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Metastatic Medullary Thyroid Cancers: Challenges in Diagnosis with Nuclear Medicine Techniques and the Role of Radionuclide Therapy

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Abstract

Medullary thyroid cancer is a rare tumor driven from neuroendocrine cells. In the last decade there has been important discoveries regarding its genetics and relationship between genotype and phenotype on familial cases. However remains unknown the best approach for patient with maintained high levels of tumor markers such as calcitonin. Most available imaging techniques are able to accurately find metastatic lesions only in advanced disease. Traditionaly, nuclear medicine images are able to find metastatic suspicious lesions before they reach the size to be considered suspicious in conventional studies such as computed tomography scans or magnetic resonance imaging. However in patients with medullary thyroid cancer the ideal radiopharmaceutical for this purpose is yet to be found. Based on the biology of the tumor, some radiopharmaceuticals have been studied for diagnosis and also for therapy in those patients. The aim of this review is to describe the radiopharmaceuticals used for diagnosis and treatment until today and the role of each of them in medical care. In conclusion, the medullary thyroid cancer is a rare tumor and the review shows that despite all studies there is still no consensus on the importance of nuclear medicine in the diagnosis and treatment of these patients. Further studies are still needed.

Keywords: Metastatic medullary thyroid cancer; Conventional scintigraphy; PET/CT; Radionuclide therapy; Review

Introduction

Medullary thyroid carcinoma (MTC) is a relatively rare cancer with peculiar issues: slow growth and highly aggressive behaviour, which makes its approach to be a challenge in clinical practice. It is originated from parafollicular cells, calcitonin-producer (Ct), making it one of the most sensitive markers used for clinical monitoring of these patients [1,2]. These tumors also produce other substances, in varying amounts, such as peptide calcitonin gene (CGRP), carcinoembryonic antigen (CEA), amyloid, somatostatin, adrenocorticotropic hormone (ACTH), corticotropin releasing hormone (CRH), peptide vasoactive intestinal (VIP), gastrin releasing peptide, prostaglandins, serotonin, catecholamine, substance P, histaminase, chromogranin A, beta-endorphin, melanin, nerve growth factor, neurotensin, neuron specific enolase, synaptophysin, kinin and kallikrein [2]. They are responsible for 4 to 9% of all thyroid tumors, however, compared to well differentiated thyroid carcinoma, they have a worse prognosis. The tumor staging, and restaging is essential since the surgery is the only curative method, and the identification of advanced disease is required in order to provid, as soon as possible, other therapeutic modalities. High plasma concentrations of Ct and/or high levels of CEA suggest the presence of residual malignant disease/ recurrence or distant metastasis [1].

Because of the tumor characteristics and the aggressive behavior of the disease numerous studies have been conducted on the diagnosis and treatment of this condition in patients with more advanced tumors (metastatic) in order to improve the quality of life and survival of patients. Therapies range from medications for symptomatic control to chemotherapy drugs, palliative treatments with radiation therapy until more recently the target therapies with or without radionuclides.

The aim of this review is to describe the diagnostic nuclear medicine imaging methods using radionuclides and the radionuclide treatment for these patients emphasizing its indications, benefits, limitations and possible side effects.

Nuclear Medicine in the Evaluation of Patients with Medullary Thyroid Carcinoma

Conventional nuclear medicine radiopharmaceuticals

Eventhough disease staging and restaging is usually evaluated by conventional morphologic imaging methods, such as ultrasound, computed tomography and magnetic resonance these methods do not provide functional data and frequently fail to reveal local or distant recurrences and metastasis [1]. In this manner the advantages of conventional nuclear medicine is the possibility to acquire functional information with planar images or tomographic approaches, such as (single photon positron emission–(SPECT) or SPECT/CT [3].

The most studied radiopharmaceuticals for conventional nuclear medicine imaging in metastatic MTC are technetium-99m-(V)-dimercaptosuccinic acid (^{99m}Tc-V-DMSA), ^{201}Thalium chloride (^{201}Tl), ^{99m}Tc-sestamibi, iodine-131/iodine-123-metaiodobenzylguanidine (^{123}I/^{131}I-MIBG) and somatostatin receptors labelled with Indium-111 (^{111}In) or Technetium-99m (^{99m}Tc) [4-7].

^{99m}Tc-V-DMSA scans can be used in the evaluation of the the primary tumor, as well as in tumor recurrence, with sensitivities ranging from 19% to 88%. Its advantage is the use of ^{99m}Tc as the radionuclide. Technetium-99m is a widely used radioactive tracer isotope in Nuclear Medicine. It's gamma ray energy of about 140 keV is convenient for detection. The fact that both its physical and biological half-life are very short leads to very fast clearing from the body after the study. A further advantage is that the gamma is a single energy, not accompanied by beta emission, and that permits more precise alignment of imaging detectors. The usually protocol performed is the intravenous injection of 370 MBq (10 mCi) of 99mTc-V-DMSA within 10 min of the preparation. Using a large field of view gamma camera, images are usually acquired 2 hours after the injection. It has been postulated that ^{99m}Tc-V-DMSA resembles phosphate ion in its distribution pattern, and that this is the mechanism by which the radiopharmaceutical accumulates in MCT. Although the precise mechanism for its uptake is yet to be clarified [8]. However, based in several reports, nowadays ^{99m}Tc-V-DMSA scans are not recommended for these patients as other imaging techniques can offer more reproductible results with higher sensitivity [4,5,9,10].

Metaiodobenzylguanidine (MIBG) is an analogue of guanethidine, similar in structure to norepinephrine. The MIBG can be labeled with iodine-123 or iodine-131 (^{123}I/^{131}I). ^{131}I emits a principal gamma photon of 364 keV (81% abundance) with a physical half-life of 8.04 days. It also emits beta particles with maximum and mean energies of 0.61 MeV and 0.192 MeV, respectively. ^{123}I is a gamma emitting radionuclide with a physical half-life of 13.13 hours. The principal gamma photon is emitted at 159 keV (83% abundance). ^{123}I-MIBG, because of its physical properties, is more suitable for imaging and ^{131}I-MIBG for treatment purposes. ^{123}I-MIBG can be used for diagnosis of neuroendocrine tumors, particularly neuroblastoma and pheochromocytoma, and also MTC, however is not highly recommended for MTC tumors as it has low sensitivity in these type of cancer [6,7,11]. ^{131}I-MIBG may be preferred for imaging when estimation of tumour uptake and retention measurement is required for MIBG therapy planning. For diagnosis purposes the radiopharmaceutical is administered by slow intravenous injection (at least 5 minutes) in a peripheral vein. The recommended activity administered to adults is 40-80 MBq (1.2-2.2 mCi) for ^{131}I-MIBG and for ^{123}IMIBG 400 MBq (10.8 mCi). The referred known side effects of MIBG are tachycardia, pallor, vomiting, abdominal pain and depend directly on the administered activity. Before the administration of the radiopharmaceutical a thyroid blockage must be done to avoid thyroid uptake. Furthermore many classes of medicines may theoretically interfere with MIBG uptake and storage and they have to be known before imaging and/or therapy and must be interrupted. Allergy reactions are very rare when slow injection is used. The phisiological biodistribution of MIBG is bladder and urinary tract (because of its excretion), liver, spleen, lungs, salivary glands, skeletal muscles and myocardium. Normal adrenal glands are seen in up to 15% of cases when using ^{131}I-MIBG and in up to 75% of cases if using ^{123}I-MIBG [12]. For treatment purposes usual single-administered activities range between 3.7 (100 mCi) and 11.2 GBq (300 mCi). The administered activity may be modified for medical reasons such as tumour burden or according to local legislation. Because several therapeutic doses may be required to achieve objective response, these activities are often repeated at widely different intervals, according to individual needs. The main criteria for activity reduction are myelosuppression, impaired renal function and no clinical response [13].

The MTC cells also express somatostatin receptors, which makes it possible to use analogues of somatostatin labeled with radionuclides. The most widely used radiopharmaceutical was indium-111-pentetreotide that is a [^{111}In-DTPA-D-Phe] conjugate of octreotide (Octreoscan® [10]. Then other radiopharmaceuticals labeled with technetium-99m were developed and became routine tracers. The most used somatostatin analogues labeled with technetium-99m are ^{99m}Tc-HYNIC-TATE (HYNIC0, Tyr3, Thr8) octreotide, using ethylenediamine-N,N′-diacetic acid as a coligand, ^{99m}Tc-N-α-(6-hydrazinonicotinoyl)-octreotide (^{99m}Tc-EDDA/HYNIC-TOC), ^{99m}Tc-N4-[Tyr3]octreotate (^{99m}Tc-Demotate) and Tyr3-octreotate (TATE). These have high affinity for somatostatine receptor subtype 2 (SSTR2) and some affinity for SSTR5 and are useful in assessing the carcinoid tumor, pheochromocytoma, paraganglioma, insulinoma, gastrinoma and glucagonoma. Tyr3-octreotate (TATE) differs from the Tyr3 -octreotide (TOC) in that the terminal threonine replaces threoninol. The terminal threonine results in a higher receptor binding and better internalization, with the consequence that tumour uptake of the tracer is intense. In vitro studies revealed that TATE, whether chelated with DTPA or DOTA, shows 14- to 17-fold higher affinity to SSTR2 than octreotide and 8- to 10-fold higher affinity than TOC [13]. They are rapidly cleared from the blood. Excretion is almost entirely through the kidneys and also by hepatobiliary excretion and elimination via the faeces. As somatostatin receptors are expressed by many neuroendocrine and non-neuroendocrine cells of the body, different organs may be imaged by somatostatin receptor scintigraphy including liver, spleen, pituitary, thyroid and some times adrenal glands [13]. The use of 111In as the radionuclide has some disadvantages in comparison to ^{99m}-Tc compounds with respect to its supplement, high cost, suboptimal imaging properties, and low resolution because of its medium energy and relatively high radiation dose to the patient [14]. In some studies there is a 50-70% sensitivity in detecting these tumors using these radiopharmaceuticals. It is believed that the uptake grade is directly related to high levels of Ct and CEA. This implies that somatostatin receptors can be detected in vivo in different forms of MTC [15-18].

The sensitivity rates of the most used radiopharmaceuticals for MTC in conventional nuclear medicine for ^{201}Tl chloride, ^{99m}Tc-sestamibi, ^{99m}Tc-(V)-DMSA, and ^{123}I/^{131}I-MIBG are 63%, 47–83%, 68–95%, and 31%, respectively, and somatostatin analogues sensitivities were reported to be between 37% and 71% [3]. In several series it was shown that ^{201}Tl and ^{99m}Tc-sestamibi have no role in the detection of medullary thyroid carcinoma metastases and restaging protocol [3,8,18].

However, the sensitivity of these imaging modalities, when compared to PET imaging, needs to be revised downwards because some lesions can be only a few millimetres in size and therefore are not detectable by conventional nuclear medicine techniques as they provides lower resolution images and inferior quantitation [18].

PET/CT Radiopharmaceuticals

More recently the use of positron emission tomography with (PET) or without computed tomography (PET/CT) associated in the evaluation of thyroid tumors is being studied. The main radiotracer used in oncology is the fluorodeoxyglucose (FDG), an analogue of glucose that accumulates in different kinds of tumors with increased glycolytic metabolism. It is labeled with fluorine-18 (^{18}F), a radioisotope that has a short half-live of 110 minutes (^{18}F-FDG). ^{18}F-FDG biodistribution varies according to glucose metabolism and

fasting time. The ideal scanning protocol recommends for at least 6 hours of fasting. The physiological uptake is observed in brain, liver and salivary glands. Kidneys, urinary tract and bladder are also seen because ^{18}F-FDG is not reabsorbed at proximal tubules in kidneys. The uptake of ^{18}F-FDG in neoplastic cells correlates with lower differentiation and high proliferative activity. Neuroendocrine tumors generally show an indolent course, and hence low uptake of ^{18}F-FDG [19-21]. These tumors, however, when they undergo dedifferentiation and become more aggressive with increased cell proliferation, may show an increase in uptake of ^{18}F-FDG [22,23].

The PET/CT with ^{18}F-FDG can be an important tool in patients with biochemical evidence of recurrence. Treglia et al. [23] performed a meta-analysis of 24 studies which evaluated the performance of PET or PET/CT with ^{18}F-FDG to detect recurrence of MTC [18,23]. The study indicated that the overall detection rate was 75% when the calcitonin level was greater than 1000 ng/ml and 40% when it was lower than 150 ng/ml. Likewise, detection rates were 69% higher when CEA was 5 ng/ml and 45% when it was less than or equal to 5 ng/ml. The detection rates were 26% when the doubling time of calcitonin was greater than 24 months and 67% when the doubling time was less than 24 months. In relation to CEA, detection rates were 33% when its doubling time was greater than 24 months and 91% when less than 24 months [18,23]. The relatively low detection rate of disease in patients with low levels of calcitonin is probably resulting in a smaller mass of microscopic tumor or disease volume [20]. Other studies also corroborate that ^{18}F-FDG PET/CT imaging is more sensitive in patients with rapidly progressive disease than in patients with slowly rising calcitonin levels, although this is not always supported by literature evidence [20,22]. Because of this evidence recently studies indicate ^{18}F-FDG PET/CT should be included in targeted therapy evaluation, especially when ^{18}F-FDG is correlated with disease aggressiveness, as in MTC. In MTC, it may be a useful tool to predict therapy success as ^{18}F-FDG uptake probably reflects dedifferentiated tumour cells with a higher glucose metabolism and a significant decrease in this uptake after therapy would represent responsive disease [21,24]. ^{18}F-FDG PET before and after treatment, might be the best procedure, in progressive MTC, to stratify patients for specific therapies and assess drug efficacy as it is a non invasive and reproductible method that can scan the whole body at once [21,25].

In the latest MTC review published it was advised that preoperative ^{18}F-FDG PET/CT imaging is not indicated in the routine evaluation and follow up of patients with MTC. The main recommendations for the use of ^{18}F-FDG PET/CT imaging are: when conventional imaging techniques are either negative or inconclusive or if there is a persistent elevated Ct level (more than 150 pg/ml 3 months post thyroidectomy) or CEA beyond 30 ng/ml [22,25].

Another PET radiotracer that has been investigated for MTC's imaging is 6-[^{18}F]-L-fluoro-L-3, 4-dihydroxyphenylalanine (^{18}F-DOPA). It is believed that the accumulation of ^{18}F-DOPA in the MTC is based on the fact that they harbour L-type amino acid transporter system that mediate cellular uptake of the radiopharmaceutical and an intracellular decarboxylation takes place with the help of L aromatic amino acid decarboxylase [25]. Several studies have shown that ^{18}F-DOPA PET/CT have higher sensitivity rates when compared to ^{18}F-FDG PET/CT [25-28]. In recently studies it was described that persistent cervical disease needs further surgical procedures that are optimized if guided by imaging. In this manner ^{18}F-DOPA PET/CT, is the most useful PET tracer in detecting persistent MTC [25]. However it is not available worldwide and it has been shown that actual protocols need to be modified for patients with MTC in order to identify the best imaging time as it was referred that tumor uptake of ^{18}F-DOPA may decrease approximately 40% between early and delayed images [25].

Similarly to somatostatin analogues labeled with ^{111}In and ^{99m}Tc it has been developed somatostatin analogues labeled with gallium-68 (^{68}Ga) for PET imaging, such as DOTA, Tyr3-Octreotate (DOTATATE) and DOTA-D-Phe1-Tyr3-Octreotide (DOTATOC) with high affinity for somatostatin receptors [29,30]. ^{68}Ga is a cost-effective and convenient positron emitting alternative for conventional radionuclides, since it can be eluted from a ^{68}Ge/^{68}Ga generator twice daily. Its main limitation is the need of relatively rapid PET imaging as it has a short half-life of 67.7 min [31]. It has the same biodistibution as octreotide, except for up to 15% of the patients that present physiological uptake in pancreas head. Several studies have proven that as ^{18}F-FDG PET/CT, ^{68}Ga-DOTATATE is an efficient imaging modality in the staging and restaging of MTC patients with increased Ct and CEA for localizing recurrent or metastatic disease [4,31]. The main limitation of the technique is that some lesions may have similar degrees of uptake of the liver and may be missed during evaluation [32].

Pre-clinical studies with novel radiopharmaceuticals such as cholecystokinin-2 (CCK-2) peptides labelled with ^{68}Ga and Cupper-64 (^{64}Cu) (PET radionuclides) are under investigation and preliminary data shows promissing results. The advantage of the ^{64}Cu is the possibility for PET imaging at later time points as it has a half-life of 12.7 hours. Its uptake is based in the premisse that in MTC CCK-2 receptors are overexpressed. Therefore, CCK-2 receptors serve as targets for peptide receptor radionuclide imaging of these tumors by PET radiopharmaceuticals [33].

One study compared ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT in 18 patients with MTC and showed that the sensitivity was slightly lower for the ^{68}Ga-DOTATATE (72% vs. 78%), eventhough it was not statistically significant (p=0.056) [34].

In a retrospective study comparing ^{18}F-DOPA PET/CT, ^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE PET/CT in 18 patients with residual or recurrent MTC and high levels of calcitonin, it was observed that ^{18}F-DOPA PET/CT was superior in the detection of the lesions as it was more sensitive. However ^{18}F-FDG PET/CT showed to be more valuable in the prognosis of patients with MTC recurrence, suggesting complementary roles for the two radiotracers [21,27,28]. On the other hand ^{68}Ga-DOTATATE PET/CT has the advantage of identifying potential subjects for radionuclide therapy [28,34].

An ongoing clinical study is evaluating a new generation of pretargeting agents, the anti-CEA, anti-HSG trivalent humanized BsMAb TF2 and a histamine peptide labelled with ^{68}Ga, in MTC patients with abnormal Ct serum levels, and promissing results are expected [21,24].

Amino acid tracer 3-O-methyl-6-^{18}F Fluoro-DOPA (^{18}F-OMFD) is another new agent that has been tried in patients with MTC recurrence. In a study comparing ^{18}F-FDG, ^{18}F-DOPA and ^{18}F-OMFD PET/CT there was correlation in the detection of lesions with ^{18}F-FDG and ^{18}F-DOPA while ^{18}F-OMFD was found to have no diagnostic impact in these patients [21,24].

Other PET tracers that may be useful in detecting recurrence of metastatic disease in MTC patients are Carbon-11(^{11}C)-hydroxyl

tryptophan and ^{11}C-DOPA, but further investigations are still needed [21,24].

Eventhough a lot of new radiotracers are being developed to evaluate MTC they are not worldwide available and are not yet stablished to be used in routine practice as ^{18}F-FDG, but they are showing promissing results in clinical trials and might became powerful tools in the new theranostic era.

Radionuclide Target Therapies: Future Perspectives

The best treatment for patients with metastatic or inoperable MTC is still a challenge what makes a multidisciplinary approach essential. After aggressive surgery, 40% of patients have persistent disease and about 10%, with undetectable postoperative Ct develop tumor recurrence. At this point treatment options are scarce and not worldwide available. The most used systemic chemotherapy scheme are dacarbazine, doxorubicin and 5-fluorouracil single or in combination and they have shown low efficacy with only partial biochemical responses in 10 to 20% of cases [34-37].

The first nuclear medicine therapy approach was the use of ^{131}I-MIBG. There are few studies envolving the response of ^{131}I-MIBG treatment in patients with MTC. The last review published showed a relatively good response only in patients with lesions avid for the radiopharmaceutical, with transient and auto-limiting side effects. They showed two patients with no other therapeutic option and low MIBG uptake in the screening scintigraphy that acchieved stable disease. In a series of 13 patients that underwent ^{131}I-MIBG therapy in 4 they observed partial response and in 4 they showed stable disease. The most frequent side effect was thrombocytopenia [37].

Due to the low response rates obtained with conventional treatments and MIBG therapy, new therapeutic approaches have been studied in an attempt to improve the efficiency of treatment in patients with metastasis and recurrence MTC. In the last decades a lot of improvement was observed in the diagnosis and treatment with target therapy of various solid tumors, including MTC. Based on the tumor overexpression of somatostatin receptors and on symptomatology control observed with the use of these drugs it was possible to develop therapeutic approaches using somatostatin analogues associated with radionuclides (peptide receptor radionuclide therapy-PRRT), enabling not only diagnosis but also target therapies [15,38,39].

Somatostatin is a peptide regulator with two bioactive forms, somatostatin-14 and somatostatin-28, produced by neuroendocrine cells in the brain and are responsible for neurotransmission modulation [40]. In 1979, Bauer synthesized the octreotide a synthetic octapeptide somatostatin derivative (peptide), which contains essential amino acids for binding to its cell receptor (SSTR) present in the pituitary and other tissues. They were isolated, cloned and sequenced some SSTR subtypes. The subtype 2 is present in MTC [41].

The size reduction and stabilization of the peptide against enzymatic attack resulted in a more biologically stable structure. Comparing the half-lives, the octreotide is about 30 times greater than the endogenous somatostatin. Somatostatin analogues have been successfully used in the symptomatic management of patients whose tumors express these receptors [41].

The main advantages of PRRT over systemic therapy are selectivity (as they have high affinity to somatostatin receptor subtype 2) and relatively lower toxicity. Besides that, due to the radionuclides characteristics patients may be discharged from the hospital in the same day. The most studied peptides labelled with radionuclides yttrium-90 or lutetium-177 (^{90}Y or ^{177}Lu) are [DOTA, Tyr3] octreotide (DOTATOC), DOTA-lanreotide (DOTALAN), and [DOTA, Tyr3]-octreotate (DOTATATE). The difference between Tyr3-octreotate (octreotate) and Tyr3-octreotide (octreotide) is the replacemnent of threoninol in the terminal threonine, that provides higher receptor binding, better internalisation, and greater tumour irradiation [39,42]. DOTATOC, DOTALAN and DOTATATE are chelant agents used in the labelling process of peptides with radionuclides. It is well known that the side effects most observed in these patients is directly related to the type of the ligand. Somatostatin analogues labelled with ^{90}Y or ^{177}Lu are secreted to glomeruli and reabsorbed in proximal canaliculi, what leads to an increased kidney irradiation. In this manner the administration of aminoacids to protect the kidneys decreased substancially which concerns about renal side effects [39,42].

Yttrium-90 is a decay product of strontium-90 which makes up about 5% of the nuclear daughter isotopes when uranium is fissioned. It is a pure beta emitter, with half-life of 64 hours with a maximum range of tissue irradiation of 12 mm. The high energy of this radioisotope (935 keV) is sufficient to achieve direct tumour effects [39,42,43].

Lutetium-177 is a member of a family of chemical elements known as the lanthanides. It has a half-life of 6.7 days, and β-emissions of 497 and 133 keV, and γ-emissions of 208 (11%) and 113 keV (7%), with a maximal tissue penetration of 2 mm. Somatostatin analogues labelled with 177Lu have low tissue penetration and currently have proven more effective in lesions smaller than two centimeters [39,42].

The first reports about treatment with radiolabelled somatostatin analogues in patients with neuroendocrine tumors are dated of the early 1990s. The first labelled peptide used was ^{111}In-DTPA-octreotide with promising results specially in symptomatic control, but very low rates of partial remissions was observed. However the acquired experience showed the occurrence of severe toxicities such as bone marrow suppression, and even myelodysplastic syndrome in patients treated with high activities of >100 GBq, as well as renal insufficiency and transient liver toxicity. In this manner researchers were awared of these side effects and prophylactically kidneys protection was made with the administration of specific aminoacids (infusion of arginine and lysine) and a closely follow up of the patients which concerns of hematological and hepatic parameters was made declining considerable the side effects when peptides labeled with ^{90}Y and ^{177}Lu were applied [43].

In phase I and II trials it became clear that for larger lesions ^{90}Y-labeled somatostatin analogues may be more effective, and ^{177}Lu-labeled somatostatin analogues have better responses for smaller tumors, and furthermore combination may be the best approach [39,42]. Several groups have also advocated the feasibility of locoregional, such as intraarterial administration of radiolabeled somatostatin analogues with promissing results showing a better relation tumor/health tissues uptake. In this manner tumor heterogeneity seems to be a predictor of outcome in patients selected to PRRT. In a "theranostic" approach, assessment of textural parameters may help in selecting patients who might benefit from combined PRRT [31,39,42,43].

In a recenty study it was evaluated the low response to PRRT in some patients with MTC. They observed that if the patients were referred to PRRT after a ^{68}Ga-DOTATOC PET/CT some lesions may

be diagnosed but will not be treated with ^{177}Lu-DOTATATE as ^{68}Ga-DOTATOC shows a very high affinity for SSTR 2 and 5, while ^{177}Lu-DOTATATE has high affinity for SSTR2 mainly. To solve this problem it was developed [^{111}In,^{90}Y-DOTA]-1-Nal3-octreotide (^{111}In, ^{90}Y-DOTANOC) that shows high binding affinity to SSTR2, SSTR3, and SSTR5. These findings are probably due to selective SSTR3 and 5 expression rather than type 2 in some of MTC patients. Another speculation, although unlikely, could be the occurrance of stunning effect because of the pre-dose PET/CT scan before PRRT [44].

The use of combined therapy of chemotherapy and PRRT is now a reality. The clinical trials have shown that it may lead to increased anti-tumoral efficacy and another way to improve PRRT. The first study of success and that was proven to be safe evaluated the use of 5-fluorouracil (5-FU) and PRRT. After that, a randomized trial was made to evaluate the use of PRRT with ^{177}Lu combined with capecitabine in patients with gastroenteropancreatic neuroendocrine tumors. They demonstrated tumor control and stabilization in 94% of the 33 included patients. Three patients had to discontinue the chemotherapy due to angina capecitabine-induced (grade 3 side effect), but were able to complete the PRRT cycles. These are important issues as we can expect similar results in MTC. Other studies were published using capecitabine and ^{90}Y radioimmunotherapy and ^{111}In-octreotide radiopeptide therapy [31,39,42].

Although these promissing results after PRRT are encouraging, complete remission is rare and eventually recurrence can be observed. Retreatment with PRRT as salvage therapy may be considered, with no additional serious side effects, when better alternatives are not available [39,42].

The best advocated for these patients is the combination of the screening with scintigraphy or PET/CT using somatostatin receptor and ^{123}I-MIBG in order to determine which radionuclide therapy is the best according to the tumor caractheristics [9,37].

Post PRRT Side Effects

Most usual side effects observed post PRRT treatment are consider mild and auto-limited and rarely are observed grades 3 and 4 (WHO criteria) of toxicity. Nausea or, more rarely, vomiting is related to the concomitant administration of nephro-protective amino acids. More subacute side effects are related to the radiopeptide itself, such as fatigue, hematologic or renal toxicity, mild hair loss (observed with peptides labelled with ^{177}Lu), impairment of male fertility or, more rarely, an exacerbation of a pre existing clinical disease [31,39,42,43,44].

The hematological toxicity, occurring within 4-6 weeks after therapy, of grades 3 or 4 of leucocytes, granulocytes, or platelets is usually transient when it occurs [31,39,42,45].

Myelotoxicity is a rare condition and long-term serious side effect after PRRT and is mostly due to bone marrow suppression after high doses of PRRT where the estimated radiation dose for bone marrow is 3 Gy [39]. Besides that most patients demonstrating toxicity had pre existent risk factors [39].

It is described that toxic renal failure can occur from two to five months or up to several years after therapy [39,42]. With properly renal protection cases of acute severe, end-stage, renal damage are currently very rare. However, despite kidney protection, loss of kidney function can occur after PRRT, with a creatinine clearance loss of about 3.8% per year for ^{177}Lu-octreotate and 7.3% per year for ^{90}Y-DOTATOC [39].

Most of the reported serious side effects of PRRT are probably due to heavily pre-treatment these patients were exposed to. In this manner these events are rare and the causal relationship with PRRT may be controversial [39,42,45].

PRRT Response and Quality of Life after treatment

Several studies were performed to evaluate the efficacy of PRRT using ^{177}Lu and/or ^{90}Y. Most studies show that when different protocols of ^{90}Y-DOTATOC treatment are used, the response to treatment increases up to 4–33%, much better rates when compared to other therapies, including therapy with ^{111}In-DTPA-octreotide [34,39,42]. In some studies up to 78% of success (remission or stabilization) was observed is patients who received the whole planned therapy regimen [39,42]. However differences in treatment protocols such as cycle doses and administered cumulative activities, as well as differences in patient characteristics (included tumor types, patient performance status, tumor sizes) make it virtually impossible to compare these studies.

Regarding quality of life Vaisman et al. [34] showed that eventhough a small number of patients with MTC were evaluated all the responders had improvement in global health status and pain after PRRT with ^{177}-Lu-octreotate. In other studies theses results were corroborated as a significantly improvement after therapy with ^{177}Lu-DOTATATE was observed [34].

To our knowledge there is a lack of information about median Progression Free Survival (PFS) and median Overall Survival (OS) after PRRT in patients with MTC.

Other systemic therapies

Medullary thyroid cancer is a highly vascular tumor and has an increase expression of vascular endothelial growth factor (VEGF) which is assciated with invasiveness and cell proliferation. In recent years, some drugs that inhibit VEGF receptors showed antiproliferative effects on metastatic lesions leading to stabilization or even shrinkage of previously progressive disease. There are two phase III trials [45,46] showing that PFS was better in patients taking Vandetanib vs placebo (30.5 vs 19.3 months, $p<0.001$) and Cabozatinib vs placebo (11.2 vs 4 months, $p<0.001$). Those 2 drugs have been recently approved by FDA for progressive metastatic medullary thyroid cancer. However, none of these treatments were able to promote complete remission and cure of the disease and had some important side effects such as ECG alterations, diarrhea and hypertension [45,46]. PRRT was also effective in stabilizing disease in SSTR positive patients with fewer side effects [34]. Further studies are needed to clarify if maybe PRRT could be used as an option for SSTR positive patients, in early stage of progression, before systemic therapy.

Conclusion

Nuclear medicine techniques are very promissing as they can be used for diagnosis, to select the patient for the best therapy and also individualize therapy for MTC metastatic disease. These techniques became more accurate over the past years due to the possibility to combine functional images with CT scans and MRI, and the discovery of new radiopharmaceuticals.

Furthermore, there is no curable treatment for these patients until today and most of the approved therapeutic options carry a very large and potentially fatal profile of side effects that dismisses quality of life. Based on the tumor biology, some patients might benefit from PPRT with fewer side effects and a possible improvement in quality of life. Future studies are needed to evaluate long term outcomes such as the impact in PFS and OS in these group.

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