



Anti-Tumour Treatment

Systemic treatment and management approaches for medullary thyroid cancer

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ABSTRACT

Although rare, medullary thyroid cancer (MTC) exemplifies the value that ever-expanding knowledge of molecular pathways and mechanisms brings to managing challenging cancers. Although surgery can be curative for MTC in many patients, a substantial proportion of patients present with locoregional or distant metastatic disease. Once distant disease occurs, treatment options are limited, and conventional cancer treatments such as cytotoxic chemotherapy are of minimal benefit. Biomarkers such as calcitonin and carcinoembryonic antigen are important correlates of disease burden as well as predictors of disease progress, including recurrence and survival. MTC is either sporadic (~75%) or inherited (~25%) as an autosomal dominant disease. Regardless, germline and somatic mutations, particularly in the rearranged during transfection (*RET*) proto-oncogene, are key factors in the neoplastic process. Gain-of-function *RET* mutations result in overactive proteins that lead to abnormal activation of downstream signal transduction pathways, resulting in ligand-independent growth and resistance to apoptotic stimuli. Specific *RET* mutation variants have been found to correlate with phenotype and natural history of MTC with some defects portending a more aggressive clinical course. Greater understanding of the consequence of the aberrant signaling pathway has fostered the development of targeted therapies. Two small-molecule tyrosine kinase inhibitors, vandetanib and cabozantinib, are currently available as approved agents for the treatment of advanced or progressive MTC and provide significant increases in progression-free survival. Since there have been no head-to-head comparisons, clinicians often select between these agents on the basis of familiarity, patient characteristics, comorbidities, and toxicity profile.

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Introduction

Thyroid cancer is the most common endocrine malignancy, with more deaths annually than all other endocrine malignancies combined. A total of 64,300 new cases of thyroid cancers are estimated to be diagnosed in the United States in 2015 [1]. Cancer of the thyroid is the 5th most common cancer in females, with 49,350 new cases projected in 2016 [1]. Among all malignancies

tracked and recorded by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program between 2006 and 2010, the most rapid increase in incidence was in thyroid cancer, with 5.4% and 6.5% increase in men and women, respectively [2]. Overall, the annual increase in rate in the United States was 5.1% per year from 2003 to 2012 [1]. The mortality rate from thyroid cancer, however, has been relatively stable for the same period [1]. Worldwide, 298,000 new cases were estimated in 2012, accounting for approximately 2.0% of new cancers [3]. From 2006 to 2010, the marked increase observed in thyroid cancer incidence in the United States is likely the consequence of a number of contributing factors, including improved diagnostic identification and detection as well as a true increase of unclear etiology or possibly the result of exposure to radiation or environmental carcinogens [1,4,5].

The main histologic subtypes of thyroid cancer are differentiated (papillary, follicular, and Hürthle), medullary, and anaplastic. Of these, papillary thyroid cancer (PTC) is the most common sub-

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type. Based on a series of nearly 54,000 cases treated in the United States between 1985 and 1995, PTC accounts for approximately 80% of all thyroid malignancies [6]. PTC is followed by follicular thyroid cancer, which accounts for approximately 11% of all cases. In the past, medullary thyroid cancer (MTC), a rare subtype, was estimated to comprise less than 5% of thyroid cancers [6,7]. More recent data now places this estimate at less than 2% [8]. Anaplastic thyroid cancer, one of the most aggressive and rapidly fatal cancers, represents the least common form of thyroid cancer at approximately 2% of all thyroid malignancies [6,7].

This review focuses on MTC, which arises from the neural crest-derived, calcitonin-secreting, parafollicular C cells of the thyroid gland [9]. Recent advances in the understanding of the underlying molecular pathogenic pathways of MTC have led to the development of targeted therapies that confer improved outcomes for patients with advanced progressive metastatic disease that is not amenable to local interventions such as surgical resection or ionizing radiation [10,11]. This review will present an overview of the clinical and molecular characteristics of MTC and how these factors help define current management approaches, especially the use of targeted therapies, for advanced MTC.

Demographics and survival

The median age at diagnosis of MTC is approximately 50 years [12]. Analysis of the clinical and demographic characteristics of 1252 patients with MTC showed that 87% were white and 60% were females [12]. Overall, survival in MTC is strongly influenced by age and stage at diagnosis [8,12], with reported overall 10-year survival rates ranging from 70% to 90% and 56% to 87% at 5 years based on the results of several studies [13–15]. Patients younger than 40 years at the time of diagnosis had a significantly higher adjusted survival rate than older patients [12,16]. Additionally, patients whose tumors are confined to the thyroid gland had a 10-year survival rate of 96% [12]. The 10-year survival rate decreased to about 75% with regional disease spread, and to 40% with distant metastases [12,14,17].

Sporadic and hereditary MTC

Most cases of MTC (approximately 75–80%) are sporadic, with inherited or hereditary forms of MTC accounting for the remainder [9,18]. Multiple endocrine neoplasia (MEN) 2A and MEN 2B are inherited, autosomal, dominant diseases with generally high but variable penetrance and phenotypic expression of MTC [19]. Mutations in the rearranged during transfection (*RET*) proto-oncogene are considered central to the pathogenesis of both hereditary and sporadic forms of MTC and constitute an early oncogenic event that drives tumorigenesis [18,20]. *RET* mutations have been reported in approximately 50% of patients with sporadic MTC, but frequencies vary substantially [8,21,22]. The presence of *RET* mutations appears to predict a poor prognosis compared with the absence of such a mutation [7,8,22–24]. In addition, other non-*RET* somatic mutations have been reported in cases of sporadic MTC, adding to the complexity of this condition [8].

Inherited MTC includes 2 variants of the MEN type 2 syndrome (A and B). Another form of inherited MTC, familial medullary thyroid cancer (FMTC), historically was classified as a freestanding syndrome, but the classification is in flux and it is now recommended that it be considered one of the variants of MEN 2A [7,8,25]. MEN 2A, the most common subtype of MEN 2, accounts for about 95% of all MEN 2 cases [8,9,25]. MTC is a dominant feature of MEN 2A, occurring in virtually all patients [8]. Other components of the syndrome include pheochromocytoma, present in approximately 50% of patients, and hyperparathyroidism, which

occurs in 25–35% of patients. The overall clinical manifestation is variable, depending on the specific mutations in the *RET* gene that underlie the disease [25]. FMTC lacks any of the other hereditary extrathyroidal endocrine tumors commonly observed in patients with MEN 2 syndrome [8,25].

About 5% of hereditary MTC cases occur in the setting of MEN 2B, which manifests primarily as MTC along with pheochromocytoma occurring in about 50% of patients [9]. Patients with MEN 2B typically exhibit a marfanoid body habitus and musculoskeletal manifestations. They may develop enteric ganglioneuromas, mucosal neuromas, and ocular abnormalities [8,26,27]. Gastrointestinal symptoms such as bloating, abdominal pain, constipation alternating with diarrhea, and megacolon are common, particularly in younger patients [25,26]. The frequencies of characteristic clinical manifestations of MTC-associated syndromes reported in recent reviews are presented in Table 1 [18,28].

Sporadic MTC most commonly presents as a solitary, unilateral thyroid nodule or a palpable cervical lymph node [25,29], whereas hereditary MTC tends to be multicentric and bilateral, involving the upper to middle parts of the thyroid lobes [25,29]. Involvement of cervical lymph nodes is an early and common manifestation in the clinical course of the disease, with 35–50% or more of patients presenting with positive cervical lymph nodes [9,29–31]. In one early report, more than 75% of patients with palpable MTC tumors had associated lymph node metastases [32]. Distant metastatic spread of MTC frequently involves the mediastinal nodes, lung, liver, and bones [9]. The liver is the most frequent site of metastasis; it may be involved in up to 90% of patients [33].

Molecular aberrations and therapeutic targets in MTC

Greater understanding and ongoing research of the molecular pathways and mechanisms underlying the pathogenesis and progression of MTC have led to new treatment options for patients with advanced disease. Genetic alterations in MTC have been extensively studied [18,19,21,34,35]. The genetic defect in MTC involves the *RET* proto-oncogene located on chromosome 10, which encodes for a receptor tyrosine kinase that transduces growth and differentiation signals in developing tissues, including those of the neural crest and urogenital system [19,36–39]. *RET* activation stimulates signal transduction cascades such as the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K/Akt/mammalian target of rapamycin [mTOR]), and c-Jun N-terminal protein kinases (JNK) pathways that play critical roles in regulating cell proliferation, differentiation, motility, apoptosis, and survival [35,37].

RET mutations are called gain-of-function mutations because they cause overactive proteins and abnormal activation of downstream signal transduction pathways, resulting in ligand-independent growth and resistance to apoptotic stimuli [35,40]. There is a strong genotype-phenotype correlation between specific *RET* mutations and clinical behavior and manifestation [19,34]. The most commonly reported germline *RET* mutations and their associated clinical manifestations are shown in Fig. 1 [21]. Clinicopathologic studies have provided an important framework for correlating tumor genotype with patient phenotype [41–43]. *RET* mutations are known to occur in codons 609, 611, 618, and 620 in exon 10 or in codon 634 in exon 11 in 95% of patients with MEN 2A, whereas the presence of germline codon 634 mutation is associated with manifestation of hyperparathyroidism and pheochromocytoma [25]. The frequency of pheochromocytoma varies depending on the specific *RET* codon mutation, ranging from 0% for codon 611, 4% for codon 609, 9% for codon 620, 22% for codon 618, and 50% for codon 634 [44]. A codon 634 mutation is almost always associated with cutaneous lichen amyloidosis in

Table 1
Estimates^a of the frequency of characteristic clinical manifestations in hereditary MTC syndromes [18,28].

Clinical Manifestation	FMTC		MEN 2A		MEN 2B	
	%		%		%	
	Ferreira et al. [18]	Links et al. [28]	Ferreira et al. [18]	Links et al. [28]	Ferreira et al. [18]	Links et al. [28]
MTC	100	100	95	100	>90	100
Pheochromocytoma	0	0	30–50	10–60	45	50
Hyperparathyroidism	0	0	10–20	10–30	0	0
Marfanoid habitus	0	0	0	0	65	100
Intestinal ganglioneuromatosis	0	0	0	0	100	60–90
Mucosal neuromas	0	0	0	0	NR	70–100

FMTC, familial medullary thyroid cancer; MEN, multiple endocrine neoplasia; MTC, medullary thyroid cancer; NR, not reported.

^a Estimates vary between sources as indicated by more than 1 set of values.

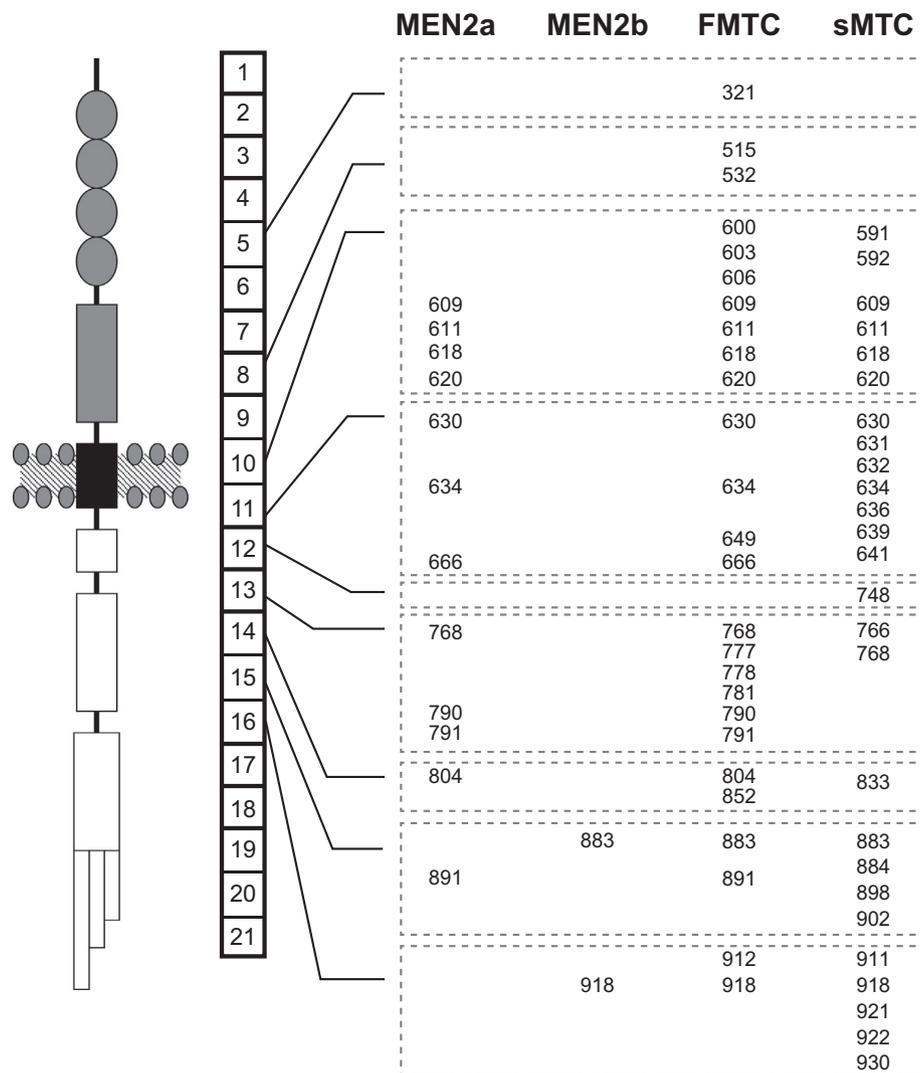


Fig. 1. Overview of the RET receptor, the gene with its exons, and the most common mutations in hereditary and sporadic MTC. Recreated with permission from Tacaliti A, Silveti F, Palmonella G, Boscaro M. Genetic alterations in medullary thyroid cancer: diagnostic and prognostic markers. *Curr Genomics* 2011; 12: 618–25 [21].

MEN 2A, whereas Hirschsprung disease is observed in association with MEN 2A patients harboring mutations in the cysteine codons in exon 10, including codon 609 (15%), 611 (5%), 618 (30%), and 620 (>50%) [45,46]. The majority of patients with MEN 2B harbor the M918T mutation in exon 16 and less commonly the A883F mutation in exon 15. Tumors harboring the A883F mutation follow a less aggressive course than those with an M918T mutation [47]. Rare double *RET* mutations, such as those involving codon V804M and Y806C are associated with atypical presentation of MEN 2B, in

which patients present at an older age and with tumors that behave less aggressively compared with the more typical presentation of MEN 2B, which is associated with the most aggressive tumor behavior [48,49]. Comprehensive reviews have been published that detail the various genetic alterations affecting the *RET* gene as reported in patients with MEN 2A and MEN 2B [25,34].

Another molecular aberration, overexpression of vascular endothelial growth factor (VEGF)-2 receptors, has been described in MTC and is associated with increased metastasis [50,51]. Muta-

tions in *MET*, a proto-oncogene that encodes the receptor for hepatocyte growth factor and aberrant expression of *MET* protein, have been reported in MTC [52,53]. The epidermal growth factor receptor (EGFR) has also been reported to be frequently overexpressed in cancer cells [54]. Similar to *RET*, EGFR is a transmembrane tyrosine kinase receptor involved in the activation of MAPK and the PI3K/Akt pathway [55]. Depending on the specific *RET* mutation present, the interactions of *RET* mutations and abnormalities in expression and function of EGFRs can be complex and are not fully understood [54].

Other molecular targets that may be important in the pathogenesis of MTC include the fibroblast growth factor receptor (FGFR), which is overexpressed in MTC. Blockade of FGFR results in decreased proliferation of MTC [56]. Additionally, the *RAS* family of genes, which encodes the *RAS* protein, an upstream signal relay from membrane-associated tyrosine kinase receptors through the PI3K/Akt pathway, has been found to be mutated especially in sporadic MTC. Mutations in *RAS* appear to be mutually exclusive of *RET* abnormalities [40,57]. Fig. 2 illustrates the molecular pathways implicated in the pathogenesis of MTC and the targeted agents that are currently approved or in clinical development for the treatment of advanced MTC [10].

Diagnosis and monitoring

Preoperative diagnosis of MTC is typically established using a combination of tissue-based cytomorphologic assessment with samples obtained by fine needle aspiration biopsy of a suspicious thyroid nodule, along with demonstrable elevation of serum-based biomarkers, such as serum calcitonin and carcinoembryonic antigen (CEA) [8,29,58]. Serum calcitonin is a well-established, specific, and highly sensitive biomarker employed throughout the trajectory of disease, from diagnosis through surgical management and postresection surveillance monitoring, to evaluating prognosis [8,59–61]. CEA is also a useful biomarker found to be elevated in more than 50% of patients with MTC. CEA can be elevated when preoperative calcitonin levels are negative [29], and it tends to be elevated in patients with poorly differentiated tumors [62]. Levels of these biomarkers correlate with burden of disease and, postoperatively, can indicate the presence of residual disease [59,63]. Calcitonin levels greater than 100 pg/mL are considered to have a 100% positive predictive value for the presence of MTC [59], whereas CEA blood levels of approximately 30 ng/mL suggest regional spread to draining lymph node basins; levels greater than 100 ng/mL are consistent with more distant spread to nonregional lymph nodes [64]. Rising blood levels of calcitonin may be the first sign of tumor recurrence, often becoming detectable before other signs of progression [62]. The doubling time of both calcitonin and CEA is a clinically useful endpoint because it correlates with outcomes such as survival, recurrence, and the time interval between surgery and clinically detectable recurrence [65–68]. A meta-analysis of published works showed that a doubling time of 0–1 year had higher prognostic value than doubling times of more than 1 year [67]. Meijer and colleagues found 5- and 10-year survival rates for patients with a calcitonin doubling time of less than 1 year to be 36% and 18%, respectively, whereas patients with doubling times of 1 year or more had 5- and 10-year survival rates of 98% and 95%, respectively. Five- and 10-year survival rates associated with CEA doubling times less than 1 year were 43% and 21%, respectively, whereas CEA doubling times greater than 1 year were associated with 100% survival at both 5 and 10 years [67].

DNA analysis for the *RET* germline mutation has become standard-of-care and is part of the initial work-up following a diagnosis of MTC [8,60]. The optimal preoperative imaging modality and extent depend on various factors including hereditary status

of the disease, patient age, and calcitonin and CEA levels (Fig. 3) [8,60]. Ultrasound of the cervical neck enables the definition of the degree of thyroid gland involvement as well as the presence of pathologically enlarged regional lymph nodes. Although convenient and very safe, the sensitivity of preoperative cervical ultrasound is quite modest. Ultrasound was shown to be falsely negative for central neck involvement in 14% of patients with MTC and for ipsilateral node involvement in another 17% [69]. Imaging procedures, such as contrast-enhanced computed tomography (CT) of the neck and chest, dedicated magnetic resonance imaging (MRI) of the liver, axial MRI, and bone scintigraphy are recommended to evaluate for metastatic disease when calcitonin levels are above 500 pg/mL, neck disease is extensive, and if signs or symptoms of distant metastases are present [8].

Surgical management of MTC

It is recognized that surgery currently offers the sole opportunity for cure of MTC. As many as 50% of patients, however, present with locoregional spread; another 10–15% may have distant metastases at the time of initial presentation [9]. Patients with MTC can be classified into 3 prognostic and management groups: patients with localized disease without evidence of metastases to regional lymph nodes in whom surgical cure is possible, patients with metastatic disease limited to the neck in which surgical cure may be possible but not always attained, and patients with distant metastasis in which the disease has spread outside the neck and for which surgery is not curative.

Surgical extirpation of the thyroid gland and associated cervical and mediastinal adenopathy remain the mainstay of initial treatment of MTC [8,60]. Total thyroidectomy with bilateral central compartment neck dissection is recommended because of the high rate of associated adenopathy in the central compartment. Lateral neck dissection is indicated if there is radiologic evidence of disease. Partial median sternotomy may be indicated if there is extensive mediastinal adenopathy [70]. Retrospective analysis of the impact of surgery in the setting of distant disease spread showed resection of intrathoracic thyroid metastasis was generally safe and provided survival benefit, especially in patients with disease-free interval ≥ 3 years and those diagnosed at < 45 years of age [70]. Outcomes from these surgeries have been reported as satisfactory with the overall goal being macroscopic control of disease [71,72]. Thus, most patients undergo thyroidectomy either as definitive curative intervention or as a debulking procedure for the purpose of reducing potential future complications [73]. It is good clinical practice to measure serum calcitonin and CEA levels within 2–6 months after surgery to assess for residual disease. Although detectable serum calcitonin within weeks of surgery may portend evidence of persistent disease, a high serum calcitonin value at 6 months or beyond post thyroidectomy is stronger evidence for residual disease. While overall prognosis is good—with many patients experiencing long-term survival—disease progression can be variable depending on disease status at diagnosis as well as the lethality of underlying mutations, which may be unknown.

Residual and recurrent disease

Approximately 50–80% of patients with MTC who undergo thyroidectomy with curative intent continue to have persistently high serum calcitonin levels that indicate the presence of residual disease [60]. The degree to which serum calcitonin is elevated may shed light on the extent and location of the residual disease. For example, calcitonin values that are less than 150 pg/mL 2–3 months after surgery usually indicate persistent locoregional dis-

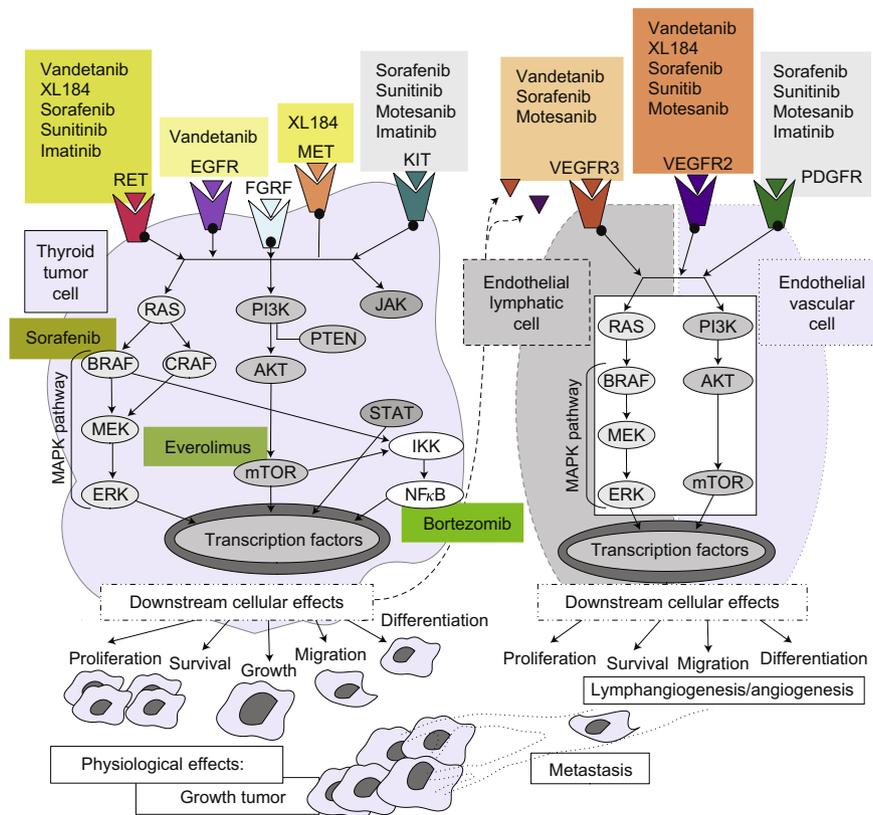


Fig. 2. Tyrosine kinase receptors and downstream effectors. AKT, protein kinase B; BRAF, proto-oncogene B-Raf; CRAF, proto-oncogene c-RAF; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; IKK, inhibitor of nuclear factor kappa-B kinase; JAK, Janus kinase; KIT, proto-oncogene c-Kit; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/ERK kinase; MET, proto-oncogene C-Met; mTOR, mammalian target of rapamycin; NFκB, nuclear factor kappa-B kinase; PDGFR, platelet-derived growth factor receptors; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RET, rearranged during transfection proto-oncogene; STAT, signal transducer and activator of transcription; VEGFR, vascular endothelial growth factor receptor. Recreated with permission from Giunti S, Antonelli A, Amorosi A, Santarpia L. Cellular signaling pathway alterations and potential targeted therapies for medullary thyroid carcinoma. *Int J Endocrinol* 2013; 2013: 803171 [10].

ease [60]. This finding should at minimum warrant a neck ultrasound to identify possible residual disease in the thyroid bed or in the draining lymph nodes. Calcitonin levels greater than 150 pg/mL at 2–3 months postsurgery indicate a higher probability of distant metastatic disease. In addition to a neck ultrasound, patients with this level of biochemical elevation should undergo contrast-enhanced CT or MRI of the neck, chest, and abdomen including the liver [8,60]. If calcitonin levels are highly elevated and routine imaging indicated above failed to reveal site of persistent disease, bone scan and MRI of the axial skeleton can also be considered. Salvage surgery is usually indicated for inadequate surgical resection and for localized recurrent disease that is visible on imaging, especially if there are associated local compressive effects on the trachea or major vessels [8,60]. In the setting of recurrent disease, the decision to proceed with repeat surgery is predicated on the extent of locoregional disease, the presence or absence of metastatic disease, and the risk of surgical complications [74,75]. Surgical excision of residual or locally recurrent MTC may lead to reduced calcitonin levels in many patients and normalization of the calcitonin levels in up to about one-third of patients [74,76]. Local compressive symptoms may be relieved and morbidity decreased if reoperative surgery is performed by an experienced surgeon. This approach must be balanced with the potential for delaying systemic therapy postoperatively during the healing process, especially in the face of incomplete debulking surgery. Regardless of the potential benefit of repeat surgical intervention, active surveillance offers a reasonable option for a significant proportion of patients with persistent, asymptomatic, small-volume locoregional disease.

Medical management of advanced metastatic disease

Cytotoxic chemotherapy

Patients with symptomatic and progressive metastatic disease who are not candidates for local intervention such as surgery or radiotherapy may be considered for systemic therapy. Previously, systemic therapy relied on the use of cytotoxic chemotherapy for advanced MTC with disappointing results [8]. Cytotoxic regimens comprising dacarbazine along with other agents such as cyclophosphamide, vincristine, or 5-fluorouracil have been employed for the treatment of MTC but failed to provide survival benefits, and the regimens are associated with significant toxicity [35]. Current practice guidelines recommend cytotoxic chemotherapy in limited circumstances such as patients with rapidly progressive disease, those who are not eligible for clinical trials or tyrosine kinase inhibitors (TKIs), or those who have progressed on a TKI [8,60].

Radionuclide therapy

Unlike differentiated thyroid cancer, which arises from follicular thyroid epithelium, MTC, a neuroendocrine tumor, arises from the parafollicular cells. Follicular thyroid epithelium has high avidity for iodine, but parafollicular cells are unable to directly take up iodine. Thus, conventional iodine (I)-131 treatments are of no benefit in MTC. In contrast, MTC can take up peptides and amines, hormonal building blocks [77,78]. This characteristic of MTC provides a rationale for radionuclide therapy. A guanethidine derivative,

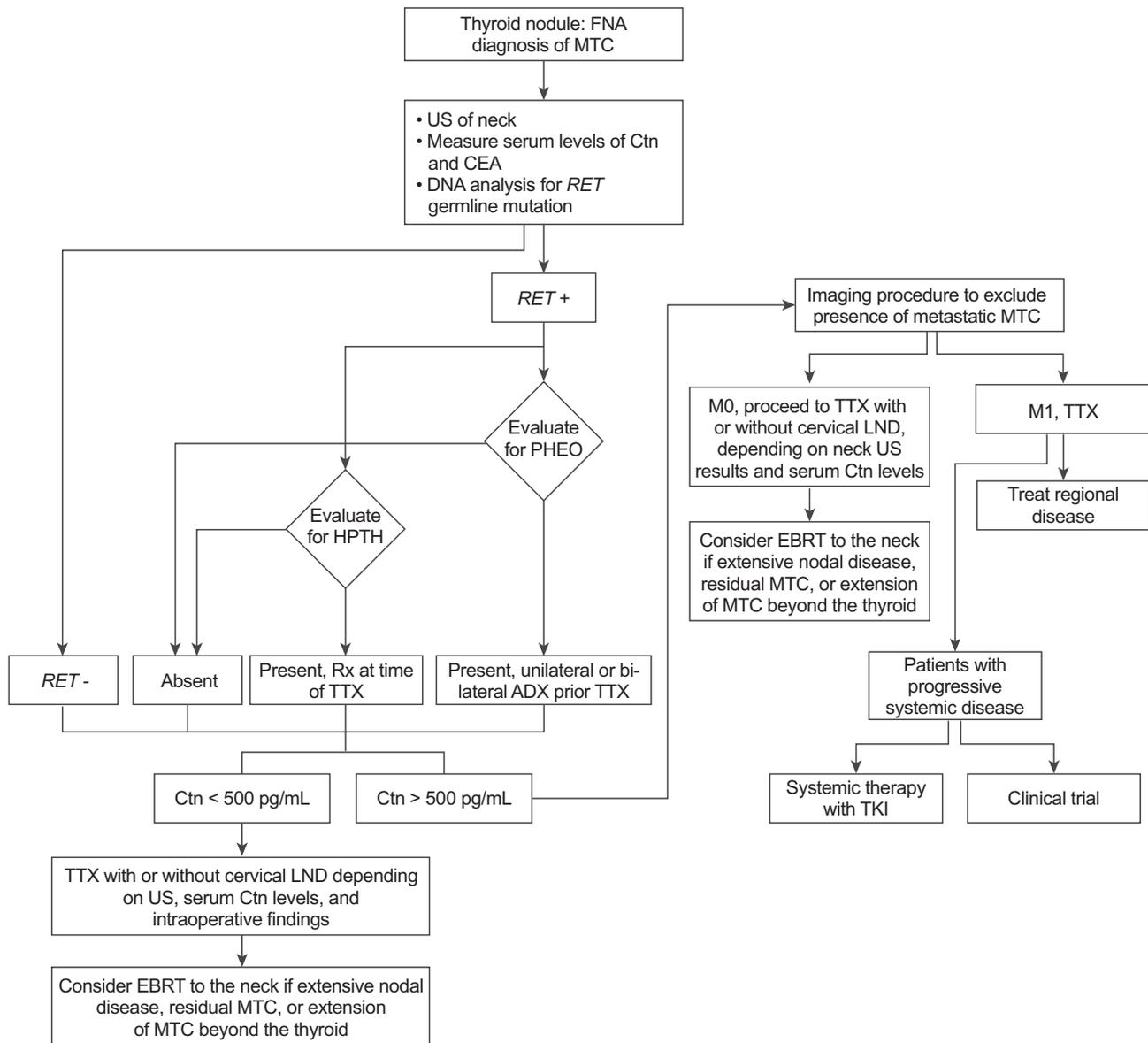


Fig. 3. Treatment algorithm for MTC. Management of patients with a thyroid nodule and histologic diagnosis of medullary thyroid carcinoma. ADX, adrenalectomy; Ctn, calcitonin; CEA, carcinoembryonic antigen; EBRT, external beam radiotherapy; FNA, fine-needle aspiration; HPTH, hyperparathyroidism; LND, lymph node dissection; MTC, medullary thyroid carcinoma; M, metastatic MTC; PHEO, pheochromocytoma; RET, rearranged during transfection; Rx, prescription/medication; TKI, tyrosine kinase inhibitor; TTX, total thyroidectomy; US, ultrasound. Reprinted with permission from Wells SA Jr, 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: 567–610 [8].

metaiodobenzylguanidine (MIBG) is similar to norepinephrine and can be taken up by neurocrest-derived cells. MIBG linked to a high-energy isotope of I-131 is a Trojan horse approach to intracellular delivery of lethal doses of I-131 in a targeted fashion. Neoplastic cells have variable capacity to process MIBG efficiently, and consequently, the efficacy of MIBG-based therapy in advanced MTC is quite variable, with tumors in only about one-third of patients with MTC showing strong MIBG uptake [79,80]. MIBG labeled with I-131 is currently employed mainly for symptom palliation. Although objective responses in terms of tumor shrinkage are limited to only about 30–35% of patients, symptoms may be alleviated in up to 60% of treated patients, at least temporarily [78,80]. The uptake of indium (In)-111 pentetate and I-123-labeled MIBG in MTC tumors has been proposed as a predictive strategy to identify patients likely to respond to octreotide therapy [78,81].

Targeted therapy

The identification of genetic and associated molecular mechanisms and pathways underlying MTC pathogenesis (discussed above) led to the evaluation of targeted biologic agents for the treatment of advanced MTC. The expectation that biologically targeted agents will interfere with critical pathways required for cancer cell survival and proliferation and translate into clinical benefit has been demonstrated in prospective, placebo-controlled, randomized clinical trials. The initial clinical studies of targeted agents in MTC exploited the important role of increased angiogenesis and aberrant *RET* signaling shown to be prevalent in MTC. To date, a large number of phase 2 clinical studies have been conducted, including studies on sorafenib, sunitinib, vandetanib, cabozantinib, pazopanib, and lenvatinib, among others. TKIs possess overlapping profiles in terms of their inhibitory activity against receptor tyrosine kinases implicated in the pathogenesis of MTC such as *RET*,

EGFR, VEGFR, and FGFR (Fig. 2) [10]. Based on the demonstration of promising clinical efficacy in phase 2 clinical trials, definitive phase 3 studies required for regulatory approval have been conducted in some of these agents. To date, there have been two phase 3 studies comparing the efficacy of TKIs to placebo [82,83]. The results of these 2 studies led to the approval by the U.S. Food and Drug Administration (FDA) of vandetanib in April 2011 [84] and cabozantinib in November 2012 [85] for the treatment of symptomatic or progressive MTC in patients with unresectable, locally advanced, or metastatic disease (vandetanib); or progressive, metastatic MTC (cabozantinib) [11,86].

The efficacy and safety of vandetanib in patients with hereditary (*RET* mutations), locally advanced, or metastatic MTC were evaluated in two phase 2 trials (hereditary only) and one phase 3 clinical trial [82,87,88]. Robinson and colleagues found that vandetanib given at a flat dose of 100 mg daily resulted in a partial response (PR) in 16% and stable disease for at least 24 weeks in 53% of treated patients [87]. Wells and colleagues demonstrated that vandetanib 300 mg daily led to a PR in 20% and stable disease in 53% with a median progression-free survival (PFS) of 27.9 months (95% confidence interval [CI], 19.4 – not estimable) [88]. A subsequent multicenter, randomized, placebo-controlled crossover phase 3 study (ZETA) in 331 patients with hereditary and sporadic forms of MTC was conducted [82]. Patients treated with vandetanib had a statistically significant prolonged PFS (hazard ratio [HR] 0.46; 95% CI, 0.31–0.69; $P < .001$). The median PFS in the vandetanib group had not been reached but was predicted to be 30.5 months (based on fitting a Weibull model) compared with 19.3 months in patients treated with placebo. The objective response rate was 45% in the vandetanib group versus 13% in the placebo group. In this study, the most common adverse events (AEs) (>20%) in the vandetanib group were diarrhea (56%), rash (45%), nausea (33%), hypertension (32%), headache (26%), fatigue (24%), and decreased appetite (21%). QT prolongation occurred in 14% of patients. Grade 3 or higher toxicities occurring in more than 5% of vandetanib-treated patients were diarrhea (11%), hypertension (9%), QT prolongation (8%), and fatigue (6%) [82]. Owing to the risk of QT prolongation, routine electrocardiograms should be obtained at baseline and regularly after initiation of treatment with vandetanib. Furthermore, it is recommended that anti-arrhythmic drugs (eg, amiodarone, disopyramide, and others) as well as drugs that prolong the QT interval (eg, chloroquine, clarithromycin, and others) be avoided. Due to the potentially life-threatening cardiac toxicity, vandetanib approval came with the requirement for a risk evaluation and mitigation strategy (REMS) program for all prescribers [11].

Cabozantinib has also been studied in phase 1 and phase 3 studies. A phase 1 dose-escalation study that enrolled 37 patients with a variety of solid tumors or lymphomas included MTC patients with progressive disease as its largest cohort [89]. The MTC cohort achieved an objective response (PR only) of 29% (95% CI, 15–45%). The majority of patients (68%) had a PR or stable disease lasting at least 6 months. Based on these encouraging results, a large ($N = 330$) multicenter, randomized, placebo-controlled phase 3 study (EXAM) of patients with histologically confirmed, unresectable, locally advanced, or metastatic MTC was conducted [83]. The median PFS was significantly longer in cabozantinib-treated patients (11.2 months) compared with the placebo group (4.0 months; HR 0.28; 95% CI, 0.19–0.40; $P < .001$). A PR was seen in 28% of patients on cabozantinib but 0% of patients treated with placebo [83]. Cabozantinib treatment was associated with grade 3 or 4 toxicities in 69% of patients compared with 33% for the placebo group. The most frequent grade 3 or 4 toxicities in cabozantinib-treated patients were diarrhea (16%), palmar-plantar erythrodysesthesia (12.6%), and fatigue (9.3%). The AEs deemed typical of VEGF pathway inhibition were hypertension, hemorrhage,

fistula formation, and gastrointestinal perforation, all of which occurred with greater frequency in cabozantinib-treated patients than in placebo patients [83]. This toxicity profile may make cabozantinib less suitable for elderly patients for whom the prevalence of cardiovascular risk factors is generally higher.

It is not appropriate to compare results of the ZETA and EXAM studies because of important design differences between the 2 trials [82,83]. Most notable is the difference in study populations enrolled in the 2 studies. The EXAM study enrolled only patients with progressive MTC (within 14 months of enrollment), whereas the ZETA study permitted both patients with progressive disease and those with stable metastatic disease. Furthermore, patients in the ZETA study, but not the EXAM study, were allowed to cross over to active treatment. Finally, different *RET* mutation variants are known to have differing impact on overall prognosis, so differences in the distribution of patients across various prognostic *RET* mutation variants in the 2 studies could also have impacted outcomes. The estimated median PFS with vandetanib is numerically longer than with cabozantinib; however, there is no reliable evidence at this time to support any claim of superiority of one approved agent over the other. The choice of which agent to use should depend upon careful consideration of a patient's comorbid conditions and the toxicity profile that the patient is willing to bear.

Although higher level evidence required for regulatory approval is lacking, professional guidelines support the use of other small-molecule kinase inhibitors, such as sunitinib, sorafenib, and pazopanib, in patients who have progressed on vandetanib or cabozantinib, or if neither of these approved agents is appropriate for the patient [60]. Neither sunitinib nor sorafenib is currently approved by the FDA for treating MTC. However, in a phase 2 study that enrolled 35 patients with differentiated thyroid cancer and MTC, sunitinib treatment resulted in PR in 28% and stable disease in 46%. It is worth noting that only 7 of the 35 had a diagnosis of MTC, and efficacy by different histologic subtypes of thyroid cancer was not presented [90]. In another phase 2 study that enrolled 16 patients, sorafenib treatment resulted in PR in 6.3% (95% CI, 0.2–30.2%) and stable disease in 87.5% (95% CI, 61.7–99.5%) [91].

Other targeted treatments previously evaluated or currently under clinical study for advanced MTC (Table 2) include the mTOR inhibitor, everolimus, as well as other TKIs [92]. In a phase 2 study, treatment with everolimus reduced calcitonin and CEA levels by at least 50% relative to baseline in 3 and 4 of 9 patients with MTC, respectively [92]. Another phase 2 study evaluated the efficacy of lenvatinib in patients with advanced MTC [93]. In this study, 26 of the 59 patients (44%) had received anti-VEGFR therapy. The objective response rate was 35% (95% CI, 17–56%) for those who received prior anti-VEGFR therapy and 36% (95% CI, 20–55%) for those who did not. All were PRs. The median PFS for each of these groups, respectively, was 7.3 months (95% CI, 4.0–NE) and 12.9 months (95% CI, 7.1–NE) [93].

Selecting among therapeutic options in advanced MTC

Currently, the most important determinants for selecting systemic therapy in patients with advanced MTC are safety considerations because of potential dose-limiting toxicities associated with TKI therapy. Therefore, selection should be guided by patient characteristics, comorbidities, and other treatments, as well as by disease status and tumor features. Unfortunately, little consensus exists as to how to select a specific treatment as first line, and recent guidelines do not specify between vandetanib and cabozantinib [8,94]. Although benefits to patients with and without *RET* mutations have been seen with TKIs, mutation analysis cannot yet indicate which patients are most likely to benefit from targeted

Table 2
Clinical trials of targeted therapy in MTC. Source: clinicaltrials.gov.

Registration number	Phase	Title and intervention	Estimated enrollment	Study design	Outcomes	Status	URL
NCT01856920	2	A Phase 2 Study of GI-6207 in Patients With Recurrent Medullary Thyroid Cancer (anti-CEA vaccine)	34	Randomized	Calcitonin levels/time to progression	Recruiting	http://ClinicalTrials.gov/show/NCT01856920
NCT01730638	1/2	ImmunoPET for Patients With Medullary Thyroid Carcinoma	24	Open label	Pharmacokinetics and imaging	Recruiting	http://ClinicalTrials.gov/show/NCT01730638
NCT02114658	2	Sorafenib Phase 2 Study for Japanese Anaplastic or Medullary Thyroid Carcinoma Patients	18	Open label	Safety, efficacy, pharmacokinetics	Active, not recruiting	http://ClinicalTrials.gov/show/NCT02114658
NCT01270321	2	A Trial of Pasireotide and Everolimus in Adult Patients With Radioiodine-Refractory Differentiated and Medullary Thyroid Cancer (mTOR plus somatostatin analog)	90	Randomized	Efficacy	Active, not recruiting	http://ClinicalTrials.gov/show/NCT01270321
NCT01155258	1	Temsirolimus and Vinorelbine Ditartrate in Treating Patients With Unresectable or Metastatic Solid Tumors (dose-finding in a wide array of tumors)	19	Open label	Side effects, dose-finding, efficacy	Active, not recruiting	http://ClinicalTrials.gov/show/NCT01155258
NCT01013597	2	Trial of LBH589 in Metastatic Thyroid Cancer (panobinostat)	33	Open label	Efficacy and safety	Completed	http://ClinicalTrials.gov/show/NCT01013597
NCT00121628	2	A Phase 2, Open-label Study of AMG 706 to Treat Subjects With Locally Advanced or Metastatic Thyroid Cancer (motesanib)	184	Open label (various thyroid tumors)	Efficacy	Completed	http://ClinicalTrials.gov/show/NCT00121628
NCT01874873	2	Phase 2 Study of Anlotinib in Advanced Medullary Thyroid Carcinoma	47	Open label	Safety and efficacy	Active, not recruiting	http://ClinicalTrials.gov/show/NCT01874873
NCT00784303	2	Evaluating the Safety and Efficacy of Oral E7080 in Medullary and Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancers, Stratified by Histology (lenvatinib)	116	Open label	Safety and efficacy	Completed	http://ClinicalTrials.gov/show/NCT00784303
NCT00389441	2	Study of AG-013736 in Patients With 131I-Refractory Thyroid Cancer (axitinib)	52	Open label (does not specify MTC)	Efficacy	Completed	http://ClinicalTrials.gov/show/NCT00389441
NCT01856920	1	A Phase 2 Study of GI-6207 in Patients With Recurrent Medullary Thyroid Cancer (yeast-derived anti-CEA vaccine)	34	Open label	Safety and efficacy	Recruiting	http://ClinicalTrials.gov/show/NCT01856920

CEA, carcinoembryonic antigen; MTC, medullary thyroid cancer; mTOR, mammalian target of rapamycin.

treatment. Best supportive measures should always be undertaken and tailored to the patient's presentation for symptom control or for progressive disease that is not amenable to further systemic treatment. Supportive care can include, but is not limited to, agents to relieve bone pain and/or strengthen bone, antidiarrheal medication, correction of electrolyte imbalances, and ongoing management of comorbidities.

Conclusions and future directions

Many patients with hereditary and sporadic MTC present with incurable disease, and treatment for progressive MTC is palliative. General principles that should be considered when managing patients include evaluation and consideration of the presence of progressive disease, symptomatic disease despite best supportive care or localized therapy, or MTC-related symptoms (eg, diarrhea) not controlled with standard treatments.

The rapidly expanding understanding of the molecular pathways responsible for MTC development has fostered the discovery of promising molecularly targeted therapies that reduce tumor size

and may result in disease stabilization and symptomatic improvement. With the advent of small-molecule kinase inhibitors, patients with unresectable or advancing disease now have new options for disease control.

No direct comparisons of vandetanib and cabozantinib have been undertaken; therefore, current findings cannot differentiate these treatments in terms of efficacy. The overall differences between these agents in terms of AEs and/or toxicities may serve as a basis to select one treatment over the other for specific patients. Continued research is needed to better understand the relative benefit-risk of current treatments for MTC and to develop new, potentially more effective, and perhaps curative treatments.

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