Medical Management of Metastatic Medullary Thyroid Cancer

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Abstract

Medullary thyroid cancer (MTC) is an aggressive form of thyroid cancer, which occurs in both heritable and sporadic forms. Discovery that mutations in the *RET* protooncogene predispose to familial cases of this disease has allowed for presymptomatic identification of gene carriers and prophylactic surgery to improve the prognosis of these patients. A significant number of patients with the sporadic type of MTC and even with familial disease, still present with nodal or distant metastases, making surgical cure difficult. Over the past several decades, many different types of therapy for metastatic disease have been attempted, with limited success. Improved understanding of the molecular defects and pathways involved in both familial and sporadic MTC has resulted in new hope for these patients with the development of drugs targeting the specific alterations responsible. This new era of targeted therapy with kinase inhibitors represents a significant step forward from previous trials of chemotherapy, radiotherapy, and hormonal therapy. Although much progress has been made, additional agents and strategies are needed to achieve durable, long-term responses in patients with metastatic MTC. This article reviews the history and results of medical management for metastatic MTC from the early 1970s up until the present day.

INTRODUCTION

Medullary thyroid cancer (MTC) comprises 5 to 10% of all thyroid cancers.[1] MTC arises from the parafollicular C cells of the thyroid gland, which originate in the neural crest. The disease progresses from C cell hyperplasia (CCH), often with elevated calcitonin levels, to microscopically invasive carcinoma, then grossly evident carcinoma.[2] Like other neuroendocrine tumors, MTC can elaborate a variety of products such as calcitonin (CT), carcinoembyonic antigen (CEA), serotonin, and chromogranin A that may cause symptoms such as diarrhea in patients with metastatic disease. In the context of CCH and MTC, the secretion of calcitonin predominates and can be used to confirm the diagnosis,[3] indicate treatment efficacy,[4] and monitor for disease progression or recurrence.[5]

Medullary thyroid cancer develops sporadically in 60 to 75% of cases,[3,6] or as a result of a germline mutation in the <u>re</u>arranged during <u>t</u>ransfection (*RET*) protooncogene, as is seen in multiple endocrine neoplasia types 2A and 2B (MEN2), and familial MTC syndrome (FMTC). MTC often progresses in an indolent fashion with a 15-year survival of 85%, but

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has a tendency to spread to locoregional lymph nodes early, making surgical cure difficult.[7] Total thyroidectomy and lymphadenectomy result in biochemical cure (normalization of calcitonin and CEA) only 40% of the time.[7,8] Even when biochemical cure is achieved, approximately 9% of patients will later develop recurrent disease.[8] For patients with sporadic MTC, total thyroidectomy and at minimum, central neck dissection, is performed upon histological confirmation of the disease. Patients with known *RET* mutations are offered prophylactic thyroidectomy and lymphadenectomy in childhood or upon discovery of the mutation.[9] Due to the difficulty in achieving surgical cure, medical treatment for residual micrometastatic disease and recurrent disease are critical for long-term survival. Unfortunately, the relative rarity of the disease makes clinical trial design and patient accrual difficult. Thus, much of our knowledge about medical treatment of MTC rests upon small prospective series and retrospective reports.

The advent of targeted small-molecule kinase inhibitor drugs has revolutionized medical treatment of medullary thyroid cancer (MTC). Drugs such as vandetanib and cabozantinib produce disease regression in a significant portion of patients, and can extend progression-free survival in advanced, unresectable MTC.[10,11] Other multikinase inhibitors such as sunitinib and sorafenib also offer hope to MTC patients progressing on other treatments, and ongoing clinical trials continue to evaluate additional agents. This review seeks to update readers on the recent developments in targeted small-molecule therapies for medical management of MTC. It also attempts to provide an overview of the major radioactive and chemotherapeutic regimens that preceded them, and remain as treatment options in MTC, as well as some of the many other therapies that have been tried with limited success in this previously treatment-refractory disease.

TYROSINE KINASE INHIBITORS

The first indication of the promise of small-molecule kinase inhibitors came from the class prototype, imatinib. Targeting the mutant BCR-ABL tyrosine kinase in chronic myeloid leukemia, imatinib dramatically improved response rates of CML patients in blast crisis, and significantly forestalled progression from the chronic phase in long-term studies.[12,13] Imatinib also targets the mutated c-KIT receptor responsible for gastrointestinal stromal tumor (GIST), and use of imatinib after resection of high-risk GISTs had similarly impressive results, with 5-year survival improving from 35% to 83%.[14] These encouraging studies suggested a role for small-molecule inhibitors in MTC.

Like CML and GIST, oncogenic transformation in MTC occurs due to a mutation causing constitutive activation of a signaling pathway. The causative genetic region for autosomal dominant MEN2A was mapped by genetic linkage to chromosome 10 in the late 1980s,[15,16] and mutations in the (*RET*) gene were determined to cause MEN2A, MEN2B, and FMTC in the early 1990s.[17–22] In sporadic MTC, somatic *RET* mutations occur in 40–65% of tumors.[11,23] While many different *RET* mutations can lead to MEN2 syndromes, the most prevalent mutations include C634R in MEN2A and M918T in MEN2B.[24] The M918T mutation also represents the most common somatically-occurring mutation in sporadic MTC.[23] RET is a membrane-bound receptor tyrosine kinase involved in renal and enteric nervous development and is activated by any of four glial-derived neurotrophic factor

(GDNF) molecules.[25] While RET activation principally induces the RAS-RAF-MEK-ERK mitogen-activated protein kinase (MAPK) pathway, RET can also activate phosphatidylinositol-3-kinase/Akt (PI3K/Akt), janus-activated kinase/signal transducers and activators of transcription (JAK/STAT), and jun-N terminal kinase (JNK), among other pathways (Figure 1).[25–27] In MTC, RET mutations lead to substrate-independent dimerization of the receptor causing constitutive activation, unrestricted signaling, and ultimately, cancer.[25,28]

Although it could be readily appreciated that MTC shared similar mechanisms of molecular pathogenesis to cancers treatable with imatinib, research into CML, melanoma, and papillary thyroid cancer helped spur development of MAPK and related pathway inhibitors.[25,29] In addition to RET, interactors with the MAPK pathway include receptors for vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF).[30] Gain-of-function mutations in BRAF kinase, a downstream target of RET and key effector in the MAPK pathway, occur in nearly 60% of melanoma cell lines and 45% of human papillary thyroid cancers.[31–33] With aberrant activation of the MAPK and related pathways recognized as causative events in human cancers affecting a large number of patients, intensive research efforts have produced small molecule inhibitors with activity at multiple receptors and at multiple steps of these pathways, from receptor to effector kinases (Table 1). While much of this research has focused on papillary thyroid or other cancers, several kinase inhibitors have been evaluated for activity in medullary thyroid cancer, with two, vandetanib and cabozantinib, currently approved by the FDA for MTC.

Vandetanib was the first kinase inhibitor approved for treatment of symptomatic metastatic medullary thyroid cancer.[34] Initially developed as an orally-available VEGFR-inhibitor, vandetanib was found to prevent activation of RET receptors with common mutations and to block MTC tumor growth in mice.[35] Two less-common *RET* mutants, V804M and V804L, demonstrate resistance to vandetanib inhibition of RET.[36] In 2010, results of a phase-II study showed that treatment of with 300mg of vandetanib daily induced objective responses in 6 of 30 patients (20%) with unresectable locally advanced or metastatic hereditary MTC.[37] Stable disease or objective responses occurred in 22 of 30 patients (73%), and 80% saw reductions in serum calcitonin. Estimated PFS was 27.9 months. A second study of 100mg daily vandetanib treatment in patients with advanced hereditary MTC reported similar results, with 13 of 19 patients (68%) having stable disease or partial objective responses.[38] In both trials, diarrhea, rash, and fatigue were the most common adverse events, and QTc prolongation requiring dose-reduction occurred.[37,38]

Supported by the results of these initial trials, investigators initiated a phase-III randomized, double-blind trial of vandetanib 300mg daily versus placebo in unresectable locally advanced or metastatic medullary thyroid cancer.[10] Included were 331 patients with sporadic or hereditary MTC. In this trial, vandetanib significantly prolonged PFS, with an estimated median PFS of 30.5 months in the vandetanib treatment group compared to 19.3 months in the placebo group (p<0.001). Objective radiologic responses occurred in 45% of treatment vs. 13% of placebo groups (p<0.001), and disease control rates were 87% in treatment vs. 71% in placebo groups (p=0.001). No overall survival benefit was noted due to

inadequate event numbers, and possibly because 93% of patients who progressed while receiving placebo elected to crossover to open-label vandetanib. Additionally, all but one objective responses in the placebo group occurred after crossover. Toxicities were common, and 35% of patients required dose-reductions due to adverse events. Grade 3 and higher adverse events included diarrhea (11%), hypertension, (9%), QTc prolongation (8%), and fatigue (6%). Although not observed in the trial, torsades de pointes has been reported and QTc monitoring is essential during vandetanib treatment.[39]

A potential problem with VEGFR-inhibitor treatment is development of resistance or diminished response due to blockade-induced upregulation of related pathways.[40] Cabozantinib, or XL184, is an orally-available multi-kinase inhibitor with activity against MET, VEGFR2, RET, and others.[41] Its developers proposed its broader inhibition of important kinases, particularly MET, which can be upregulated in MTC, as offering potential to avoid treatment failures due to targeting VEGFR alone.[40,41] In cell culture and animal models, cabozantinib prevented phosphorylation of its target kinases, reduced cell proliferation, and limited angiogenesis, tumor invasiveness, and metastasis of multiple cancer cell lines.[41] In a phase-I trial of cabozantinib, of 37 patients with advanced or recurrent medullary thyroid cancer, 10 (29%) demonstrated objective partial responses, and 68% had stable disease or objective response at 6 months.[40]

The efficacy of cabozantinib for prolonging progression-free survival was shown in a phase-III randomized, double-blind trial of cabozantinib in progressive medullary thyroid cancer.[11] In this manufacturer-sponsored trial, 330 patients with advanced or recurrent MTC were randomized to cabozantinib 140mg daily or placebo until intolerable toxicity or progression. Patients receiving cabozantinib had significantly longer progression-free survival than those receiving placebo (median PFS 11.2 vs. 4.0 months, $p<0.001$), and this advantage applied both to patients with and without *RET* mutations. Objective radiographic responses were observed in 28% of cabozantinib versus 0% of placebo patients ($p<0.001$). Although not enough deaths had occurred to fully evaluate overall survival, despite the large advantage in progression-free survival among treated patients, investigators observed no difference in overall survival, with death occurring in 21 (10%) patients in the cabozantinib arm and 10 (9%) of patients in the placebo arm. This was not due to crossover, as crossover upon progression was forbidden by the study protocol, and patients receiving any other additional cancer therapy were censored. Adverse events were frequent with cabozantinib treatment. Grade 3 or 4 adverse events, defined as severe or life-threatening/disabling,[42] including hemorrhage, fistulas, and gastrointestinal perforation occurred in 69% of cabozantinib patients versus 33% in the placebo group, while "serious adverse events," defined as imminently life-threating or resulting in death (which were reported separately from grade 3 and 4 events),[43] occurred in 42.1% of cabozantinib patients versus 22.9% of placebo patients. Overall, 79% of cabozantinib-treated patients required dose-reductions due to adverse events. Due to a requirement for radiographically-evident disease progression for inclusion in this trial, which was not required for the phase-III trial of vandetanib, patients in the cabozantinib trial may have had more advanced disease, although this too was influenced by crossover (placebo group PFS 4.0 months vs. 19.3 months in the vandetanib trial placebo group).[10,11] This difference and the protocol difference regarding whether

treatment crossover was allowed, complicate direct comparison of the two trials, both in terms of outcomes and side-effect profiles.

Current National Comprehensive Cancer Network (NCCN) guidelines now recommend that clinicians consider either vandetanib or cabozantinib for medical therapy of advanced, unresectable MTC.[44] After failure of these agents, the guidelines recommend considering two additional agents, sorafenib or sunitinib, or enrollment in a clinical trial.[44] The evidence for sorafenib and sunitinib in MTC is not as robust as for the other drugs, but small studies have demonstrated efficacy of both in medullary thyroid cancer.

Sorafenib is a multi-kinase inhibitor that is FDA-approved for treatment of renal cell and hepatocellular cancers.[45] Although developed for B-RAF and C-RAF inhibition, sorafenib also potently inhibits several other pathways and kinases including VEGFR, PDGFR, and both wild-type, mutant, and V804M and V804L resistant-mutant RET.[27] A phase-I study evaluating treatment with sorafenib and the farnesyl-transferase inhibitor (affecting RAS kinase) tipifarnib reported a dramatic objective response in a sporadic, *RET*-mutation-positive MTC patient.[27] Later follow-up with 13 MTC patients enrolled in the same study revealed a 38% rate of partial responses and 69% overall disease control (partial response + 6 month stable disease) rate.[46] A phase-II study evaluated 21 MTC patients treated with 400mg twice-daily sorafenib without tipifarnib. All patients experienced stable disease and some tumor shrinkage, with 2 having objective partial responses.[45] Durable stable disease of at least 6 months occurred in 11 patients (52%).[45] Adverse events were frequent with 76% of patients requiring dose-reductions and grade 3 or higher complications occurring in 13 patients (62%). The most common serious adverse events were hand-foot-skin reaction, hypertension, diarrhea, and infection.[45] A non-randomized, retrospective study of Spanish thyroid cancer patients treated with sorafenib found a 47% response rate among 15 MTC patients.[47] Additional small studies and case-reports support the consideration of sorafenib in MTC, although additional randomized studies are needed.[34,48,49]

Sunitinib is a multi-tyrosine kinase inhibitor with activity against VEGFR1 and 2, c-KIT, FLT3, PDGFR, and RET.[50] On the basis of its inhibitory spectrum, Kelleher and McDermott in 2008 reported treating a patient with metastatic MTC with sunitinib, leading to marked reduction of tumor size by imaging and improvement in clinical symptoms[51]. Another group reported a patient with advanced MTC whose dramatic response to sunitinib permitted surgical resection of his disease, despite the absence of a detectable *RET* mutation.[52] A phase-II trial testing 37.5mg daily sunitinib included 7 patients with metastatic MTC and found objective responses in 3 of 6 with radiologically-evaluable lesions (50%) and stable disease in 2 for a disease control rate of 71% in this small sample.[50] More than 10% of all treated patients experienced grade 3 or higher toxicities of fatigue, diarrhea, hand/foot syndrome, and leuko/neutropenia.[50] Both sorafenib and sunitinib effectively block phosphorylation of the *RET* V804M mutant, which confers resistance to vandetanib and reduced effectiveness of cabozantinib.[53]

Other tyrosine kinase inhibitors have been assessed for treatment of MTC. The class-prototype imatinib has limited inhibitory activity against RET, and two open-label trials treated a total of 24 MTC patients with imatinib. In these trials, no objective responses were

observed, whereas treatment incurred significant toxicity, and use of imatinib has stalled in MTC.[54,55] Gefitinib represents another drug with efficacy in a different cancer type that was explored in MTC. Gefitinib is an EGFR inhibitor with activity in EGFR-mutant non-small cell lung cancer, however when tested in a phase-II trial which enrolled four patients with MTC, no objective responses were noted.[56]

Axitinib is an orally-available kinase inhibitor with relative specificity to VEGFR1–3.[57] A phase-II trial treated 60 patients, including 11 with MTC, with 5mg of axitinib twice daily. Partial response or stable disease occurred in 5 (45%). Adverse events included fatigue and diarrhea, which were common. Twelve percent of all treated patients experienced grade 3 or higher hypertension, and no other serious toxicity occurred in more than 5% of patients. Interestingly, axitinib's activity in MTC occurs without inhibition of RET. Another orally-available multi-kinase inhibitor, motesanib, demonstrates activity against VEGFR1–3, PDGFR, and KIT, but does not inhibit mutant RET.[58] A phase-II trial enrolling 91 MTC patients found that although only 2 patients achieved objective partial radiographic responses, 76% of treated patients achieved "clinical benefit", defined as objective response or durable stable disease.[58] Both *RET* mutation-positive and negative patients achieved durable stable disease, with higher rates (62%) among *RET* mutation-negative than mutation-positive (42%) patients.[58] Grade 3 and 4 adverse events occurred in 38% and 3% of patients, with gallbladder toxicity occurring in 8 of 91 patients (9%).[58]

Ponatinib, a newer multikinase inhibitor, shows broad inhibitory activity across a wide range of kinases. In particular, ponatinib shows strong inhibition at low drug concentrations of BCR-ABL and RET, with anti-RET potency at least 100–1000 times greater than those for vandetanib, cabozantinib, or motesanib.[53] *In vitro* studies demonstrate that ponatinib inhibits phosphorylation and signaling through multiple pathways, and besides BCR-ABL and RET, ponatinib blocks VEGFR2, PDGFRα, SRC, KIT, FGFR1, and FLT3.[59] Two recent studies support ponatinib's potential for efficacy in MTC. In cell culture, low concentrations of ponatinib prevent phosphorylation of RET and its downstream target ERK1/2,[53] and mice injected with MTC cell line tumors show significantly inhibited tumor growth with ponatinib treatment.[59] Notably, ponatinib shows *in vitro* activity against kinases with common inhibitor-resistance mutations, including the *BCR-ABL* T315I mutant, *FLT3* F691I mutant, and *RET* V804 and Y806 mutants.[53,59] Additionally, although rare, some patients do carry *RET* V804 and Y806 mutations, which confer resistance to vandetanib and reduce cabozantinib effectiveness by blocking the RET ATP-ase active site where these inhibitors bind.[53] By exploiting a slightly different mechanism of activity – binding and stabilizing the inactive receptor state – ponatinib could offer an alternative after initial treatment options have failed.[53] While such a broad spectrum of activity could theoretically lead to greater efficacy, recent clinical trials of ponatinib in CML raised serious safety concerns. The phase-II PACE trial observed high rates of arterial thrombotic events, including cardiovascular (7.1%), cerebrovascular (3.6%), and peripheral vascular (4.9%) thrombosis.[60] Ponatinib sales and clinical trials were suspended in late 2013 after United States Prescribing Information adverse event surveillance identified a 17.1% rate of arterial thrombotic events,[60] and the current drug label contains a black-box warning citing a rate of arterial and venous occlusion of "at least 27%" in ponatinib-treated patients.[61] Although

ponatinib can once again be prescribed for CML under a risk evaluation and mitigation strategy, reports of fatal arterial thrombotic events continue, and its future in MTC appears doubtful.[62]

Neither vandetanib nor cabozantinib shows a definitive correlation between *RET* mutational status and efficacy.[63] Phase-II trials of cabozantinib identified patients with and without *RET* mutations who showed tumor shrinkage.[40] In the phase-III vandetanib trial, patients with sporadic MTC who had the *RET* M918T mutation had a higher response rate than those who did not (54.5 vs. 30.9%), but the investigators' inability to determine the mutational status of 45% of the study patients due to inadequate tissue specimens, limited overarching conclusions regarding genotype and response to treatment.[10] Patients receiving motesanib, which functions principally through VEGFR inhibition, had a higher rate of partial responses and stable disease (8% and 62%) in *RET* mutation-negative patients than in mutation-positive patients (0% and 42%).[58] Further complicating genotype-phenotype correlations, axitinib offers minimal if any inhibition of RET,[57] yet still achieved stable disease or objective responses in 45% of MTC patients, while gefitinib achieved no responses through targeting EGFR.[56] Although *RET* mutations are sufficient to induce neoplasia in MEN2 patients, aberrant activity of VEGFR and MET is also observed in MTC.[40,58] Lack of a strong connection between the presence of an activating *RET* mutation and response to treatment, or drug activity against RET, highlights the contributions that blockade of additional receptors besides RET, especially VEGFR, make to clinical efficacy of these drugs[63]. Thus, despite the appeal of "rational" treatment, the pathways representing the most important targets for clinical effectiveness may not be the same as those presumed based on our understanding of MEN2. Further research could improve understanding of signal transduction when considered as complex networks, rather than as discrete and sequentially proceeding pathways, improving future efforts to target therapeutics.

Although there are now options for patients with metastatic MTC, the question of optimal medical management will likely remain open for the time being. No randomized trial has yet demonstrated an overall survival benefit in MTC with targeted agents, and their toxicities and expense are considerable.[63] Head-to-head studies directly comparing therapies are lacking, but could elucidate the relative benefits of different agents. Over the next several years, longer follow-up of patients included in recent trials will become available to determine effects on overall survival, studies of additional agents will accrue, and continuing research will further illuminate the cellular networks involved in response to treatment.

CYTOTOXIC CHEMOTHERAPY

Prior to introduction of current kinase inhibitor-based therapies, chemotherapy and radiation formed the mainstay of medical MTC treatment. While recent advances in small-molecule therapies have largely supplanted these regimens, they remain in consideration for refractory cases, and research continues to improve the sensitivity of MTC cells to them. As kinase inhibitors display mostly cytostatic, rather than cytocidal effects, a need persists for effective agents to eliminate cancerous cells.

Doxorubicin and dacarbazine-Standard cytotoxic chemotherapy agents have been employed in management of metastatic MTC for more than 30 years with mixed results. Doxorubicin (Adriamycin) and dacarbazine (DTIC) are the two agents with the most extensive track record, and dacarbazine is currently recommended as a treatment option for patients with disseminated, symptomatic disease.[44]

Doxorubicin was first tested in MTC patients in the 1970s. Two case series[64,65] and one small prospective study[66] documented the response of advanced MTC to doxorubicin administered as a single agent. The results of the case series were split. One reported a robust anti-tumor effect[64] but the other only minor tumor shrinkage.[65] The prospective study was more encouraging, as 3 of 5 MTC patients responded to treatment and demonstrated significantly better overall survival than those patients that did not respond.[66]

Thereafter, doxorubicin was studied in combination with a number of other agents. In 1985, Shimaoka *et al.* combined doxorubicin with cisplatin in a multi-institutional, prospective, randomized controlled trial of advanced thyroid cancer. Ten of 84 patients had MTC—4 of which were treated with doxorubicin alone, and 6 treated with the combination regimen. Disappointingly, only 1 MTC patient in the doxorubicin-only arm, and 2 in the combination arm demonstrated partial tumor responses, defined as decrease in total tumor volume of more than 50%. There were no complete responses.[67] Sridhar *et al.* also tested doxorubicin in combination with cisplatin, but included only 1 MTC patient in a study of neuroendocrine cancers. The patient with MTC did relatively well—demonstrating a partial response lasting 58 weeks—but treatment was eventually discontinued due to doxorubicin-mediated cardiac toxicity.[68]

In 1990, Scherubl *et al.* attempted to build on previous work by testing doxorubicin combination regimens in a phase II clinical trial. In this study, vindesine and cisplatin were added to doxorubicin and administered to 20 patients with advanced thyroid cancer, 10 of whom had MTC. Of MTC patients, 1 had a partial tumor response, 6 had stable disease and 3 progressed. The authors declared this combination ineffective for treatment of advanced thyroid cancers.[69] Droz *et al.* used a range of chemotherapeutics in patients with advanced non-anaplastic thyroid cancers but included only a small number of MTC patients in each group. Investigators observed partial tumor responses in the MTC patients in the doxorubicin-only arm, but these were short lived and many patients experienced cardiac toxicity.[70] Although doxorubicin induces partial morphologic tumor responses in a reasonable proportion of MTC patients, its use is severely limited by cardiac toxicity, and thus it is not an ideal chemotherapeutic agent for patients with advanced MTC.

Dacarbazine (DTIC), an alkylating agent, was first used as a single agent chemotherapeutic for MTC in the 1980s. The first case reports boasted dramatic reductions in metastatic tumor burdens (though these lasted less than 1 year) and thus encouraged further investigation of this drug's efficacy in advanced MTC.[71,72] The first DTIC/5-FU combination trial achieved partial responses in 3 of the 5 MTC patients included in the study. These responses lasted 8 to 10 months. A fourth patient achieved stable disease. Given the encouraging tumor responses and a limited number of grade I and II side effects, this study served as the basis for testing DTIC combinations in larger numbers of patients with MTC.[73]

The DTIC combination trials that followed failed to achieve results that would suggest the drug's utility as a standard adjuvant treatment of advanced MTC. DTIC was combined in various ways with cyclophosphamide, vincristine, streptozocin, and epirubicin. Though no trial included more than 20 MTC patients, most reported moderate success with one-third to one-half of patients achieving partial tumor responses or stable disease for an average of 1 year.[74–78] Despite the results of these trials, of the major antineoplastic agents studied, DTIC is the only one currently recommended for patients with disseminated symptomatic MTC by the National Comprehensive Cancer Network.[44]

Capecitabine-Capecitabine is a 5-FU prodrug that is converted in target tissues by thymidylate phosphorylase and selectively accumulates in tumors, rather than plasma or muscle tissue. Capecitabine interferes with DNA synthesis by inhibiting thymidylate synthase, preventing tumor cell proliferation.[79] Widespread experimentation with 5-FU in other neuroendocrine cancers, availability of capecitabine via oral administration, and the promise of trials evaluating capecitabine in colorectal and breast cancers, has led to use of this drug in metastatic MTC.[80] Thus far, only case reports exist, and in these, concurrent use of other agents obscures capecitabine's effects. Nevertheless, disease stabilization in most patients has been reported.[80–82]

EXTERNAL BEAM RADIATION

External beam radiotherapy (EBRT) has been used sporadically in the treatment of MTC for more than 40 years, but is not currently considered standard treatment. As with other methodologies, there are limited clinical trials to guide decision-making about the indications for EBRT. Most of what is known about the efficacy and safety of EBRT for MTC is derived from small, single institution experiences.

Prior to 1990, a number of small series reported contradictory conclusions about the utility of EBRT as adjuvant treatment for MTC. In 1977, Steinfeld treated 4 MTC patients with EBRT and achieved local control of their disease lasting 3 to 6 years. He recommended that EBRT be used to treat MTC, and further suggested that the modality be tested in combination with chemotherapy.[83] Samaan *et al.* published a contradictory retrospective study in 1988. In this series, 57 patients with advanced MTC treated with total or subtotal thyroidectomy followed by EBRT were compared to patients treated with surgery only. The group treated with EBRT had worse survival than those treated with thyroidectomy only.[84]

The largest series examining EBRT in MTC was published in 1990 by Jensen *et al.* This multicenter retrospective review included 5,287 patients, 200 of whom had MTC. Approximately 30% of MTC patients were offered some sort of adjuvant treatment, although the specific number receiving EBRT was not reported. The authors found that nearly equal proportions of patients with MTC at each disease stage were offered EBRT. Analysis of the entire MTC cohort demonstrated that patients undergoing surgery followed by EBRT had 100% 5-year survival, whereas patients who only had surgery had a 91% 5-year survival. When the cohort was divided by disease stage, EBRT conferred a survival advantage in patients with regional disease, but not in patients with distant metastases.[85] Given their large sample size, this study serves as one of the foundations for the ATA

recommendation to offer EBRT to post-thyroidectomy MTC patients at high risk for locoregional recurrence.[9]

Another large series examining EBRT in patients with MTC was published in 1996. This was a retrospective, single center series looking at patients diagnosed and treated for MTC from 1954 to 1992. The study included 72 patients with MTC, 43 of whom received EBRT. At this institution, the indications for EBRT in the context of MTC included (1) residual microscopic disease after thyroidectomy, (2) presence of tumor within 2 mm of the resection margin, (3) extraglandular invasion or lymph node involvement, and (4) elevated post-operative CT (in the absence of distant metastases). Patients received a variety of radiation protocols. The most important finding in this series was that in patients at high risk for locoregional recurrence, EBRT seemed to confer a significantly longer 10-year relapse-free rate compared to those that only had surgery (p = 0.049).[86] This study provided support for Jensen *et al*'s suggestion that EBRT is indicated in those patients at high risk for locoregional recurrence.

Nearly a decade later, Schwartz *et al*. published a single institution series that included 34 patients with MTC treated with total thyroidectomy, appropriate neck dissection and EBRT between the years 1995 and 2004. Indications for adjuvant EBRT were gross or microscopic residual disease, soft tissue extension, nodal disease, or mediastinal involvement. There were 4 locoregional failures in this cohort, all occurring within 26 months of completion of EBRT. Five-year disease specific survival was 62%, and overall survival was 56%. The 5-year relapse-free rate was 87%. These results supported a role for EBRT in patients at high risk for local recurrence in the adjuvant setting. The authors emphasized that this type of control was especially important in patients with MTC, even those with distant metastases, as they tend to live a long time with disease and good locoregional control can confer a better quality of life.[87]

The most recent study examining the use and utility of EBRT in MTC patients was published in 2010 by Martinez *et al*. This analysis was conducted using the SEER cohort (1988 – 2004), and included 534 patients with MTC. All patients had been treated with total thyroidectomy with at least one lymph node excised at the time of surgery. Patients with distant metastases were excluded. Interestingly, EBRT did not affect overall survival when all patients were examined, nor when the subset of patients with lymph node-positive disease were analyzed.[88]

Currently, the American Thyroid Association suggests that EBRT be used in patients post-operatively who are at high risk for locoregional recurrence, as well as be offered to patients with extensive M1 disease as a palliative treatment.[9]

RADIOACTIVE IODINE

Radioactive iodine (RAI) has been useful in the treatment of differentiated thyroid cancer since the 1940s,[89] but is largely ineffective in MTC. In differentiated thyroid cancers, follicular cells concentrate radioactive ^{131}I through a sodium iodide symporter on the cell surface, permitting damage to the cancer cell by the emitted β particle. Though C cells do not concentrate iodine,[90] they can be damaged by exposure to radioactive ^{131}I by virtue of

the bystander effect.[91–94] RAI treatment has been offered to MTC patients with positive post-operative thyroid scans or persistently elevated calcitonin, as these are signs that thyroid tissue was left behind after surgery. It is possible that the residual tissue is a mixture of C cells and iodine-concentrating follicular cells, and thus small foci of MTC may be eradicated by the β particles emitted from neighboring follicular cells.

Though initial case reports were promising,[95,96] the utility of this modality has not been borne out in modern practice. Saad *et al.* published the M.D. Anderson experience with RAI in MTC in 1983. In this series, there was no difference in disease course, recurrence rate, or overall survival between 15 MTC patients who underwent RAI and 84 patients treated with surgery alone.[97] In 2006, Erdogan *et al.* published a series (n=7) suggesting that RAI may be useful as an adjuvant treatment for MTC in patients with persistently elevated calcitonin and residual microscopic disease. Their conclusions were based on the finding that 2 of 3 patients with localized disease and 1 of 4 patients with locoregional disease achieved biochemical cure after treatment with RAI. However, their conclusions were limited by their small study population and short follow up interval, which was a maximum of five years.[98]

The most recent RAI series by Meijer *et al.*[99] is the largest and supports the suggestion made 30 years earlier that RAI is not an effective adjuvant treatment for MTC. This multicenter, retrospective analysis compared 232 patients with local or locoregional MTC treated with surgery only to 61 matched patients that were also given post-operative RAI. Investigators attempted to standardize the surgical treatment received by the patients by only including those patients that underwent surgery according to the American Thyroid Association guidelines set forth in 2009.[9] In these groups, they found no difference in disease-free or disease-specific survival. These findings held when they performed the same analysis for the subgroup of patients with hereditary, clinically apparent MTC. Patients with MTC still occasionally receive RAI when medical therapies, such as cytotoxic chemotherapy fail, but current evidence indicates this is unlikely to provide much benefit. There has been renewed interest in "resensitizing" thyroid cells refractory to treatment with RAI by using kinase inhibitors in follicular-origin thyroid cancer, but these experiments have not yet gained ground in MTC.[100,101]

SOMATOSTATIN ANALOGUE-BASED REGIMENS

Somatostatin is an endogenous peptide that inhibits many secretory or proliferative cellular functions by binding to a somatostatin receptor (SSTR) expressed on cells of neural crest origin. The endogenous peptide has a short half-life, but longer-lasting synthetic analogues allow imaging and treatment of a variety of neuroendocrine tumors (NETs). Octreotide, the most widely used analogue, binds primarily to SSTR type 2 (SSTR2), which is the most commonly expressed receptor subtype on gastrointestinal (GI) NETs and on MTC cells.[102] Octreotide suppresses hormonal secretion by NETs, thereby alleviating symptoms, reducing biomarker levels, and occasionally causing tumor stabilization.[103] Given the drug's success in treating patients with GI NETs, it has also been tried in patients with MTC.

In 1990 Mahler *et al.* reported 3 patients with metastatic MTC treated daily with escalating doses of octreotide delivered via a subcutaneous pump. In 2 patients, both with MEN2A, CT

levels dropped below baseline and remained at normal levels for 15 and 17 months. In addition, these patients reported improvement in symptoms, providing support for the use of the drug in MTC patients with symptoms refractory to other treatments.[104] Two years later, Modigliani *et al.* published a trial including 14 patients with MTC and persistently elevated CT. These patients were stratified into high or low risk groups based on their pre-treatment CEA levels and given a daily infusion of 0.5 mg of octreotide for 90 days. In contrast to Mahler *et al.,* this group found that treatment with octreotide was not associated with a sustained decrease in CT levels, nor did the drug cause significant tumor stabilization or regression. In fact, in the high risk group of patients, only 1 patient had a slight drop in CT, and all demonstrated progressive disease by imaging.[105]

These early disappointing results led investigators to experiment with octreotide combined with other antineoplastic therapies. Two different trials from the same Italian group combined octreotide with recombinant interferon-alpha 2b (IFNα2b), as this adjunct had been tried in other neuroendocrine tumors with positive results.[106] The first trial, published in 1996, treated MTC patients for a total of 12 months with three times daily injections of octreotide and three times weekly injections of IFNα2b. Two of 8 patients enrolled in the study dropped out due to the side effects from IFNα2b treatment. The remaining 6 had no significant tumor response, but did have decreases in their CEA levels.[107] Their second trial was published in 2000 and included 7 patients with symptomatic and advanced MTC. This time, patients were treated with lanreotide, another long-acting somatostatin analogue, in combination with IFNα2b. Tumor responses were better in this trial, with 3 patients demonstrating disease stabilization after 6 months of treatment, and 2 patients showing minor ($< 25\%$) tumor regression. The two remaining patients continued to progress throughout treatment. Six of 7 patients had improvement of their symptoms. Despite the slightly improved outcomes compared to the previous trial, the authors concluded that IFNα2b was not a helpful adjunct to MTC treatment with somatostatin analogues as it caused unpleasant side effects in most patients and failed to have much effect on tumor growth.[108]

The most recent trial examining the utility of a somatostatin analogue for MTC treatment enrolled 22 patients with advanced MTC and treated all with either octreotide or octreotide LAR (the long-acting formulation). Thirteen patients in this group also received chemotherapy (n = 6), EBRT (n =2), or a combination of the two (n = 5). In the group of 13 patients treated with a somatostatin analogue plus additional treatments, 12 had subjective tumor responses—5 partial responses and 7 had stabilizations. In the group treated only with somatostatin analogues (n = 9), 6 had objective tumor responses—3 partial responses, and 3 stabilizations. There was no significant difference in the overall survival seen in the 2 different groups, and thus the authors reiterated what others had already found: somatostatin analogues may be helpful controlling symptoms in advanced MTC, but they do not appear to significantly affect tumor burden.[109]

PEPTIDE RECEPTOR RADIATION THERAPY

Peptide receptor radionuclide therapy (PRRT) was first developed to treat somatostatin receptor-expressing tumors, but has now expanded to use other receptors, such as

cholecystokinin (CCK) receptors A and B. This treatment relies on the binding of a radiolabeled ligand to its respective receptor expressed on a tumor's surface to produce a cytotoxic effect. Patients eligible for this treatment should have advanced cancer with inoperable metastases.[110] In MTC, PRRT targeting SSTR2 and CCK-A or –B has been tried, as MTC expresses both receptors at high levels.[102,111]

The only prospective study using CCK-B/gastrin receptor-based PPRT treated 8 patients with advanced MTC with the radioligand ^{90}Y-DTPT-D-Glu-minigastrin.[112] Patients were injected with the radioligand at 4 to 6 week intervals and given escalating doses until toxicity limited further increases. Overall, 2 patients developed partial remissions and 4 had stable disease. Unfortunately, the regimen proved relatively toxic as 1 patient (the patient demonstrating the best response) went on to develop chronic myelogenous leukemia as well as grade I nephrotoxicity, and another developed chronic renal failure. Other PRRT trials in patients with MTC have all used radiolabeled somatostatin analogues that bind to SSTR2. Bodei *et al*. published their experience with SSTR PRRT in 21 MTC patients in 2004.[113] Patients received varying cumulative doses of ^{90}Y-DOTATOC, but regardless of dose, all were pretreated with amino acid solutions to prevent nephrotoxicity. They found that 67% of their patients derived a clinical benefit from PRRT—manifest as either an objective tumor response or stabilization of tumor burden. Two patients had complete responses, with the duration of clinical benefits ranging from 3 to 40 months. None of these patients suffered permanent renal toxicity. The authors were encouraged by the moderate responses in their patients, but noted that the patients treated in this study were the least likely to derive benefit from the treatment, as their tumor burdens were too great for optimal ^{90}Y radiation effect.[113]

In 2007, a group in Basel, Switzerland published results from a phase II trial examining the efficacy of ^{90}Y-DOTATOC treatment in 31 patients with stage IV MTC (M1 disease) who had progressed within the last 12 months and had visible radiolabeled somatostatin analogue uptake on Octreoscan.[114] Patients were treated with ^{90}Y-DOTATOC until they failed to respond to treatment. Treatment response was gauged based on alteration of CT doubling time, toxicity, and overall survival. Patients who demonstrated significant lengthening of their CT doubling time were characterized as 'responders." In this cohort, there were 18 responders (58.1%) and 13 nonresponders (41.9%). PRRT responders demonstrated significantly longer survival than nonresponders as measured both from the time of MTC diagnosis (108 months vs. 80 months) and from the time of ^{90}Y-DOTATOC treatment (74.5 months vs. 10.8 months). Interestingly, there was no correlation between PRRT response and uptake on pretreatment Octreoscan, suggesting that Octreoscan may exclude patients from treatment that could actually benefit. As in other PRRT trials, some patients developed nephrotoxicity as a consequence of treatment, 4 of which were permanent toxicities. Though this study used changes in CT doubling time rather than objective tumor response by imaging to gauge benefit, the difference in survival between responders and nonresponders support the conclusion that PRRT has a positive effect on advanced MTC and is thus worthy of further study.[114]

The most recent report of PRRT for metastatic MTC evaluated both ^{90}Y and ^{177}Lu labeled somatostatin analogues.[115] A total of 16 patients with advanced non-radioiodine-avid thyroid cancer were enrolled, 8 of whom had metastatic MTC. Patients received up to 5

treatments of PRRT. Of the patients with MTC, 4 maintained stable disease, 1 developed a partial remission, and 1 continued to progress. Two patients were lost to follow up. The patient with partial remission also had decreased CT levels, whereas those that progressed saw their CT levels increase. In this trial, only mild hematologic toxicity was seen, and all cases were reversible. Of the entire cohort, patients with MTC demonstrated the most promising responses to treatment, supporting the Swiss group's conclusion that PRRT is a worthwhile addition to MTC treatment and warrants a phase III study.[115]

EXPERIMENTAL TREATMENTS

A number of other treatments are in the early stages of development for the treatment of advanced MTC, and will hopefully impact future management. Histone deacetylase inhibitors increase ^{125}I accumulation in follicular cells and cause apoptosis. Reports of its use in 3 patients with MTC have been published, and in each case only disease stabilization was achieved. It is now being tried as a chemosensitizing agent.[116–123] Thalidomide is known for its antiangiogenic properties and has been tried in 7 MTC patients in a phase II trial. Due to severe side effects, only 5 completed the study. A partial tumor response was achieved in only 1 patient.[124–130] Plitidepsin is an antibiotic that can induce apoptosis and has been used to treat 1 patient with MTC. The patient had a partial response to treatment, with a 52% reduction in their nodal disease. A phase II trial is now underway.[131] Radioimmunotherapy, a targeted treatment that uses bispecific anti-CEA monoclonal antibodies which also bind a radiolabeled hapten (^{131}I or[90]Y-DOTA), has been reported in approximately 100 MTC patients. Most patients have stable disease with treatment, but a handful of minor tumor responses have been reported, as well as 1 complete response.[132–138] Vaccination with dendritic cells pulsed with MTC-specific antigens has also been attempted. A trial in 7 MTC patients resulted in 1 objective tumor response and 2 biological responses.[139,140]

SUMMARY

For much of its history, medullary thyroid cancer has proven refractory to most medical therapies. Although DTIC or doxorubicin can produce tumor responses in a subset of MTC patients, no large trials demonstrating survival benefits exist. Nevertheless, until recently they were the only options showing any effectiveness, and they still may play a role when MTC fails with other treatments. Other therapies such as somatostatin analogues may relieve symptoms in some patients, but do not alter the disease course. External beam radiation and radioactive iodine are mostly ineffective. Additional chemotherapeutic combinations, novel agents, immunotherapy, and other drugs have all been tried in MTC, but were ineffective or remain in the early phases of development. Given the long record of failures in managing this frustrating disease, the high rates of partial response and disease stabilization with small-molecule kinase inhibitors mark an important shift in MTC treatment. Evidence from large randomized trials showing improved progression-free survival supports using drugs such as vandetanib and cabozantinib as first-line agents for symptomatic metastatic MTC. Sorafenib and sunitinib may also produce improvement in patients failing first-line drugs. Despite better progression-free survival, however, cytostatic rather than cytotoxic effects predominate with these kinase inhibitors, and their impact on overall survival remains to be

demonstrated. Moreover, their adverse events are frequent and often serious. While the challenge posed by metastatic MTC has not been solved by currently-available kinase inhibitors, patients have more options than ever before. Research in the next few years will likely add additional kinase-inhibitors for patients progressing on or developing resistance to existing drugs, and the search continues for agents with greater efficacy and cytotoxicity for MTC cells.

Acknowledgments

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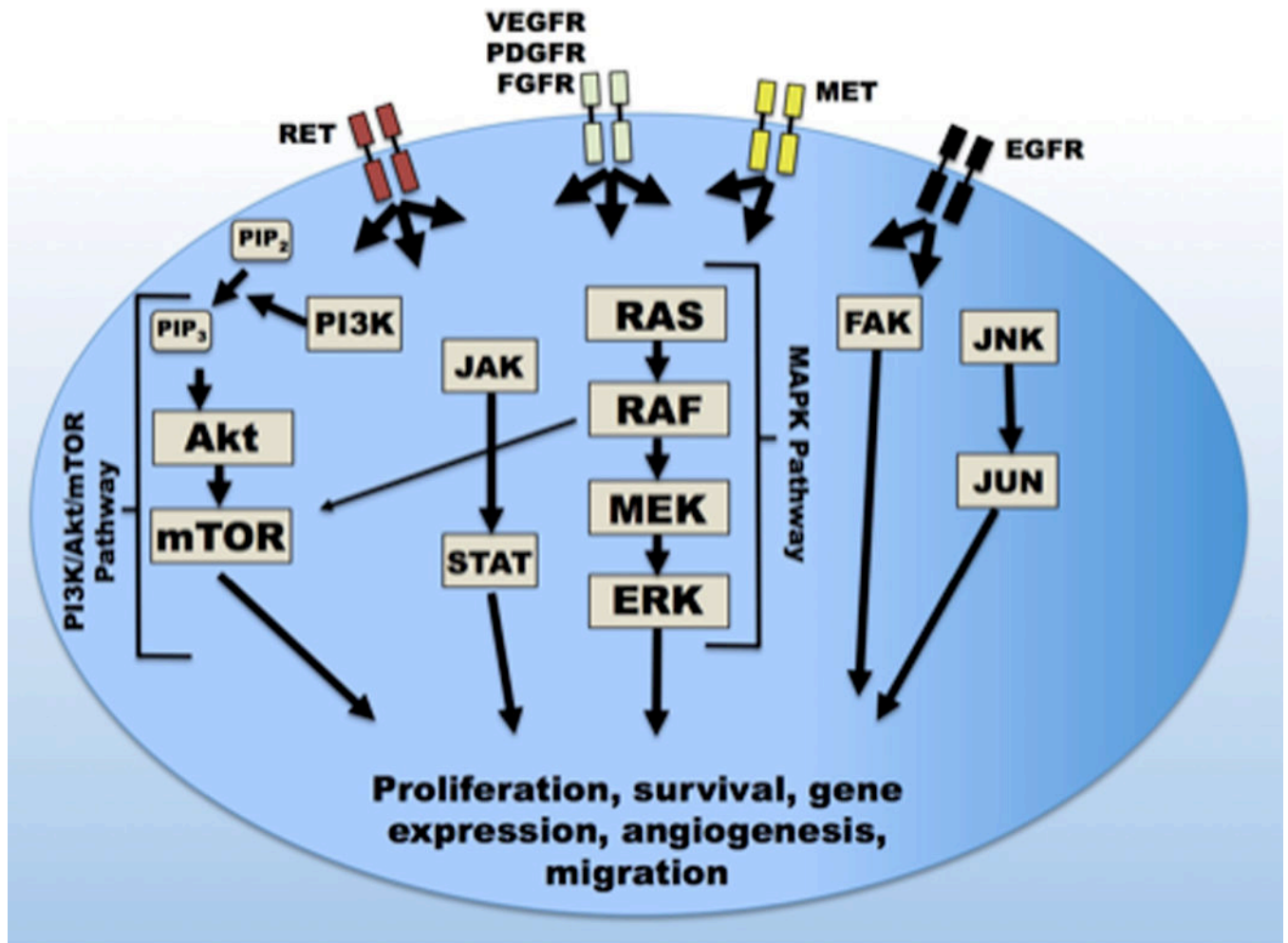
Figure 1.
Receptors and pathways in medullary thyroid cancer. Kinase inhibitors block the activity of rearranged during transfection (RET), vascular endothelial growth factor receptor (VEGFR), and other receptors, inactivating the mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K), and other pathways. Extensive interpathway cross-talk exists. Arrows indicate pathways most commonly associated with each receptor, however, most receptors interact with additional pathways to varying extents. Abbreviations: mTOR: mammalian target of rapamycin; PIP_2: phosphatidylinositol bisphosphate; PIP_3 phosphatidylinositol trisphosphate; JAK: janus-activated kinase; STAT: signal transducers and activators of transcription; FAK: Focal adhesion kinase; JNK/JUN: jun-N-terminal kinase/JUN protein; RET: Rearranged during transfection kinase; PDGFR: Platelet-derived growth factor receptor; FGFR: Fibroblast growth factor receptor; MET: Mesenchymal epithelial transition factor/hepatocyte growth factor receptor; EGFR: Epidermal growth factor receptor.

Table 1

Selected drugs targeting pathways involved in medullary thyroid cancer

Drug	Alternative Name	Targets	Selected trials
Vandetanib	ZD6474	VEGFR2, VEGFR3, EGFR, RET, PDGFR[25,35]	MTC Early Phase[37,38] Phase-III: 331 MTC patients[10]
Cabozantinib	XL184	MET, VEGFR2, RET, KIT, AXL, FLT3[41]	MTC Phase-I[40] Phase-III: 330 MTC patients[11]
Sorafenib	BAY 43–9006	RAF, RET, VEGFR1-3, PDGFR, KIT, FLT3[27,39]	Phase-I: 1 MTC patient[27] 13 MTC patients[46] Phase-II: Thyroid cancer; 1 MTC patient;[141] 21 MTC patients[45]
Sunitinib	SU11248	VEGFR1,2, PDGFR, RET, KIT, FLT3, CSF1R[39,50]	Phase-II: Thyroid cancer including 7 MTC patients[50]
Axitinib	AG-013736	VEGFR1-3, much lower for KIT, PDGFR[57]	Phase-II: Thyroid cancer including 11 MTC cases[57]
Motesanib	AMG 706	VEGFR1-3, PDGFR, KIT[58]	Phase-I: 1 MTC patient[142] Phase-II:91 MTC patients[58]
Ponatinib	AP24534	BCR-ABL, SRC, FLT3, KIT, FGFR1, PDGFR, VEGFR2, RET[59]	MTC cell culture, animal model[59] MTC cell culture, comparison with other MTC agents[53] Phase-II: CML – High rate of arterial thrombotic events[60]
Imatinib	STI571	BCR-ABL, PDGFR, CSF1R, KIT, lower activity against RET[54,55]	Phase-II: MTC[54,55]
Gefitinib	ZD1839	EGFR[56]	Trial including 4 MTC patients[56]

Abbreviations: MTC: Medullary thyroid cancer; AXL: AXL receptor tyrosine kinase; BCR-ABL: Breakpoint cluster region-Abelson tyrosine-protein kinase; CML: Chronic myeloid leukemia; CSF1R: Colony stimulating factor-1 receptor (c-Fms); EGFR: Epidermal growth factor receptor; FGFR: Fibroblast growth factor receptor; FLT3: fms-related tyrosine kinase 3; KIT: c-Kit/Stem cell factor receptor; MET: Mesenchymal epithelial transition factor/hepatocyte growth factor receptor; PDGFR: Platelet-derived growth factor recptor; RAF: Rapidly accelerated fibrosarcoma kinase; RET: Rearranged during transfection; SRC: Avian sarcoma viral oncogene homolog; VEGFR: Vascular endothelial growth factor receptor