



Recent Updates on the Management of Medullary Thyroid Carcinoma

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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor derived from the thyroid C cells producing calcitonin. MTC accounts for 0.6% of all thyroid cancers and incidence of MTC increased steadily between 1997 and 2011 in Korea. It occurs either sporadically or in a hereditary form based on germline rearranged during transfection (*RET*) mutations. MTC can be cured only by complete resection of the thyroid tumor and any loco-regional metastases. The most appropriate treatment is still less clear in patients with residual or recurrent disease after initial surgery or those with distant metastases because most patients even with metastatic disease have indolent courses with slow progression for several years and MTC is not responsive to either radioactive iodine therapy or thyroid-stimulating hormone suppression. Recently, two tyrosine kinase inhibitors (TKIs), vandetanib and cabozantinib, are approved for use in patients with advanced, metastatic or progressive MTC. In this review, we summarize the current approach according to revised American Thyroid Association guidelines and recent advances in systemic treatment such as TKIs for patients with persistent or recurrent MTC after surgery.

Keywords: Thyroid cancer, medullary; Tyrosine kinase inhibitors; Molecular targeted therapy; Adverse event

INTRODUCTION

In the past 2 decades, the incidence of thyroid cancer has been rapidly increasing worldwide [1-3]. In Korea in particular, thyroid cancer was the most commonly diagnosed cancer in 2013 [4]. The most common histological subtype that has been contributing to the increase in the incidence of thyroid cancer is papillary thyroid carcinoma derived from thyroid follicular cells [3,4]. Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor derived from the thyroid C cells that produce calcitonin. MTC occurs both as a sporadic form and as a hereditary form as part of multiple endocrine neoplasia (MEN) type 2. Ac-

ording to recent Surveillance, Epidemiology, and End Results (SEER) data, MTC accounts for 1% to 2% of all thyroid cancers in the United States [5]. On the other hand, in Korea, MTC accounts for 0.6% of all thyroid cancers but the incidence of MTC has increased steadily between 1997 and 2011 [6].

Although the 5-year relative survival rate for all thyroid cancers in Korea was over 100% [4], Jung et al. [7] recently reported that the 5- and 10-year survival rates for MTC were 92% and 87%, respectively. It is generally recognized that MTC can be cured only by complete resection of the thyroid tumor and any loco-regional metastases. However, the most appropriate treatment is less clear in patients with residual or recurrent disease

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after initial surgery or those with distant metastases because most patients, even those with metastatic disease, have an indolent course with slow progression for several years and MTC is not responsive to either radioactive iodine therapy or thyroid-stimulating hormone suppression [5]. This review mainly discusses the recent advances in medical treatment such as tyrosine kinase inhibitors (TKIs) for patients with persistent or recurrent MTC after surgery.

SURGERY AS PRIMARY THERAPY

All patients with a preoperative diagnosis of MTC should undergo detailed neck ultrasonography (US) and measurement of serum calcitonin and carcinoembryonic antigen (CEA). Basal serum calcitonin concentrations usually correlate with tumor burden but also reflect tumor differentiation in MTC. Thus, total thyroidectomy and dissection of cervical lymph node (LN) compartments, depending on serum calcitonin levels and neck US findings, is standard treatment for patients with MTC [5]. In addition, establishing whether the patient has germline rearranged during transfection (*RET*) mutation or sporadic disease is crucial because patients with MEN type 2 can have pheochromocytoma or primary hyperparathyroidism, or both. If the patient has pheochromocytoma, adrenalectomy should be prioritized before thyroidectomy [8].

For patients with MTC confined to the neck and no evidence of involved cervical LN on preoperative imaging studies and no evidence of distant metastases, total thyroidectomy with LN dissection in the central compartment is recommended as the preferred initial treatment [5]. However, prophylactic central neck LN dissection is not required in patients with small intrathyroidal MTCs with a preoperative calcitonin level <20 pg/mL, because there is virtually no risk of LN metastases when the preoperative serum basal calcitonin level is less than 20 pg/mL (normal reference value, <10) [9]. An important issue is whether lateral LN dissections should be performed in the absence of clinically or ultrasonographically detectable LN metastases as part of the primary surgery. In patients with MTC and no evidence of neck metastases on US, and no distant metastases, dissection of LN in the lateral compartments (levels II to V) may be considered based on serum calcitonin levels according to the revised American Thyroid Association (ATA) guidelines as a grade I recommendation [5]. For patients with MTC confined to the neck and cervical LNs, total thyroidectomy, dissection of the central LN compartment, and dissection of the involved lateral neck compartments should be performed. When preoperative

imaging shows positive results in the ipsilateral neck compartment but negative results in the contralateral neck compartment, contralateral neck dissection should be considered if the basal serum calcitonin level is greater than 200 pg/mL [5].

MANAGEMENT OF LOCALLY ADVANCED OR METASTATIC MEDULLARY THYROID CARCINOMA

In patients with locally advanced or metastatic disease at initial presentation, total thyroidectomy with dissection of involved LN compartments is usually recommended in most patients. In these cases, less aggressive surgery in the central and lateral neck may be appropriate to preserve speech, swallowing, parathyroid function, and shoulder mobility because the goals of surgery are largely palliative. External beam radiotherapy (EBRT), systemic medical therapy, and other nonsurgical therapies such as radiofrequency ablation (RFA), cryoablation, or embolization should be considered to achieve local tumor control. The eradicated surgical approach should be individualized based upon the patient's wishes, life expectancy, and other medical comorbidities [5].

MANAGEMENT OF PERSISTENT OR RECURRENT MEDULLARY THYROID CARCINOMA

Serum calcitonin and CEA should be measured 3 months after surgery to detect the presence of residual disease [5]. Patients who have normal serum CEA and undetectable serum calcitonin values are considered biochemically cured and have an excellent prognosis [10-12]. Postoperative biochemical remission is the best predictive factor for recurrence-free survival [7]. For patients with persistent hypercalcitoninemia, further evaluation depends upon the serum calcitonin concentration (150 pg/mL). In addition, calcitonin and CEA doubling times are useful tumor markers, because they are predictive of outcomes and aggressive tumor behavior [13]. Calcitonin and CEA doubling time calculator are readily available from the ATA web site (<http://www.thyroid.org/professionals/calculators/thyroid-cancer-carcinoma/>).

Treatment options for patients with recurrent or residual disease include observation and active surveillance; surgical resection; EBRT; other directed therapies including RFA, cryoablation, and embolization; and systemic therapies such as chemotherapy, molecular targeted therapy, and immunotherapy. The management approach for these patients mainly depends on

various clinical factors including whether the disease can be localized, the volume of the disease, metastatic locations threatening vital structures, the presence of disease associated symptoms, or likelihood of clinically significant structural progression [5,8].

Patients with detectable calcitonin and/or abnormal CEA levels without structurally identifiable disease can be best followed up with observation instead of systemic therapy. Routine use of postoperative EBRT as adjuvant therapy is not recommended, even if the postoperative calcitonin and CEA values are abnormal in patients without gross residual disease [5]. EBRT should be selectively used because it can limit future surgical intervention due to the induction of fibrosis and it can reduce the quality of life of the patient. Thus, postoperative adjuvant EBRT to the neck and mediastinum should be considered in patients at high risk for local recurrence (microscopic or macroscopic residual MTC, extrathyroidal extension, or extensive LN metastases), and those at risk of airway obstruction [5].

For patients with persistent or recurrent loco-regional MTC without distant metastases, surgical resection including compartmental dissection of image-positive or biopsy-positive disease in the central or lateral neck compartments should be considered to prevent invasion into surrounding major structures [5,14,15]. In addition, locally recurrent MTC can be managed with careful observation without surgery, depending on the risk of the tumor threatening vital structures and other patient factors such as tumor burden, disease symptoms, patient age, and comorbidities [8]. In view of this, active surveillance is the best management option for most MTC patients with persistent, asymptomatic subcentimeter LN metastases. However, for patients with unresectable gross residual disease in the thyroid bed or cervical soft tissue, EBRT is considered to improve loco-regional control. Although large-volume solitary metastatic lesions in the lungs, liver, or brain should be considered for surgical resection, EBRT is also indicated for treating multiple brain metastases and mediastinal metastases, palliation of painful bone metastases, and decreasing the risk of fracture [5].

SYSTEMIC THERAPY: CYTOTOXIC AGENTS AND TYROSINE KINASE INHIBITORS

Progressive or symptomatic metastatic MTC that cannot be treated with surgery, local management, or radiotherapy should be considered as a candidate for systemic therapy. In general, traditional cytotoxic agents (dacarbazine-based combination

therapy with doxorubicin, cyclophosphamide, or 5-fluorouracil) should not be considered as the first-line therapy for patients with persistent or recurrent MTC because of their limited benefit and toxicity [5,16]. Activating germline mutations of the *RET* proto-oncogene, a tyrosine kinase receptor, are found in almost all patients with MEN2A and MEN2B. Somatic *RET* mutations have been documented in approximately 50% to 60% of sporadic MTC cases. Somatic RAS mutations have also been found in MTC patients without somatic *RET* mutations [17,18]. In addition, vascular endothelial growth factor (VEGF) receptors (VEGFR-1 and VEGFR-2) are often overexpressed in MTC tumor cells and vascular endothelium [19]. Because angiogenesis plays a crucial role in growth and metastasis of tumors, increased VEGF expression promotes thyroid cancer cell growth, LN metastasis, local invasion, and enhanced distant metastasis [19,20]. Thus, the most successful agents target both the VEGFRs and tyrosine kinases. Although several TKIs have been evaluated in clinical trials, both vandetanib and cabozantinib were recently approved for treatment of advanced, metastatic or progressive MTC on the basis of phase 3 clinical trials [21,22].

Table 1 summarize phase 3 clinical trials of vandetanib and cabozantinib versus placebo in patients with advanced MTC. Vandetanib is a once-daily oral TKI that selectively targets the RET, VEGFR-2, VEGFR-3, epidermal growth factor receptor [23,24]. In a randomized, double-blind, placebo-controlled multicenter phase 3 trial (Zactima Efficacy in Thyroid Cancer Assessment [ZETA] trial), patients with locally advanced or metastatic MTC were randomized 2:1 to vandetanib 300 mg/day ($n=231$) or placebo ($n=100$). The results of this study showed better progression-free survival (PFS) in the vandetanib group compared to placebo (30.5 months vs. 19.3 months; hazard ratio [HR], 0.46; $P<0.001$). In addition, vandetanib showed significantly high rates of objective response (45% vs. 13% for placebo, $P<0.001$), disease control (87% vs. 71%, $P=0.001$), and calcitonin biochemical response (69% vs. 3%, $P<0.001$). However, no complete response (CR) was reported in both arms. Overall survival (OS) was not significantly different between two arms because unmasking and crossover was permitted at the time of disease progression and OS data were immature since only 15% of patients had died at the PFS cutoff. The final survival analysis will be performed when sufficient number of deaths have occurred. Of interest, patients with sporadic MTC harboring a somatic *RET* M918T mutation had a higher response rate to vandetanib than patients without this mutation (54.5% vs. 32%) [21].

Diarrhea, hypertension, prolongation of the corrected QT

Table 1. Summary of Phase 3 Clinical Trials of Vandetanib and Cabozantinib versus Placebo in Patients with Advanced Medullary Thyroid Carcinoma

Variable	Vandetanib	Cabozantinib
Targets	VEGFR, RET, EGFR	VEGFR, RET, c-MET
Clinical trial	ZETA study	EXAM study
No. of patients	331	330
Randomization (drug vs. placebo)	2:1, crossover allowed	2:1, crossover not allowed
Radiologic progression before enrolment	Not requested	Yes (within 14 mo)
Previous treatment, %	40	38
Previous TKIs, %	Unknown	20
Distant metastasis, %	94	95
Hereditary disease, %	10	6
RET mutation positive, %	38	45
RET 918, %	Not available	35
Follow-up duration, mo	24	14
Results		
Median progression-free survival, mo	30.5 vs. 19.3 (HR, 0.46; $P < 0.001$)	11.2 vs. 4.0 (HR, 0.28; $P < 0.001$)
Objective response rate, %	45 vs. 13	28 vs. 0
Complete response rate, %	0	0
Stable disease, %	Not available	48.1 vs. 50
Survival, mo	Not available	27 vs. 21
Biochemical response, %	69 vs. 3	45 vs. 0
Safety		
Toxic effects (\geq grade 3), %	55 (24)	69 (33)
Most common adverse events at least grade 3	Diarrhea, hypertension, QTc prolongation, fatigue	Diarrhea, palmar-plantar erythrodysesthesia, fatigue
Deaths, %	2 vs. 2 (placebo)	5.6 vs. 2.8 (placebo)

VEGFR, vascular endothelial growth factor receptor; RET, rearranged during transfection; EGFR, epidermal growth factor receptor; c-MET, hepatocyte growth factor receptor; ZETA, Zactima Efficacy in Thyroid Cancer Assessment; EXAM, Efficacy of XL184 (cabozantinib) in Advanced Medullary Thyroid Cancer; TKI, tyrosine kinase inhibitor; HR, hazard ratio; QTc, corrected QT.

(QTc) interval (> 500 ms), and fatigue were the most commonly reported (incidence $> 5\%$) adverse events at least grade 3 in this trial [21]. QTc is defined as QT interval adjusted for heart rate. QTc prolongation is characterized either in absolute (> 500 ms) or relative terms (> 30 ms change from baseline in QTc interval). Although no case of Torsades de Pointes was reported in ZETA trial, clinician should be remember that a baseline electrocardiogram with QTc measurement must be recorded prior to initiation of vandetanib, and it should not be given to patients with a baseline QTc > 450 ms (United States prescribing information) or > 480 ms (European Union summary of product characteristics). Vandetanib should be withheld if the QTc interval is longer than 500 ms until it returns to 450 ms [25].

Cabozantinib is also a once-daily oral TKI that selectively tar-

gets the RET, VEGFR-2, hepatocyte growth factor receptor (c-MET) [26]. In a randomized, double-blind, placebo-controlled multicenter phase 3 trial (Efficacy of XL184 [cabozantinib] in Advanced Medullary Thyroid Cancer [EXAM] trial), patients with progressive according to response evaluation criteria in solid tumors (RECIST), metastatic, or locally advanced MTC were randomized 2:1 to cabozantinib 140 mg/day ($n=230$) or placebo ($n=100$). Unlikely vandetanib in ZETA trial, patients were never unmasked and were not permitted to crossover to open-label drug. The results showed median PFS was significantly improved from 4.0 months (placebo) compared to 11.2 months (cabozantinib) (HR, 0.28; $P < 0.0001$). Benefits in PFS were observed in all subgroups studied. The overall response rate was 28%. OS was not statistically different between the two

arms despite not permitting for crossover [22]. However, a very recent study reported statistically significant difference in OS between patients with *RET* M918 mutations who received cabozantinib compared with placebo (44.3 months vs. 18.9 months; HR, 0.60; 95% confidence interval, 0.38 to 0.95) [27].

Most common side effects of cabozantinib included diarrhea, abdominal discomfort, palmoplantar erythrodysesthesia, fatigue, hypertension, and headaches. Rare but serious adverse events include gastrointestinal perforation and fistula, hemorrhage, thromboembolic events, poor wound healing, osteonecrosis of the jaw, and reversible posterior leukoencephalopathy syndrome [22,28]. Thus, the FDA issued an important warning for cabozantinib about gastrointestinal fistulas and life-threatening bleeding.

Because neither TKIs is curative, vandetanib and cabozantinib are administered to treat patients with advanced MTC until the patient exhibits radiological progression or develops intolerable adverse events. Although TKIs are generally better tolerated compared to cytotoxic agents, many patients experience adverse events. Thus, cautious and aggressive management of adverse events is required to optimize therapy, maintain compliance, and avoid potentially life-threatening toxicities, including QTc prolongation or gastrointestinal perforation and fistula formation [28]. In addition, patients treated with TKIs require careful monitoring of thyroid function to detect TKI-induced thyroid dysfunction because they are at increased risk for developing hypothyroidism [29,30].

These TKIs have only a moderate antitumor effect, while also having significant toxic effects. Therefore, it is important to carefully select patients who should be considered for kinase inhibitors for MTC. According to the 2015 revised ATA guidelines, in patients with a significant tumor burden and symptomatic or progressive metastatic disease according to RECIST, treatment with TKIs targeting both *RET* and *VEGFR* tyrosine kinases should be considered as systemic therapy [5]. TKIs should be considered for patients with metastatic tumors at least 1 to 2 cm in diameter, growing by at least 20% per year, or for patients with symptoms related to multiple metastatic foci that cannot be treated with surgery or EBRT.

Vandetanib is available and under reimbursement coverage by the National Health Insurance system from November 2015 in Korea. However, the use of cabozantinib is not yet approved in Korea. Therefore, to date, vandetanib can be considered as the first targeted therapy for patients with advanced, symptomatic metastatic MTC in Korea. In addition, clinicians try to enroll these patients in available ongoing clinical trial. Active clin-

ical trials can be identified at www.clinicaltrials.gov.

Sorafenib shows a partial response in patients with advanced MTC in previous clinical studies [31,32]. Sunitinib also showed a partial response or stable disease in open-label phase 2 trials [33,34]. Thus, sorafenib and sunitinib could be considered for use in selected, advanced MTC patients who cannot tolerate or who are not responsive to vandetanib or who are unable to participate in available clinical trials.

Several studies have evaluated the effect of the synergistic action of an antineoplastic agent combination including proteasome inhibitors (bortezomib) and a cytotoxic agent (irinotecan) [35-39]. Recently, it has been suggested that the concomitant targeting of *RET* and mechanistic target of rapamycin (mTOR) may represent a new therapeutic approach in MTC because deregulation of the phosphoinositide 3-kinase/Akt/mTOR pathway seems to contribute to the tumorigenic activity of *RET* proto-oncogene mutations [40]. The role of cancer immunotherapies and tumor vaccines is being studied in MTC, but as yet has had a limited role and little clinical application [41-44].

CONCLUSIONS

The primary treatment for MTC is extensive and curative surgical resection. Treatment options for patients with recurrent or residual MTC include observation and active surveillance, surgical resection, EBRT, other directed local therapies (such as RFA, cryoablation, embolization), and systemic therapies. To date, vandetanib and cabozantinib targeting both *RET* and *VEGFR* as systemic molecular targeted therapy can be considered in advanced, symptomatic metastatic patients with MTC. However, neither vandetanib nor cabozantinib is curative, and, it is critical to weigh the risks and benefits of treatment. These drugs should not be used in patients with only increased calcitonin and CEA in the blood and no structural evidence of disease. In addition, these TKIs should not be used in patients with small tumor masses without any evidence of progression on imaging studies, who are generally asymptomatic, who have multiple comorbidities with poor performance, and who have contraindications for treatment such as cardiac disease, arrhythmias, or uncontrolled hypertension. Because long-term treatment may be needed, clinicians should keep in mind recognizing and managing their side effects and the titration of the drug dose. Of note, education and information for these drugs should be provided to the patients. Because TKI monotherapy shows a relatively low rate of partial responses, the absence of a CR, and drug resistance, further studies are needed to develop either more effec-

tive single TKIs, or sequential approaches or to identify ideal combinations of therapeutic targets that have a synergistic effect with less toxicity.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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