Medullary thyroid carcinoma

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Purpose of review
To summarize recent developments in the diagnosis and management of patients with medullary thyroid cancer (MTC), with a focus on pathogenesis, systemic therapy, and future directions.

Recent findings
The addition of mutational analysis to cytological assessment of thyroid nodules has improved the diagnostic accuracy of MTC. The discovery of new genomic alterations and overexpression of certain factors allows for improved prognostication in MTC and provides potentially new therapeutic agents. New data suggest that tumor environment may be more immunogenic than previously thought in a subset of MTCs with identification of a new MTC-specific antigen leading to a revival of investigating immune-based therapy for this disease. The newly approved selective rearranged during transfection (RET0-inhibitors, selpercatinib and pralsetinib, offer promising results, and tolerability for patients with *RET*-mutated MTC; however, the development of resistance mechanisms may be problematic.

Summary
MTC has witnessed remarkable advancements in recent years. Our new understanding of some of the driver mutations in MTC allows for therapeutics with more tolerable adverse event profiles. However, there is still a need for more effective treatment strategies for subsets of patients without actionable mutations and for those who develop resistance to currently available therapies.

Keywords
pathogenesis, prognosis, resistance, RET-inhibitor, treatment

INTRODUCTION

Medullary thyroid cancer (MTC) is a rare cancer that arises from the neuroendocrine parafollicular C-cells of the thyroid gland comprising up to 3% of all thyroid cancers [1]. In recent years, mutational analysis has been instrumental in improving the diagnostic accuracy of MTC from cytological samples as well as in directing systemic therapy in patients with advanced MTC. As all hereditary MTC harbor a germline *RET* mutations and almost half of sporadic cases have a somatic rearranged during transfection (*RET*) mutation, the selective RET-inhibitors are a welcome addition to therapeutic options for our patients. A better understanding of resistance mechanisms and the pathogenesis of non-*RET*-mutated MTC is needed for the development of more effective novel therapies to target this subset of patients.

ADVANCEMENTS IN DIAGNOSTIC AND STAGING EVALUATION

MTC is typically diagnosed by US-guided fine-needle aspiration (FNA) biopsy of a thyroid nodule. Cytological diagnosis of MTC is challenging and the diagnosis is missed about half the time so other techniques are often needed to make the diagnosis [2]. Using RNA sequencing, the Afirma Genomic Sequencing Classifier has been previously shown to have 100% specificity and sensitivity in identifying MTC among 211 indeterminate FNA samples [3]. The Afirma Xpression Atlas is an add-on test that reports nucleotide variants and fusions across 511 cancer-associated genes. When applied to MTC-positive FNA samples, it was able to identify a variant or fusion in 44–87% of all samples, 64% of which may be actionable in terms of available targeted therapies [4,5,6▪]. Similarly, use of pairwise miRNA expression analysis of ThyraMIR accurately classified all MTC samples, even in indeterminate cytological findings [7].

Once the diagnosis of MTC is made, preoperative systemic imaging is recommended depending

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KEY POINTS

- The addition of GSC and miRNA expression analysis to cytological assessment of thyroid nodules has improved the diagnostic accuracy of MTC.
- The use of 68Ga-positron emission tomography/computed tomography may be a useful imaging modality when tumor markers are rising and conventional imaging is unrevealing for new or progressing lesions.
- The discovery of new genomic alterations in genes such as *CDKN2C, FAT1/FAT4* and overexpression of certain factors such as IGFBPP2, ATF4, DLL3 and COX-4 led to more aggressive forms of MTC and present opportunities for investigating other therapeutic agents.
- Recent studies have identified several novel immune co-inhibitory receptors and an MTC-specific antigen (GFR-α4) restricted to normal C-cells; thus, combinatorial approaches including immune checkpoint inhibitors or evaluation of CAR-T therapy may be worth exploring in MTC.
- The newly approved selective rearranged during transfection (RET)-inhibitors, selpercatinib and pralsetinib, offer promising results and tolerability for patients with *RET*-mutated MTC; however, the development of resistance mechanisms may be problematic.
- There remains an unmet need for more effective and curative treatment strategies to address *RAS*-mutated MTC and the clinical heterogeneity of MTC.

on preoperative calcitonin levels and/or concerning clinical features. Given that many patients with MTC require lifelong imaging surveillance, multiple studies have evaluated the role of a single whole-body imaging technique in detecting persistent or recurrent disease. It has been previously shown that positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography (^{18}F-fluorodeoxyglucose positron emission tomography [PET]/computed tomography [CT]) and 6-fluoro-(18F)-L3,4-dihydroxyphenylalanine (18F-DOPA) PET/CT are less sensitive than conventional imaging modalities [8–10]. More recently, and due to its binding to somatostatin receptors, use of gallium-68 (68Ga) radiolabeled somatostatin analog peptides in PET/CT has shown promising results in surveillance of neuroendocrine tumors. In a recent prospective study evaluating 30 patients with MTC and comparing 68Ga-PET/CT to conventional imaging modalities, 68Ga-PET/CT was superior to bone scan in detecting bone metastases but inferior to other imaging modalities at all other disease sites [11]. This may be a useful imaging modality when tumor markers are rising and conventional imaging is unrevealing for new or progressing lesions [12].

NEW PROGNOSTIC INDICATORS OF BEHAVIOR

Pathologic grading

In a recent analysis, large tumor size, tumor necrosis, a high mitotic index, presence of nodal disease predicted poor outcomes, specifically worse disease-specific survival (DSS) and progression-free survival (PFS), with tumor necrosis and mitotic activity being independent predictors for worse DSS [13▪].

Tumor markers

Recent publications have identified additional tumor markers, other than calcitonin and carcinoembryonic antigen, as possible poor prognostic indicators. A positive serum Ca19.9 and a short Ca19.9 DT of less than 1 year were predictive of mortality but not for progressive disease in patients with advanced MTC [14▪]. The average structural tumor volume DT has also been shown to be of worse prognosis, with a DT $\leq$1 year conferring a worse overall survival [15▪].

PATHOGENESIS, PROGNOSTIC MARKERS AND RATIONALE FOR TREATMENT OPTIONS

Pathogenic drivers in MTC include overexpression of tyrosine kinase receptors (VEGFR, EGFR, MET) which upregulate intracellular signaling pathways. The most common molecular alteration in MTC is *RET* mutation in almost all hereditary and in about half of the sporadic MTC tumors [16]. In sporadic MTC, *RAS* mutations are the second most common being present in approximately 14% [16]. *RET* and *RAS* mutations are nearly mutually exclusive, with *RAS* mutations being detected in about 70% of *RET* wild-type tumors. The understanding of these pathogenic drivers and pathways led to development of several multikinase inhibitors, and the approval of cabozantinib and vandetanib for the treatment of progressive metastatic and advanced MTC. Their inability to significantly inhibit the RET receptor without intolerable toxicities led to the development and eventually approval of the two highly selective RET-inhibitors, selpercatinib and pralsetinib, as well as other RET-inhibitors.

Several more recent studies demonstrated additional alterations, such as copy number loss of the *CDKN2C* gene located on chromosome 1p, RB tumor suppressor pathway and mTOR pathway

are associated with worse prognosis in MTC [17–18,19▪]. Other studies have evaluated epigenetics, overexpression of miRNA as a potential mediator of pathogenesis. Preclinical studies have shown that cyclin-dependent kinase-inhibitors may be potential therapeutic targets in MTC [20–22].

In a recent study using whole genome and whole transcriptome sequencing in a small set of tumors, it was noted that *FAT1/FAT4* genomic alterations were frequent in sporadic MTC. Additionally, based on gene expression profile, two molecular subtypes with different biological behavior were identified: the mesenchymal-like subtype characterized by epithelial–mesenchymal transition, and the proliferative-like subtype associated with enrichment of cell cycle pathways [23]. Another recent study showed that CD133 expression, a stem cell marker, was associated with more aggressive MTC [24▪].

A recent study showed that *RET* protooncogene promotes the expression of IGFBPP2, which in turn increased cell survival and migration of MTC cells [25▪]. High levels of IGFBP2 was associated with worse clinical characteristics and poor survival in MTC. It was also noted that *RET* may promote VEGFR2 expression in MTC. It was previously shown that *RET* promotes cell survival through phosphorylation-dependent degradation of ATF4 and that overexpression of ATF4 leads to *RET* ubiquitination and were associated with worse outcomes in patients with MTC [26].

The expression of DLL3 (Delta-like ligand 3), an inhibitory NOTCH ligand, was recently investigated in 59 sporadic MTC tumors. A high DLL3 expression correlated with more aggressive features such as stromal desmoplasia and lymph node metastases [27▪]. This may be also a relevant therapeutic target as the DLL3-targeting antibody, rovalpituzumab tesirine, showed promising activity in neuroendocrine tumors with DLL3 expression of more than 50% [28▪].

Cytochrome coxidase (COX-4), a regulator of oxidative phosphorylation is expressed in malignant thyroid tumors compared with controls. It was demonstrated that oxidative phosphorylation may play an important role in metastatic progression of *RET*-mutant MTCs. Further studies to assess COX-4 as a potential therapeutic target should be investigated [29▪].

It was initially believed that immune checkpoint inhibitor (ICI) therapy is not very effective in the treatment of MTC. It was recently demonstrated that MTC tumors may be more immunogenic that previously thought. Immune infiltration was observed in 49% and 90% of primary and metastatic tumors, respectively with CD8+ cells being the dominant T-cell subtype, whereas CD4+ T cells were sparse. Myeloid infiltrate was common, especially CD163+ macrophages (M2 type) leading to suppression of antitumor immune response. PD-L1 was expressed at low levels (1–5%) in approximately one-third of patients [30]. In another recent large study including 200 samples, several immune co-inhibitory receptors such as T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) were expressed in almost half of MTC tumors, followed by PD-1 and cytotoxic T-lymphocyte antigen 4 (CTLA-4), both detected in about 12% of MTC tumors. Others such as lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin and ITIM domain (TIGIT) were detected in low frequencies (3%). Based on new evidence, it is very possible that a subset of MTC tumors are immunogenic and treatment with immunotherapy targeting TIM-3 as single agent or in combination with PD-1/PD-L1 and CTLA-4 antibodies may be reasonable to consider [31▪▪].

Chimeric antigen receptor (CAR)-modified T cells (CAR-T) therapy has been limited in solid tumors due to the lack of target antigens. The glial-derived neurotrophic factor (GDNF) family receptor alpha 4 (GFRα4) was recently discovered as a potential target antigen as it is expressed in MTC and is restricted to C-cells. GFRα4-directed CAR-T immunotherapy is currently being evaluated for the treatment of MTC [32▪].

UPDATES IN THE MANAGEMENT OF MEDULLARY THYROID CANCER

Surgery

Total thyroidectomy with central lymph node dissection is recommended as an initial surgery for patients with MTC [1]. However, there continues to be controversy regarding lateral neck dissection (LND). In a recent study, it was noted that prophylactic ipsilateral LND for patients without structural disease in the lateral neck did not result in improved outcomes, such as recurrence in the neck, development of distant metastases or overall survival [33]. Untreated microscopic lymph node disease did not increase the risk of distant metastasis [34▪]. These data suggest that aggressive surgical approach to control microscopic neck disease may not affect clinical outcomes and may result in more morbidity.

A recent case report also highlights the significance of neoadjuvant targeted therapy to allow for R0 surgical resection in patients with advanced MTC. A patient with initially unresectable *RET*-mutated MTC was treated with selpercatinib with a significant response to allow for complete surgical resection [35▪].

Radiation therapy

External beam radiation therapy (EBRT) for MTC following initial surgery remains controversial. A recent database analysis showed that EBRT was not associated with improved outcomes [36▪▪]. The decision to proceed with EBRT to the neck should be carefully weighed with the potential for increased complications, specifically fistulas, should these patients require multikinase inhibitor therapy with antiangiogenic properties.

The combination of EBRT with targeted systemic therapy with vandetanib or cabozantinib in mouse models resulted in an increased therapeutic effect with larger reduction in tumor volume and longer time to progression [37]. Future studies should evaluate this approach.

Systemic therapy

The characteristics of multikinase inhibitors (cabozantinib, vandetanib) and RET-inhibitors (selperatinib, pralsetinib) are summarized in Table 1. This section will describe the more recently approved selective RET-inhibitors and emergent mechanisms of resistance. Selective RET-inhibitors were developed with the intention of targeting both activating *RET* mutations in MTC (>60%) and *RET*-fusions which can be found in non-MTC (papillary, poorly differentiated, anaplastic; 10–20%) and more rarely in nonsmall cell lung cancer (NSCLC, 2%), and other malignancies [38,39]. In addition to targeting the most common somatic *RET* M918T mutation and other pathogenic *RET* mutations or deletions, these inhibitors are able to overcome the gatekeeper *RET* V804L/M mutations, which are known to convey resistance to both cabozantinib and vandetanib [40,41].

Selpercatinib (previously called LOXO-292)

In the LIBRETTO-001 phase 1/2 trial, the overall response rates (ORR) of selpercatinib in patients with *RET*-mutated MTC who had prior treatment with cabozantinib and/or vandetinib ($n = 55$) and naïve to prior therapy ($n = 88$) were 69% (95% CI, 55–81) and 73% (95% CI, 62–82), respectively [42▪▪]. The 1-year PFS was 82% for patients who received prior targeted therapy and 92% for treatment-naïve patients. Three of 11 patients with gatekeeper *RET* V804 mutations had responses to selpercatinib. The study drug was well-tolerated overall with 30% of the entire study population of 531 *RET*-altered cancers requiring a dose reduction due to a treatment-related adverse event (TRAE) and 2% ($n = 12$) discontinued the study drug due to TRAEs. Most common TRAEs were low-grade and consisted of dry mouth (39%), hypertension (30%), increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (28% and 26%, respectively), and fatigue (25%). The two most common Grade 3 and 4 TRAEs were hypertension (12%) and increased liver enzymes (AST 8%, ALT 11%). Selpercatinib was approved by the United States Food and Drug Administration (FDA) in May 2020 for *RET*-mutant MTC and *RET*-fusion non-MTC and NSCLC.

Pralsetinib (previously called BLU-667)

In the ARROW phase 1/2 trial, pralsetinib for *RET*-mutant MTC demonstrated an ORR of 60% (95% CI, 46–73) in patients who received prior cabozantinib and/or vandetanib ($n = 55$) and 71% (95% CI, 48–89) in treatment-naïve patients ($n = 21$) [43▪▪]. The 1-year PFS was 75% in previously treated patients and 81% in treatment-naïve MTC patients with median PFS not reached in either group at the time of analysis.

Table 1. Characteristics of currently approved systemic therapies for patients with advanced MTC

	Vandetanib [50,51]	Cabozantinib [52]	Selpercatinib [42▪▪]	Pralsetinib [43▪▪]
Response rate (%)	45	28	69 (prior Rx) 73 (naïve)	60 (prior Rx) 71% (naïve)
Median PFS (months)	19.3	11.2 (estimated)	Not reached	Not reached
1-year PFS (%)	–	47.3	82 (prior Rx) 92 (naïve)	75 (prior Rx) 81 (naïve)
AEs – grade ≥ 3 (%)	Diarrhea (11) Hypertension (9) QTc Prolongation (8) Fatigue (6)	Diarrhea (15.9) Palmar-plantar erythrodysesthesia (12.6) Decreased weight/appetite (4.7)	Hypertension (12) Increased ALT (11) Increased AST (8)	Hypertension (17) Neutropenia (14) Lymphopenia (12) Anemia (10) Leukopenia (8)
Drug discontinuation rate (%)	12	16	2	4

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTC, medullary thyroid cancer; PET, positron emission tomography; PFS, progression-free survival.

Responses were seen in 83% (5 out of 6) of patients with *RET* gatekeeper mutations. Similar to selpercatinib, pralsetinib was associated with mostly low-grade TRAEs: decreased white blood cell count (34%), neutropenia (34%), increased AST (34%), hypertension (33%), anemia (29%), constipation (28%), asthenia (26%), increased ALT (23%), hyperphosphatemia (22%), and lymphopenia (20%). The most common Grade 3/4 TRAEs were hypertension (17%), and complete blood count abnormalities (neutropenia 14%, lymphopenia 12%, anemia 10%, and leukopenia 8%). Although both selpercatinib and pralsetinib are highly selective for aberrant RET, each has relatively lower potency against VEGFR2 and can lead to hypertension in patients, requiring monitoring, medical management or dose-reduction of the RET-inhibitor. Dose reduction due to a TRAE occurred in 46% of the thyroid cancer patients treated with pralsetinib with 4% ($n = 5$) discontinuing treatment due to TRAEs. Pralsetinib was approved by the FDA in December 2020 for *RET*-mutant MTC and *RET*-fusion non-MTC, in addition to NSCLC.

Although there is no clear guidance currently on what agent should be used as first-line therapy in patients with advanced *RET*-mutant MTC, physicians should consider the patient's tumor mutation type, comorbidities, interfering medications, and other contraindications when selecting appropriate systemic therapy. A multicenter, randomized ongoing phase 3 trial comparing the safety and efficacy of selpercatinib with standard of care multikinase inhibitor (vandetinib or cabozantinib) in treatment-naïve *RET*-mutant MTC may provide evidence to which should be considered as first-line therapy (ClinicalTrials.gov Identifier: NCT04211337). The primary outcome is evaluating treatment failure-free survival, which takes into account treatment discontinuation due to unacceptable toxicity, as well as progression of disease or death from any cause.

Mechanisms of resistance

Mechanisms of progression of disease while on systemic therapy are not fully understood.

As described earlier, *in vitro* studies showed that the *RET* V804L/M gatekeeper mutation confers resistance to cabozantinib and vandetanib by preventing these molecules from inserting into the ATP-binding pocket of the kinase portion of the RET receptor [40,41]. In addition, emergent *RET* V804 gatekeeper mutations have been described in MTC patients treated with vandetanib and/or cabozantinib correlating with progressive disease on drug therapy [44,45]. Resistance to vandetanib has also been noted with an S904F mutation in the activation loop of the RET kinase domain [46].

Pralsetinib and selpercatinib have been optimized to avoid the gatekeeper resistance mechanism. However, emergent *RET* mutations at the solvent front (G810C/R/S/V) and hinge region (Y806C/N) have been associated with progression of disease and resistance to selpercatinib in patients with RET-altered NSCLC and MTC after having initial partial responses with treatment [47▪▪,48▪▪]. Subbiah and colleagues showed that these solvent front and hinge *RET* mutations also led to resistance to pralsetinib in cell cultures. Other resistance mechanisms to the selective RET-inhibitors include development of *MET* and *KRAS* amplifications [45,49▪▪]. Even though these resistance mechanisms occur infrequently, it is important to check for development of new mutations when progression occurs after an initial response to therapy. Other next-generation RET-inhibitors are in development or in early stages of clinical trials and will hopefully be able to bypass these emergent resistance mechanism. TPX-0046 does have inhibitory activity against the solvent front *RET* G810 mutation but, unfortunately, does not inhibit the gatekeeper *RET* V804 mutation.

CONCLUSION

Advances in the treatment of MTC over the past decade have been truly remarkable. Between 2011 and 2020, 4 agents were approved for advanced progressive MTC with the recent approval of 2 highly potent RET-inhibitors that have well-tolerated side effect profiles compared with the multikinase inhibitors. Understanding other pathogenic mechanisms may lead to developing novel therapeutic agents.

These promising developments are offset by continued unmet needs for development of new barriers to effective, long-term disease control. Although our *RET*-mutated MTC patients have an expanded compendium of treatment options, our patients with *RAS*-mutations or no identifiable driver mutations are limited to multikinase inhibitors which convey more side effects, which can be dose-limiting and less effective. Additionally, the emergence of resistance mechanisms while on systemic therapies is highly problematic. Long-term consequences of potent RET inhibition are unknown and need to be considered. Finally, despite new selective treatments demonstrating high response rates, agents with curative intent have remained elusive.

Continued investigation into other pathogenic drivers is essential for greater understanding of the heterogeneity of clinical behavior amongst patients with MTC. There is an urgent need for development

of more effective therapies which can address tumoral heterogeneity and resistance mechanisms. Further investigation evaluating the most effective strategies to treat this rare but chronic disease is needed with consideration of combination therapies targeting different pathways to elicit high response rates while minimizing toxicities.

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