to guarantee higher tumor uptake and metabolic stability of the compound; a possible solution is represented by the co-administration of a peptidase inhibitor, since these enzymes (such as NEP or Neutral EndoPeptidase) are responsible of the rapid *in vivo* degradation of the radiopharmaceutical, thus its somatostatin resembling molecular structure. (20)

Being a pansomatostatin, ^{111}In-[DOTA]-LTT-SS28 showed its capability to bind all SSTR subtypes (SSTR-1 to SSTR-5), but here there is a pivotal molecular difference with KE88: LTT-SS28 showed an agonist effect on SSTR-2, SSTR-3 and SSTR-5, stimulating their activation and subsequent (effective) internalization of the ligand-receptor complexes.

The preclinical study of Maina's group has provided very interesting and promising results, that only a clinical study can crown in order to explain its potential. (64)

Moreover, as we previously affirmed, the conception of internalization is pivotal for the effectiveness of PRRT, because of the necessity of collecting inside the cell a certain amount of radiations.

This conception was quite revolutionized by Ginj et al. (21) preclinical study, when receptor affinity and internalization capability of ^{111}In-DOTA-SST2-ANT (a radiolabeled SST-2 **antagonist**) was compared to ^{111}In-DOTA-TATE (a radiolabeled somatostatin SST-2 **agonist**): while the latter presented a higher receptor binding capability (affinity), the first

radiopharmaceutical showed a far higher internalization rate and tumor retention. Tumor to kidney ratios (after 4 hours from the injection) were measured, reporting, respectively, 2.7 and 1.4 values.

This preclinical finding opens to further considerations and hypothesis on the possible involvement of somatostatin antagonists in PRRT (but also in nuclear diagnostics), in the future, but other studies are strictly needed. (64)

GLUCAGON-LIKE PEPTIDE 1 RECEPTOR TERGETING PEPTIDES

Low SSTR (especially SSTR-2) expression in several neuroendocrine tumors, such as insulinomas, has always represented a challenge in order to outline an efficient PRRT strategy, because of the lack of useful radiopharmaceuticals able to bind targeted cells and being internalized by the latter. For this reason, different radiotracers have been studied, making advantage of the different receptor density and types available on the tumor surface, in particular the one the most interesting is GLP-1R (Glucagon-Like Peptide 1 Receptor). This receptor has been identified as an overexpressed molecule not only in insulinoma itself, but also in pheochromocytomas and gastrinomas (the latter is the most frequent histotype among functional P-NETs). (65)

Several preclinical studied were led to analyze various combination of radionuclides and ligands. Regarding specifically insulinomas, compounds that showed great results were ^{111}In-DTPA-Lys^{40}-exendin-4 and, in particular, **(Lys^{40}[Ahx-DTPA-^{111}In]NH$_2$)exendin-4**, in other words radiopharmaceuticals derived by the conjugation of ^{111}In, DTPA and exendin analogues, able to provide satisfactory TBR (Tumor to Background Ratio). Furthermore, (Lys^{40}[Ahx-DTPA-^{111}In]NH$_2$)exendin-4 displayed also the ability to repress insulinoma's growth, in a study conducted in mice.

Now, let's explain the main subsequent downside of these peptides' employment: post-PRRT long-term kidney toxicity, resulting also in compromising conditions of renal failure, due to the high radiopeptide renal uptake, retaining it in the parenchyma. How to solve this problem, since the convenient premises of these drugs? It has been studied that the co-infusion of albumin fragments, gelofusin and/or lysine has the ability to decrease renal uptake; this result was observed in both aforementioned peptides and this solution opens new possibilities of clinical PRRT studies for both of them.

Finally, recent prospective studies have shown also the capabilities of another radiopharmaceuticals, this time combined with SPECT/CT procedures, applying it in nuclear diagnostics: **^{111}In-DOTA-exendin-4**. The drug provided grate results in depicting insulinomas targeting GLP-1Rs, potentially giving to this radiopharmaceutical the opportunity to be employed also in peptide therapy, with the subsequent need of further adjustments and related studies.

As later discussed, PRRT has not only been applied strictly to NENs, but the application fields are various and very heterogeneous, especially for oncologic diseases. Following paragraphs will explain better these topics, involving breast and cancer carcinomas, in addition to medullary thyroid carcinomas, proliferating endothelial cells and EGFR-dependent cancers. (66)

GASTRIN-REALISING PEPTIDE RECEPTOR TARGETING PEPTIDES

PRRT has been applied also in breast and prostate cancers, taking advantage of their surface expression of GRP-Rs (Gastrin-Releasing Peptide Receptors), utilizing specific ligands able to interact with them. Appropriately and variously radiolabeled **bombesin** analogues (that can act as agonists or antagonists, depending on the specific molecule) have been analyzed in this context: (67)

- **^{99m}Tc-demobesin-1**: this was one of the most promising bombesin analogues (a bombesin

antagonist), presenting a high tumor uptake in addition to an *in vivo* pancreatic excretion, due to its expression of GRP-Rs.

- **^{99m}Tc-RP527** and **^{99m}Tc-(Leu13)bombesin** both have been studied in prostate cancer patients, reporting promising results in depicting primary and metastatic lesions, such as secondary bone tumors.
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From a nuclear imaging perspective, besides experiments with SPECT, PET has lesser been studied, even if reported results were encouraging.

CCK-2 RECEPTOR TARGETING

Colecistokinine-2/gastrin receptors (CCK-2/gastrin-R) expression has been found in several neoplasms: mainly in medullary thyroid carcinoma (MTC, in which the receptor is overexpressed in more than 90% of cases) and in a consistent number of cases in stromal ovarian cancers, astrocytomas, SCLC (lung microcytoma) and other neoplastic diseases. These tumors, especially MTC, shows low density SSTR-2 expression, making inefficient somatostatin peptides (both in diagnostics and PRRT), and the condition is even worse in malignant cases, where the expression can be even absent. (68)

In addition to CCK analogs, also other kind of molecules have been tested, such as gastrin and minigastrin analogues, showing promising results in terms of targeting affinity towards CCK-2 receptors.

The association of CT and GRS represented the most accurate approach in depicting metastatic lesions in medullary thyroid cancer, to the point that they suggested the latter could even become the best scintigraphic imaging modality in this kind of patients; it is important to note that clinical studies regarding the employment of CCK-2-based radiopharmaceutical in PRRT have not been completed, even if their results are really promising. (69)

$\alpha_v\beta_3$ INTEGRIN TARGETING

Neoplasms are characterized by a deep dysregulation in cell proliferation, resulting in the production of a large number of neoplastic cells: this condition implies the need for a huge amount of nutrients in order to support this cell population, otherwise they would start to die. This is the reason of the marked angiogenesis process associated to neoplasms.

New capillary vessels, or simply "neovessels", after all, are not exactly equal to quiescent capillary vessels: in fact, it has been demonstrated that proliferating endothelial cells express $\alpha_v\beta_3$ integrin receptors, in order to interact with extracellular matrix, but this characteristic is absent in quiescent endothelial cells. This peculiarity makes them particularly interesting from a diagnostic and therapeutic perspective in neoplasms diseases.

The first step was to synthetize a peptide able to interact with these receptors: **cyclic RGD analogues**; RGD stays for arginine-glycine-aspartic acid, representing the standardized abbreviation letter which identify each amino acid, and this molecule is the one that physiologically interacts with $\alpha_v\beta_3$ integrin receptors.

Cyclic RGD analogues have been conjugated to several chelators (DOTA and DTPA) and radionuclides (^{111}In, ^{68}Ga, ^{64}Cu and ^{18}F for diagnostic utilization with SPECT and PET, ^{90}Y and ^{177}Lu for PRRT). For example, ^{18}F-galacto-RGD was employed to demonstrate the expression of $\alpha_v\beta_3$ integrin receptors in humans. (70)

The highest results in terms of binding affinity and tumor uptake were displayed by tetrameric RGD peptides and tetrameric RGD dendrimer, even if they also showed an increased renal retention, representing a serious risk for kidneys' integrity. For this reason, the group found an alternative approach with the intraperitoneal administration of these drugs, reporting better tumor-to-kidney ratios in addition to satisfactory tumor growth inhibition, even compared to intravenous injection of these radiopharmaceuticals, confirming their high potential in PRRT. (70)

EPIDERMAL GROWTH FACTOR RECEPTOR TARGETING

EGFR (Epidermal Growth Factor Receptor) overexpression has been described in several neoplasms, including NETs: breast, gastric, bladder, NSCLC are all examples of neoplastic diseases that present this molecule on their cell surface, a sign of their malignant and aggressive behavior. (71)

Several studies have been led with the purpose of evaluating EGFR ligands analogue as effective ligands to insert into the composition of radiopharmaceuticals, having a PRRT approach in mind.

The main disadvantages related to these radiopharmaceuticals are represented by the side effects due to their EGF agonistic activity, such as nausea and vomiting, fever, diarrhea, hypotension, chills), especially manifested by patients during dose escalating studies. (71)

As an alternative, it was thought to utilize radiolabeled antibodies (Ab) able to target EGFRs, both in diagnostics and therapy, but their main problem is related to their molecular dimension (about 150 kDa), meaning increased systemic retention a low penetration in tissues.

CONCLUSIONS

Detection of gastroenteropancreatic neuroendocrine tumours and monitoring of treatment response relies mainly on morphological imaging such as computed tomography (CT) and magnetic resonance imaging (MRI). (72-75) Molecular imaging techniques also in combination with CT (hybrid imaging) greatly benefit patient management, including better localization of occult tumours and better staging. Despite exciting results and progress made during last decades, both diagnostic and therapeutic applications of radiolabeled peptides in NENs and other diseases, the path is far to be complete. Several studies are needed in order to completely validate the efficacy and the possibilities of various radiopharmaceuticals, but current results are really promising. (76)

Their application in benign diseases also represents another important goal to reach.

This kind of techniques can also be identified with the quintessence of nuclear medicine, thanks to its diagnostic functional nature, in addition to applications in peptide receptor radionuclide therapy; also its non-invasive nature is a great characteristic, even if locoregional treatments could undergo radical changes, but always keeping in mind the strategy's effectiveness and feasibility for the patient.

The theragnostic approach is the key in these maladies, representing the sweet point in patients affected by inoperable oncologic disease. (77) The real challenge is to make these procedures, especially the newer and more promising ones, available in clinical routine as soon as possible, but the premises (in particular, regarding their efficiency and accuracy) are more than exciting.

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