Clinical Roundtable Monograph

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New and Emerging Therapeutic Options for Thyroid Carcinoma

Discussants

Jatin P. Shah, MD
Chief, Head and Neck Service
Elliot W. Strong Chair in Head and Neck Oncology
Memorial Sloan Kettering Cancer Center
Professor of Surgery
Weill Medical College of Cornell University
New York, New York

Gary L. Clayman, DMD, MD
Professor of Surgery, Department of Head and Neck Surgery
Chief of Head and Neck Endocrine Surgery
Alando J. Ballantyne Distinguished Chair of Head and Neck Surgery
Medical Director for Health Care Providers
The University of Texas MD Anderson Cancer Center
Houston, Texas

Lori J. Wirth, MD
Assistant Professor
Medical Director of the Center for Head and Neck Cancers
Department of Medicine
Harvard Medical School
Assistant Professor of Medicine
Massachusetts General Hospital
Boston, Massachusetts

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Abstract: The incidence of thyroid cancer has increased in the past few decades. Most patients with follicular cell–derived tumors present with well-differentiated carcinomas, and they have an excellent prognosis following treatment. Between 10% and 15% of tumors will mutate into more aggressive variants, such as tall-cell carcinoma and insular carcinoma. Some patients will present with poorly differentiated carcinomas requiring aggressive surgery and adjuvant therapy. The management plan for patients with thyroid carcinoma is based on the tumor type and prognostic risk factors. There is controversy regarding whether all thyroid cancers require treatment. In most cases, the initial treatment for differentiated thyroid cancers is surgical. Radioactive iodine (RAI) was established as adjuvant therapy more than 50 years ago, but data show that many patients do not respond to this therapy or develop RAI-refractory disease, which is associated with a poor prognosis. Until recently, there were no specific targeted systemic therapies available for patients with RAI-refractory thyroid cancer. The US Food and Drug Administration has recently approved 2 systemic agents for RAI-refractory disease: sorafenib and lenvatinib. These approvals have paved the way for the clinical development of other targeted therapies, with many showing promising results in patients with RAI-refractory disease.

This activity is supported by an independent educational grant from Eisai Inc.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and nurses involved in the management of patients with thyroid carcinoma.

Statement of Need/Program Overview

Most cases of newly diagnosed thyroid cancers are low-risk, well-differentiated papillary carcinomas found at an early stage. These patients have an excellent prognosis. The initial treatment for differentiated thyroid carcinomas is usually surgical. The extent of surgery is tailored to the extent of the tumor and the patient's risk group. Radioactive iodine (RAI) was established as adjuvant therapy more than 50 years ago, but data show that many patients do not respond to this therapy or develop RAI-refractory disease, which is associated with a poor prognosis. Until recently, doxorubicin was the only treatment option approved by the US Food and Drug Administration (FDA) for RAI-refractory patients with metastatic differentiated thyroid carcinomas. Doxorubicin is associated with low objective response rates and high toxicity, and it has little to no impact on overall survival. The emergence of newer targeted therapies ended the era of cytotoxic chemotherapy as the primary treatment for patients with RAI-refractory differentiated thyroid carcinomas. The FDA approved the targeted agents sorafenib in 2013 and lenvatinib in 2015 for the treatment of RAI-refractory differentiated thyroid carcinomas. These approvals have led to the clinical development of other targeted therapies, with many showing promising results in patients with RAI-refractory disease.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the traditional treatment approaches for patients with differentiated thyroid carcinoma based on risk stratification
- Identify patients who might benefit from treatment with recently approved targeted agents
- Integrate the use of recently approved agents into the management course
- Apply strategies to manage the adverse events associated with novel targeted therapies for thyroid carcinoma
- Describe future research directions for therapies in thyroid carcinoma based on recent clinical data

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Thyroid Carcinoma: Epidemiology, Histology, and Diagnosis

Jatin P. Shah, MD

The incidence of thyroid cancer has risen in recent years. In the United States, the incidence increased at an annual rate of 5.4% in men and 6.5% in women from 2006 to 2010.[1] Whether this increase represents a true rise in incidence—or early discovery of subclinical disease—is a matter of discussion. Early diagnoses of subclinical disease are also becoming more common throughout the world.[2] This increase has generated significant interest in the management of thyroid cancer.

Pathophysiology

Thyroid cancer begins in the follicular cell of the thyroid gland. There are 2 types of cells located within the thyroid parenchyma: the follicular cells and the supporting cells (also called the *C cells*). Cancers derived from follicular cells are generally differentiated thyroid carcinomas (DTC). Although these cancers are not usually aggressive, they can eventually mutate into more aggressive variants.

Thyroid cancer progresses according to a well-defined tumor progression model (Figure 1).[3] Approximately 85% of patients present with DTC, and they have an excellent prognosis following treatment. Between 10% and 15% of tumors will mutate into more aggressive variants of thyroid carcinoma (Figure 2). These tumors may present with tall-cell features or as tall-cell thyroid carcinoma, and they have a biologic behavior that requires more aggressive surgical intervention and adjuvant therapy. Notably, these patients could be candidates for novel therapies if their disease is unresectable or refractory to radioactive iodine (RAI).

When the same stimulus that initiated the cancer continues, the tumors may mutate into poorly differentiated carcinomas. Approximately 10% of thyroid cancers may present with these features, and they carry a worse prognosis requiring more aggressive interventions, both surgically and nonsurgically. These cancers are generally refractory to RAI and have a higher risk of cause-specific mortality.

Fewer than 2% of thyroid cancers present as anaplastic carcinomas.[4] Most mortality in thyroid cancer occurs in patients with anaplastic carcinoma. It is a uniformly fatal cancer.

Etiology

Thyroid cancer has no established etiologic factors, although exposure to radiation has been implicated for several decades.

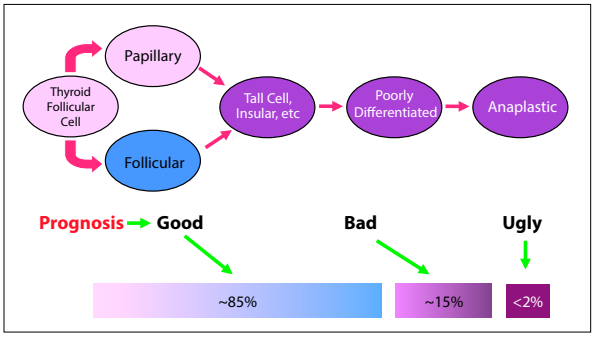

Figure 1. Thyroid cancer progresses according to a well-defined tumor progression model. Data from Wreesmann VB et al. *Am J Pathol.* 2002;161(5):1549-1556.[3]

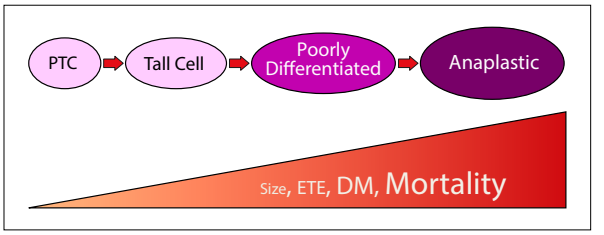

Figure 2. A small proportion (approximately 10%) of papillary carcinomas will undergo progression to more aggressive variants. As the tumor progress to more aggressive variants, it leads to clinical manifestations of progression and increased mortality.

DM, distant metastases; ETE, extrathyroid extension; PTC, papillary thyroid carcinoma.

The phenomenon of radiation exposure leading to increased incidence of thyroid cancer was documented following the atomic bomb exposure in Hiroshima and Nagasaki during World War II.[5] More recently, it was shown after the Chernobyl accident, which was followed by a steep rise in thyroid cancer among children exposed to the radiation fallout.[6] There is evidence that exposure to low-dose radiation during childhood (such as in patients receiving therapeutic radiation for leukemia/lymphoma) is associated with an increased incidence of thyroid cancer.[7] There is also evidence to show an increased risk of thyroid cancer in children treated with low-voltage radiation for acne. Although the incidence of thyroid cancer is higher after radiation exposure, the biological behavior of the disease is similar in both radiation-exposed and nonradiation-induced thyroid cancer. Therefore, although radiation exposure is important for triggering

the disease, it does not appear to play a role in determining the aggressiveness of the malignancy.

Epidemiology

Thyroid cancer is most frequently encountered in younger age groups.[8] Across the literature, age at onset appears as a bell-shaped curve, with the highest incidence in the second, third, and fourth decades of life. Within the past 2 decades, however, there has been a rise in the incidence of thyroid cancer during the fourth and fifth decades of life.[9] The increased diagnoses may be attributable to incidental findings of tumors on imaging studies, such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), performed for other reasons.

In the United States, occult thyroid cancers are reported with an incidence of approximately 10% at autopsy among people who died of other causes.[10] This incidence rises in various geographic regions of the world. In Finland, the autopsy incidence of occult papillary carcinoma is 35%.[11] These cancers likely had been present in the thyroid glands of these people throughout a portion of their life, without ever becoming clinically significant. These findings raise a controversial issue regarding whether all thyroid cancers should be diagnosed and treated. Data from the US autopsy study would suggest that there are more than 38 million people unknowingly living with papillary carcinoma. If overdiagnosis and treatment of these subclinical cancers continues, then in years to come, the autopsy incidence of occult thyroid cancers will probably decrease. Whether all thyroid carcinomas need to be treated is currently under debate.

Diagnosis

Typically, thyroid cancer is diagnosed after intrathyroid nodules are discovered on routine imaging (eg, on an MRI performed for a whiplash injury or an ultrasound performed on carotid arteries). The majority of such patients with thyroid cancer have no symptoms at the time of initial diagnosis. When symptoms do arise, they are usually caused by invasion of an adjacent structure by the primary tumor or metastatic progression to a lateral neck lymph node. A minority of patients present with locally advanced thyroid cancer (often poorly differentiated or anaplastic carcinoma). These patients may present with either symptoms of a mass in the neck, a feeling of pressure in the neck, or a choking sensation. Occasionally, patients present with hoarseness caused by paralysis of the vocal cords resulting from invasion of the recurrent laryngeal nerve. Some patients may also experience hemoptysis or airway obstruction from tumors growing into the trachea and compromising the airway. In some patients, the only symptom is a lump in the neck that turns out to be a metastatic lymph node.

A series of tests can be performed to diagnose and assess the primary tumor. The tests most relevant to decision-making in this disease are an ultrasound of the thyroid gland and a fine-needle aspiration biopsy. All other tests are relatively peripheral and subsequent to the establishment of the diagnosis of cancer.

Following confirmation of the diagnosis, and depending on the size and extent of the tumor, further radiologic workup may be necessary. Anatomic imaging studies, such as CT or MRI, are usually required in those patients who have an extensive primary tumor (such as a T3 or a T4 primary tumor) with invasion of adjacent structures or in patients who present with extensive nodal metastases.

Some clinicians believe that a CT scan should not be performed with the contrast dye. Use of iodine-containing contrast dye for imaging studies will delay the administration of RAI treatment, but this delay is not necessarily detrimental to the long-term outcome of the patient. In fact, detailed and accurate anatomic assessment of the primary tumor and its invasion to local structures is crucial for the surgeon to be able to perform a definitive and complete operation and achieve an R0 resection. Thus, when necessary, contrast dye should be used to obtain a good structural study.

Histology

Fortunately, the majority of newly diagnosed thyroid cancers are well-differentiated papillary carcinomas that are easily treatable and highly curable, and they respond well to therapy. In the past 2 decades, more than 80% of patients with newly diagnosed thyroid cancer had tumors less than 2 cm in diameter.[9] This relatively small size implies that the cancer is at an early stage and associated with an excellent prognosis.

DTC can present with a papillary pattern or a follicular pattern, resulting in a diagnosis of either papillary carcinoma or follicular carcinoma. Most tumors are heterogeneous with both histologies—papillary and follicular—which is why they were formerly referred to as *mixed papillary and follicular carcinomas*. Current classification, however, is based on the predominance of the histologic pattern. Within DTC, there are variants of papillary carcinoma. For example, a follicular variant of papillary carcinoma is diagnosed when the follicular histology is predominant.

Prognosis

The prognosis in DTC depends on a variety of factors that are related to the patient and the tumor (Figure 3).[12-16]

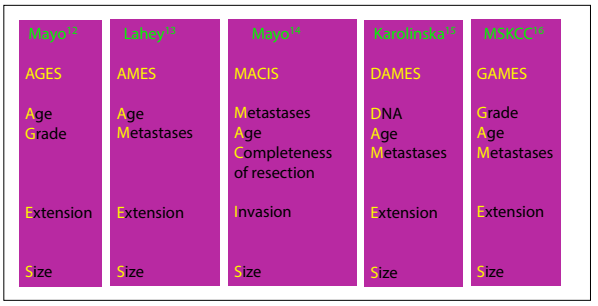

Figure 3. Prognostic factors independently impacting outcomes in differentiated thyroid carcinoma based on multivariate analyses from the Mayo Clinic,[12,14] Lahey Clinic,[13] the Karolinska Institute,[15] and the Memorial Sloan Kettering Cancer Center (MSKCC).[16]

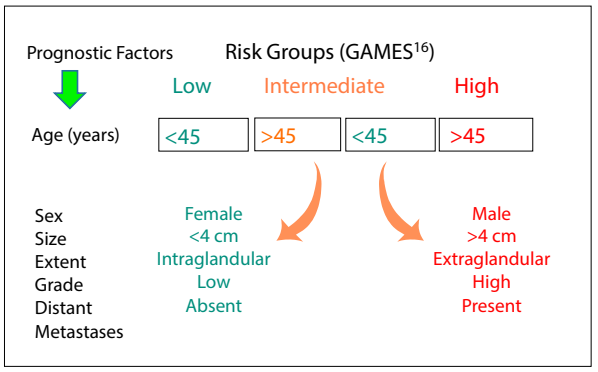

Figure 4. The identification of prognostic factors led to the development of risk group stratification, which categorizes patients into low-risk, intermediate-risk, and high-risk groups. GAMES, grade, age, metastases, extension, size. Based on a multivariate analysis from the Memorial Sloan Kettering Cancer Center.[16]

Patient age is an important prognostic factor.[8,17] Patients who are younger (generally considered <45 years) have an improved prognosis compared with older patients. In patients younger than 45 years, the 10-year survival rate is 98% to 99%. In contrast, mortality rates reach 20% to 25% among patients older than 70 years.

Histologic grade is another important factor for prognosis, with well-differentiated tumors having a better prognosis compared with poorly differentiated tumors.[8] Similarly, extrathyroid extension is an independent factor impacting outcome.[8] Patients with minor extension (T3) outside the thyroid gland have a relatively better outcome compared with those who have major extension (T4a) involving the adjacent structures, such as the recurrent laryngeal nerve, the trachea, the larynx, and the esophagus.

Tumor size is also of prognostic value.[8] With increasing size, the risk of local recurrence starts to rise, which may eventually have a potential negative impact on survivorship. Presence of distant metastases is also an obvious and independent predictor of outcome.

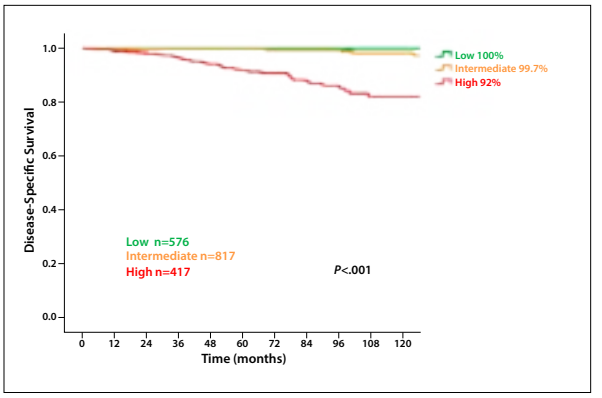

Figure 5. Disease-specific survival according to risk group stratification according to the GAMES system from the Memorial Sloan Kettering Cancer Center.[16] GAMES, grade, age, metastases, extension, size.

Risk Group Stratification

The identification of prognostic factors led to the development of risk group stratification, which categorizes patients into low-risk, intermediate-risk, and high-risk groups.[18] This stratification allows clinicians to tailor the initial treatment, including the extent of surgery, as well as the need for adjuvant postoperative therapy and the intensity of subsequent follow-up care. The low-risk category consists of patients who are young and female, with intraglandular tumors that are smaller than 4 cm, and who show no evidence of distant metastases (Figure 4). The 5-year survival rate in low-risk patients following treatment is near 100% (Figure 5).[4] The high-risk category includes patients who are older and male, with extraglandular tumors larger than 4 cm that have a high-grade histology or evidence of distant metastases. These patients require aggressive surgery. There should also be consideration of elective treatment of regional lymph nodes and adjuvant therapies with RAI, external radiation therapy, or newer systemic agents.

There are 2 groups of patients in the intermediate-risk group category. One group consists of younger patients with tumors that have poor histology or a gross extrathyroid extension. The second group includes older patients with small intrathyroidal differentiated tumors. Management should be tailored to the patient and the tumor in the intermediate group, to avoid overtreating the patient.

Disclosure

Dr Shah has no conflicts of interest to report.

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Local Treatment of Differentiated Thyroid Carcinoma

Gary L. Clayman, DMD, MD
Professor of Surgery, Department of Head and Neck Surgery
Chief of Head and Neck Endocrine Surgery
Alando J. Ballantyne Distinguished Chair of Head and Neck Surgery
Medical Director for Health Care Providers
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Surgery remains the mainstay of treatment for differentiated thyroid cancers. The efficacy of surgical therapy varies based on several factors, including extent of differentiation, nodal spread, and soft tissue extension. Ultrasonography is required to assess the need for surgery and evaluate the areas that require attention. When disease is identified within the thyroid gland during ultrasound, evaluation should also include the cervical lymph nodes. Nodal disease under the thyroid gland and central compartment is one of the primary areas of lymphatic drainage.

Any suspicious nodes must undergo needle biopsy if the results would change the extent of surgery. When lateral neck lymph nodes are present, not all require biopsy; confirmation of disease can be based on results from just representative areas. During ultrasonography, suspicious lymph nodes are difficult to appreciate in the presence of thyroiditis because they can appear similar to metastatic lymph nodes. Intraoperative frozen section analysis can determine whether the central compartment lymph nodes are involved in patients with thyroiditis.

The Use of Radioactive Iodine

The original indications for the use of RAI in differentiated thyroid cancer date to the 1940s, when it was shown that this therapy could treat soft tissue extension and lymph node metastases, which increase the rates of local and regional recurrence.[1] RAI became a mainstay of therapy in patients with distant metastases. It was soon recognized, however, that many patients did not respond

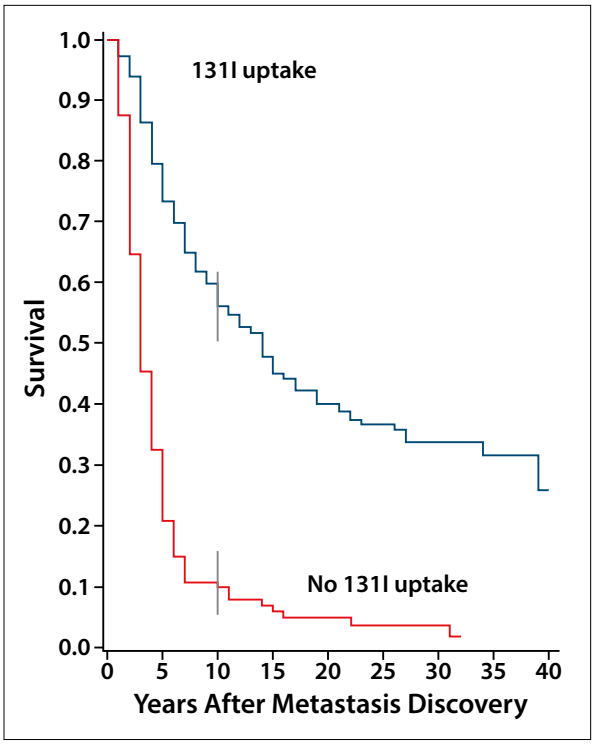

Figure 6. Nonavid tumors are unlikely to benefit from treatment with radioactive iodine. Adapted from Durante C et al. *J Clin Endocrinol Metab.* 2006;91(8):2892-2899.[3]

to treatment with RAI.[2] Currently, RAI tends to be used in patients who have tumors with pathologic extrathyroidal extension, cancer that has spread to the lymph nodes, or distant metastases. The new American Thyroid Association (ATA) guidelines, which will be available later in 2015, are expected to recommend that RAI therapy be used in patients with involvement of multiple lymph nodes, soft tissue extension, or distant metastases.

Relapsed, Recurrent, or Refractory Disease

Disease that reoccurs after confirmation of local regional control on imaging studies is known as relapsed or recurrent. Patients who are refractory to RAI have been described by several terms, including resistant, nonresponsive, and nonavid.

Nonavid Tumors

The term *nonavid* describes tumors that failed to absorb a sufficient amount of RAI during diagnostic procedures or post-therapy scintigraphy. It is also possible for tumors to retain their avidity for RAI but to receive too little radiation for a meaningful clinical response. Tumors may be resistant to RAI if the clearance is too rapid or the retention is inadequate. Nonavid tumors are unlikely to benefit from treatment with RAI (Figure 6).[3,4] Avidity has recently become more important with the US Food and Drug Administration (FDA) approval of 2 systemic therapies—sorafenib and lenvatinib—for patients with progressive disease that is refractory to RAI.[5,6] Some patients may require RAI scanning to confirm tumor nonavidity before consideration of systemic therapy.

Persistent Disease

Disease that has not been extirpated by surgery is described as persistent. In prospective studies, rates of persistent disease reached 11% among patients with stage 1 or stage 2 thyroid carcinoma.[7] In some patients, the diseased tissue was left behind intentionally because excision was thought to pose greater risk of morbidity than the disease itself. Other patients have local extension of gross disease. Patients with persistent disease must undergo reevaluation to determine the risk of progression associated with these local or regional disease processes.

Local Treatment

Recurrent or Persistent Differentiated Thyroid Cancer

Patients with persistent recurrent or refractory differentiated thyroid cancer may have disease within the primary site, meaning the thyroid parenchyma itself; nodal disease; or soft tissue disease. Patients with primary site recurrence are at highest risk of invasion into the local organs, including the larynx, trachea, and esophagus, which can lead to significant morbidity.

Patients ages 50 years or older with locally invasive tumors have a higher risk of distant metastases and mortality from the disease.[8] In older patients with extensive disease, surgery itself is often inadequate. Even if the disease is completely resected (an R0 resection), there is the potential for microscopic disease, especially when organ preservation has been sought. These patients require combined modality therapy consisting of surgery, RAI, and external beam radiation. Retrospective studies have established the efficacy of this approach.[9-11]

Soft Tissue Disease

In soft tissue disease, radiofrequency and external beam radiation therapy can be used in the local environment. Radiation therapy can also be used for distant sites, for example, isolated metastases outside of the cervical areas. There are no randomized trials evaluating the use of radiofrequency cryoablations or percutaneous ethanol in the management of these locoregional recurrent diseases. Most studies continue to suggest that therapies for nodal recurrence in the cervical area be restricted to patients who are not candidates for surgical extirpation of the disease. In the rare circumstances in which surgery for nodal

recurrent disease is likely to be associated with high morbidity, radiofrequency or percutaneous ethanol injection are options. Therapy with percutaneous ethanol injection can require multiple injections on different occasions, but they tend to be well tolerated.[12] A mean of 2 ethanol ablation procedures are usually required to control the disease process, and the control rates are acceptable. Radiofrequency cryoablation and percutaneous ethanol injections are appropriate for management of isolated or multiple lymph nodes that are not suited for a surgical approach. These procedures are not used for previously untreated regional lymphatics.

RAI therapy for soft tissue metastasis and nodal metastasis in the neck is an option for patients with subclinical disease. There may be some patients, particularly children or young adults, with gross disease that may be controlled with RAI. In these circumstances, it is necessary to consider the potential morbidity of local regional extirpation of disease, especially when iodine avidity is expected. RAI therapy could be used as an adjuvant to surgery. Close observation is necessary to determine how these patients respond to systemic management of what may be gross disease in the cervical area.

Less Favorable Histologies

Differentiated thyroid cancer histologies with less favorable outcomes include the tall cell variant, Hürthle cell carcinomas, and disease that is poorly differentiated.[13] Regional and local recurrence can occur in these patients. The histology, pathology (including soft tissue extension), and quality of the surgical excision (whether R0 or R1 resections) must be considered during the initial surgery. Adjuvant treatment may be needed to prevent the devastating local regional recurrences that can be seen in these patients.

Disclosure

Dr Clayman has served on the medical advisory board of Eisai Pharmaceuticals.

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Targeted Therapy for Advanced or Metastatic Differentiated Thyroid Carcinoma

Lori J. Wirth, MD

After a patient develops RAI-refractory DTC, the chances of survival rapidly decrease compared with patients who are RAI-sensitive. A study of 444 patients with metastatic DTC who were treated with RAI demonstrated survival differences according to whether the patient's tumors exhibited RAI uptake on imaging.[1] The 10-year rate of overall survival was 92% among patients who responded to RAI, but dropped to 19% in patients who did not.

RAI-refractory patients may have unresectable recurrent disease in the neck, distant metastasis, or both; eventually, patients will experience disease-related symptoms and may ultimately die from disease progression. Until 2013, the only FDA-approved treatment option for RAI-refractory patients with metastatic DTC was doxorubicin. Recently, the treatment landscape changed dramatically with the FDA's approval of sorafenib, the first targeted therapy with an indication for metastatic DTC.[2] This approval has paved the way for the clinical development of other targeted therapies, with many showing promising results in RAI-refractory patients.

Goals of Therapy

Often in the course of thyroid cancer, from the time of initial diagnosis throughout treatment, the goals of therapy are curative. In advanced RAI-refractory DTC, this is usually no longer the case, unfortunately. It is essential, therefore, for the clinician to review realistic goals for treatment of late-stage DTC with the patient. These goals are primarily palliative, and may include prolonging life, preventing disease progression, minimizing symptoms, and improving quality of life.

Candidates for Systemic Treatment

Several patient- and disease-related factors should be taken into account when systemic therapy for RAI-refractory DTC is considered. First, the disease should be confirmed as truly RAI-refractory. Some patients with advanced DTC, even those with metastatic disease, are candidates for RAI.[3] However, between 10% and 15% of patients with DTC go on to develop RAI-refractory disease or have RAI-refractory disease de novo.[4] RAI offers no benefit in patients with RAI-refractory tumors.[3] A commonly used definition of RAI-refractory DTC includes the presence of at least 1 structural lesion that shows no RAI uptake on whole body scanning or disease progression within 1 year following a treatment dose of RAI, even if RAI uptake was present on whole body scanning.[5] Some DTC patients may have some lesions that take up RAI and other lesions that do not. By definition, these patients are also considered to have RAI-refractory disease. It is important to confirm that the radioiodine study was performed with the appropriate thyroid-stimulating hormone stimulation and iodine preparation.

As was discussed earlier in this monograph, tumor histology is closely associated with prognosis; certain subtypes are associated with more aggressive disease. Thyroid cancers are comprised of a wide variety of histologies, with most falling under the classification of DTC. Although the histologic subtype may carry prognostic significance, most clinical trials enroll patients with all DTC subtypes, and in general, activity with targeted agents has been seen across all of them. Therefore, although histologic subtype may be important from a disease state viewpoint, it does not necessarily influence whether systemic therapy is needed.

Patients with RAI-refractory DTC exhibit a wide range of clinical courses. Some patients experience very slow tumor growth over time and have a long life expectancy. Other patients experience rapid tumor progression, quickly develop symptomatic disease, and may have a short survival. The disease course is an important factor when determining whether a patient is a candidate for systemic therapy. Patients with rapidly progressive disease are candidates for systemic treatment.[6] Other potential candidates for systemic treatment include patients who are symptomatic from their disease. In contrast, patients with a low disease burden that is very slowly progressive over time may be better managed with observation alone. Patients under active surveillance should be followed with serial imaging studies and thyroglobulin measurements (in the absence of antithyroglobulin antibodies) to monitor disease activity. Appropriate thyroid-stimulating hormone suppression, as tolerated, is also an important component of care for all patients with advanced DTC.

The extent and location of recurrent disease is an important consideration for determining whether a patient should begin systemic therapy. For example, if

a patient has recurrent disease limited to a single lesion, surgery may be a better option than systemic treatment, even if that focal lesion proves to be RAI-refractory. The site of disease recurrence may also be a critical factor. For example, treatment may be indicated for even a small tumor in the neck if it is threatening to compromise the function of the larynx, trachea, or esophagus. Systemic therapy may also be appropriate for patients with lytic bone lesions, who are at risk of pathologic fracture and other bone-related events.

Role of Traditional Chemotherapy

In general, there is no role for cytotoxic chemotherapy in DTC. Older studies investigating cytotoxic chemotherapy were typically small, phase 2 trials conducted at single institutions.[7] In these studies, chemotherapy yielded rather low response rates and high toxicity. The median survival, when reported, was short.[8] The most widely studied cytotoxic agent in DTC is doxorubicin, which until recently was the only FDA-approved treatment for RAI-refractory thyroid cancer. Response rates seen with doxorubicin ranged from 0% to 22%, and combination therapy did not prove to be superior to single-agent use.[6]

Guidelines and Recommendations

Several guidelines are available to help inform decisions regarding the management of patients with DTC. However, 2 of the most widely used guidelines—from the ATA and the European Society for Medical Oncology (ESMO)—were released before the FDA approval of the first targeted agent for RAI-refractory DTC. The ATA guidelines are currently under revision.[3] The most recent ATA guidelines list the preferred hierarchy of treatment for metastatic DTC as surgical excision of locoregional disease (if appropriate), 131I therapy for RAI-sensitive disease, external beam radiation, watchful waiting (in patients with stable or slowly progressive asymptomatic disease), and experimental trials (especially for patients with significantly progressive macroscopic refractory disease). Targeted therapies are not discussed. Updates to the ATA guidelines will likely address the role of new targeted agents in the treatment of advanced DTC.

ESMO guidelines, published in 2012, state that chemotherapy is no longer indicated in metastatic DTC based on its lack of efficacy.[9] ESMO guidelines instead recommend that patients should be enrolled in experimental trials with targeted therapy.

Guidelines from the National Comprehensive Cancer Network (NCCN) represent the most recently updated guidelines available in thyroid cancer.[6] As such, the FDA-approved targeted agent sorafenib is recommended for consideration for the treatment of progressive and/or symptomatic metastatic DTC not amenable to RAI therapy. NCCN guidelines further state that several other small-molecule kinase inhibitors (such as axitinib, pazopanib, sunitinib, and vandetanib) can be considered for patients in this setting if clinical trials or other systemic therapies are not available or appropriate, although these agents are not approved by the FDA for this indication. Additionally, the NCCN guidelines state that cytotoxic chemotherapy has been shown to have minimal efficacy for the treatment of advanced DTC.

Potential Therapeutic Targets

The emergence of newer targeted therapies over the last decade ended the era of cytotoxic chemotherapy as the primary treatment for patients with RAI-refractory DTC. DTC is rich in "druggable" targets. In fact, the rate of targetable molecular abnormalities harbored in thyroid cancers is among the highest in solid tumors.

A number of molecular abnormalities identified in DTC play important roles in angiogenesis, a hallmark feature of thyroid cancer. Altered signaling through vascular endothelial growth factor (VEGF)–mediated pathways is considered one of the key drivers of oncogenesis.[10] The importance of upregulation of the VEGF pathway is supported by preclinical data, as well as by studies showing that VEGF expression correlates with the proliferative index of thyroid cancers and nodal metastasis. Additionally, increased VEGF expression correlates with worse progression-free survival (PFS).

Another common molecular abnormality in DTC, particularly in papillary thyroid cancer, is *RET*/*PTC* gene rearrangement.[7] This rearrangement results in constitutive activation of the RET tyrosine kinase, which in turn activates the mitogen activated protein kinase (MAPK) pathway. In a large-scale study of the genomic landscape of 496 papillary thyroid cancers by the Cancer Genome Atlas Research Network, *RET*/*PTC* rearrangement was found in 6.8% of tumors, representing the most common gene fusion in thyroid cancer.[11]

Two other pathways with demonstrated importance in DTC are the RAS/RAF/MAPK and the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathways. Both pathways are frequently upregulated in DTC, to differing degrees among the various histologic subtypes. *BRAF* and *RAS* mutations are the most common mutations in thyroid cancer, and are essentially mutually exclusive.[7]

The *BRAF* V600E mutation is the most common molecular alteration in all of thyroid cancers. *BRAF* gene mutations occur in approximately 45% to 60% of papillary thyroid cancers.[7,11] The *BRAF* V600E mutation is also found in poorly differentiated and anaplastic thyroid

cancers. It does not occur in follicular thyroid cancer. Preclinical studies suggest that altered *BRAF* signaling has a significant oncogenic role in these cancers. This mutation results in constitutive activation of the *BRAF* kinase, upregulating the MAPK signaling pathway. The presence of *BRAF* V600E correlates with more aggressive pathologic features of papillary thyroid cancer, including extrathyroidal extension, lymph node metastasis, and refractoriness to RAI. In some reports, the *BRAF* V600E mutation has also been associated with a more advanced stage at diagnosis and greater risk of recurrence and death.[12,13] There are conflicting data on whether the presence of a *BRAF* mutation impacts PFS or overall survival. However, in one of the largest and most comprehensive studies to date, this mutation was found to correlate with an increase in mortality among patients with thyroid cancer.[14] In this retrospective study of 1849 patients from 7 countries, conducted between 1978 and 2011, the mortality rate was 5.3% for patients who harbored the *BRAF* V600E mutation, compared with 1.1% for patients who were *BRAF* V600E–negative ($P<.001$). Overall, it appears that the presence of the *BRAF* V600E mutation in papillary thyroid cancers has clinical significance.

RAS mutations are the most common abnormalities in follicular thyroid cancer, occurring in approximately 45% of cases.[7] These mutations are also seen in adenomas. Therefore, the presence of the mutation is not necessarily diagnostic for an invasive follicular thyroid carcinoma. *RAS* mutations do occur in papillary thyroid carcinomas, as well, particularly in the follicular variant. *RAS* mutation leads to upregulation of both the RAS/RAF/MAPK and the PI3K/AKT/mTOR signaling pathways, whereas *BRAF*-mutant tumors are driven more strongly by the MAPK pathway alone.

Other molecular alterations occurring at a low frequency in thyroid cancers include *PTEN* mutations and gene fusions involving PAX8/PPAR-γ and *ALK*. Molecular alterations of *ALK* in thyroid cancer are of particular interest, given the availability of *ALK*-targeted therapies in non–small cell lung cancer. Another infrequent but potentially important molecular alteration is a mutation in the *TERT* gene promoter. Retrospective analysis of 507 papillary thyroid cancers showed that high-risk clinicopathologic features are concentrated in those tumors that harbor mutations in both *BRAF* and *TERT*.[15] This finding correlated with disease-free survival; patients with *BRAF* and *TERT* mutations alone had recurrence rates of 25.8% and 47.5%, respectively, whereas patients with both mutations had a recurrence rate of 68.6%. The negative impact of both mutations on tumor biology was confirmed by analysis from the Cancer Genome Atlas Research Network.[11] These studies suggest that the presence of *TERT* promoter mutations, in addition to other driver mutations in DTC, may help identify patients who have high-risk disease and are at risk for recurrence.

Clinical Trials for RAI-Refractory DTC

The DECISION Trial

The DECISION (Study of Sorafenib in Locally Advanced Metastatic Patients With Radioactive Iodine Refractory Thyroid Cancer) trial led to the approval of sorafenib as the first targeted agent for the treatment of progressive disease in patients with RAI-refractory DTC. Sorafenib is an oral multitargeted kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, RET (including RET/PTC), RAF (including *BRAF* V600E), and platelet-derived growth factor receptor β (PDGFRβ). DECISION was a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial that evaluated the efficacy and safety of sorafenib in the treatment of RAI-refractory DTC.[16] Between November 2009 and August 2011, a total of 419 patients were randomized in a 1:1 ratio to treatment with either sorafenib (400 mg twice daily) or placebo. All patients had locally advanced or metastatic RAI-refractory DTC that had progressed within 14 months by investigator review before study entry. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2; adequate bone marrow, liver, and renal function; and a serum thyroid-stimulating hormone concentration of less than 0.5 mIU/L. Patients who had received prior cytotoxic chemotherapy or targeted therapy were excluded. More than half of patients in each arm had papillary tumor histology. Other histologies included Hürthle cell, follicular non–Hürthle cell, and poorly differentiated disease. At the time of disease progression, as assessed by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, patients were unblinded. Those on placebo were offered the opportunity to cross over and begin treatment with sorafenib.

The primary endpoint of DECISION, PFS, was met (Figure 7).[16] Patients in the sorafenib arm showed a significant improvement in median PFS vs the placebo arm (10.8 vs 5.8 months, hazard ratio [HR] 0.59; 95% CI, 0.45-0.76; $P<.0001$), resulting in a 41% reduction in the risk of progression or death with sorafenib. Notably, the PFS benefit was observed across all prespecified subgroups, including age, sex, geographic region, tumor histology, lung or bone metastasis, ^{18}F-fluorodeoxyglucose (FDG) uptake, and number and size of tumor lesions. Overall survival (OS) was not significantly different between the sorafenib and placebo arms (HR, 0.80; 95% CI, 0.54-1.19; $P=.14$). This result was not unexpected, as 71.4% of patients in the placebo arm crossed over to open-label sorafenib at the time of disease progression. At the time of primary data analysis cutoff (in August 2012), median OS had not been reached.

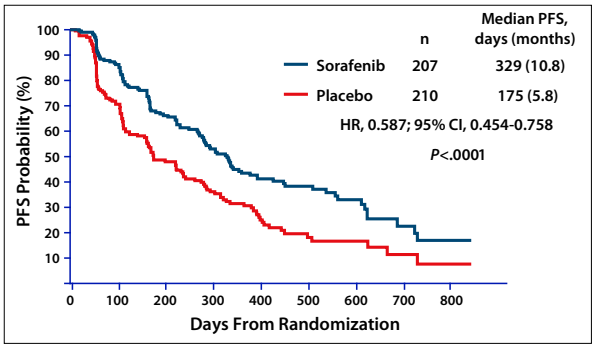

Figure 7. Progression-free survival as assessed by independent central review in the DECISION trial, which compared sorafenib and placebo in patients with locally advanced or metastatic radioactive iodine–refractory differentiated thyroid carcinoma. DECISION, Study of Sorafenib in Locally Advanced Metastatic Patients With Radioactive Iodine Refractory Thyroid Cancer; HR, hazard ratio; PFS, progression-free survival. Adapted from Brose MS et al. *Lancet*. 2014;384(9940):319-328.[16]

The objective response rate was 12.2% with sorafenib and 0.5% with placebo (*P*<.0001), and the median duration of response in sorafenib-treated patients was 10.2 months. Beyond responses, the waterfall plot showed that a majority of patients experienced some degree of tumor shrinkage as best response, with 41.8% of patients achieving stable disease lasting 6 months or longer.

The majority of adverse events were grade 1 or 2 in severity. Among sorafenib-treated patients, the most frequently reported adverse events included hand-foot skin reaction (76.3%), diarrhea (68.6%), alopecia (67.1%), rash or desquamation (50.2%), fatigue (49.8%), weight loss (46.9%), and hypertension (40.6%). Serious adverse events included secondary malignancy (4.3%), dyspnea (3.4%), and pleural effusion (2.9%). Adverse events led to dose interruptions in 66.2% of patients on sorafenib, dose reductions in 64.3%, and discontinuation of sorafenib in 18.8%, with hand-foot skin reaction being the most common cause for dose interruptions and withdrawals.

Although the adverse events associated with sorafenib were primarily mild to moderate in severity, they have the potential to significantly impact quality of life, especially in light of the duration of treatment, with most patients expected to remain on therapy for many months. Overall, the side effects associated with sorafenib are not negligible, and they should be carefully managed. Rare but important adverse events include an increased risk of bleeding and thromboembolic disease, gastrointestinal perforation, and aerodigestive fistula. In fact, some patients with thyroid cancer, such as those with disease present in the neck or upper chest, or those who receive regional radiotherapy to these sites, may be at particular risk of developing aerodigestive fistula.

The SELECT Trial

SELECT (Study of [E7080] Lenvatinib in Differentiated Cancer of the Thyroid) was a randomized, double-blind, multicenter, phase 3 trial evaluating lenvatinib, an oral multitargeted kinase inhibitor of the VEGF receptors 1, 2, and 3; fibroblast growth factor receptors 1 through 4; PDGFRα; RET; and KIT in patients who have RAI-refractory DTC.[17] The 329 patients were randomized in a 2:1 fashion to receive lenvatinib (24 mg/day) or placebo. To be eligible for the study, patients had RAI-refractory DTC with evidence of progressive disease within the 12 months before study entry, as confirmed by independent radiology review. Patients also had an ECOG performance status between 0 and 2, and adequate bone marrow, renal, and liver function. One prior VEGF-targeted therapy was allowed.

Similar to the design of DECISION, patients were unblinded at the time of disease progression, and those on placebo were offered open-label lenvatinib. PFS, the primary endpoint in SELECT, improved by nearly 15 months with lenvatinib compared with placebo (18.3 months vs 3.6 months [HR, 0.21; 99% CI, 0.14-0.31; *P*<.001]).[17] The PFS benefit with lenvatinib was observed in all prespecified patient subgroups. Importantly, 25% of patients had received prior therapy with VEGF agents; PFS was significantly improved with lenvatinib among these patients as well (median, 15.1 months vs 3.6 months with placebo), indicating that lenvatinib has efficacy in the second-line setting, as well as the first-line, for metastatic RAI-refractory DTC. Median OS had not been reached in either treatment arm at the time of data analysis.[17] As in DECISION, patient crossover from the placebo arm to open-label lenvatinib, which was permitted at the time of disease progression, may impact the ability to detect an overall survival benefit. Patients in the lenvatinib arm experienced a 65% objective response rate, which included 4 complete responses. Durable stable disease 23 weeks or longer was seen in an additional 15.3% of patients, and only 6.9% of patients on lenvatinib progressed during the study period.

The most frequently occurring treatment-related adverse events of any grade in the lenvatinib arm included hypertension (67.8%), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), decreased weight (46.4%), and nausea (41.0%).[17] As with sorafenib, dose holds and dose reductions were utilized in conjunction with supportive care to manage adverse events. A total of 14.2% of lenvatinib-treated patients discontinued the study drug owing to adverse events. In the lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered by the investigator to be drug-related.

Based on these highly significant results, lenvatinib was granted FDA approval for the treatment of progres-

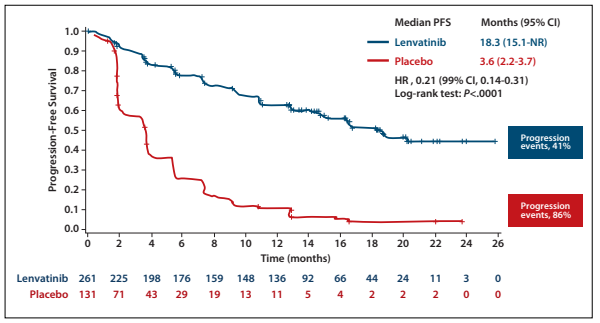

Figure 8. Progression-free survival in the SELECT trial, which compared lenvatinib and placebo in patients with radioactive iodine–refractory differentiated thyroid carcinoma. HR, hazard ratio; NR, not reached; PFS, progression-free survival; SELECT, Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid. Adapted from Schlumberger M et al. *N Engl J Med*. 2015;372(7):621-630.[17]

sive RAI-refractory DTC in February 2015. In fact, the unprecedented activity of lenvatinib—as demonstrated by the lengthy PFS benefit and very high, durable response rate—may now begin to call into question the recent trend in which patients with RAI-refractory DTC first undergo prolonged periods of active surveillance, with a delay in the start of VEGF-targeted therapy for as long as possible in order to avoid the side effects that accompany treatment. With activity as robust as that seen with lenvatinib, studies investigating earlier vs later initiation of treatment are needed.

Phase 2 Study of Vandetanib

Vandetanib is an oral multitargeted kinase inhibitor that is selective against RET, the VEGF receptor, and the epidermal growth factor receptor. In April 2011, vandetanib was approved for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced, or metastatic disease.

In RAI-refractory DTC, vandetanib was investigated in a randomized, double-blind, multicenter, placebo-controlled, phase 2 study.[18] The 145 patients were randomized to treatment with either vandetanib (300 mg/day) or placebo. Prior treatment with other targeted agents and tyrosine kinase inhibitors, with the exception of vandetanib, was allowed. Baseline patient characteristics were well balanced between the vandetanib and placebo arms.

The primary study endpoint, PFS, was significantly prolonged with vandetanib vs placebo (11.1 months vs 5.9 months [HR, 0.63; 95% CI, 0.43-0.92; 2-sided *P*=.017]), as confirmed by independent central review. This improvement was a consistent finding among all patient subgroups, including age, lung or bone metastasis site, prior RAI uptake, presence of metastatic lymph nodes, and tumor histology. At the time of data cutoff, OS was not significantly different between the treatment arms (HR, 0.92; 99.24% CI, 0.4-2.15; *P*=.80).[18] The objective response rate was 8% with vandetanib, and all responses were partial.

The most common adverse events associated with vandetanib included diarrhea (74%), hypertension (34%), QTc prolongation (23%), rash (25%), acne (27%), and decreased appetite (26%).[18] Adverse events leading to discontinuation of the study drug were more frequent with vandetanib (33%) than placebo (6%). The most common were QTc prolongation (7%) and diarrhea (5%).

The positive results of this phase 2 trial led to the development of a phase 3 study, VERIFY (Vandetanib Efficacy in RAI-Ineligible Refractory Thyroid Cancer), comparing vandetanib with placebo for the treatment of patients with RAI-refractory DTC.[19] This international, multicenter trial, with a planned enrollment of 238 patients, is underway. The estimated primary completion date is August 2015.

Phase 2 Study of Pazopanib

Pazopanib is another multitargeted kinase inhibitor that targets VEGF receptors, platelet-derived growth factor receptors, and KIT, among other kinases. A phase 2 trial evaluated pazopanib in patients with metastatic and rapidly progressive RAI-refractory DTC.[20] A total of 39 patients were enrolled (37 were evaluable) into this single-arm study between February 2008 and January 2009. All patients were treated with pazopanib (800 mg/day). Enrollment criteria included disease progression within 6 months before study enrollment. Up to 2 prior systemic therapies were allowed. Other eligibility criteria included an ECOG performance status between 0 and 2 and adequate organ function. Tumor histologies included papillary (40.5%), follicular (29.7%), and Hürthle cell (29.7%).

The primary study endpoint, objective response, was 49%.[20] All responses were partial. Responses were observed in 73% of patients with follicular tumors, 45% of patients with Hürthle cell tumors, and 33% of patients with papillary tumors. Responses were durable, with a 66% likelihood of lasting for longer than 1 year. Tumor size decreased from baseline in most patients (Figure 9). The 1-year OS rate was 81%, with median OS not yet reached. The 1-year PFS rate was 47%, and the median PFS was 11.7 months.

Dose reductions of pazopanib owing to adverse events occurred in 43% of patients. The most frequent adverse events (any grade) were fatigue (n=29), skin and hair hypopigmentation (n=28), diarrhea (n=27), and nausea (n=27).

Phase 2 Study of Axitinib

Axitinib is a potent and selective second-generation inhibitor of VEGF receptors. It is currently approved in the United States, the European Union, and elsewhere for the treatment of advanced renal cell carcinoma after failure of prior systemic therapy. Axitinib has been studied in several

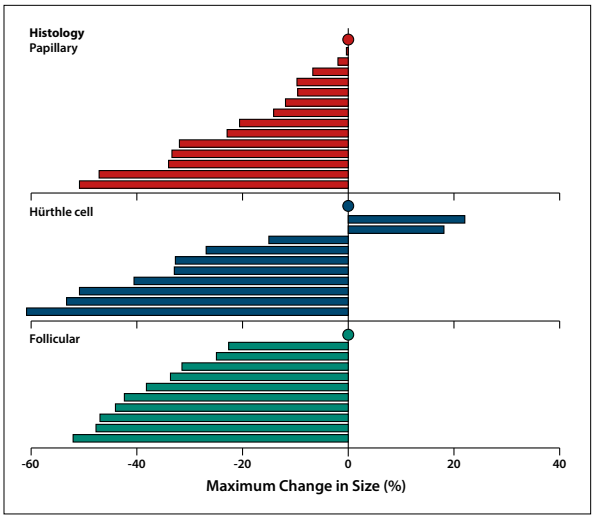

Figure 9. Changes in tumor size in a phase 2 trial of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers. Adapted from Bible KC et al. *Lancet Oncol.* 2010;11(10):962-997.[20]

phase 2 trials of DTC. The most recently reported of these trials enrolled 52 patients with metastatic or unresectable, locally advanced RAI-refractory medullary thyroid carcinoma or DTC.[21] All patients received single-agent axitinib (5 mg twice daily). The objective response rate was 35%; all of these responses were partial. In addition, 18 patients had stable disease lasting at least 16 weeks. Median PFS was 16.1 months, and median OS was 27.2 months.

The most common grade 3 or higher adverse events associated with axitinib included fatigue, dyspnea, diarrhea, decreased weight, pain in extremity, hypertension, decreased appetite, palmar-plantar erythrodysesthesia, hypocalcemia, and myalgia.[21] Quality of life was maintained during treatment with axitinib. There were no reports of significant deterioration in symptoms or symptom-related interference in daily life.

Phase 2 Study of Everolimus

Everolimus, an inhibitor of the mTOR protein, was evaluated in an open-label phase 2 trial. Patients with metastatic thyroid cancer (33 patients with DTC; 10 patients with medullary thyroid cancer; 5 patients with anaplastic thyroid cancer) who had experienced progression within 6 months of study enrollment were treated with everolimus (10 mg once daily).[22]

Median PFS in the DTC group was 16.0 months.[22] Disease was stable for 6 months in 18 patients and for at least 12 months in 10 patients. Median OS had not been reached at the time of data analysis, but the 1-year survival rate was 76%. A partial response was reported in 1 patient.

What may be most notable about this trial was the report of an impressive, durable, partial response in a patient with anaplastic thyroid cancer.[22] Whole genome sequencing of this patient showed a loss-of-function mutation in the tuberous sclerosis 2 (*TSC2*) gene, which is a negative regulator of mTOR.[23] This finding, not previously noted in anaplastic thyroid cancer, reinforces the notion that analysis of extraordinary responders to targeted therapies is critical to optimizing precision medicine approaches for each and every cancer patient.

The most common treatment-related adverse events included fatigue, stomatitis, and infections. Grade 3 adverse events included infection (5 patients), weight loss (3 patients), leukopenia (3 patients), thrombocytopenia (3 patients), fatigue (3 patients), hypophosphatemia (2 patients), stomatitis (2 patients), pneumonitis (1 patient), and thrombosis (1 patient). Grade 4 hypercholesterolemia was reported in 1 patient, as was grade 4 leukopenia.

Everolimus and other mTOR inhibitors are being studied in combination with sorafenib in several phase 2 studies that will mature in the near future.[24-26]

Phase 2 Study of Vemurafenib

The potential activity of BRAF targeting in RAI-refractory DTC is of great interest, given that the most common driver mutation seen in thyroid cancer is *BRAF* V600E. To this end, vemurafenib, currently approved for the treatment of metastatic melanoma, is the first BRAF inhibitor to be investigated in DTC. A total of 51 patients with RAI-refractory papillary thyroid cancer harboring a *BRAF* V600E mutation were enrolled in a phase 2 clinical trial.[27] Patients were assigned to cohort 1 (n=26) if they were naive to tyrosine kinase inhibitor therapy or cohort 2 (n=25) if they had been previously treated with a tyrosine kinase inhibitor. Patients in both cohorts were treated with vemurafenib (960 mg twice daily).

The primary endpoint, best overall response, was 35% in cohort 1 and 26% in cohort 2.[27] All of these responses were partial. The clinical benefit rate (defined as complete responses, partial responses, and stable disease of at least 6 months) was 58% in cohort 1 and 36% in cohort 2. Median PFS was 15.6 months for patients in cohort 1, and 6.8 months for patients in cohort 2.

The toxicity profile was generally consistent with that seen with vemurafenib treatment in melanoma patients. Exceptions included higher rates of weight loss, dysgeusia, anemia, increased creatinine, and liver laboratory abnormalities.[27] Common adverse events included rash, fatigue, weight loss, and increased bilirubin.

Studies to Reverse RAI-Refractory Thyroid Cancer

Because the 2 most common mutations encountered in thyroid cancer involving *BRAF* and *RAS* both activate

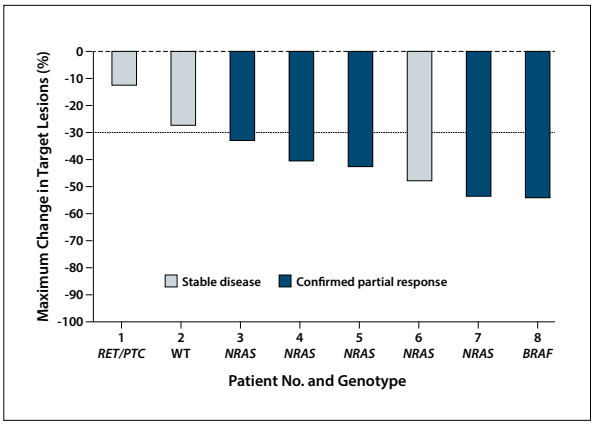

Figure 10. Maximum change in target lesions (relative to baseline) in patients who received therapeutic radioiodine in a study of the MEK 1/2 inhibitor selumetinib. Adapted from Ho AL et al. *N Engl J Med*. 2013;368(7):623-632.[29]

the MAPK pathway, which can lead to suppression of thyroid-specific gene expression and loss of ability to take up iodine, inhibiting this pathway with specific targeted agents in order to redifferentiate iodine-refractory thyroid cancers to resensitize them to radioiodine is an appealing therapeutic strategy.[28] In a novel proof-of-concept study, the MEK 1/2 inhibitor selumetinib was evaluated for its ability to reverse RAI-refractory metastatic thyroid cancer.[29] Patients were treated with single-agent selumetinib (75 mg twice daily), and 4 weeks later underwent a 124I PET scan. If dosimetry calculations by 124I PET indicated that a therapeutic dose of 131I could be successfully delivered, therapeutic RAI was administered while the patient continued to receive selumetinib. Among 20 evaluable patients, selumetinib increased the uptake of 124I in 12 patients. Of these 12 patients, 8 reached the dosimetry threshold for RAI therapy, including all 5 patients with *NRAS* mutations. Among the 8 patients who were treated with RAI, 5 achieved a partial response and 3 achieved stable disease (Figure 10). No grade 3 or higher treatment-related adverse events were reported.

These encouraging results led to the development of other studies, including the ASTRA (Adjuvant Selumetinib for Differentiated Thyroid Cancer, Remission After RAI) trial.[30] This multicenter, double-blind, randomized, international, phase 3 trial is comparing selumetinib vs placebo as pretreatment to RAI in patients who have undergone surgical resection of DTC and who are at high risk of recurrence based on clinicopathologic features. The primary study endpoint is the rate of complete remission. The estimated primary completion date is July 2015.

The BRAF-specific inhibitor dabrafenib has also been investigated for its potential to redifferentiate tumors and resensitize them to RAI in a small pilot study. This study enrolled 10 patients with RAI-refractory *BRAF* V600E–positive papillary thyroid cancer; all patients were treated with single-agent dabrafenib (150 mg twice daily) for 25 days before a low-dose 131I whole body scan.[31] Six patients demonstrated new RAI uptake on whole body scan after pretreatment with dabrafenib, and went on to receive a 150 mCi dose of RAI. Of these, 2 patients achieved partial responses, and 4 patients had stable disease at 3 months. The only significant adverse event was squamous cell carcinoma of the skin, which occurred in 1 patient. Therefore, encouraging early data suggest that MAPK pathway inhibition can indeed reverse insensitivity to RAI, opening up a new avenue of treatment with the potential to benefit a large number of RAI-refractory DTC patients with a well-tolerated and brief course of therapy.

Incorporating Novel Agents into Treatment

Several important clinical trends have emerged in trials of targeted agents in RAI-refractory DTC. These points should be considered when incorporating novel agents into the treatment strategy for patients with thyroid cancer. One key observation involves the balance of toxicity with efficacy in patients with a relatively long life expectancy, who may be receiving therapy for many months. Once patients are started on therapy, optimal management of side effects is critical. For example, hypertension can occur early during treatment with VEGF receptor inhibitors, even within the first 2 weeks of initiating treatment. Thus, frequent and early monitoring of blood pressure is essential. Antihypertensive therapy, rather than dose adjustment, should be the first approach to hypertension when it emerges or worsens during a patient's course of treatment. Unfortunately, at present, data are limited regarding which antihypertensive agent is the best to use in patients who develop hypertension while receiving this class of drugs. Dose holds and reductions are built into the system of administering these therapies. However, maintaining dose density could be an important factor in the efficacy of VEGF receptor tyrosine kinase inhibitors. Thus, the first approach to managing side effects with therapy is generally with supportive care, but it may be necessary to hold and reduce the dosage when symptom management alone is not enough.

A team approach, with nursing and other support staff educated in symptom management, may offer patients the most comprehensive support. Patients should be encouraged to ask for help when needed. It may also be important to bring a nutritionist into the patient's treatment team early, particularly because adverse events can include weight loss, diarrhea, anorexia, and nausea. Foods that might be typically suggested to help mitigate weight loss (eg, ice cream and other dairy products, fatty foods) may exacerbate a patient's diarrhea. It can be difficult to balance the

dietary modifications necessary to minimize diarrhea while maintaining weight and nutrition. Nutritional consultation early in the course of therapy may help.

Lastly, when to initiate treatment with a targeted kinase inhibitor is an individualized decision for each patient. More data are ultimately needed in order to determine whether patients obtain the most benefit from earlier vs later initiation of treatment. For now, however, initiating targeted therapy for advanced DTC should be considered for patients with confirmed RAI-refractory disease that is progressive throughout a time frame of at least 12 to 14 months. Symptomatic disease certainly warrants consideration of therapy, as does rapidly progressive disease. Beyond these factors, when to start therapy remains an individualized decision likely best made by the treating clinician and patient on a case-by-case basis.

Disclosure

Dr Wirth has received consulting income from AstraZeneca, Eisai, Loxo, and Ashion.

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New and Emerging Therapeutic Options for Thyroid Carcinoma: Q&A Discussion

Gary L. Clayman, DMD, MD, and
Lori J. Wirth, MD

H&O What are some unmet needs in differentiated thyroid carcinoma?

Gary L. Clayman, DMD, MD The treatment of differentiated thyroid cancer is evolving. Currently, the only adjuvant treatments for patients at high risk of recurrent disease are external beam radiation therapy and RAI, and many of these patients are nonavid. New approaches are needed for neoadjuvant treatment and adjuvant treatment with systemic therapy.

Lori J. Wirth, MD One major unmet need is how to get the treatment right for each patient. There are patients with thyroid cancer who are going to do quite well over time. With the present paradigms, we may be overtreating these patients. In contrast, there are other patients who are not going to do well, and we need to be sure not to undertreat them. More effective therapies are needed for those patients.

There has been progress with the risk stratification strategy. The ATA stratifies patients into categories of low, intermediate, and high risk. In the future, molecular profiles of tumors may allow us to better delineate high-risk patients from very low-risk patients, and adjust the decision-making process accordingly.

Because of the rarity of advanced thyroid cancer, international collaboration is needed to determine the best management strategies. The current paradigm for demonstrating benefit in clinical trials is not feasible in populations with rare but actionable mutations, such as those in AKT, P10, MTRAK, and ALK arrangements. A new framework is needed that can demonstrate efficacy of molecularly targeted agents, so that we can make these therapies available to patients on an individualized basis. In oncology, we are starting to use basket trials, such as MATCH (Molecular Analysis for Therapy Choice Program), which was recently launched by the National Cancer Institute.

As Dr Clayman mentioned, future treatment will likely include RAI resensitization for patients with distant metastatic disease. We are currently developing strategies for after surgery among patients with nonmetastatic disease and a high risk of recurrence despite adjuvant RAI. Immunotherapy, particularly for patients with advanced iodine-refractory disease, is another expected area of research.

We have made progress on treating differentiated thyroid cancer across the entire spectrum of disease, from low-volume disease to advanced iodine-refractory disease. There are now 2 new drugs approved for the iodine-refractory population, and more are expected. There has been more limited progress with anaplastic thyroid cancer. It is necessary to redouble our efforts in the management of patients with anaplastic thyroid cancer. Unfortunately, the current paradigms are not good enough in most cases. There had been great progress in developing new systemic therapies for medullary thyroid carcinoma, but the field has been quiet recently. More research is needed in the management of these patients.

Disclosures

Dr Clayman has served on the medical advisory board of Eisai Pharmaceuticals. Dr Wirth has received consulting income from AstraZeneca, Eisai, Loxo, and Ashion.

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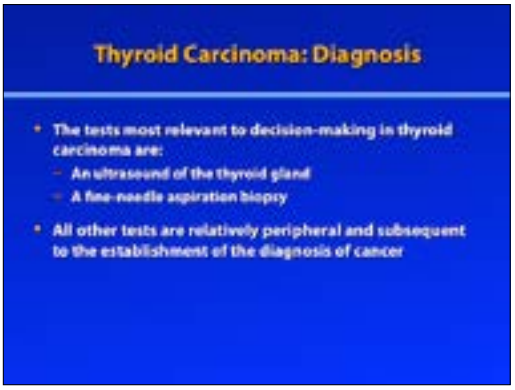

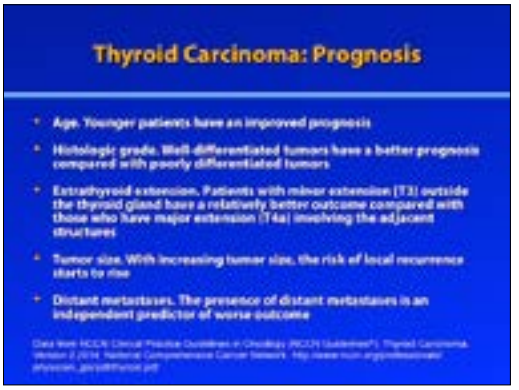

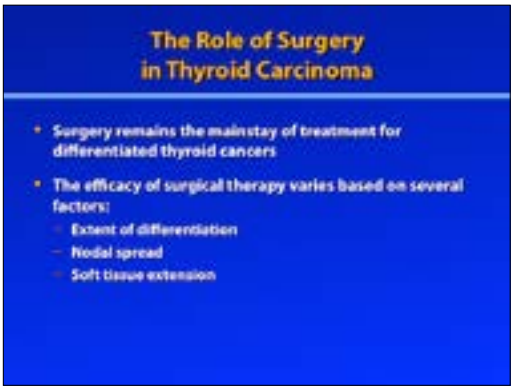

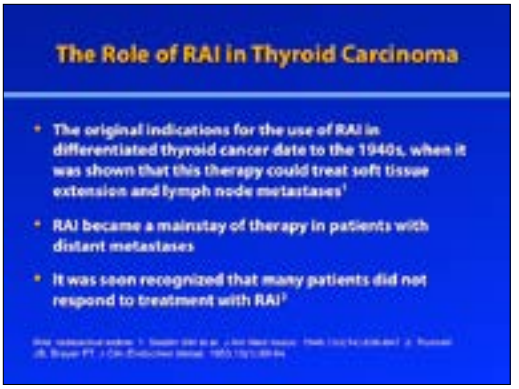

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New and Emerging Therapeutic Options for Thyroid Carcinoma

CME Post-Test: *Circle the correct answer for each question below.*

1. In the United States, thyroid cancers are reported with an incidence of approximately __ at autopsy among people who died of other causes.

   a. 5%
   b. 10%
   c. 15%
   d. 20%

2. What scenario typically leads to the diagnosis of thyroid carcinoma?

   a. Intrathyroid nodules are discovered on routine imaging
   b. The patient presents with airway obstruction
   c. The patient presents with hoarseness
   d. The patient presents with a mass in the neck

3. Should contrast dye be used in a CT scan performed during radiologic workup of a patient with thyroid cancer?

   a. Yes
   b. No

4. A mean of __ ethanol ablation procedures are usually required to control the disease process.

   a. 2
   b. 3
   c. 4
   d. 5

5. Approximately how many patients with differentiated thyroid carcinoma are refractory to radioactive iodine?

   a. 10% to 15%
   b. 20% to 25%
   c. 30% to 35%
   d. 40% to 45%

6. Which organization has the most recently updated guidelines in thyroid cancer?

   a. American Thyroid Association
   b. American Society of Clinical Oncology
   c. European Society for Medical Oncology
   d. National Comprehensive Cancer Network

7. In the DECISION trial, sorafenib was associated with a progression-free survival of:

   a. 8.1 months
   b. 10.8 months
   c. 12.2 months
   d. 13.6 months

8. In the SELECT trial, lenvatinib was associated with a progression-free survival of:

   a. 12.4 months
   b. 14.8 months
   c. 16.9 months
   d. 18.3 months

9. In a phase 2 trial of pazopanib in patients with metastatic and rapidly progressive RAI-refractory DTC, the objective response rate was:

   a. 29%
   b. 39%
   c. 49%
   d. 59%

10. Which agent is a BRAF inhibitor being investigated in differentiated thyroid carcinoma?

    a. Axitinib
    b. Pazopanib
    c. Vemurafenib
    d. Vandetanib

Project ID: 10442

Evaluation Form: New and Emerging Therapeutic Options for Thyroid Carcinoma

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 10442**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Medical ❒ Surgery/Surgical Oncology ❒ Oncology, Radiation

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week who have thyroid carcinoma?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Describe the traditional treatment approaches for patients with differentiated thyroid carcinoma based on risk stratification

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Identify patients who might benefit from treatment with recently approved targeted agents

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Integrate the use of recently approved agents into the management course

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Apply strategies to manage the adverse events associated with novel targeted therapies for thyroid carcinoma

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Describe future research directions for therapies in thyroid carcinoma based on recent clinical data

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented

❒ My current practice has been reinforced by the information presented

❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

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I certify my actual time spent to complete this educational activity to be:

❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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