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REVIEW

Cabozantinib for the Treatment of Advanced Medullary Thyroid Cancer

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ABSTRACT

Introduction: Patients with advanced medullary thyroid cancer (MTC) have poor prognoses and limited treatment options. Improved knowledge about molecular aberrations associated with MTC and the availability of novel targeted tyrosine kinase inhibitors (TKIs) have led to new potential treatment modalities. Cabozantinib is an oral multitargeted TKI with activity against multiple receptors including RET, vascular endothelial growth factor receptor type 2 (VEGFR2), and MET that has been evaluated in MTC in the preclinical and clinical arenas.

Methods: This article reviews unmet clinical needs in advanced MTC. The authors consider novel agents that have been studied in MTC, with a focus on the investigational agent cabozantinib. Up-to-date clinical data of cabozantinib in MTC are discussed.

Results: Recent clinical evaluation suggests that cabozantinib is the first agent to prolong progression-free survival in patients with progressive MTC. These findings indicate that cabozantinib may be an effective therapy in advanced MTC. No improvement in overall survival has been demonstrated but data are not mature.

Conclusion: Cabozantinib may be an effective treatment option for patients with advanced MTC and is worthy of further evaluation.

Keywords: Cabozantinib; Endocrinology; Medullary thyroid cancer; Oncology; Targeted therapy; Tyrosine kinase inhibitors

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INTRODUCTION

Medullary thyroid cancer (MTC) is a rare thyroid carcinoma, accounting for only 5–8% of thyroid cancers overall [1]. MTC can be inherited or sporadic; in both types, mutations in the *RET* proto-oncogene play a central role in pathogenesis. Approximately 25% of MTC

is inherited as a germline mutation in the (rearranged during transfection) proto-oncogene and is referred to collectively as multiple endocrine neoplasia type 2 (MEN2). Depending on the mutation, MTC can be the only finding (familial MTC) or it can be associated with other tumors including pheochromocytoma in 50% of cases (MEN2A and MEN2B). About 75% of MTCs are sporadic; somatic mutations in *RET* have been reported in 50% of sporadic cases. In *RET*-mutated sporadic MTC, the M918T somatic mutation has been reported in 50–85% of patients; data suggest that this mutation is a negative predictor of cancer remission and survival [2–4]. Key mutations in wild-type *RET* MTC are under investigation. Mutations in *H-RAS* or *K-RAS* have been observed in some wild-type *RET* MTC [5]. An activating *BRAF* mutation and *MET* gene amplification have also been reported [6].

MTC is generally more aggressive than the more common differentiated thyroid cancer. Multivariate analysis of the Surveillance, Epidemiology, and End Results (SEER) registry has suggested that survival in MTC depends strongly on the stage of disease and age at diagnosis [7]. Patients with cancer confined to the thyroid gland have 10-year survival rates of approximately 95.6%. The 10-year survival rates decrease to 75.5% in patients with regional disease. Patients with metastatic disease have markedly worse clinical courses; the 10-year survival in patients with distant disease is only 40% with an overall survival of about 36 months. In addition, multivariate analysis suggests that the risk of dying from MTC increases by 5.2% for each additional year of age at diagnosis in a continuous manner. The prognosis is especially poor in patients greater than 65 years of age [7].

Cabozantinib is a novel multitargeted tyrosine kinase inhibitor (TKI) with potent activity against MET, vascular endothelial growth factor receptor type 2 (VEGFR2), and RET. Activation of these receptors and downstream pathways has been implicated in MTC initiation and progression [6]. Receptor inhibition therefore serves as a rational approach to anticancer therapy. Encouraging recent data suggest that cabozantinib will likely change the landscape of available therapies for advanced MTC. This review will discuss the unmet needs in advanced MTC and current investigational and approved therapeutic agents. We will then describe cabozantinib, with a focus on preclinical and up-to-date clinical data on this promising new targeted therapy.

MATERIALS AND METHODS

A comprehensive literature search was used to collect relevant sources for this review. An online search using PubMed was performed using the keyword terms "XL184" and "cabozantinib." After deleting duplications, references related to cancers other than MTC were excluded. Ten references were reviewed. Other PubMed searches included clinical trials for MTC with each of the following terms individually, "sorafenib, sunitinib, imatinib, axitinib, motesanib, or vandetanib."

Abstracts from sessions of the American Society of Clinical Oncology (ASCO) were searched for the terms "XL184" and "cabozantinib." Of 23 abstracts, 19 not related to MTC were excluded and four were included. Powerpoint slides from oral presentations at ASCO of two included abstracts were also reviewed. ASCO abstracts were also searched using the terms "medullary thyroid cancer" with each of the following terms individually, "sorafenib, sunitinib, imatinib, axitinib, motesanib, or vandetanib."

Additional sources included product information from AstraZeneca on the agent

vandetanib and up-to-date text books focused on thyroid diseases.

UNMET NEEDS IN ADVANCED MTC

Patients with progressive MTC whose disease is not controlled with surgery are in need of additional therapy. Until recently, treatment options have been extremely limited and have included external beam radiotherapy (EBRT) to control local cervical disease and/or cytotoxic chemotherapy for systemic disease.

Data supporting the use of EBRT in MTC are limited as there have been no prospective studies of its use in this cancer. However, retrospective data suggest that EBRT may improve locoregional control in high-risk patients [8–10]. Importantly, analysis of SEER data showed no survival benefit in node-positive patients who underwent EBRT [11]. Side effects from EBRT, including mucositis, dysphagia, and potential tracheal stenosis and esophageal stricture need to be carefully weighed against possible benefits.

Cytotoxic chemotherapy has generally been ineffective in controlling MTC. Doxorubicin, used alone or in combination with other agents, has been the most used cytotoxic agent and is approved by the United States Food and Drug Administration (US FDA) for thyroid cancer treatment. In most cases, response rates with single-agent doxorubicin are poor and toxicity can be high [12]. Combination chemotherapy has not been shown to have an advantage compared to single-agent therapy [12].

Because MTC is a neuroendocrine tumor, the somatostatin receptor may be expressed. Somatostatin analogs, such as octreotide and lanreotide, had been employed alone or in combination with interferon-alpha. These agents have been shown to improve symptoms in some reports, especially diarrhea and flushing that can be seen in advanced disease, but minimal to no change in tumor mass has been observed [12–14], suggesting that, at least alone, somatostatin analogs are not effective therapies for advanced MTC.

The development of targeted therapies, agents that block known aberrancies in cancer pathogenesis, has provided a novel avenue for potential treatments for patients with advanced MTC. Targeted agents, including sorafenib, sunitinib, imatinib, axitinib, and motesanib, have all been investigated in advanced MTC with variable response rates and outcomes [6, 15–24] (Table 1). For example, of 16 patients with advanced sporadic MTC treated with sorafenib, a multitargeted agent with activity against BRAF, CRAF, VEGFR, RET, and platelet-derived growth factor receptor (PDGFR), one (6.3%) had a partial response (PR) and nine patients (56%) had stable disease (SD) for more than 6 months [18]. Of 24 evaluable patients with advanced MTC who received sunitinib, a TKI with activity against RET, VEGFR2, PDGFR, and c-Kit, eight patients (35%) had a PR with a median duration of response of 37 weeks and 13 patients (57%) had SD with a median duration of 32 weeks [19]. A total of 24 patients with advanced MTC were treated with imatinib, a TKI with activity against RET, Bcr-Abl, PDGFR, c-Fms, and c-Kit, in two phase 2 trials [15, 16, 25]. No objective responses were observed, but four patients had SD greater than 24 months.

One of the biggest breakthroughs for patients with advanced MTC came with the development of vandetanib, an oral TKI that targets RET, VEGFR, and epidermal growth factor receptor (EGFR) (Table 1). Clinical efficacy was initially observed in a phase 2 trial of vandetanib in patients with advanced hereditary MTC. Of 30 patients who received vandetanib 300 mg daily, six patients (20%) experienced a PR and 22 patients (73%) had SD for ≥24 weeks [22, 26]. In another phase 2 study

Table 1 Clinical trials with tyrosine kinase inhibitors in medullary thyroid cancer (MTC)

Agent	Target	Phase	No. of patients	PR (%)	24 week SD (%)	Median PFS
Imatinib [15]	RET, Bcr-Abl, PDGFR, c-Fms, c-Kit	2	9	0	56	--
Imatinib [16]	RET, Bcr-Abl, PDGFR, c-Fms, c-Kit	2	15	0	27%	--
Motesanib [17]	VEGFR1–3, RET, PDGFR	2	91	2	48	48 weeks
Sorafenib [18]	BRAF, CRAF, VEGFR, RET, PDGFR	2	16	6.3	56	17.9 months
Sunitinib [19]	VEGFR1–3, RET, PDGFR, c-Kit	2	24	33	46	49 weeks
Axitinib [20]	VEGFR1–3	2	11	18	--	--
Vandetanib [21, 22] 300 mg	VEGFR2, RET, EGFR	2	30	20	73	--
Vandetanib [23] 100 mg	VEGFR2, RET, EGFR	2	19	16	53	--
Vandetanib [22]	VEGFR2, RET, EGFR	3	231 vandetanib, 100 placebo	45% vs. 13% (vandetanib vs. placebo)	--	Not reached; predicted 30.5 months
Cabozantinib [6]	VEGFR2, RET, MET, c-Kit, AXL, FLT3	1	37	29	41	--
Cabozantinib [24]	VEGFR2, RET, MET, c-Kit, AXL, FLT3	3	219 cabozantinib, 111 placebo	28% vs. 0% (cabozantinib vs. placebo)	--	11.2 vs. 4.0 months (cabozantinib vs. placebo)

EGFR epidermal growth factor receptor, *FLT3* fms-like tyrosine kinase 3, *PDGFR* platelet-derived growth factor receptor, *PFS* progression-free survival, *PR* partial response, *SD* stable disease, *VEGFR2* vascular endothelial growth factor receptor type 2

of vandetanib in advanced hereditary MTC, 19 patients received vandetanib 100 mg daily. A PR was observed in three patients (16%) and SD lasting ≥24 weeks was reported in 10 patients (53%) [23].

Promising early results in phase 2 evaluation led to a phase 3 randomized, double-blinded trial of vandetanib compared to placebo in 331 patients with measurable, unresectable locally advanced or metastatic hereditary or sporadic MTC [22]. Patients were not required to have evidence of progression to enroll. Patients who received vandetanib had significantly longer progression-free survival (PFS) compared with placebo. Median PFS had not been reached in the vandetanib group but was predicted at 30.5 months. Of note, the median PFS in the placebo group was 19.3 months, suggesting that some enrolled patients did not need therapy. Patients treated with vandetanib also had statistically significant improvements in objective response rates (ORR), disease control rate, and biochemical response. No change in overall survival (OS) was observed. However, because the study allowed open-label vandetanib therapy at objective disease progression, it would be unlikely to see a difference in OS [22].

Vandetanib was approved by the US FDA in April 2011, becoming the first targeted therapy approved for any thyroid cancer treatment. However, the drug is not without toxicities, the most significant being QT prolongation and risk for torsades de pointes. The product information reads, "Vandetanib can prolong the QT interval. Torsades de pointes and sudden death have been reported in patients receiving vandetanib" [27]. Safety concerns led to the development of the Vandetanib Risk Evaluation and Mitigation Strategy (REMS) Program. Healthcare providers and pharmacies wanting to prescribe and dispense vandetanib must complete the training program, which focuses on decreasing the risk for developing QT prolongation. Beyond this serious potential toxicity, other adverse events occurred. Approximately 12% of patients in the phase 3 trial who received vandetanib discontinued therapy due to adverse events [22]. In addition, not all patients with MTC responded to vandetanib therapy and many that did respond eventually progressed. There is no approved proven therapy for this group of patients.

Clinical experience with cabozantinib suggests that this agent may help fulfill unmet needs in advanced MTC.

MECHANISM OF ACTION

Cabozantinib is a potent inhibitor of RET, VEGFR2, and MET with half-maximal inhibitory concentration values of 5.2 ± 4.3, 0.035 ± 0.01, and 1.3 ± 1.2 nmol/L, respectively [28]. Activation of these proteins and downstream mediators has all been implicated in MTC initiation and progression. Cabozantinib also has activity against other TKIs including c-KIT, AXL, and fms-like tyrosine kinase 3 (FLT3).

RET encodes a transmembrane tyrosine kinase, comprising of an extracellular, transmembrane and cytoplasmic domains, which, as discussed earlier, is mutated in hereditary MTC and up to 50% of sporadic MTC. Under normal conditions, wild-type RET receptor is activated by the glial cell line-derived neurotrophic factor (GDNF) family. GDNF binds with a glycosylphosphatidylinositol (GPI)-anchored coreceptor; this links two RET proteins resulting in autophosphorylation of each RET molecule and receptor activation [29]. Activation of RET leads to stimulation of multiple downstream pathways, including the mitogen-activated protein kinase and the phosphoinositide 3-kinase/protein kinase B pathways, which act to promote cell growth, proliferation, cell survival, and differentiation.

Point mutations in *RET* leading to constitutive protein activation can result in uncontrolled cell growth and tumor initiation.

VEGFR activation, which leads to angiogenesis, has been implicated in tumor progression in many cancers. Vascular endothelial growth factor-A (VEGF-A), a key player in angiogenesis, exerts its effects by binding to VEGFR1 and VEGFR2. In response to ligand binding, the VEGFR activates a network of distinct downstream signaling pathways, including the phosphoinositide 3-kinase/protein kinase B pathways. Endothelial proliferation is thought to occur mainly via signaling through VEGFR2, which is highly expressed by endothelial cells; the role of VEGFR1 is not fully understood [30]. Immunohistochemical staining of paraffin-embedded MTC samples demonstrated overexpression of VEGF-A, VEGFR1, and VEGFR2 in over 90% tumors studied, suggesting a role of VEGFR activation in tumor progression [30]. Studies differ in whether VEGF-A expression and/or serum VEGF levels correlate with the clinical extent of MTC [30–33].

The *MET* proto-oncogene encodes the MET tyrosine kinase receptor. Activation of the receptor via binding of hepatocyte growth factor (HGF), a pro-migratory, mitogenic cytokine, mediates the invasive growth of epithelial cells. Upon ligand binding to HGF, MET is phosphorylated at multiple residues with subsequent catalytic activation of signaling cascades involved in cell proliferation, migration, and invasion [34]. Evaluation of MTC pathological specimens has shown that MET and HGF are coexpressed in a subset of MTCs, suggesting autocrine/paracrine circuits may be involved [35].

Inhibition of VEGFR2 and MET may give cabozantinib an advantage over other VEGFR inhibitors. In mouse models, cabozantinib treatment resulted in decreased tumor and endothelial cell proliferation, increased apoptosis, and dose-dependent inhibition of tumor growth in a number of tumors, including a model of MTC with an activating *RET* mutation [6, 28]. One potential problem observed with VEGFR2 targeting inhibitors is that they promote metastasis in preclinical models. This may result from increased signaling through MET [36, 37]. Preclinical data suggest that cabozantinib does not promote metastasis or tumor invasiveness following intravenous tumor cell inoculation [28]. These observations may be due to simultaneous MET and VEFGR2 targeting, which may help block alternative pathway signaling and, therefore, may provide more sustained anticancer effect.

PHARMACOKINETICS

A phase 1 study of cabozantinib in patients with solid tumors used a 3 + 3 dose escalation design to evaluate different schedules of administration and formulations of cabozantinib, including an intermittent dosing (5 days on, 9 days off) with a suspension formulation, continuous fixed daily dosing with a suspension formulation, and continuous daily dosing with capsules [6]. Cabozantinib was found to accumulate in the body with repeat daily dosing. Terminal half-life values of cabozantinib with repeat daily dosing was 91.33 ± 33.3 h (mean ± SD) and apparent steady-state plasma levels were reached by day 15. Steady-state clearance for the 175 mg capsule dose derived from repeat dose data was 4.2 ± 1.5 L/h.

CLINICAL EXPERIENCE

Clinical interest in cabozantinib heightened with early data from the phase 1 dose-escalation study of cabozantinib in patients with advanced solid tumors [6]. Primary endpoints included evaluation of safety, pharmacokinetics, and

maximum tolerated dose (MTD) determination. Eligible patients were required to have hereditary or sporadic disease that was locally advanced or metastatic. Prior therapy, including treatment with VEGFR and RET inhibitors, was allowed. The initial study included 13 patients with MTC; given clinical activity, this cohort was expanded to 37 patients with MTC. The MTD was 140 mg daily. Of 35 patients with MTC with measurable disease, 10 (29%) had a confirmed PR and 17 (49%) experienced tumor shrinkage of 30% or more. Five of the 10 responders had a PR at the first radiologic assessment. The median time to response was 49.5 days and the median duration of response had not been reached. Importantly, three of the 10 responses (30%) occurred in patients who had failed prior TKI therapies, including RET inhibitors. Fifteen (41%) of 37 patients with MTC had SD for at least 6 months. Tumor shrinkage or SD was seen in 12 of 15 patients with somatic M918T *RET* mutations, a mutation that is associated with poor outcome. There was no clear correlation between *RET* mutational status and clinical response [6].

Cabozantinib was generally well-tolerated, but 77 patients (90%) had at least one adverse event. The most common adverse events included gastrointestinal toxicity such as diarrhea, decreased appetite, nausea, vomiting, increased liver enzymes, and mucositis. Other adverse events were fatigue, palmar-plantar erythrodysesthesia (PPE), and hypertension. One pulmonary embolism was reported.

Early promising data from the phase 1 study of cabozantinib in MTC led to an international, double-blind, randomized, placebo-controlled phase 3 trial (cabozantinib [XL184] in Advanced Medullary Thyroid Cancer [EXAM]) of cabozantinib in MTC [24]. Design and endpoints were agreed upon with the US FDA and European regulatory authorities. Patients were required to have locally advanced or metastatic MTC with evidence of Response Evaluation Criteria in Solid Tumors (RECIST) progression within 14 months of screening, making the patient population different from the phase 3 trial with vandetanib. Subjects were randomized 2:1 to receive cabozantinib 140 mg daily (n = 219) or placebo (n = 111), and were followed until progression or unacceptable toxicity. Tumor assessment occurred every 12 weeks. No cross-over or unblinding was allowed at progression. The primary outcome was PFS as determined by an independent review facility. The study was designed to have 90% power to detect a 75% increase in PFS. Secondary outcome measures included ORR and OS.

A total of 330 patients were enrolled. *RET* mutation status was positive in 48%, negative in 12%, and unknown in 39% of subjects. A total of 21% of subjects had received prior TKI therapy. Bone metastases were reported in 51% of patients. Patients receiving cabozantinib had statistically significant PFS prolongation of 7.2 months. Median PFS for cabozantinib and placebo were 11.2 months and 4.0 months, respectively (hazard ratio 0.28, confidence intervals [CI] 0.19–0.40, $P < 0.001$). In addition, the 1 year PFS rate for patients receiving cabozantinib was 47.3% versus 7.2% in patients receiving placebo. Subset analysis including *RET* mutation status, prior TKI use, and presence of bone metastases also showed improved PFS with cabozantinib. ORR was 28% versus 0% for cabozantinib versus placebo ($P < 0.0001$). Median duration of response was 14.6 months in the cabozantinib group. Although the final analysis has not been done, no improvement in OS has been observed. Significant adverse events (treatment vs. placebo) included diarrhea, PPE, fatigue, hypocalcemia, and hypertension. The pathophysiology of higher rates of hypocalcemia in the treatment group has yet to be fully elucidated [24].

CHANGE IN LANDSCAPE OF THERAPY

Data from the EXAM trial suggest that cabozantinib has significant activity in advanced and progressive thyroid cancer and may serve as a potential treatment modality in this disease. Whether mature data suggest that cabozantinib improves OS will be important as no treatments have been shown to improve OS in advanced MTC.

If cabozantinib is approved for use, the treatment paradigm for advanced MTC remains uncertain. First, there are not clear indications as to when targeted therapy should be initiated. The phase 3 trial with vandetanib did not require progressive disease, whereas the phase 3 trial with cabozantinib did [22, 24]. It is not known whether the benefits outweigh the risks in both groups. In addition, debate exists whether patients with radiographic stable disease but rising calcitonin and carcinoembryonic antigen should be treated and how tumor marker doubling time should factor into decision making. Finally, burden of disease remains an issue that has not been explored. It is unknown whether patients with low levels of disease benefit from early treatment or whether these patients should be monitored for the development of more substantial metastases.

If cabozantinib is approved for use in patients with progressing disease, clinicians will be further challenged as to whether vandetanib or cabozantinib should be used as first-line therapy. For safety reasons, patients at risk for prolonged QT interval should likely be treated with cabozantinib, but this will apply to a small minority of patients. Cabozantinib has its own set of toxicities that are not completely benign and need to be considered. In addition, some patients who failed vandetanib respond to cabozantinib, but whether the converse is true has not been evaluated.

The crux of the problem is that advanced MTC is a heterogeneous disease process; this explains why some patients respond to some TKIs and others do not. Understanding genetic aberrations in tumors that respond and do not respond to therapy is a necessary area of research. As this is better understood, more comprehensive study of tumor genetics will hopefully lead to better matching of cancer with an appropriate therapy. However, this is likely some time away. For now, clinicians will have to discuss potential benefits and toxicities with their patients in order to create individualized treatment plans.

CONCLUSION

Cabozantinib is the first agent to show improved PFS in progressive MTC, representing a major breakthrough for advanced MTC therapy. Whether this agent will improve OS in this rare disease remains unknown. Nonetheless, cabozantinib offers clinicians a novel and effective tool to help patients with MTC. More research is needed to understand which patients with MTC are likely to benefit most from cabozantinib and from targeted therapy in general.

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