New Directions in the Systemic Treatment of Metastatic Thyroid Cancer

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About 30,000 new cases of thyroid cancer are diagnosed annually in the United States.[1] The incidence among men has risen more dramatically than any other malignancy in recent years (2.4% annual increase).[2] Thyroid cancers arise from one of two cell types, namely follicular and parafollicular cells.

ABSTRACT: Medical oncologists have traditionally had little to offer patients with metastatic radioactive iodine–resistant thyroid cancer. The 3-year survival rate of patients with differentiated thyroid cancer is less than 50%, with little response obtained from standard cytotoxic chemotherapies. In recent years, however, huge advances have been made in understanding the molecular pathways and cellular pathogenesis of this disease. This knowledge has in turn led to the development of a range of targeted therapies, some specific to thyroid cancer genetic alterations such as the RET/PTC translocation, and others that exploit general malignant properties such as angiogenesis. This review highlights novel targeted agents for the treatment of differentiated and medullary thyroid cancers being studied at this time, and the results of recently published trials. We propose that such patients should be managed, whenever possible, within a clinical trial, in order to access the most promising new drugs for thyroid cancer. In cases where trials are unavailable, we recommend off-label use of the currently available oral multikinase inhibitors such as sorafenib and sunitinib rather than traditional chemotherapies.

About 30,000 new cases of thyroid cancer are diagnosed annually in the United States.[1] The incidence among men has risen more dramatically than any other malignancy in recent years (2.4% annual increase).[2] Thyroid cancers arise from one of two cell types, namely follicular and parafollicular cells.

Differentiated and undifferentiated tumors originate in follicular cells. Fortunately, the majority of patients present with differentiated carcinoma, which includes papillary, follicular, and Hürthle cell variants. The poorly differentiated or undifferentiated category includes anaplastic thyroid cancer, an aggressive tumor that is largely chemotherapy resistant. Medullary thyroid cancer arises from parafollicular or C cells and may be familial or sporadic.

Most patients with differentiated thyroid cancer are managed successfully with a combination of surgery, radioactive iodine (RAI), and long-term thyroid hormone–suppression therapy. This has led to a 20-year overall survival rate of almost 90% for thyroid cancers.[3] The prognosis is grim, however, for patients with poorly differentiated thyroid cancers, which have less RAI avidity (and therefore less sensitivity), and for those with anaplastic/undifferentiated tumors, which are refractory to RAI. Locoregional control of relapsed thyroid cancer is best managed by a multidisciplinary team and can include therapies such as surgery, endobronchial laser ablations, and external-beam radiation with or without chemotherapy.

Over time, 25% to 50% of metastatic differentiated thyroid cancers can lose functional iodine-concentrating ability and become insensitive to treatment with RAI.[4] Less than 50% of this subgroup of patients is alive at 3 years.[5-7] These same patients have historically obtained little benefit from cytotoxic chemotherapy,[8] augmenting the need for novel therapies. This review will focus on systemic treatments for patients with radioactive iodine–resistant thyroid cancer that has metastasized distantly.

Radioactive Iodine

Both normal and malignant differentiated thyroid cells possess a unique sodium iodide symporter which allows concentration of beta-emitting radiolabeled iodine. The symporter is found at lower levels within malignant thyroid tissue[9] and therefore iodine depletion and thyroid-stimulating
hormone (TSH) elevation are used to achieve sufficient uptake of iodine to ensure effective therapy. Radioactive iodine (RAI) has no activity in undifferentiated thyroid cancer but can prolong disease-free and overall survival in patients with metastatic differentiated thyroid cancer, in whom its use is associated with 5-year survival rates of about 50%. However, approximately 25% of patients will have persistent disease after initial therapy. Additional responses can be seen with re-treatment. Treatment works best when the volume of disease is small or microscopic. RAI has limited efficacy against central nervous system metastases, and at the doses usually used in the treatment of metastatic thyroid cancer, can have several significant side effects including salivary gland dysfunction, bone marrow suppression, and secondary hematopoietic malignancies.

Radioactive Iodine Resistance, an Evolving Role for Positron-Emission Tomography

It is important both prognostically and therapeutically to define RAI resistance, and this is currently done in one of two ways. The first is in the setting of a negative RAI whole-body scan obtained after TSH stimulation. Care should be taken to avoid close or contemporaneous use of iodinated contrast with computed tomography and RAI scanning, as this can cause false-negative results. TSH elevation can be induced by either thyroid hormone withdrawal or by administration of human recombinant TSH (thyrotropin alfa, Thyrogen).

More recently, investigators have used 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) to localize distant sites of disease and thereby diagnose RAI resistance. Thyroid carcinomas with low iodine avidity tend to have a higher glucose metabolism and are more likely to be positive on FDG-PET imaging. RAI has been shown to have little or no therapeutic effect on FDG-avid tumors. Conversely, tumors that concentrate RAI well are unlikely to be active on FDG-PET. FDG avidity may be the most practical and reproducible definition of RAI-resistant disease and has a reported median sensitivity and specificity of 77% and 78%, respectively.

Molecular Pathways in Thyroid Cancer

Thyroid cancer provides an excellent model for the study of tumor-initiating genetic events. Cancers of this area harbor several highly prevalent genetic alterations, some of which are unique. A well known example is the RET proto-oncogene, which codes for a cell membrane receptor tyrosine kinase. RET is expressed in parafollicular C cells but not in follicular cells. However, in follicular cells it can be activated by a chromosomal translocation known as the RET/PTC rearrangement. RET/PTC is found in approximately 20% of adult sporadic papillary carcinomas. A point mutation in RET is found commonly in parafollicular C cell-derived medullary thyroid carcinomas.

FIGURE 1

MAPK Signaling Pathway

An activation mutation in the gene encoding for the B-type Raf kinase (BRAF) can lead to activation of the mitogen-activated protein kinase (MAPK) signaling pathway (Figure 1, Table 1). Point mutations of the BRAF gene are found in 45% of thyroid papillary carcinomas. This mutation is mutually exclusive with other common genetic alterations, supporting an independent oncogenic role. The RAS gene also activates MAPK, among other signaling pathways. In malignant cells, point mutations within discrete domains of the RAS gene result in permanent activation of the mutant protein and corresponding activation of downstream signaling pathways. Point mutations of RAS
seem to occur in all types of thyroid follicular cell-derived adenomas and carcinomas, suggesting that RAS mutations represent an early event in thyroid tumorigenesis.[29]

TABLE 1

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<th>Average Prevalence of Mutations in Thyroid Cancer and Potential Drugs Targeting the Mutations</th>
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<td>Together, mutations involving one of these three genes (RET/PTC, BRAF, or RAS) are found in &gt; 70% of papillary carcinomas and they rarely overlap in the same tumor.[28,30,31] The prevalence of mutations commonly found in thyroid cancers is shown in Table 1.</td>
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<td>PAX8-PPAR is a rearrangement leading to the fusion of the PAX8 gene, which encodes a paired domain transcription factor and the peroxisome proliferator-activated receptor PPAR gene.[32] PAX8-PPAR is found in about 35% of follicular carcinomas and a small number of Hürthle cell (oncocytic) carcinomas.[33-35] It has been suggested that follicular carcinomas may develop by at least two distinct molecular pathways, initiated by either PAX8-PPAR or RAS mutations, because these two are rarely seen in the same tumor.[34]</td>
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<td>Inactivating point mutations of the tumor-suppressor gene p53 are rare in patients with differentiated thyroid carcinomas but are commonly seen in anaplastic thyroid cancer.[36,37] Deregulation of intracellular levels of beta-catenin is an early event in the development of a variety of cancers. Beta-catenin mutations are mostly found in undifferentiated thyroid carcinomas.[38] The pathways that are deregulated due to activation and or inactivation by the genes outlined above provide attractive therapeutic targets for thyroid cancer. These have been the basis for many rational clinical trials and drug development in recent years. Interest has also grown in several modulators of angiogenesis that have been successfully exploited in other cancers. Vascular endothelial growth factor (VEGF) is a key regulator of tumor-induced endothelial cell proliferation and vascular permeability. Elevated levels of VEGF are seen in thyroid cancers compared with normal thyroid tissue.[39-41] Higher VEGF levels correlate with later disease stage, large tumor size, nodal involvement, extrathyroidal invasion, and distant metastases.[42] Investigators have also studied the expression of epidermal growth factor receptor (EGFR) in anaplastic thyroid cancer cell lines and have highlighted the potential of EGFR-targeting therapies.[43] Activation of EGFR signaling can upregulate the production of VEGF in human cancer cells.[44,45] EGFR overexpression has been shown to correlate with a decrease in recurrence-free thyroid cancer survival.[46]</td>
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**Targeted Therapies in Thyroid Cancer**

**Sorafenib**

Many of the key oncogenic events in thyroid cancer are activating mutations of signaling pathways involving tyrosine kinases, making kinase inhibitors a rational choice of anti-thyroid cancer therapy. One such multitargeted kinase inhibitor with known activity against VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), RET, and BRAF is sorafenib (Nexavar), which is currently approved by the US Food and Drug Administration (FDA) for the treatment of renal cell
carcinoma and hepatocellular carcinoma. TABLE 2

Summary of Trial Results of Sorafenib and Sunitinib in Thyroid Cancer

In a recent phase II study of 30 patients with differentiated or medullary thyroid cancer who took sorafenib at a dose of 400 mg twice a day orally, an overall clinical response (defined as either a partial response or stable disease) was seen in 77%, and the median progression-free survival was 79 weeks (Table 2). Approximately 23% experienced a partial response by Response Evaluation Criteria in Solid Tumors (RECIST). The most common treatment-related adverse events included fatigue, rash, diarrhea, palmar-plantar erythema, musculoskeletal pain, and weight loss. One patient with medullary thyroid cancer experienced grade 4 liver toxicity, which may have been treatment-related, and died.[47]

Similar results and side effects were recorded in a further small study,[48] which suggested that sorafenib has significant antitumor activity in patients with advanced thyroid cancer and warrants further study in this group.

Sunitinib

Much enthusiasm has been generated following recent studies using sunitinib (Sutent), an oral agent with inhibitory activity against RET, VEGFR, and PDGFR, and thus the potential to be active in both differentiated and medullary thyroid cancers.[49-51] Sunitinib is FDA approved for renal cell cancer and imatinib (Gleevec)-refractory gastrointestinal stromal tumors.

In the largest study of sunitinib in thyroid cancer to date, 43 patients with radioactive iodine–resistant disease were treated with sunitinib, 50 mg daily, on a 4-week-on/2-week-off schedule. Among patients with differentiated carcinomas, 13% achieved a partial response and 68% had stable disease. In contrast, 83% of patients with medullary thyroid carcinomas had stable disease (Table 2). This was a heavily pretreated group of patients, and reported adverse effects were similar to those seen with sorafenib but also included neutropenia in 49% and thrombocytopenia in 16%.[49]

Motesanib Diphosphate

Motesanib diphosphate (AMG 706) is a potent, oral multikinase inhibitor that targets VEGF, PDGFR, KIT, and RET receptors and has both antiangiogenic and antitumor activity. In a small subgroup analysis of a phase I trial, three thyroid cancer patients treated with motesanib had a partial response and three experienced disease stabilization.[52] This prompted a large open-label, phase II study in which 93 patients with progressive, locally advanced or metastatic, radioiodine-resistant differentiated thyroid cancer were treated with 125 mg of motesanib administered once daily. Stable disease was achieved in 67% of the patients and was maintained for 24 weeks or longer in 35%. The most common treatment-related adverse events were diarrhea (59% incidence), hypertension (56%), fatigue (46%), and weight loss (40%).[53]

Axitinib

Axitinib is a potent, selective, orally administered inhibitor of VEGF receptors 1, 2, and 3. It is more than 10-fold less potent for inhibiting PDGFR and cKIT in cell-based assays, and this relative selectivity, in combination with the recognized importance of angiogenesis in thyroid cancer, made it an excellent choice for further study in this disease.

A recent, multi-institutional study assessed its safety and activity in 60 patients with thyroid cancer of any histology that was resistant to iodine-131. The drug was given at a dose of 5 mg twice daily. Partial responses were observed in 30% of patients, and stable disease lasting at least 16 weeks was reported in another 38%. Median progression-free survival was over 18 months.[54] These results are more impressive when we consider that the majority of patients were male and had metastatic disease, which are risk factors for poor prognosis. Common treatment-related adverse events were fatigue, diarrhea, nausea, anorexia, hypertension, stomatitis, weight decrease, and headache, but very few high-grade events were recorded.

Vandetanib
Vandetanib (ZD6474, Zactima) is another novel tyrosine kinase inhibitor that acts as a potent and reversible inhibitor of ATP binding to VEGF and EGF receptors.[55] The drug has also demonstrated selective inhibition of RET-dependent thyroid tumor cell growth in vitro.[56] This provided the rationale for studying the activity of vandetanib in hereditary medullary thyroid cancer, which is associated with findings in family members of point mutations in the RET proto-oncogene. The most recent phase II study of this drug in patients with locally advanced or metastatic hereditary medullary thyroid cancer enrolled 19 patients. Preliminary results showed a partial response in two patients, and stable disease for at least 24 weeks in six patients (ie, a disease control rate of 42.1%).[57] A randomized, placebo-controlled, international phase III study of vandetanib in medullary thyroid cancer is currently accruing.

The studies discussed above show a renewed interest in refractory thyroid cancer management and suggest that small-molecule inhibitors offer promising prospects for the treatment of these patients. Several other multtargeted tyrosine kinase inhibitors are in development. We would propose treatment of refractory thyroid cancer patients in a clinical trial wherever possible, and where studies are unavailable, off-label use of the currently available oral multikinase inhibitors such as sorafenib and sunitinib. A summary of drugs in development that may target pathways involved in thyroid cancer is shown in Table 1.

**EGFR Inhibitors**

Gefinitib (Iressa) is a tyrosine kinase inhibitor of the epidermal growth factor receptor, approved in the United States for locally advanced or metastatic non–small-cell lung cancer after failure of first-line chemotherapies. Preclinical data support a role for EGFR inhibition in thyroid carcinomas, and in particular, anaplastic thyroid cancer.[58] The most recent study of the drug in radioactive iodine–refractory thyroid cancers of all histologic subtypes failed to show any objective responses among 25 patients.[59] Approximately 32% of patients experienced a reduction in tumor volume that did not meet criteria for a partial response, but some had prolonged periods of stable disease, suggesting biologic activity.

Another logical therapeutic intervention is the monoclonal antibody to EGFR, cetuximab (Erbitux). This agent has previously shown synergism with chemotherapy such as irinotecan in the treatment of patients with colorectal cancer.[60] This same combination has demonstrated synergistic inhibition of the growth of orthotopic anaplastic thyroid carcinoma xenografts in nude mice but has yet to be studied in humans.[61]

**Vascular-Disrupting Agents**

Combretastatin A4 phosphate is a novel drug whose precise mechanism of action is unknown. It is structurally similar to colchicine and causes antitumor effects by binding tubulin and disrupting vascular supply within tumors. In combination with paclitaxel, combretastatin A4 phosphate demonstrated excellent antineoplastic activity against anaplastic thyroid cancer in a nude mouse xenograft model.[62] When given to patients with advanced cancer in a phase I trial, a single patient with anaplastic thyroid cancer had a complete response that lasted more than 30 months after treatment. No traditional “cytotoxic” side effects such as myelotoxicity, stomatitis, or alopecia were noted. However, tumor pain occurred in 10% of treatment cycles.

It is possible that combretastatin, in addition to disrupting tumor vasculature, may cause transient changes in other vascular beds—two episodes of acute coronary syndrome were noted among 25 patients treated on this trial.[63] Preliminary data from a subsequent phase II study failed to obtain any objective responses, but a number of patients achieved disease stabilization.[64] A phase III trial of this agent in combination with carboplatin and paclitaxel chemotherapy is currently accruing.

**Cytotoxic Chemotherapy and Attempts to Improve Traditional Therapies**

Traditional cytotoxic chemotherapies have been studied with variable and usually poor responses in $^{131}$I-resistant thyroid cancers. Single-agent doxorubicin (the most studied chemotherapy drug) provides partial response rates in the 10%-37% range.[65,66] Trials of other drugs such as cisplatin and paclitaxel have not yielded improved response rates, and combination regimens have merely increased toxicity.[66,67] Because of the minimal efficacy associated with cytotoxic treatment, the National Comprehensive Cancer Network guidelines, among others, recommend enrollment in clinical trials for such patients.[68]

Attempts have also been made to enhance or prolong the beneficial effects of $^{131}$I using all-trans retinoic acid (ATRA) to “redifferentiate” metastatic thyroid cancer. Chinese investigators treated 11
patients with dedifferentiated thyroid cancer using 1 mg/kg/d of ATRA followed by radioactive iodine. They obtained mixed responses. A British study has failed to demonstrate clinically significant 131I uptake after administration of the retinoid.[69,70]

**Antiangiogenic Therapies**

An area of growing interest involves the use of the antiangiogenic drugs thalidomide (Thalomid) and lenalidomide (Revlimid) to target hypervascular thyroid carcinomas. Of 28 evaluable patients with refractory, differentiated thyroid cancer who received thalidomide in a phase II trial, 18% obtained a partial response and 32% experienced stable disease.[71] Early results of a phase II study of lenalidomide in the same population also showed this agent to be well tolerated, with 22% of 21 patients achieving a partial response and 44% experiencing disease stabilization.[72]

**Other Promising Agents and Areas for Further Study**

Enhanced knowledge of the epigenetic pathways involved in carcinogenesis has led to discovery of the importance of acetylation of histone tails and hypermethylation of DNA in regulator regions. Dysregulated histone deacetylase (HDAC) activity has been found in a number of cancers, and HDAC inhibitors have demonstrated anticancer effects.[73,74] HDAC inhibitors have depressed the growth of thyroid cancer cell lines in vitro, providing a rationale for the potential use of these drugs in the clinic.[75]

Preliminary studies suggest a role for DNA methylation in the loss of human sodium iodide symporter expression in thyroid carcinomas, as well as a potential application for chemical demethylation therapy in restoring responsiveness to therapeutic radioiodide.[76]

**Conclusion**

The prognosis for patients with metastatic radioactive iodine–resistant thyroid cancer remains poor. Recent progress in understanding the molecular pathways involved, however, has rekindled an interest in targeted treatment of this challenging disease. Many of the new studies discussed here are still in early phases, and further large, randomized trials are required. It is evident that the landscape of treatment for this group is evolving rapidly, and there is an ever-increasing role for the medical oncologist. In the absence of strong phase III data, we strongly propose that patients be enrolled in clinical trials wherever possible. Moreover, the currently available oral multikinase inhibitors such as sorafenib and sunitinib should be the off-study treatment of choice for patients with metastatic radioiodine-insensitive thyroid cancers.

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**References:**


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