ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Emerging Treatments in Thyroid Cancer

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H&O How common is thyroid cancer?

SS Thyroid cancer is the most rapidly increasing diagnosed malignancy. It is currently the fifth most common cancer diagnosed in women. In 2012, an estimated 55,000 people in the United States will be diagnosed with some type of thyroid cancer. According to the last formal prevalence estimate from the National Cancer Institute, just over 400,000 patients are living with thyroid cancer in the United States.

H&O Are there any known risk factors in thyroid cancer?

SS Little is known about risk factors for the development of the various forms of thyroid cancer. Most patients with thyroid cancer have the differentiated subtype, which derives from the follicular epithelium responsible for making thyroid hormone. Radiation exposure is the only known trigger for the development of differentiated thyroid cancer.

Medullary thyroid cancer, a neuroendocrine form of the disease, accounts for only about 5% of all cases. In approximately 20% of patients, medullary thyroid cancer is familial and associated with inherited syndromes of medullary cancer or multiple endocrine neoplasia. However, 80% of patients have sporadic disease that is associated approximately half the time with a particular somatic gene mutation in the tumor. What triggers the mutation to occur is unknown as well.

H&O What are the mortality rates in thyroid cancer?

SS Most patients diagnosed with thyroid cancer live long enough to die from something else. The relative survival is excellent for localized differentiated thyroid cancer confined to the thyroid gland; the 10-year relative survival rate is close to 100%. However, for patients who are older at the time of diagnosis, with larger tumors that are locally invasive and particularly metastatic to distant sites, the risk of mortality is significantly high. At the other end of the spectrum is anaplastic thyroid cancer, which probably affects a little more than 500 people in the United States each year. It is virtually uniformly fatal, with a median survival of only about 3 months despite any particular approach to therapy.

H&O How is thyroid cancer diagnosed?

SS In most patients, it is diagnosed on the basis of a fine-needle aspiration of a thyroid nodule that is either palpated by a physician or detected incidentally by an imaging modality, such as ultrasound. These incidental findings may account for the rapid rise in the reported incidence of thyroid cancer. The increased rate of diagnosis in women is most likely because small, intrathyroidal tumors are being detected incidentally with imaging modalities, such as carotid ultrasound used to evaluate for atherosclerotic disease. There have also been increases in the larger forms of the disease. Again, most of these

diagnoses are based on a fine-needle aspiration. In some cases, if fine-needle aspiration yields suspicious criteria but is not diagnostic for malignancy, the patient may undergo a thyroidectomy to establish a formal diagnosis.

H&O What are the traditional treatment approaches?

SS For patients with differentiated thyroid cancer, thyroidectomy is probably the most important and curative intervention. Adjuvant radioactive iodine has been in use since the 1940s, but to a large degree, it has fairly weak levels of supportive evidence. More recently, the use of radioactive iodine as adjuvant therapy for differentiated thyroid cancer has declined. Radioiodine is still useful in the setting of metastatic differentiated thyroid cancer, as it is currently the only intervention that is curative for the small group of patients with this disease.

Another treatment is thyroid hormone suppression therapy, which uses thyroid hormone to make the patient iatrogenically thyrotoxic—hopefully subclinically, but at least enough to lower the levels of trophic thyroid-stimulating hormone so that growth of metastatic disease is suppressed. External beam radiation is occasionally of value in the treatment of microscopic residual disease or in an adjuvant mode after surgery for invasive cancer in the neck. For medullary thyroid cancer, surgery has been the mainstay and the only curative intervention. Unfortunately, most patients do not achieve a biochemical cure even with aggressive surgery. However, in most cases, thyroidectomy and central neck dissection are appropriate first steps.

For distant metastatic disease, in the last year we have seen the approval of vandetanib (Caprelsa, AstraZeneca), the first chemotherapeutic agent that improves progression-free survival in thyroid cancer. So there is now an approved approach to treating metastatic disease that can be of some clinical benefit, although as of yet it has not been demonstrated to improve overall survival.

H&O Which multikinase inhibitors are being studied for thyroid cancer?

SS There is a broad array of multikinase inhibitors attacking both tyrosine kinases and other kinases. The primary target for most of the therapies that have been evaluated and appear to be effective is the vascular endothelial growth factor (VEGF) receptor. However, most of the inhibitors are multi-targeted, and in addition to the VEGF receptor, other targets include the platelet-derived growth factor (PDGF) receptor and c-kit, which may be less relevant in thyroid cancer. Many of these agents also inhibit some of the oncogenes that are found to be activated in papillary carcinoma, such as the RET/PTC oncogene. Because the activation of these oncogenes appears to be relatively uncommon in patients with metastatic or advanced disease, their value as a target for chemotherapy is unclear. Some of the agents target *BRAF*, which is of interest because *BRAF* mutations are found in approximately 40% of papillary thyroid cancers and have been epidemiologically associated with more advanced and aggressive disease.

There are ongoing clinical trials of selective B-Raf inhibitors, such as vemurafenib (Zelboraf, Genentech/Daiichi-Sankyo) and dabrafenib (GlaxoSmithKline). However, there are no publications describing significant experience in thyroid cancer with these kinds of agents.

Lenvatinib (Eisai Co) is a small-molecule, tyrosine kinase inhibitor. At the 2011 American Society of Clinical Oncology (ASCO) annual meeting, I presented results of an open-label, multicenter phase II study of lenvatinib (24 mg/day) in 58 patients with radioiodine-refractory, advanced differentiated thyroid cancer. At 14 months of follow-up, 59% of patients achieved a partial response, as assessed by the study investigators. Stable disease was observed in 36% of patients, and median progression-free survival was 13.3 months. Progressive disease occurred in 5% of patients. Adverse events were manageable and consisted mostly of hypertension, proteinuria, fatigue, and gastrointestinal complaints.

Sorafenib (Nexavar, Onyx/Bayer) has been used a great deal in patients with thyroid cancer on the basis of several published phase II studies. There is an ongoing randomized phase III trial to determine whether sorafenib improves progression-free survival as compared with placebo. For patients with medullary cancer, as I mentioned, vandetanib is a chemotherapeutic agent that targets the VEGF receptor EGFR, in high doses, and RET. Cabozantinib (Exelixis), which targets the c-Met oncogene in addition to VEGF-R and RET, may have a slightly different mode of action in achieving response than vandetanib. As reported at the 2012 ASCO meeting, in a cohort of patients with rapidly progressive disease, cabozantinib was associated with a marked increase in progression-free survival as compared to placebo (11.2 months vs 4.0 months, respectively).

H&O Which biomarkers are important in thyroid cancer?

SS Historically, thyroglobulin has been used as a biomarker for differentiated throat cancer, and calcitonin and the carcinoembryonic antigen have been used for medullary cancer. These biomarkers are generally used in early-stage disease. The elimination of detectable levels of thyroglobulin and calcitonin is part of the definition for

biochemical evidence of cured disease. Thyroglobulin and calcitonin are also followed sequentially in these patients to monitor for recurrence or progression of disease. Their value as biomarkers to monitor response to chemotherapy is less well-established at this point, particularly so for calcitonin in medullary cancer.

All of the kinase inhibitors that target RET have a direct suppressive effect in calcitonin gene transcription that may not necessarily correspond with tumor response to the drug. Other potential biomarkers of keen interest that are currently being studied include circulating tumor cells, thyrotropin receptor mRNA, and circulating B-Raf mutant DNA.

H&O Are there new treatment options on the horizon?

SS Most of the current work involves single-agent kinase inhibitors. There is some early work being done in combination trials, and a soon-to-be initiated randomized trial of a B-Raf inhibitor versus a B-Raf and an MEK inhibitor, so additive regimens are beginning to be studied. Certainly, the ways in which some of the kinase inhibitors might synergize with more traditional cytotoxic or immunotherapeutic agents is of great interest.

I am currently chairing a new group that aims to provide valuable support to innovative research and clinical trials. The International Thyroid Oncology Group (ITOG) is comprised of approximately 50 thyroid cancer investigators from around the world. ITOG will hopefully launch its first clinical trial sponsored by the National Cancer Institute later this year.

H&O What are some areas of research in thyroid cancer?

SS There is much focus on medullary cancer, in particular trying to identify the genetic causes of the disease in patients without RET mutations, a scenario found in at least 60% of the sporadic cases of the disease. Another important area is the nature of the events that lead to aggressive and progressive metastatic disease. As I mentioned, most patients with thyroid cancer do very well, sometimes even without any treatment at all. What distinguishes those patients who have relatively indolent, nonlethal disease from patients who go on to experience significant morbidity and/or die from thyroid cancer remains an unknown and important area for research.

Suggested Readings

Carr LL, Mankoff DA, Goulart BH, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. *Clin Cancer Res*. 2010;16:5260-8526.

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