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Systemic treatment and management approaches for medullary thyroid cancer

Vinicius Ernani [a,1], Mukesh Kumar [a,1], Amy Y. Chen [b,2], Taofeek K. Owonikoko [a,*]

[a] Department of Hematology/Medical Oncology, Emory University School of Medicine, Winship Cancer Institute, 1365-C Clifton Road NE, Atlanta, GA, USA
[b] Department of Otolaryngology, Head and Neck Surgery, Emory University School of Medicine, Winship Cancer Institute, 1365-A Clifton Road NE, Atlanta, GA, USA

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ABSTRACT

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

Introduction

Thyroid cancer is the most common endocrine malignancy, with more deaths annually than all other endocrine malignancies combined. A total of 64,300 new cases of thyroid cancers are estimated to be diagnosed in the United States in 2015 [1]. Cancer of the thyroid is the 5th most common cancer in females, with 49,350 new cases projected in 2016 [1]. Among all malignancies tracked and recorded by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program between 2006 and 2010, the most rapid increase in incidence was in thyroid cancer, with 5.4% and 6.5% increase in men and women, respectively [2]. Overall, the annual increase in rate in the United States was 5.1% per year from 2003 to 2012 [1]. The mortality rate from thyroid cancer, however, has been relatively stable for the same period [1]. Worldwide, 298,000 new cases were estimated in 2012, accounting for approximately 2.0% of new cancers [3]. From 2006 to 2010, the marked increase observed in thyroid cancer incidence in the United States is likely the consequence of a number of contributing factors, including improved diagnostic identification and detection as well as a true increase of unclear etiology or possibly the result of exposure to radiation or environmental carcinogens [1,4,5].

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

* Corresponding author at: Department of Hematology/Medical Oncology, Winship Cancer Institute, 1365-C Clifton Road NE, Atlanta, GA 30322, USA.
E-mail addresses: vinicius.ernani@emory.edu (V. Ernani), mukesh.kumar@emory.edu (M. Kumar), achen@emory.edu (A.Y. Chen), twowonik@emory.edu (T.K. Owonikoko).
[1] Department of Hematology/Medical Oncology, Winship Cancer Institute, 1365-C Clifton Road NE, Atlanta, GA 30322, USA.
[2] Department of Otolaryngology, Head and Neck Surgery, Emory University School of Medicine, Winship Cancer Institute, 1365-A Clifton Road NE, Atlanta, GA 30322, USA.

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

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

Demographics and survival

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

Sporadic and hereditary MTC

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

Inherited MTC includes 2 variants of the MEN type 2 syndrome (A and B). Another form of inherited MTC, familial medullary thyroid cancer (FMTC), historically was classified as a freestanding syndrome, but the classification is in flux and it is now recommended that it be considered one of the variants of MEN 2A [7,8,25]. MEN 2A, the most common subtype of MEN 2, accounts for about 95% of all MEN 2 cases [8,9,25]. MTC is a dominant feature of MEN 2A, occurring in virtually all patients [8]. Other components of the syndrome include pheochromocytoma, present in approximately 50% of patients, and hyperparathyroidism, which occurs in 25–35% of patients. The overall clinical manifestation is variable, depending on the specific mutations in the *RET* gene that underlie the disease [25]. FMTC lacks any of the other hereditary extrathyroidal endocrine tumors commonly observed in patients with MEN 2 syndrome [8,25].

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

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

Molecular aberrations and therapeutic targets in MTC

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

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