Acta Clin Croat (Suppl. 1) 2020; 59:50-59

doi: 10.20471/acc.2020.59.s1.06

Review

MEDULLARY THYROID CANCER – FEATURE REVIEW AND UPDATE ON SYSTEMIC TREATMENT

Nina Dabelić[1], Tomislav Jukić[1,2] and Ana Fröbe[1,3]

[1]Department of Oncology and Nuclear Medicine, Sestre Milosrdnice University Hospital Centre, Zagreb, Croatia;
[2]University of Zagreb, School of Medicine;
[3]University of Zagreb, School of Dental Medicine

SUMMARY – Medullary thyroid carcinoma (MTC) is a rare malignancy that originates from parafollicular (C cells) of the thyroid and accounts for 2-4% of all thyroid malignancies. MTC may be sporadic or inherited, the latter as part of the MEN 2 syndromes. Germline mutations in the *RET* proto-oncogene (REarranged during Transfection) are driver mutations in hereditary MTC, whereas somatic *RET* mutations and, less frequently, *RAS* mutations, have been described in tumor tissues of sporadic MTC. Genetic screening for germline mutations in *RET* proto-oncogene identifies gene carriers of germline mutations. That enables primary prevention (the avoidance of disease onset by total prophylactic thyroidectomy), or at least secondary prevention (early detection) of the disease. Radical surgery with complete tumor resection is still pivotal in attaining cure for MTC. Despite recent advances, the treatment of advanced, metastatic, and progressive MTC remains challenging. Metastatic MTC can have an indolent clinical course; therefore, it is necessary to assess which patient to cure and when to initiate the treatment. Multidisciplinary boards of various specialists involved in the diagnostics and therapy of the patients with MTC in highly specialized centers with a high volume of patients provide optimal patient management. Multikinase inhibitors (MKI) vandetanib and cabozantinib were approved for the treatment of progressive or symptomatic metastatic/unresectable MTC. Although these treatments have been shown to improve progression-free survival (PFS) with higher overall response rates (ORR) compared with placebo, no MKI has been shown to increase the overall survival (OS) yet, except in the subgroup of patients with *RETM918T*-mutations on cabozantinib therapy. As these drugs are nonselective, significant off-target toxicities may occur. Recently, next-generation small-molecule tyrosine kinase inhibitors (TKIs) have been developed. These highly selective RET-inhibitors are specifically designed for highly potent and selective targeting of oncogenic RET alterations, making them promising drugs for the treatment of advanced MTC. The selective RET-inhibitor selpercatinib has been very recently registered for the treatment of *RET*-mutated thyroid cancer.

Keywords: medullary *thyroid cancer; RET proto-oncogene, molecular targeted therapy; treatment; update*

Introduction

Epidemiology

Medullary thyroid carcinoma (MTC) is a rare type of thyroid malignancy and a member of the neuroendocrine type of tumors. MTC arises from parafollicular cells, or C cells, derived from the neural crest, which produce calcitonin, which serves as a specific MTC-tumor marker, as well as some other peptides, including carcinoembryonic antigen (CEA) which is used as a non-specific tumor marker in MTC.

MTC accounts for less than 5% (2-4%) of all thyroid cancers[1]. According to current SEER (Surveillance, Epidemiology, and End Results) data, medullary thyroid carcinoma accounts for 1-2% of thyroid cancers in the United States, which is much lower than

Correspondence to: *Nina Dabelić*, Dpt of Oncology and Nuclear Medicine, Sestre Milosrdnice University Hospital Centre, Vinogradska 29, 10000 Zagreb, Croatia
E-mail: nina.dabelic@kbcsm.hr

previously cited, primarily due to the significant increase in the relative incidence of papillary thyroid carcinoma (PTC) over the last several decades[2].

MTC mostly occurs in the fifth or sixth decade of life when sporadic, but earlier in the cases of hereditary disease. MTC is extremely rare in children, except for the hereditary forms, making the probability of a hereditary form very high. In contrast with thyroid epithelial cell tumors, the female to male ratio is nearly equal.

Approximately 35% of patients with MTC with palpable thyroid nodules have cervical metastases. Roughly 10% (7-23%) have distant metastases at disease presentation[3]. However, distant metastases appear during follow-up in approximately 20-40% of patients with MTC. Distant metastases are the leading cause of MTC-related death[4]. Recent data shows lower disease-specific mortality rates, probably due to earlier discovery of metastatic disease[5]. The reported 10-year MTC-related mortality rates vary from 13.4% to 38.0%[5].

The stage of the disease at diagnosis and the possibility of radical surgical resection are the most important factors in achieving cure in MTC. The classical main prognostic factors in MTC are age, tumor size, local and distant metastases, somatic M918T mutations, calcitonin, and CEA doubling times[6].

Etiology

Inherited tumors are part of the MEN2 syndromes, which are transmitted in families as autosomal dominant traits due to activating germline point mutations of the *RET* proto-oncogene.

The predominant driver mutations in MTCs are *RET* (REarranged during Transfection) and *RAS* proto-oncogene mutations that are detected in approximately 90% of MTCs[7]. *RET* mutations can occur sporadically as somatic mutations in tumor tissue or can be inherited as germline mutations[8]. In the latter case, they are associated with hereditary MTCs.

Patients with MEN2A syndrome can have medullary thyroid cancers, pheochromocytomas, and parathyroid hyperplasia or adenomas. Previously considered a separate entity, FMTC (familial medullary thyroid cancer) is today considered a variant of MEN2A syndrome. Patients with MEN2B have medullary thyroid carcinoma, mucosal neuromas, pheochromocytomas which are usually bilateral and often malignant, occasionally *cafe-au-lait* spots, and possibly Gardner's syndrome (mucocutaneous pigmented nevi and small intestinal polyps). Some of these features result in a distinct phenotype known as marphanoid.

Germline mutations of the *RET* proto-oncogene cause hereditary cancer, whereas somatic *RET* mutations are frequently present in sporadic MTC tumor tissues. *RET* encodes a transmembrane receptor; point-activating *RET* mutations promote continuous phosphorylation of a distinct set of tyrosine residues, triggering intracellular signaling pathways responsible for cell survival, differentiation, and proliferation. *RET* is activated by point mutation in MTC, as opposed to PTCs (papillary thyroid cancer) where it is activated by chromosomal rearrangement.

In FMTC, germline mutations in specific functional regions of *RET* are found in almost all patients. In MEN 2A and FMTC, mutations are typically located within the cysteine-rich region in the extracellular domain. Almost 90% of MEN 2A mutations are present in a single codon, codon 634. In contrast, in FMTC they are more evenly distributed along the cysteine-rich region. In MEN 2B, the vast majority of germline mutations occur in the intracellular tyrosine kinase domain of *RET,* in codon 918.

In sporadic MTCs, somatic mutations of the *RET* gene in tumor tissue can be detected in approximately 50% (20-80%) of patients. Almost all of those affect codon 918, although they have also been identified in a few other gene regions. Mutations in this codon 918 are thought to be a predictor of a poor prognosis[9].

Germline *RET* mutations, either *de novo* or in previously unrecognized families with hereditary MTCs, can be present in patients with apparently sporadic MTCs. Therefore, screening for germline *RET* mutations and genetic counselling should be offered to all newly diagnosed patients with MTC.

If germline *RET* mutation in a patient with MTC is detected, screening for *RET* oncogene mutation in the blood is the first step in family members at risk[10]. Neck ultrasound and calcitonin measurements are indicated in mutation carriers to assess the possible presence of the disease. Every mutation carrier with either a thyroid mass or elevated calcitonin levels should receive an immediate thyroidectomy. If no thyroid nodule is detected and the serum calcitonin is normal according to the reference range for the specific age

group, prophylactic thyroidectomy should be considered at the appropriate age, depending on the mutation type found (usually according to the ATA-criteria) in order to take out the thyroid gland before the disease is initiated[11]. The recommended age for total prophylactic thyroidectomy in carriers of germline *RET* mutations varies depending on the type of mutation. The most aggressive germline *M918T* mutation requires total thyroidectomy as early as within the first year of life. Surgery can be postponed until age five in high-risk *C634F* and *A883F* mutations, unless there is an increase in calcitonin levels. Carriers of other mutation types should be monitored from age five onwards by measuring calcitonin levels and performing neck US, and prophylactic thyroidectomy may in some cases even be avoided or at least postponed to a more mature age; the decision should be made based on genetic counselling of the parents[12].

In MEN2A, the tumors follow a rather benign course somewhat similar to that of follicular cancer and can usually be controlled by surgery. MEN2B tumors are much more aggressive and often cause death in the second or third decade of life[13].

MTCs caused by specific germline *RET* mutations have a very different median age of disease onset (but mostly occurring from early childhood to early adulthood, depending on the driver mutation), as well as different tumor aggressiveness. MTCs, as part of the MEN 2B syndrome, are very aggressive malignancies. In contrast, hereditary MTCs as part of MEN 2A syndrome (including FMTC) have a more indolent clinical course compared with the sporadic MTCs[14]. However, if somatic RET mutations, especially RET M918T, are present in sporadic MTCs, their biologic behavior is more aggressive compared with the ones without it[15].

Clinical presentation

Hereditary MTC is usually multicentric, bilateral, and associated with C-cell hyperplasia, while sporadic MTC is unicentric and unilateral.

Approximately 35% of patients with MTC with palpable thyroid nodules already have cervical metastases. Roughly 10% (7-23%) have distant metastases at disease presentation[3]. However, distant metastases appear during follow-up in approximately 20-40% of patients with MTC and are the leading cause of MTC-related death. The symptomatic clinical disease will occur in approximately 30-60% of patients with MTC with evidence of persistent disease after initial treatment at different time intervals during the subsequent follow-up, depending on the persistent tumor volume and progression rate.

MTC biologic behavior varies widely; from indolent in some cases, to rapidly progressive in others. Tumor marker doubling times can rather reliably predict biologic behavior. Currently approved systemic therapies for MTC still do not provide prolongation of overall survival. Therapy should be initiated in symptomatic disease, lesions close to vital structures, high-tumor burdens, and/or rapid (within one year) disease progression on imaging (as defined by RECIST 1.1 criteria)[16,17].

Advanced MTC is associated with the secretion of the variety of peptides (serotonin, histaminase, vasoactive intestinal peptide, prostaglandins, kinins, etc.) causing clinical symptoms such as flushing or diarrhea that disrupt patient quality of life and needing management.

In inherited MTC, symptoms related to other endocrine neoplasia within MEN2 syndromes can appear and should be treated accordingly.

Diagnosis

In pathology, MTC is sometimes referred to as "the great mimic" because of its morphological heterogeneity and the ability to resemble virtually all other primary thyroid tumors. Therefore, calcitonin expression is mandatory for the pathohistological diagnosis of MTC.

Calcitonin and CEA serum levels have valuable diagnostic, prognostic, and predictive value as markers in MTC. Their serum concentrations directly correlate with the C-cell mass. Preoperative calcitonin levels strongly correlate to tumor diameter, while postoperative levels are a valuable indicator of the probable extent of the disease[18]. Calcitonin levels exceeding 500 pg/mL are suggestive of distant metastatic disease, and patients should be submitted to additional imaging diagnostics. Postoperative serum calcitonin should be measured 60-90 days after total thyroidectomy.

Patients that are considered "biochemically cured" with postoperative basal calcitonin levels within the normal range have a 10-year survival rate of 97.7%.

However, biochemical recurrence occurs within 7.5 years in about 3% of them.

Carcinoembryonic antigen (CEA) is a non-specific tumor marker for MTC. It is usually measured in gastrointestinal malignancies, and therefore MTC is sometimes discovered during follow-up of those patients as an incidental finding. However, the primary use of CEA in MTC is in monitoring for potential disease progression in already diagnosed and treated MTC.

Doubling times of the postoperative basal levels of tumor markers calcitonin and CEA are defined as the time intervals in which the marker levels have doubled, and have been established as prognostic markers in MTC[19]. Doubling times of tumor markers calcitonin and CEA accurately predict tumor behavior, recurrence rates, and cancer-related death. A calcitonin doubling time that exceeds six months is associated with a 5-year survival rate of 92% and 10-year survival rate of 37%. The prognosis in patients with MTC is much worse in patients with shorter doubling times: a 5-year survival rate of 25% and 10-year survival rate of 8%, respectively. However, in aggressive, progressive, and poorly differentiated MTCs, calcitonin values may actually decrease in time while the CEA levels and doubling time increases, the latter being often considered a more accurate predictor of rapidly progressive MTC.

Serial tumor marker levels measurements provide useful information on the doubling times. Calcitonin doubling times should be based on at least four consecutive measurements in the same laboratory using the same assay, preferably over a 2-year time period. Clinically relevant disease is rarely detected if calcitonin levels are below 150 pg/mL. However, increase in calcitonin and CEA levels raises the likelihood of structural disease[6].

Except for the tumor markers, diagnostic procedures used in the diagnosis, assessment of the therapeutic efficacy, and follow-up of MTC-patients may include, according to clinical findings: neck ultrasonography (US) with fine-needle aspiration (FNA) and calcitonin levels measurements in FNA-washouts, and contrast-enhanced CT or MRI of the neck and chest with US of the abdomen in suspicious findings[20]. Workup for distant metastases is indicated in suspicious clinical findings and/or serum calcitonin levels exceeding 500 pg/mL and may include CT and/or MRI of the chest and abdomen, bone scintigraphy, F-DOPA-PET/CT (if available, with high sensitivity and specificity for MTC, in contrast to FDG-PET/CT)[21]. Although FDG-PET/CT is not recommended in the staging of the indolent MTCs due to generally low avidity for FDG, it can be useful for assessing advanced, especially dedifferentiated and rapidly progressive disease[22].

Today, scintigraphy with 131-I-MIBG or tectrotide (octreotide) has less importance than in previous years. However, positive findings on 131-I-MIBG or expression of somatostatin receptors could prove as a therapeutic target in the absence of other, more effective therapeutic options or when they are exhausted. When the feasibility of radionuclide therapy is being explored, gallium-68 (^{68}Ga) somatostatin analogue PET/CT, as the newer imaging procedure than octreotide/tectrotide scintigraphy, can provide information of the expression of somatostatin receptors.

Screening for pheochromocytoma and hyperparathyroidism is necessary for the assessment and follow-up of all patients with confirmed or suspected MEN 2A syndrome until germline mutations are excluded.

MTC treatment

Surgical management – Total thyroidectomy with central (region VI) lymph node neck dissection is the surgical standard of care and the only curative treatment for MTC. Additionally, unilateral or bilateral cervical lymph node dissection is performed if needed, based on the imaging, serological (tumor markers), and/or intraoperative findings. Patients with recurrent local/regional disease in the neck and mediastinum are candidates for repeat neck surgery with either curative or palliative intent, and some patients may also benefit from external beam radiation therapy (EBRT)[5]. Surgery in patients with MTC should be performed by surgeons with substantial experience in this field, especially when lateral neck dissection is needed.

Radiotherapy – External beam radiotherapy (EBRT) is indicated in the presence of extensive local/locoregional disease, residual tumor, and/or extranodal tumor extension[23]. However, there is no evidence of the OS benefit with the addition of **adjuvant EBRT** in completely resected disease, only better locoregional disease control in patients at high risk of cervical re-

lapse. There is therefore no consensus on the indications for adjuvant EBRT.

Palliative radiotherapy has its role, especially in the presence of painful bone metastases and/or risk of pathologic fractures[24].

Systemic therapy

No effective curative therapeutic option exists for patients with locally/locoregionally advanced inoperable disease and/or distant metastases[25]. Unfortunately, **chemotherapy** regimens have only limited response rates, and the data from clinical studies on efficacy are insufficient, given the retrospective design, small patient cohorts, and the of robust evaluation response criteria such as RECIST. The most active drug has been doxorubicin, alone or in combination with cisplatin, which achieved the response rate of approximately 20%[26].

Upon planning the therapeutic strategy for metastatic MTC, one should keep in mind that metastatic MTC can have an indolent clinical course with a favorable long-term outcome; however, this is the case in only a portion of patients[27]. The others may have a rapidly progressing disease that requires immediate therapy and close follow-ups. Asymptomatic patients with low-burden indolent MTC can be followed-up without therapy. On the other hand, those with the symptomatic, high-burden, rapidly progressing disease, or with lesions associated with a high risk of serious complications (i.e. brain metastases, spinal cord compression, lesions compromising the airway, bone metastases with an imminent risk of pathologic fractures) require immediate therapy[17]. Multidisciplinary collaboration (including surgeons specialized in thyroid surgery, endocrinologists, nuclear medicine specialists, oncologists, pain therapists, and palliative care personnel) of specialists with high patient volume enables the optimal care for these patients[28].

In patients with progressive (within one year on imaging according to the RECIST 1.1 criteria) and/or symptomatic metastatic disease, **systemic therapy** with targeted agents – vandetanib or cabozantinib, tyrosine kinase inhibitors – is indicated. If possible, patients should be included in clinical trials[3].

Solitary or symptomatic metastases, especially in the liver or bone, should be considered for **local treatment** (surgery, cryo-, thermo-, or chemoablation, / chemo/embolization).

Embolization or ablation can be beneficial in selected cases in order to decrease tumor burden, pain, and even refractory diarrhea associated with liver metastases[29].

Symptomatic therapy is sometimes required, especially in cases of severe diarrhea. Diarrhea, a possible paraneoplastic symptom, may appear in patients with advanced MTC due to high levels of calcitonin, VIP, or increased intestinal motility. Antimotility agents, such as loperamide, may be used to ease the symptoms. In persistent diarrhea, somatostatin analogues can alleviate the symptoms. For patients with extensive liver metastases, various types of local liver-directed therapy may reduce the calcitonin levels and consequently symptoms of diarrhea. Only rarely, paraneoplastic Cushing's syndrome can occur (in 0.7% of cases) due to the secretion of ectopic hormones CRH or ACTH.

The management of advanced, metastatic, and progressive MTC remains challenging. Patients with distant metastatic disease have a 10-year overall survival rate of <40%, compared with 75% in patients with regional metastases and 96% of patients with localized disease[30].

Over the last decades, new insights into the signaling pathways and numerous genetic aberrations involved in the pathogenesis of cancer have led to the development and use of molecular targeted therapies[31].

Protein kinases, by catalyzing the phosphorylation of the tyrosine residues in proteins, activate various intracellular signaling pathways, cell proliferation, differentiation, migration, and anti-apoptosis. Consequently, uncontrolled tyrosine kinase receptor activation is one of the main mechanisms of development and progression of malignancies.

In normal parafollicular thyroid cells, signaling pathways such as RET, RAS/MAPK, PI3K, c-MET, and mTOR regulate the wide range of intracellular processes, such as cell proliferation, differentiation, migration, and apoptosis. Various molecular-driven abnormalities in these signaling pathways are involved in thyroid carcinogenesis.

RET is a type of tyrosine kinase receptor. Inhibition of the phosphorylation of the RET protein by tyrosine kinase inhibitor (TKI) can down-regulate its downstream targets in the signaling pathway, consequently causing inhibition of tumor growth.

Tyrosine kinase inhibitors (TKIs) may provide therapeutic benefit by blocking tyrosine kinase-dependent oncogenic pathways. TKIs may inhibit one or several tyrosine kinase receptors; the latter are often called multikinase inhibitors, MKIs.

TKIs are small molecules that specifically target and inhibit the tyrosine kinases. Since RET is a form of tyrosine kinase receptor, TKIs can inhibit the phosphorylation of the RET protein, consequently leading to downregulation of its downstream targets, with subsequent inhibition of tumor growth. Although multikinase inhibitors inhibit *RET* kinase activity to some extent, their antitumor effect is mainly achieved by their strong inhibition of the key angiogenic pathway components, especially vascular endothelial growth factor receptor (VEGFR).

In the management of MTC, numerous MKIs have been evaluated in clinical trials (axitinib, apatinib, cabozantinib, gefitinib, imatinib, lenvatinib, motesanib, pazopanib, sorafenib, sunitinib, vandetanib); however, results are variable[32-36]. The majority of clinical studies reached phase 2, resulting mostly in the stabilization of the disease, while partial response rates vary from 0-50%. The most interesting results came from clinical studies with sunitinib and lenvatinib, with response rates of 50% and 36%, respectively[26].

Until very recently, only two TKIs, namely **vandetanib** and **cabozantinib**, have been approved by the FDA and the EMA for the treatment of advanced, progressive (within one year on imaging according to the RECIST 1.1 criteria), and/or symptomatic metastatic or locally/locoregionally advanced inoperable MTC, based on the results of the two phase 3 randomized multicenter clinical trials (ZETA – vandetanib registrational trial and EXAM – cabozantinib registrational trial)[37, 38]. In comparison with placebo, the therapy with these TKIs significantly prolonged progression-free survival (PFS), with better overall response rates (ORR) in patients with metastatic MTC[39, 40]. No overall survival (OS) benefit was observed, except for the prolonged OS in the subgroup of patients on cabozantinib therapy with *RETM918T*-positive MTCs (44.3 versus 18.9 months with placebo, HR 0.60)[40]. Other than this subgroup of patients, both drugs displayed *RET/RAS* status-independent efficacy. These drugs inhibit multiple tyrosine kinases that are functionally related, resulting in the disruption of their associated pathways. The kinases inhibited by vandetanib are RET, VEGFR, and EGFR, and the kinases inhibited by cabozantinib are RET, VEGFR, c-KIT, and MET. Because of the different inclusion criteria, trial designs, and the different patient populations, the results from the vandetanib and cabozantinib trials are not at all comparable. Both drugs are considered equally effective both in the first- and the second-line regimens, with no clear evidence supporting one over the other as the first-line therapeutic choice. The decision which drug to use as the first-line therapy may be based on the potential toxicity profile of the drugs, if no *RETM918T*-mutation exists. In patients with *RET918T* or *RAS*-mutant MTCs, as shown in a subgroup analysis, a significant advantage in PFS and OS was achieved with cabozantinib therapy.

However, TKI-therapy is associated with significant adverse effects, such as diarrhea, fatigue, rash, nausea, hypertension, hand-foot syndrome, and others[41]. That is probably due to wide-spread RET inhibition in "off-target" sites. This toxicity can negatively impact patient quality of life, and sometimes dose reductions or, more rarely, permanent treatment discontinuation is necessary[42]. Patients on cabozantinib therapy have increased TSH levels in almost 60% of cases during treatment; therefore, close and continuous monitoring of TSH levels is required. The prolongation of QTc-interval on ECG is rare, but severe side effect reported in approximately 8% of patients in a vandetanib registrational study. VEGF-pathway inhibition associated toxicity (hypertension, hemorrhage, gastrointestinal perforation, fistula formation) was more frequent in cabozantinib-treated patients than in the placebo group in the registrational study. Additionally, some RET disease-causing variants are non-responsive to multikinase inhibitor therapy, i.e. nonspecific RET inhibitor therapy. Some of those RET-variants also corresponds negatively to some other kinases.

Currently, novel small molecules selectively targeting RET (rather than MKIs) are in the spotlight of the ongoing phase 2 clinical trials harboring *RET* activating mutations[43].

In addition, some forms of *RET* disease-causing variants, such as *V804L* and *V804M* variants, affect the active enzymatic site of RET and can render all of the known non-specific RET-inhibitors ineffective. Moreover, the V804 residue of the RET backbone also corresponds to the gate-keeper position of some other ki-

nases, such as c-KIT, EGFR, PDGFR, and Abl. The RET-suppressing activity is essential for the antitumor effects of these selective RET-inhibitors in MTC therapy, while their antiangiogenic activity is negligible.

The most promising highly selective RET-inhibitor is an ATP-competitive small molecule called **selpercatinib (LOXO-292)**[44]. Several randomized clinical studies with selpercatinib are still ongoing. However, FDA granted accelerated approval of selpercatinib for the treatment of *RET*-altered thyroid cancer in May 2020, based on the results of the LIBRETTO-001 clinical trial. The drug is registered for the treatment of adult and pediatric patients (≥12 years of age) with advanced or metastatic *RET*-mutant MTC who require systemic therapy (as well as for the treatment of adult or pediatric patients with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine (RAI)-refractory and for the treatment of metastatic *RET* fusion-positive non-small cell lung cancer). The clinical trial, regarding the subgroup of patients with MTC, enrolled 55 patients with *RET*-altered MTC who had previously been treated with cabozantinib, vandetanib, or both, as well as 88 systemic therapy-naive patients. The response rates were 69% and 73% in the prior-treatment and no-prior-treatment groups, respectively. In the majority of patients, the responses lasted 6 months or longer. In addition, selpercatinib has various favorable pharmacokinetic properties. The most common adverse effects of selpercatinib were diarrhea, high blood pressure, and liver toxicity. Serious side effects, including abnormal heart rhythms and pneumonia, occurred in a third of study patients. Although most side effects could be managed, 5% of patients stopped treatment permanently because of serious side effects.

The other new and very promising highly selective small molecule that targets oncogenic RET alterations is **pralsetinib (BLU-667)**[45]. The first clinical results are encouraging, showing clinical benefit and a favorable safety profile in a small number of patients with MTC treated in a phase 1 clinical study. However, we should await more data on a larger number of patients in phase 2 and 3 prospective randomized clinical trials.

The role of **immunotherapy** in the treatment of patients with MTC is still under investigation[46]. MTC is not considered a very immunogenic tumor, which is a prerequisite for the efficacy of immunotherapy. Several checkpoint inhibitors, a type of immunotherapeutic agents, including pembrolizumab and nivolumab (PD-1 inhibitors), as well as ipilimumab (CTLA4-inhibitor) are being evaluated in phase 2 clinical trials for the treatment of metastatic MTC[47].

Due to the potential expression of somatostatin receptors (SSTRs) in a subset of MTC tumors, owing to its neuroendocrine origin, somatostatin analogue therapy or I-131-MIBG therapy in the previous decades and lately the **peptide receptor radionuclide therapy (PRRT)** have been used[48-50]. The prerequisite for this therapy is the positive diagnostic imaging for the clinically relevant expression of SSTRs. However, phase 2 data on Y-90-DOTATOC therapy in a small number of metastatic MTC patients showed modest clinical benefit with only 29% of responders[51]. There is also some scarce data of PRRT using Lu-177-DOTATATE, also with modest results.

There have been some attempts of radioimmunotherapy with bi-specific monoclonal antibodies, I-131-labeled bivalent hapten; however, no randomized clinical trials have been conducted. The latest ATA guidelines recommend radioisotope therapy only in the context of a clinical trial.

Numerous clinical trials for the treatment of metastatic MTC are ongoing. Some of the questions to be answered include further evaluation of the efficacy of TKIs or MKIs, especially in lower doses, or in combinations, or different administration regimens in order to minimize toxicity while achieving clinical benefit.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30. DOI: 10.3322/caac.21442.
2. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. Nat Rev Endocrinol. 2016;12(11):646-53. DOI.org/10.1038/nrendo.2016.110.
3. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(12):1856-83. DOI: 10.1093/annonc/mdz400.
4. Dal Maso L, Tavilla A, Pacini F, Serraino D, van Dijk BAC, Chirlaque MD, et al. Survival of 86,690 patients with thyroid cancer: A population-based study in 29 European countries from EUROCARE-5. Eur J Cancer. 2017;77:140-52. DOI: 10.1016/j.ejca.2017.02.023.
5. Kuo EJ, Sho S, Li N, Zanocco KA, Yeh MW, Livhits MJ. Risk Factors Associated With Reoperation and Disease-Specific

Mortality in Patients With Medullary Thyroid Carcinoma. JAMA Surg. 2018;153(1):52-9. DOI: 10.1001/jamasurg.2017.3555.

6. Meijer JA, le Cessie S, van den Hout WB, Kievit J, Schoones JW, Romijn JA, et al. Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: a structured meta-analysis. Clin Endocrinol (Oxf). 2010;72(4):534-42. DOI: 10.1111/j.1365-2265.2009.03666.x.
7. Agrawal N, Jiao Y, Sausen M, Leary R, Bettegowda C, Roberts NJ, et al. Exomic sequencing of medullary thyroid cancer reveals dominant and mutually exclusive oncogenic mutations in RET and RAS. J Clin Endocrinol Metab. 2013;98(2):E364-9. DOI: 10.1210/jc.2012-2703.
8. de Groot JW, Links TP, Plukker JT, Lips CJ, Hofstra RM. RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. Endocr Rev. 2006;27(5):535-60. DOI: 10.1210/er.2006-0017.
9. Elisei R, Cosci B, Romei C, Bottici V, Renzini G, Molinaro E, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. J Clin Endocrinol Metab. 2008;93(3):682-7. DOI: 10.1210/jc.2007-1714.
10. Elisei R, Alevizaki M, Conte-Devolx B, Frank-Raue K, Leite V, Williams GR. 2012 European thyroid association guidelines for genetic testing and its clinical consequences in medullary thyroid cancer. Eur Thyroid J. 2013;1(4):216-31. DOI: 10.1159/000346174.
11. Wells SA, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610. DOI: 10.1089/thy.2014.0335.
12. Elisei R, Romei C, Renzini G, Bottici V, Cosci B, Molinaro E, et al. The timing of total thyroidectomy in RET gene mutation carriers could be personalized and safely planned on the basis of serum calcitonin: 18 years experience at one single center. J Clin Endocrinol Metab. 2012;97(2):426-35. DOI: 10.1210/jc.2011-2046.
13. Machens A, Lorenz K, Weber F, Dralle H. Genotype-specific progression of hereditary medullary thyroid cancer. Hum Mutat. 2018;39(6):860-9. DOI: 10.1002/humu.23430.
14. Castinetti F, Waguespack SG, Machens A, Uchino S, Hasse-Lazar K, Sanso G, et al. Natural history, treatment, and long-term follow up of patients with multiple endocrine neoplasia type 2B: an international, multicentre, retrospective study. Lancet Diabetes Endocrinol. 2019;7(3):213-20. DOI: 10.1016/S2213-8587(18)30336-X.
15. Cote GJ, Evers C, Hu MI, Grubbs EG, Williams MD, Hai T, et al. Prognostic Significance of Circulating RET M918T Mutated Tumor DNA in Patients With Advanced Medullary Thyroid Carcinoma. J Clin Endocrinol Metab. 2017;102(9):3591-9. DOI: 10.1210/jc.2017-01039.
16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. DOI: 10.1016/j.ejca.2008.10.026.
17. Maia AL, Wajner SM, Vargas CV. Advances and controversies in the management of medullary thyroid carcinoma. Curr Opin Oncol. 2017;29(1):25-32. DOI: 10.1097/CCO.0000000000000340.
18. Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. J Clin Endocrinol Metab. 2010;95(6):2655-63. DOI: 10.1210/jc.2009-2368.
19. Barbet J, Campion L, Kraeber-Bodéré F, Chatal JF, Group GS. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab. 2005;90(11):6077-84. DOI: 10.1210/jc.2005-0044.
20. Trimboli P, Cremonini N, Ceriani L, Saggiorato E, Guidobaldi L, Romanelli F, et al. Calcitonin measurement in aspiration needle washout fluids has higher sensitivity than cytology in detecting medullary thyroid cancer: a retrospective multicentre study. Clin Endocrinol (Oxf). 2014;80(1):135-40. DOI: 10.1111/cen.12234.
21. Romero-Lluch AR, Cuenca-Cuenca JI, Guerrero-Vázquez R, Martínez-Ortega AJ, Tirado-Hospital JL, Borrego-Dorado I, et al. Diagnostic utility of PET/CT with. Eur J Nucl Med Mol Imaging. 2017;44(12):2004-13. DOI: 10.1007/s00259-017-3759-4.
22. Treglia G, Rufini V, Salvatori M, Giordano A, Giovanella L. PET Imaging in Recurrent Medullary Thyroid Carcinoma. Int J Mol Imaging. 2012;2012:324686. DOI: 10.1155/2012/324686.
23. Brierley J, Sherman E. The role of external beam radiation and targeted therapy in thyroid cancer. Semin Radiat Oncol. 2012;22(3):254-62. DOI: 10.1016/j.semradonc.2012.03.010.
24. Call JA, Caudill JS, McIver B, Foote RL. A role for radiotherapy in the management of advanced medullary thyroid carcinoma: the mayo clinic experience. Rare Tumors. 2013;5(3):e37. DOI: 10.4081/rt.2013.e37.
25. Hadoux J, Pacini F, Tuttle RM, Schlumberger M. Management of advanced medullary thyroid cancer. Lancet Diabetes Endocrinol. 2016;4(1):64-71. DOI: 10.1016/S2213-8587(15)00337-X.
26. Hadoux J, Schlumberger M. Chemotherapy and tyrosine-kinase inhibitors for medullary thyroid cancer. Best Pract Res Clin Endocrinol Metab. 2017;31(3):335-47. DOI: 10.1016/j.beem.2017.04.009.
27. Cabanillas ME, Hu MI, Jimenez C. Medullary thyroid cancer in the era of tyrosine kinase inhibitors: to treat or not to treat--and with which drug--those are the questions. J Clin Endocrinol Metab. 2014;99(12):4390-6. DOI: 10.1210/jc.2014-2811.
28. Ceolin L, Duval MADS, Benini AF, Ferreira CV, Maia AL. Medullary thyroid carcinoma beyond surgery: advances, challenges, and perspectives. Endocr Relat Cancer. 2019;26(9):R499-R518. DOI: 10.1530/ERC-18-0574.
29. Fromigué J, De Baere T, Baudin E, Dromain C, Leboulleux S, Schlumberger M. Chemoembolization for liver metastases

from medullary thyroid carcinoma. J Clin Endocrinol Metab. 2006;91(7):2496-9. DOI: 10.1210/jc.2005-2401.

30. Schlumberger M, Bastholt L, Dralle H, Jarzab B, Pacini F, Smit JW, et al. 2012 European thyroid association guidelines for metastatic medullary thyroid cancer. Eur Thyroid J. 2012;1(1): 5-14. DOI: 10.1159/000336977.
31. Rao SN, Cabanillas ME. Navigating Systemic Therapy in Advanced Thyroid Carcinoma: From Standard of Care to Personalized Therapy and Beyond. J Endocr Soc. 2018;2(10):1109-30. DOI: 10.1210/js.2018-00180.
32. Lam ET, Ringel MD, Kloos RT, Prior TW, Knopp MV, Liang J, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. J Clin Oncol. 2010;28(14):2323-30. DOI: 10.1200/JCO.2009.25.0068.
33. Schlumberger M, Jarzab B, Cabanillas ME, Robinson B, Pacini F, Ball DW, et al. A Phase II Trial of the Multitargeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer. Clin Cancer Res. 2016;22(1):44-53. DOI: 10.1158/1078-0432.CCR-15-1127.
34. Pennell NA, Daniels GH, Haddad RI, Ross DS, Evans T, Wirth LJ, et al. A phase II study of gefitinib in patients with advanced thyroid cancer. Thyroid. 2008;18(3):317-23. DOI: 10.1089/thy.2007.0120.
35. Locati LD, Licitra L, Agate L, Ou SH, Boucher A, Jarzab B, et al. Treatment of advanced thyroid cancer with axitinib: Phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments. Cancer. 2014;120(17):2694-703. DOI: 10.1002/cncr.28766.
36. Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, et al. A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H. J Clin Endocrinol Metab. 2014;99(5):1687-93. DOI: 10.1210/jc.2013-3713.
37. Wells SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30(2):134-41. DOI: 10.1200/JCO.2011.35.5040.
38. Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31(29):3639-46. DOI: 10.1200/JCO.2012.48.4659.
39. Trimboli P, Castellana M, Virili C, Giorgino F, Giovanella L. Efficacy of Vandetanib in Treating Locally Advanced or Metastatic Medullary Thyroid Carcinoma According to RECIST Criteria: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2018;9:224. DOI: 10.3389/fendo.2018.00224.
40. Schlumberger M, Elisei R, Müller S, Schöffski P, Brose M, Shah M, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol. 2017;28 (11):2813-9. DOI: 10.1093/annonc/mdx479.
41. Grande E, Kreissl MC, Filetti S, Newbold K, Reinisch W, Robert C, et al. Vandetanib in advanced medullary thyroid cancer: review of adverse event management strategies. Adv Ther. 2013;30(11):945-66. DOI: 10.1007/s12325-013-0069-5.
42. Resteghini C, Cavalieri S, Galbiati D, Granata R, Alfieri S, Bergamini C, et al. Management of tyrosine kinase inhibitors (TKI) side effects in differentiated and medullary thyroid cancer patients. Best Pract Res Clin Endocrinol Metab. 2017;31(3):349-61. DOI: 10.1016/j.beem.2017.04.012.
43. Araque KA, Gubbi S, Klubo-Gwiezdzinska J. Updates on the Management of Thyroid Cancer. Horm Metab Res. 2020. DOI: 10.1055/a-1089-7870.
44. Subbiah V, Velcheti V, Tuch BB, Ebata K, Busaidy NL, Cabanillas ME, et al. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol. 2018;29(8):1869-76. DOI: 10.1093/annonc/mdy137.
45. Subbiah V, Gainor JF, Rahal R, Brubaker JD, Kim JL, Maynard M, et al. Precision Targeted Therapy with BLU-667 for. Cancer Discov. 2018;8(7):836-49. DOI: 10.1158/2159-8290.CD-18-0338.
46. Naoum GE, Morkos M, Kim B, Arafat W. Novel targeted therapies and immunotherapy for advanced thyroid cancers. Molecular cancer. 2018;17(1):51. DOI: 10.1186/s12943-018-0786-0.
47. Antonelli A, Ferrari SM, Fallahi P. Current and future immunotherapies for thyroid cancer. Expert Rev Anticancer Ther. 2018;18(2):149-59. DOI: 10.1080/14737140.2018.1417845.
48. Mahler C, Verhelst J, de Longueville M, Harris A. Long-term treatment of metastatic medullary thyroid carcinoma with the somatostatin analogue octreotide. Clin Endocrinol (Oxf). 1990; 33(2):261-9. DOI: 10.1111/j.1365-2265.1990.tb00490.x.
49. Vaisman F, Rosado de Castro PH, Lopes FP, Kendler DB, Pessoa CH, Bulzico DA, et al. Is there a role for peptide receptor radionuclide therapy in medullary thyroid cancer? Clin Nucl Med. 2015;40(2):123-7. DOI: 10.1097/RLU.0000000000000628.
50. Beukhof CM, Brabander T, van Nederveen FH, van Velthuysen MF, de Rijke YB, Hofland LJ, et al. Peptide receptor radionuclide therapy in patients with medullary thyroid carcinoma: predictors and pitfalls. BMC Cancer. 2019;19(1):325. DOI: 10.1186/s12885-019-5540-5.
51. Iten F, Müller B, Schindler C, Rochlitz C, Oertli D, Mäcke HR, et al. Response to [90Yttrium-DOTA]-TOC treatment is associated with long-term survival benefit in metastasized medullary thyroid cancer: a phase II clinical trial. Clin Cancer Res. 2007;13(22 Pt 1):6696-702. DOI: 10.1158/1078-0432.CCR-07-0935.

Sažetak

MEDULARNI KARCINOM ŠTITNJAČE – PREGLED ZNAČAJKI I NOVOSTI U SUSTAVNOM LIJEČENJU

N. Dabelić, T. Jukić i *A. Fröbe*

Medularni karcinomi štitnjače (MKŠ) rijetke su zloćudne bolesti podrijetla parafolikularnih (C-stanica) štitnjače i čine oko 2-4% svih zloćudnih tumora štitnjače. MKŠ može biti sporadičan ili nasljedan, potonji kao dio MEN 2 sindroma. Nasljedne mutacije protoonkogena *RET* (od engl. *REarranged during Transfection*) pokretačke su mutacije kod nasljednih MKŠ, dok su somatske *RET* mutacije, ili, rječe, *RAS* mutacije, opisane u tumorskom tkivu kod sporadičnih MKŠ. Genetski probir na nasljedne mutacije protoonkogena *RET* identificira nosioce nasljednih genetskih mutacija. To omogućuje primarnu (sprječavanje razvoja bolesti provođenjem profilaktičke totalne tireoidektomije) ili barem sekundarnu prevenciju bolesti (rano otkrivanje MKŠ-a). Radikalna operacija s kompletnom resekcijom tumora još je uvijek ključna u postizanju izlječenja kod MKŠ. Naime, unatoč nedavnim dostignućima, liječenje uznapredovalog, metastatskog i progresivnog MKŠ-a i dalje predstavlja izazov. Metastatski MKŠ može biti indolentnog kliničkog tijeka, stoga je potrebno procijeniti kojeg bolesnika liječiti i kada liječenje započeti. Multidisciplinarni timovi različitih specijalista uključenih u dijagnostiku i liječenje bolesnika s MKŠ-om u visoko specijaliziranim centrima s velikim brojem bolesnika omogućuju njihovo optimalno zbrinjavanje. Multikinazni inhibitori (MKI) vandetanib i kabozantinib, odobreni su za liječenje progresivnog ili simptomatskog metastatskog/neresektabilnog MKŠ. Premda je ovo liječenje pokazalo dobit u preživljenju bez progresije bolesti (PFS, od engl. *Progression Free Survival*) uz veću ukupnu stopu odgovora (ORR, od engl. *Overall Response Rate*) naspram placeba, MKI nisu polučili dobit u ukupnom preživljenju (OS, od engl. *Overall Survival*), osim kod podskupine bolesnika s *RETM918T*-mutacijama na terapiji kabozantinibom. Multikinazni inhibitori su neselektivni, stoga je moguća značajna toksičnost terapije. Nedavno su razvijene nove generacije tirozin-kinaznih inhibitora (TKI). Ovi visoko selektivni RET-inhibitori specifično su dizajnirani za visoko učinkovito i selektivno ciljanje onkogenih RET alteracija, što ih čini obećavajućim lijekovima u liječenju uznapredovalog MKŠ. Selektivni RET-inhibitor selperkatinib vrlo je nedavno registriran za liječenje *RET*-mutiranih karcinoma štitnjače.

Ključne riječi: *medularni karcinom štitnjače; RET-protoonkogen; molekularna ciljana terapija; liječenje; novosti*