

## Management of Advanced Medullary Thyroid Carcinoma

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### ABSTRACT

Thyroid cancer is a common endocrine tumor that is somewhat on the increase in the United States. Medullary thyroid carcinomas are relatively uncommon thyroid malignancies. Despite the fact that medullary thyroid carcinoma is considered to be a rare disease, it is the subject of prolific research activity. Approximately three-fourths of cases of medullary thyroid carcinoma are sporadic, one-fourth is hereditary and may be a part of a multiple endocrine neoplasia 2A, 2B or a familial medullary thyroid carcinoma without associated endocrinopathies. Altered molecular pathways in tumoral cells contribute to the progression of the disease. There is no curative treatment for advanced medullary thyroid carcinoma. Currently, two new multi-tyrosine kinase inhibitors have been approved by the United States Food and Drug Administration and the European Medicines Agency. Both are recommended for the systemic treatment of selected patients with MTC. Patients who cannot benefit from multi-tyrosine kinase inhibitors could be incorporated in clinical trials using other targeted therapies. The over-expression of cholecystokinin type "brain" receptors, renamed by an International Union of Pharmacology committee as cholecystokinin type 2 receptors, was found in medullary thyroid carcinoma. Because of the fact that scintigraphy or positron emission tomography scans and peptide receptor radionuclide therapy match these type of receptors,

they could be used in alternative diagnostic procedures and targeted therapy.

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**Key words:** Medullary thyroid carcinoma; Tyrosine kinase inhibitor; Peptide receptor radionuclide therapy

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### INTRODUCTION

Thyroid cancer is the fastest-increasing cancer in both genders in the United States. 60,220 new cases were expected in 2013<sup>[1]</sup>. Risk factors for thyroid cancer are: history of goiter, thyroid cancer in the family, exposure to radiation in childhood, being female, rare genetic syndromes and abnormal genes<sup>[1]</sup>. Medullary thyroid carcinoma was described for the first time in 1959 by John B. Hazard *et al*<sup>[2]</sup>. They reported the presence of 21 cases of MTCs among 600 thyroid carcinomas removed surgically between 1926 and 1957 at Cleveland Clinic in Ohio. MTC represents 3.5% of all reviewed cases of thyroid carcinomas<sup>[2]</sup>, and is considered as a rare disease. The prevalence of MTC in the European Union is 1/14,300<sup>[3]</sup>. Despite this fact, MTC is today at the centre of prolific research activity.

### DIAGNOSIS OF MTC

MTC is usually present as a thyroid nodule<sup>[4]</sup> or a palpable cervical lymph node. The functional status of the thyroid nodule is inactive or "cold" during radioactive iodine scanning, because MTC derives from parafollicular thyroid cells which synthesize and secrete calcitonin (Ct) taking their origin from transformed neural crest-derivating C-cells. The diagnosis of MTC can be made by fine-needle aspiration biopsy (FNAB) followed by detection of amyloid and if necessary by Ct immunohistochemical staining. Ct is

considered as a tumor marker of MTC in preoperative screening and postoperative follow-up<sup>[5-7]</sup>. Routine screening of Ct should be included in the diagnostic management of a thyroid nodule<sup>[8]</sup>. Risk for MTC was estimated as extremely high when the value of basal serum calcitonin (bCt) is up to 100 pg/mL<sup>[6-7]</sup>. Approximately three-fourths of cases of MTC are sporadic, one-fourth is hereditary and may be a part of Multiple Endocrine Neoplasia (MEN) 2A, MEN 2B or Familial MTC (FMTC) without associated endocrinopathies<sup>[6]</sup>. In molecular diagnosis of MTC the presence of Rearranged during Transfection (RET) pro-oncogen germline or somatic mutation should be always investigated<sup>[9]</sup> because in hereditary MTC, RET germline mutation is found in 100% of cases and in sporadic MTC, RET somatic mutation is found in 40% of cases<sup>[9]</sup>. The behaviour of the MTC depends on its molecular profile<sup>[10]</sup>. In sporadic MTC, RET (M918T, exons 16, 10, 11) screening should be performed. If it proves negative, RAS (H-and K-RAS) somatic mutation should be also investigated<sup>[9]</sup>.

## TREATMENT OF MTC

Treatment of MTC can be surgical, systemic or both. Thyroidectomy with central compartment and ipsilateral or bilateral lateral neck dissection is the appropriate surgical treatment for MTC. Dralle and Machens<sup>[11]</sup> recommended performance of an ipsilateral lateral neck dissection with a bCt level of 20-200 pg/mL and a bilateral dissection with a bCt level of up to 200 pg/mL. Before the presence of any detectable MTC is established, prophylactic thyroidectomy could be indicated after early screening by genetic testing. According to some authors, prophylactic surgery should be performed for patients with RET mutation codons 883 (at 1 month of age), 918 (at 6 months of age), 611, 618, 620, 634 (at 5 years of age), 609, 630, 768, 790, 791, 804 and 891 (at 10 years of age)<sup>[12]</sup>. The American Thyroid Association has recommended a list of RET mutations codons and, accordingly, a treatment timetable for each of them<sup>[13]</sup>.

## PROGRESSION OF THE DISEASE AND DIAGNOSIS OF RECURRENT MTC

Among the molecular pathways that contribute to MTC tumorigenesis, heterogeneous RET mutation has been described as an important factor in the progression of the disease<sup>[14]</sup>. Tyrosine kinase receptors (TKRs) such as Epidermal Growth Factor Receptor (EGFR), Vascular Endothelial Growth Factor Receptor (VEGFR) and Hepatocyte Growth Factor Receptor (HGFR) encoded by c-MET are implicated in MTC progression<sup>[15]</sup>. Some authors have reported a frequency of 7-23% of MTC with distant metastases at first clinical presentation<sup>[13]</sup>. One to two thirds of MTC patients present clinically or radiologically recurrent disease within 10 years following initial treatment<sup>[16-17]</sup>. An increase in micro-MTCs has also been described in the literature<sup>[18]</sup>. MTC metastasizes generally in the lung, liver, bones and brain. Pain, fracture or spinal cord compression could occur with bone metastases<sup>[19]</sup>. Patients with increased bCt level during postoperative follow-up are highly suspect for recurrence of the disease and should be further investigated. CEA is the other strong tumor marker used during follow-up. However, according to some authors, surgical procedures may also induce an increase in serum doubling the times of both tumor markers<sup>[20]</sup>. A combined approach with 18F-FDG PET/CT and 18F-DOPA PET/CT or using 18F-DOPA PET/CT alone are currently the most appropriate form of investigation for detecting recurrent MTC with elevated tumor markers<sup>[21-25]</sup>.

## CURRENT TREATMENTS OF ADVANCED AND/OR SYMPTOMATIC MTC

The available treatments used for distant metastatic MTC are not curative. Vandetanib, a new multi-tyrosine kinase inhibitor (multi-TKI), is currently the systemic therapy of choice in advanced MTC. Patients with a significant MTC burden and symptomatic or progressive MTC are candidates for treatment with multi-TKIs<sup>[26]</sup>. Wells *et al*<sup>[22]</sup> reported in their randomized double-blind phase III trial that progression-free survival (PFS) rates was 30.5 months in patients treated with Vandetanib and 19.3 months in patients treated with placebo (Table 1). RET, VEGFR-2 and 3 and EGFR are targeted by this new multi-TKI. Pathways involved in tumor growth and angiogenesis are selectively inhibited by Vandetanib. Vandetanib is generally well tolerated<sup>[27]</sup>. The most important reported side-effect of Vandetanib was a prolongation of the ECG QT interval. For this reason patients need monitoring during treatment in order to detect an ECG QT prolongation. Other targeted therapies using TKIs are evaluated in ongoing clinical trials (19, table 1). Recently, Elisei *et al* reported in their phase III study that PFS was 11.2 months in patients treated by Cabozantinib and 4 months in patients treated by placebo (29, table 1). Key targets of Cabozantinib are RET, MET and VEGFR-2. Others authors also reported that treatment by Cabozantinib was effective in two patients with metastatic MTC. However they found that lower doses of Cabozantinib might be needed due to side-effects in order to improve tolerability of the therapy<sup>[28]</sup>. In their phase II study, Schlumberger *et al* reported that median PFS was 11 months in patients treated with Motesanib (TKI); Lam *et al* reported that median PFS was 17.9 months in patients treated with Sorafenib (TKI); De Souza *et al* reported that median PFS was 7 months in patients treated with Sunitinib (TKI) (Table 1).

**Table 1** Main kinase inhibitors in the treatment of medullary thyroid carcinoma.

Reference	Treatment modality	Efficacy (PFS in mths)	Drug approval	Type of study	Patient (N)
Wells <i>et al</i> <sup>[22]</sup>	Vandetanib vs Placebo	30.5 vs 19.3	FDA/EMA <sup>1</sup>	phase III	331
Elisei <i>et al</i> <sup>[29]</sup>	Cabozantinib vs Placebo	11.2 vs 4	FDA/EMA <sup>1</sup>	phase III	330
Schlumberger <i>et al</i> <sup>[30]</sup>	Motesanib	11	-/-	phase II	91
Lam <i>et al</i> <sup>[31]</sup>	Sorafenib	17.9	-/-	phase II	15
Capdevila <i>et al</i> <sup>[32]</sup>	Sorafenib	10.5		retrospective	34
De Souza <i>et al</i> <sup>[33]</sup>	Sunitinib	7	-/-	phase II	25

PFC: progression free survival; mths: months; N: number of patients; FDA: food and drug administration of the United States of America; EMA: european medicines agency.

<sup>1</sup> conditional approval by european medicines agency; -/- no yet approved.

## RESEARCH AND INVESTIGATIONAL TREATMENTS OF ADVANCED MTC

Research activities are focused on other possibilities of metastatic MTC treatment of which the efficacy and toxicity have to be evaluated.

### Phytochemicals

Withaferin A (WA), a natural product withanolide, showed anti-cancer activity through multiple cytotoxic mechanisms and also has potential therapeutic effects against neuro-degenerative and inflammatory diseases<sup>[34]</sup>. Some authors in their pre-clinical studies

used WA to demonstrate possible therapeutic effects in MTC treatment *in vitro* and *in vivo*. According to their findings, RET inhibitor activity of WA in MTC was observed<sup>[35]</sup>. Another group reported that WA used *in vitro* against anaplastic and papillary thyroid carcinomas in combination therapy with Sorafenib procured synergistic efficacy and less toxicity<sup>[36]</sup>. As mentioned above, Sorafenib was also evaluated in an ongoing clinical trial for treatment of progressive metastatic MTC<sup>[19]</sup>.

**Anticarcinoembryonic Antigen Pre-targeted Radioimmunotherapy (pRAIT)**

During pRAIT, a bispecific monoclonal antibody (BsmAb) was first administered and bound to the surface of targeted tumor cells expressing CEA. A couple of days later a radio-labeled bivalent hapten was also injected in order to attach to the BsmAb. The non-targeted radioactive hapten localized in the circulation was rapidly washed out through the kidneys. pRAIT safety and efficacy will be improved by using new-generation trivalent BsmAb (anti-CEA TF2) and histamine-succinyl-glutamine (HSG) peptides. A prospective study phase II proved efficacy of this therapy in progressive metastasized MTC. Eligible patients for pRAIT should be those with a poor prognosis because of the significant hematotoxicity of this treatment<sup>[37]</sup>.

**Peptide receptor radionuclide therapy (PRRT/PRRT)**

A very high incidence (92%) and density of CCK-B receptors was found in MTC<sup>[38]</sup>. CCK-B receptors were also expressed in stromal ovarian cancers (100%), astrocytomas (65%) and small cell lung cancers (57%)<sup>[39]</sup>. According to the high incidence and density of CCK-B receptors and radiosensitivity of the tumor, patients with MTC are most eligible for PRRT<sup>[40]</sup>. Béhé and Behr reported partial remission in two human volunteers and stabilization of the disease in four human volunteers with advanced and rapidly progressing MTC treated by 90-yttrium-labeled minigastrin derivative (90-Y-DTPA-MG0). In this study CCK-B receptors were targeted. However two patients developed nephropathy 1-2 years after PRRT (41, table 2). Radionuclide 111-indium which showed less toxicity to kidneys was used instead of 90-yttrium in other preclinical studies. Fast and effective tumoral uptake, low retention in normal tissues and stability represent the criteria for eligibility of CCK receptor-targeting peptides<sup>[42]</sup>. According to committee of the International Union of Pharmacology regarding receptor nomenclature and drug classification, the CCK-A receptor and the CCK-B receptor have been renamed CCK1 receptor (CCK1R) and CCK2 receptor (CCK2R), respectively. A somatostatin receptor subtype 2 (sst2) is expressed on the surface of the tumor cells in MTC and also represents a target for PRRT. Iten *et al* reported in their phase II clinical trial benefits

in long term survival in patients with metastasized MTC treated by (90Yttrium-DOTA)-TOC. Nine patients responded to PRRT, while 22 had no response (43, table 2). Budiawan *et al* illustrated in their study a partial remission in a patient with inoperable progressive MTC treated by (90Yttrium-DOTA)-TOC and (177Lu-DOTA)-TOC. They also reported stabilization of the disease in four patients and progressive disease in one patient (44, table 2). Bodei *et al* reported in their retrospective study complete remission in two patients treated by (90Yttrium-DOTA)-TOC, the response of which to PRRT was evaluated by conventional imagery (CT, MRI, US) and in one patient with follow-up using Ct. In the patients in which response to treatment was evaluated by Ct monitoring they found partial remission in five patients, stable disease in three patients and progressive disease in 12 patients. In patients evaluated by conventional imagery, they reported stable disease in 12 patients and no response in seven patients (Table 2).

**DISCUSSION**

Using FNAB alone (low sensitivity of cytological evaluation alone) in preoperative diagnosis of MTC could have an impact on preoperative evaluation and initial surgery in more than 50% of patients with MTC<sup>[45]</sup>. Screening of Ct should also be investigated<sup>[8]</sup>. Ct was used as a tumor marker of MTC in preoperative screening and postoperative follow-up<sup>[5-7]</sup>. Risk of MTC was estimated as extremely high with a value of basal serum calcitonin (bCt) >100 pg/mL. Patients with increased basal serum Ct level during the postoperative follow-up are highly suspect for recurrence of the disease and should be further investigated<sup>[5,7,8]</sup>. High basal serum Ct (bCt) level is not pathognomonic for MTC (normal limit: <10 pg/mL)<sup>[6,7]</sup>. CEA is the other strong tumor marker used during follow-up. A combined approach with 18F-FDG PET/CT and 18F-DOPA PET/CT was considered as currently the most appropriate investigation in detecting recurrent MTC with elevated tumor markers. 18F-FDG PET/CT may complement 18F-DOPA PET/CT in patients with aggressive MTC<sup>[21-25]</sup>. Patients may be selected by PET with a somatostatin analogue labelled with gallium-68 for PRRT targeting somatostatin receptors<sup>[23]</sup>. Budiawan *et al*<sup>[44]</sup> reported in a clinical study that 68Ga-DOTA-NOC PET/CT and 177Lu-DOTA-NOC PET/CT were used in order to evaluate the somatostatin receptor density and treatment response in patients with residual/metastatic MTC. Gotthard *et al*<sup>[46]</sup> reported in a clinical study that gastrin receptor scintigraphy (GRS) was more effective in detection of MTC than somatostatin receptor scintigraphy (SRS) and 18F-FDG PET/CT. In pre-clinical studies Von Guggenberg *et al*<sup>[47]</sup> demonstrated that cyclic DOTA-minigastrin analogs are promising candidates for gastrin receptor scintigraphy and targeted radionuclide therapy. 68Ga-

**Table 2** Main studies of PRRT in the treatment of advanced medullary thyroid carcinoma.

Reference	Treatment modality/ type of study	Trageted receptor/analogue used	Response CR/PR/SD (N)	NR/PD (N)	Patients (N)/evaluation modality
Béhé, Behr <sup>[41]</sup>	PRRT	cckB/90Y- labeled minigastrin derivative	-/2/4	-/-	8/ cckB receptor scintigraphy
Bodei <i>et al</i> <sup>[56]</sup>	PRRT/retrospective	sst/90Y-DOTATOC	2/-/12	7/-	21/ CT, MRI or, and US
	PRRT/retrospective	sst/90Y-DOTATOC	1/5/3	-/12	21/ calcitonin
Budiawan <i>et al</i> <sup>[44]</sup>	PRRT	sst/90Y- or/ and 177Lu-DOTATATE	- /1/4	-/1	8/ 68Ga sst receptor PET/CT
Iten <i>et al</i> <sup>[43]</sup>	PRRT/phase II	sst/90Y-DOTATOC	9	22/-	31/ calcitonin
GRAN-T-MTC <sup>[55]</sup>	PRRT/phase I <sup>1</sup>	cck2-gastrin/ 111In-(CPO4)	NA	NA	NA/ cck2 receptor scintigraphy

PRRT: peptide receptor radionuclide therapy; CR: complete response; PR, partial response; SD: stabilization of disease; NR: no response; PD: progression of disease; N: number of patients; cck: cholecystokinin; sst: somatostatin; CT: computed tomography scan; PET: positron emission tomography; MRI: magnetic resonance imagery; US: ultrasound; Y, yttrium; Lu: lutetium; In, indium; Ga: gallium; DOTATOC: dota 0-phe1-tyr 3 octreotide; DOTATATE: dota 0-tyr 3 octreotate; CP04: DOTA-DGlu-DGlu-DGlu-DGlu-DGlu-DGlu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH2; NA: not yet available; GRAN-T-MTC: acronym of the project.

<sup>1</sup> according to our knowledge not yet started; -: not evaluated.

DOTA-MG0 is considered as a promising tracer for PET imaging of CCK2/gastrin receptor-positive tumors, which is more effective than conventional scintigraphy<sup>[48]</sup>. Advanced MTC treatment is only palliative. The currently available therapy consists of treatment with the new multi-TKIs. Patients with a hereditary or sporadic form of MTC can both benefit from Vandetanib (TKI) whether the sporadic form of MTC is M918T positive or negative. However, PFS analyses according to the RET mutation status are still controversial, thus causing uncertainty about the degree of benefit in patients with negative or unknown RET mutation status<sup>[27]</sup>. PRRT could represent promising alternative targeted therapy for progressive MTC. PRRT targeting somatostatin receptors has been used for over 15 years as an investigational treatment of neuroendocrine tumours (NETs). Nevertheless, PRRT is still not approved by the U.S. Food and Drug Administration (FDA). Bodei *et al.*<sup>[49]</sup> reported less favourable results in PRRT targeting somatostatin receptors in treatment of MTC and dedifferentiated thyroid carcinomas. Some authors estimated that PRRT will be approved by the European regulatory body as a treatment of NETs within three years<sup>[50]</sup>. According to the high incidence and density of CCK-B receptors (CCK2R) and radiosensitivity of the tumor, patients with MTC could be the most eligible for PRRT<sup>[40]</sup>. However, Bläker *et al.*<sup>[51]</sup> reported that CCK2R expression was not detected in advanced T3-, T4- and Mx-tumor stages. According to their study, they reported that CCK2R were expressed only in non-metastatic T1- and T2-stage tumors. In another study, the case of a patient with metastasized MTC was reported showing negative GRS and pentagastrin test despite high serum bCT level. The authors of this study thought that in this case CCK2Rs are missing or cannot bind gastrin agonists. In the same study, they also observed that GRS had detected distant metastasis in a patient with MTC and claimed that GRS in combination with CT was more effective than SRS. According to their opinion, CCK2R seemed to be expressed even in cases of MTC dedifferentiation<sup>[46]</sup>. PRRT could lead to nephropathy because of high absorbed doses delivered to the kidneys. Co-infusion of renal-protective agents such as positively charged amino-acids is mandatory during PRRT<sup>[52]</sup>. Thanks to the work of COST action BM0607 of the European Union, three optimal peptides (PP-FM, MGD5, cyclo-MG1) have been designed for peptide receptor radionuclide targeting of CCK2/gastrin receptor-expressing tumors, because of their low renal uptake and high accumulation in the tumor<sup>[53]</sup>. In Lausanne, Switzerland, a prospective clinical study was made to prove the feasibility of 3D radiobiological dosimetry treatment planning of PRRT in order to reduce nephrotoxicity<sup>[54]</sup>. CCK2-related peptides used in targeted therapy continue to be studied. A promising phase I clinical trial using a novel CCK-2/gastrin receptor-localizing radiolabelled peptide probe for both diagnosis and treatment of metastatic MTC is ongoing (55, table 2). Conventional chemotherapy regimens with Doxorubicin, Dacarbazine, Capecitabine and Fluorouracil have demonstrated only limited efficacy in patients with MTC. Tumor response in patients treated by different protocols using cytostatic drugs was reported, but no benefit was found for survival<sup>[57]</sup>.

## CONCLUSION

There is no curative treatment for advanced MTC.

Conventional chemotherapy protocols have showed only limited efficacy in patients with MTC and no benefit was found for survival.

Currently, the new TKIs that received approval from the U.S. Food and Drug Administration and European Medicines Agency are considered as the first-line systemic treatment for progressive MTC. Patients with advanced MTC who cannot benefit from approved TKIs

could be incorporated in clinical trials using other targeted therapies. Because of the over-expression of CCK2 receptors in MTC (incidence and density over 90%) scintigraphy or PET/CT and PRRT targeted CCK2 receptors could represent promising alternative diagnostic tools and therapy.

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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