ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Updates in the Management of Medullary Thyroid Cancer

Mimi I. Hu, MD
Assistant Professor
Department of Endocrine Neoplasia
and Hormonal Disorders
The University of Texas
MD Anderson Cancer Center
Houston, Texas

H&O Can you provide an overview on thyroid cancer?

MH Based on last year's estimates from the American Cancer Society, approximately 44,670 new cases of thyroid cancer were diagnosed in the United States. Medullary thyroid cancer (MTC) comprises approximately 4% of all thyroid cancers, which accounted for approximately 1,340 cases in 2010. MTC is different from other thyroid cancers because it arises from the C cells of the thyroid and not the follicular epithelium. This type of cancer has no hormonal interaction with the thyroid follicular cells. Because of the different cell line that MTC originates from, it is not treated in the same way one would treat differentiated thyroid cancer, which encompasses papillary, follicular, and Hürthle cell carcinomas. Differentiated thyroid cancer is typically treated with surgery followed by radioactive iodine and thyroid hormone–suppressive therapy. However, MTC is not responsive to radioactive iodine or thyroid hormone–suppressive therapy.

In MTC, the mean overall disease-specific survival is approximately 8.6 years, but this can change drastically depending on whether the patient has regional lymph node metastases or distant metastases at the time of diagnosis. If lymph node metastases are present (considered stage III or IVA MTC), 10-year survival has been estimated to be 75.5%, and if distant metastases are present, the rate is 40%. Hence, it definitely makes a difference as to what stage the patient is at the time of diagnosis.

H&O What is the RET gene? What are the implications of RET gene mutations?

MH Approximately 25% of cases of MTC are due to a germline mutation of the *RET* proto-oncogene, which is inherited in an autosomal dominant pattern, leading to hereditary endocrine syndromes such as multiple endocrine neoplasia type 2A (MEN 2A), familial medullary thyroid cancer (FMTC), or MEN 2B. *RET* mutational analysis is recommended in patients who have a new diagnosis of MTC, even in patients who have no features suggestive of an inherited syndrome, where there is no family history of other endocrine tumors such as MTC, parathyroid adenomas, or pheochromocytoma. Approximately 6% of those patients who have apparently sporadic cases have a germline *RET* mutation, which is either due to inheritance of the mutation that has been unknown (the patient was adopted) or it arose as a de novo mutation. Knowing *RET* mutational status is highly informative. The specific codon mutation can predict the potential aggressiveness of MTC disease course and provides insight into the likelihood of developing other endocrine neoplasias, and it has implications for the patient's family members. An activating mutation of *RET* leads to a constitutively active RET tyrosine kinase receptor, which activates intracellular signaling and increased cell proliferation, differentiation, migration, and survival. Additionally, 40% of non-hereditary MTC cases will have a somatic *RET* mutation in the tumor, which can contribute to the aggressiveness of the disease.

H&O What are the different syndromes of MTC?

MH There are 3 familial syndromes in MTC: MEN 2A, MEN 2B, and FMTC. MEN 2A is a syndrome of primary hyperparathyroidism due to parathyroid hyperplasia, MTC, and pheochromocytoma. MEN 2B consists of MTC, pheochromocytoma, and mucosal/gastrointestinal neuromas, without primary hyperparathyroidism. Patients with MEN 2B have a very characteristic physical presentation with a "marfanoid" appearance with long arms and digits. Due to the development of mucosal neuromas, they have thick lips, puffy eyelids, and large, nodular tongues. FMTC, now recognized as a variant of MEN 2A, is suggested when multiple family members have MTC but no expression of hyperparathyroidism or pheochromocytoma. MEN 2A is the most common of the syndromes, followed by FMTC, with MEN 2B as the least common. Luckily, MEN 2B is the least common because it is also the most aggressive of the hereditary syndromes. MEN 2B usually presents at a much earlier age, sometimes before 1 year of age, and tends to be a lot more aggressive in terms of distant spread.

H&O What is the current management approach in MTC?

MH The management of MTC should be approached from the perspective of either prevention or first-line treatment. In the case of a patient identified to have an *RET* mutation without any evidence of disease—defined as having a normal calcitonin and no radiologic evidence of disease—a prophylactic total thyroidectomy is recommended to prevent the development of MTC. If a patient has a new diagnosis of MTC, discovered on a fine needle aspiration biopsy or during incidental thyroid surgery, the recommendation for first-line treatment is a total thyroidectomy with a central neck dissection. The most common place for the disease to spread initially, and where it is often found at the time of diagnosis, is the central neck lymph nodes. Until recently, there has been no effective medical therapy for patients who have distant metastatic disease or disease that has progressed out of the thyroid but is no longer surgically amenable. The National Comprehensive Cancer Network guidelines from February 2011 state that if patients have disseminated symptomatic or progressive disease, the preferred recommendation is to refer them to a clinical trial or to external beam radiation therapy for palliation of local symptoms, such as painful bone metastasis. If the patient cannot join a clinical trial due to logistical issues, then vandetanib (Zactima, AstraZeneca), a recently approved oral kinase inhibitor, should be considered. Off-label use of other small molecule kinase inhibitors could be considered if clinical trials or vandetanib are not available or clinically appropriate. Such options include sorafenib (Nexavar, Bayer) or sunitinib (Sutent, Pfizer), both of which are approved by the US Food and Drug Administration (FDA) for other cancers. There have also been recommendations for using chemotherapy based on several older studies from 1994–1995 investigating various combinations of dacarbazine with cyclophosphamide, vincristine, 5-fluorouracil, or streptozocin. When these studies were pooled together nonsystematically, 8 of 32 patients (24%) had a partial response. This, however, was offset by a significant amount of cardiotoxicity or nephrotoxicity. Today, the general practice among specialists in this field is not to go with cytotoxic chemotherapy, but rather to recommend a clinical trial or one of the tyrosine kinase inhibitors that are currently available.

H&O What are the challenges in treating MTC?

MH One challenge is trying to counsel newly diagnosed patients that MTC can be highly variable in its disease course. Patients can have very indolent cancers that progress slowly over years or very aggressive ones that progress within 1 year. After thyroid surgery, it is necessary to observe the patient closely, monitor the calcitonin and carcinoembryonic antigen (CEA) levels, and periodically perform radiologic imaging to determine the extent of disease and clinical course. The doubling time of the calcitonin and CEA can have prognostic value. Doubling times of more than 2 years seem to be associated with a better long-term prognosis than doubling times of less than 6 months. The other challenge is explaining to patients that if they do have disease that has spread outside of the thyroid and it is not surgically amenable, there are no therapies available to date that have curative intent. Although there has been incredible growth in pharmaceutical development showing promising results, no drug studied in the last few years has demonstrated complete response.

H&O What is vandetanib?

MH Vandetanib is one of the many small molecule tyrosine kinase inhibitors that have been developed over the last several years. Vandetanib targets vascular endothelial growth factor receptor (VEGFR) type 2 and VEGFR type 3, and it has activity on the RET receptor and, at higher concentrations, on the epidermal growth factor (EGF) receptor. It is an orally administered medication given once a day; the FDA approved it in April 2011 at a dose of 300 mg/day. It is known that angiogenesis plays a large role in the pathogenesis of MTC. Thus, by targeting the VEGFRs, we have seen partial responses in

patients. Interestingly, although vandetanib targets the RET receptor, *RET* mutational status did not determine response to treatment, such that patients with or without *RET* mutations may respond to vandetanib, indicating that off-target effects on VEGF and EGF may contribute prominently to its efficacy.

The results of a phase II study evaluating vandetanib 300 mg/day in 30 patients with hereditary MTC were presented and published last year by Dr. Samuel Wells. The patients enrolled in the study did not need to show progression prior to enrollment but did need to have a lesion that met response evaluation criteria in solid tumors for monitoring. The investigators found that 20% of patients had a partial response and 53% had stable disease, indicating a disease control rate of 73% for over 24 weeks. This study did not find any correlation of response with patients' *RET* mutation. Another phase II study treated patients with hereditary MTC with a lower dose of vandetanib (100 mg/day). This study enrolled 19 patients; 16% had a partial response and 53% had stable disease. A disease control rate of 68% was seen for over 24 weeks. When comparing the 2 studies, there was not a significant difference between the disease control rates (68% with 100 mg and 73% with 300 mg).

Following these phase II trials, there was a large, multicenter, randomized, placebo-controlled, phase III trial called ZETA (Zactima Efficacy in Thyroid Cancer Assessment) that enrolled 331 patients with either sporadic or hereditary MTC. A total of 231 patients were randomized to vandetanib and 100 were randomized to placebo; 90% of the patients enrolled had sporadic MTC. During the course of the study, if patients showed progressive disease, they were unblinded and were allowed to cross over to the active drug. The findings, presented at the 2010 American Society of Clinical Oncology annual meeting, showed a partial response of 45% in patients treated with vandetanib compared to 13% in those randomized to placebo, with no available information on stable disease. Of the 13 patients randomized to placebo, 12 had partial response after crossing over to active drug in the open-label phase of the study. In the placebo arm, the median progression-free survival (PFS) was 16.4 months, and in the vandetanib arm, the median PFS was not yet reached at the time of data analysis. However, when the curve was extrapolated, a PFS of 22.6 months was estimated, which implies that vandetanib may prolong PFS by approximately 6.2 months compared to placebo. Consistent benefit was observed regardless of germline or somatic *RET* mutational status. Additionally, the benefit was sustainable with the median duration of response not yet reached at 24 months of follow-up. These studies led to the FDA approval of vandetanib for progressive or symptomatic MTC.

H&O What side effects were seen with vandetanib?

MH The most common side effect that occurred in the phase III trial was diarrhea. This is a difficult side effect to face, because patients with MTC tend to have diarrhea as part of the paraneoplastic syndrome, so uncontrolled diarrhea can be problematic. The second most common side effect was a rash, which included photosensitivity to sunlight. Therefore, it is necessary to counsel patients on using sun protection and sunscreen while taking this medication. Dermatitis acneiform, nausea, hypertension, headache, fatigue, low appetite, and abdominal pain were also seen in more than 20% of patients. Additionally, a significant portion of patients needed their thyroid hormone replacement dose increased while on this drug.

H&O Are there any contraindications with this drug?

MH Vandetanib can lead to QTc interval prolongation, an abnormal heart rhythm. If patients have QTc prolongation, they can develop torsade de pointes, bradyarrhythmia, or even sudden death. The "black box warning" for vandetanib is to not use it in patients who may be predisposed to QTc prolongation (ie, congenital long QT syndrome, history of torsade de pointes, bradyarrhythmias, uncompensated heart failure, or untreated hypocalcemia/hypokalemia/hypomagnesemia). Thus, it is necessary to monitor calcium, magnesium, potassium, and thyroid-stimulating hormone, and to correct deficiencies. An electrocardiogram should be obtained at baseline prior to initiating the drug, then 2–4 weeks and 8–12 weeks after initiation, and every 3 months thereafter. If the QTcF—the Fridericia formula to calculate the QTc interval—is greater than 500 msec, vandetanib should be stopped and the patient should be monitored for reduction of the QTc interval down to less than 450 msec. The drug can then be restarted at a dose-reduced level. The patient should be advised to avoid taking drugs that may prolong the QTc interval while taking vandetanib. Due to this potential toxicity, vandetanib is only distributed to those prescribers and pharmacies that participate in a restricted prescription program called Risk Evaluation and Mitigation Strategy (REMS).

H&O What are some future directions for research in MTC?

MH The exciting part about being in this field is that over the course of several years, there has been a great amount of research and development in therapeutics targeting MTC and differentiated thyroid cancer.

Until recently, we had no viable options to give to our patients for systemic management. We have not yet found that one drug or combination of drugs that will lead to a cure. Identifying other targets in MTC aside from RET and VEGF is necessary. It may be that we need to consider novel combinations of agents; TKIs offer multikinase activity and may prove more effective in combination with other agents. This was partially seen in the tipifarnib and sorafenib phase I experience in MTC. The FDA approval of vandetanib for patients with progressive or symptomatic MTC has been a highly anticipated event for both physicians and patients alike. However, there are ongoing trials with other potentially beneficial treatments, such as XL184 (cabozantinib, Exelixis) and E7080 (Eisai). The future is still unknown, but it definitely has dynamic and promising prospects.

Suggested Readings

Wells SA Jr, Gosnell JE, Gagel RF, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Oncol*. 2010;28:767-772.

Natale RB, Thongprasert S, Greco FA, et al. Phase III trial of vandetanib compared with erlotinib in patients with previously treated advanced non–small-cell lung cancer. *J Clin Oncol*. 2011;29:1059-1066.

Jasim S, Ying AK, Waguespack SG, et al. Multiple endocrine neoplasia type 2B with a RET proto-oncogene A883F mutation displays a more indolent form of medullary thyroid carcinoma compared with a RET M918T mutation. *Thyroid*. 2011;21:189-192.

Hong DS, Cabanillas ME, Wheler J, et al. Inhibition of the Ras/Raf/MEK/ERK and RET kinase pathways with the combination of the multikinase inhibitor sorafenib and the farnesyltransferase inhibitor tipifarnib in medullary and differentiated thyroid malignancies. *J Clin Endocrinol Metab*. 2011;96:997-1005.

American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009;19:565-612.

National Comprehensive Cancer Network. NCCN Guidelines for Thyroid Carcinoma. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site