New Developments in Thyroid Cancer

Presented by Robert I. Haddad, MD

Abstract
Thyroid cancer is common but rarely deadly. Unfortunately, when the disease becomes refractory to radioactive iodine (RAI), few effective treatment options remain. This situation is changing, however, with the availability of multitargeted tyrosine kinase inhibitors. Cabozantanib and vandetanib, both recently FDA-approved for advanced or metastatic disease, have more than doubled progression-free survival in medullary thyroid cancer. New agents in the pipeline may yield even better outcomes, as discussed by Dr. Robert I. Haddad at the NCCN 18th Annual Conference. (JNCCN 2013;11:705–707)

"These are exciting times in thyroid cancer. Two new drugs have become available for advanced medullary thyroid cancer, and more are expected in the next few years," said Robert I. Haddad, MD, Associate Professor of Medicine at Harvard Medical School and Disease Center Leader of the Head and Neck Oncology Program at Dana-Farber Cancer Institute, Boston.

Thyroid cancer is not rare: more than 60,000 new cases are diagnosed each year in the United States and the numbers are rising, probably due to better diagnosis. Thyroid cancer deaths, however, are rare, with only about 1800 a year despite the high cancer incidence, Dr. Haddad added. Most cases of thyroid cancer are differentiated thyroid cancers (83% papillary, 11% follicular). The more aggressive anaplastic and medullary carcinomas comprise 3.3%, and 2% are other subtypes.1 All histologic subtypes are poorly responsive to chemotherapy, and patients with advanced disease that becomes refractory to radioactive iodine (RAI) have had few treatment options, although this picture is changing.

RAI-refractory distant metastases are associated with a median survival of 3 to 6 years. Oncogenic mutations in BRAF and RAS are associated with worse progression-free survival (PFS) and overall survival (OS). Expert consensus and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommend clinical trials for patients with progressive metastatic disease; if access is unavailable, the anti-angiogenic tyrosine kinase inhibitors (TKIs) can be used.

The Role for TKIs
The vascular endothelial growth factor (VEGF) pathway is important in thyroid cancer, and various tyrosine kinases are activated in the disease. Thus, there is a therapeutic role for multikinase inhibitors.

In a phase II trial of pazopanib in 39 patients with rapidly progressive RAI-refractory differentiated thyroid cancer, the response rate was 49% and the likelihood of response lasting longer than 1 year was estimated at 66%.2 In a phase II study of sorafenib, 30 patients were treated for a minimum of 16 weeks, after which 23% showed response and 53% showed stable disease lasting 14 to more than 80 weeks. Median PFS was 79 weeks.3 “I have used sorafenib extensively, and I can say that some patients do benefit,” Dr. Haddad commented. A phase III trial has been completed, but the data are not yet available.

Dr. Haddad cautioned that although TKIs can be effective in thyroid cancer, many patients with metastatic...
disease do not require treatment for many years after the diagnosis of metastases. The drugs have side effects that impact quality of life without necessarily prolonging survival; therefore, care should be taken in starting treatment, he said.

Another agent that showed promising activity in thyroid cancer is lenvatinib or E7080. In a 58-patient study, a 41% response rate was seen among patients with previous VEGF-targeted treatment and a 54% response rate was seen in TKI-naive patients. Stable disease was seen in 53% and 42%, respectively. Median time to response was 2.1 months, and median PFS was 13.3 months. Treatment-related adverse events were primarily hypertension, diarrhea and proteinuria (grade 3 in 10%). The phase III trial of lenvatinib is now complete, but data are unavailable.

**MEK Inhibitors Show Encouraging Activity**

RAI resistance means that RAI fails to incorporate into metastatic sites, and this resistance is associated with higher mortality. Preclinical studies have shown that pharmacologic inhibition of oncogenic BRAF signaling increases RAI incorporation. Recent studies suggest that MEK inhibitors might be capable of reversing RAI resistance and making RAI avid and effective. In a study recently published in the New England Journal of Medicine, the MEK1/MEK2 inhibitor selumetinib induced iodine incorporation in patients with BRAF-mutations. After stimulation with thyrotropin alfa, dosimetry with iodine-124 PET was performed before and 4 weeks after treatment with selumetinib. If the second PET indicated that a 2000 cGy or higher dose of iodine-131 could be delivered to the metastatic lesion, therapeutic RAI was given with selumetinib. Among the 20 evaluable patients, selumetinib increased the uptake of iodine in 12, and 8 of these reached the dosimetry threshold for RAI therapy.

“Selumetinib-induced iodine incorporation in RAI-refractory thyroid tumors translated to a therapeutic response with RAI,” he noted. Patients with RAS mutations may be particularly susceptible to this strategy.

**Medullary Thyroid Cancer**

Medullary thyroid cancer (MTC) accounts for 5% to 8% of thyroid cancers. Patients with distant metastases have a median survival of about 2 years. About three-quarters of cases occur sporadically, typically in the fifth or sixth decade, while 25% are hereditary. Somatic RET mutations are present in up to 65% of

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**Figure 1**  Progression free survival (PFS; primary endpoint). From Schoffski P, et al; J Clin Oncol 2012;30(15 suppl):Abstract 5508; Reprinted with permission. © 2012 American Society of Clinical Oncology. All rights reserved. Abbreviations: CI, confidence interval; HR, hazard ratio.
sporadic cases, and germline RET mutations are found in more than 95% of hereditary cancers. Hepatocyte growth factor receptor and VEGF receptor 2 pathways have been implicated in the pathogenesis of MTC.

Two drugs were recently approved for metastatic MTC: cabozantinib (2012) and vandetanib (2011). The NCCN Guidelines list both drugs as category 1 treatments for unresectable disease that is symptomatic or asymptomatic and structurally progressive. In the phase III EXAM trial, 330 patients (75% treatment-naive) were randomized to receive cabozantinib 140 mg daily or placebo. Median PFS was 11.2 months with cabozantinib versus 4.0 months for placebo; 1-year PFS was 47.3% versus 7.2%; and the hazard ratio was highly significant at 0.28 (P < .0001; Figure 1). All subgroups appeared to benefit from cabozantinib. The final OS analysis is not available yet.

In the phase III ZETA trial involving 331 patients, vandetanib similarly showed a highly significant difference in PFS (hazard ratio 0.46; P < .0001). Responses were seen in 45% of patients receiving vandetanib versus 13% with placebo (P < .0001). Almost all responses in the placebo arm occurred while patients were receiving vandetanib. Median duration of response had not been reached at 24 months of follow-up. Additionally, significant reductions in calcitonin and carcinoembryonic antigen were observed, with odds ratios for biochemical responses of 73 and 52, respectively, in the study (P < .0001).

“I have used vandetanib extensively, because it has been available longer than cabozantinib, and I have seen significant and durable responses and marked reductions in biomarker levels,” Dr. Haddad noted.

But cabozantinib and vandetanib are not without side effects, and doses may need to be reduced, he cautioned. In both the EXAM and ZETA trials, dose reductions were necessary in most patients. Vandetanib can prolong the QT interval, and cases of Torsades de pointes and sudden death were reported in clinical trials. Because of this risk, the drug is available only through the risk evaluation and mitigation strategy (REMS) program. The most effective cardiac monitoring is with EKG, not echocardiogram. More commonly, diarrhea, rash, and fatigue are reported. “Be careful with the 300 mg dose of vandetanib, and be prepared to dose-reduce,” Dr. Haddad advised.

**Anaplastic Thyroid Cancer**

Anaplastic thyroid cancer is the most aggressive and lethal histologic subtype. Treatment must be started immediately, and resection is recommended, even for palliation. Chemotherapy is generally ineffective, but it can be considered after surgery in select patients. Dr. Haddad noted, “we routinely use concurrent chemoradiotherapy in patients who undergo a complete surgical resection and our preferred regimen is weekly carboplatin and paclitaxel. Refer these patients immediately for a clinical trial if one is available. This is one of the most aggressive and lethal cancers in humans,” Dr. Haddad emphasized.

**References**