Investigational Therapies for Metastatic Thyroid Carcinoma

R. Michael Tuttle, MD, and R. Leboeuf, MD, New York, New York, and Sherbrooke, Quebec, Canada

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Abstract
Although traditional chemotherapy has yielded disappointing results in the therapy of progressive metastatic thyroid cancer, the recent development of a wide range of novel therapies targeting critical steps in the pathogenesis of thyroid cancer has led to a renewed interest in thyroid cancer clinical trials. This review provides an overview of the pathogenesis of thyroid cancer with particular emphasis on specific molecular targets that can be modulated with these novel agents. The article reviews the results for the small number of thyroid cancer patients included in published therapeutic trials and critically examines patient selection criteria for inclusion in clinical trials. Given the dramatic increase in availability of thyroid cancer clinical trials, all patients with radioactive iodine-refractory, progressive metastatic thyroid cancer should be considered for inclusion in a novel therapy trial. (JNCCN 2007;5:641–646)

With appropriate surgical resection and judicious use of radioactive iodine (RAI), the majority of patients with well-differentiated thyroid cancer will be rendered disease free with initial therapy. However, up to 25% of patients will have persistent disease after initial therapy, as shown by persistent uptake on follow-up RAI scans, structural disease on cross-sectional imaging, or, more frequently, persistently detectable serum thyroglobulin either on thyroid-stimulating hormone (TSH) suppression or after TSH stimulation. Although the majority of persistent disease is small-volume, well-differentiated thyroid cancer may grow slowly over many years without a significant impact on survival. Some thyroid cancer patients have persistent or recurrent disease that is more aggressive, resulting in higher rates of disease-specific death.

In most cases, these aggressive thyroid cancer cases can be identified on the basis of initial staging because they have a higher likelihood of gross extrathyroidal extension, aggressive histologic variants with more poorly differentiated histologies, incomplete tumor resection, or non-RAI–avid metastatic disease at presentation. However, many patients with metastatic well-differentiated thyroid cancer show pulmonary or cervical metastases that are asymptomatic and increase in size at a very slow rate over many years. Recent studies have shown the prognostic importance of fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning in patients with metastatic disease. Multivariate analysis shows that large volume FDG-avid metastatic lesions are the most significant predictor of death from disease.

Currently available systemic therapies for progressive metastatic differentiated thyroid cancers are woefully inadequate. Most traditional chemotherapy regimens use doxorubicin as a single agent and researchers report short-duration partial response rates in the 0% to 20% range with essentially no long-term remissions. The combination of doxorubicin with cisplatin resulted in similar response rates but additional toxic effects.

A few small clinical trials using mitoxantrone, etoposide, or fluorouracil have also yielded disappointing results. An improved response rate was recently reported in a small study in which carboplatinum and epirubicin was used in the setting of an elevated serum TSH in advanced poorly differentiated thyroid cancer. The effectiveness of the newer cytotoxic agents such as taxanes, gemcitabine, and type I topoisomerase inhibitors have not been carefully evaluated. Because of the dismal response rates of traditional chemotherapy, both the National Comprehensive Cancer Network...
Cancer Network (NCCN) and the American Thyroid Association (ATA) thyroid cancer guidelines recommend that patients with progressive metastatic thyroid cancer be considered for clinical trials without requiring a trial of traditional chemotherapy.10,11

The new explosion in our understanding of the molecular pathogenesis of well-differentiated thyroid cancer coupled with the sudden availability of a wide variety of targeted agents has led to an unprecedented number of clinical trials in thyroid cancer. The results of the 2 largest phase II thyroid cancer trials to date are expected to be presented in the summer of 2007, but initial reports appear promising. A list of clinical trials on thyroid cancer that are currently enrolling participants is available at the ATA’s Web site (http://www.thyroidtrials.org) and at the National Cancer Institute’s Web site (http://www.cancer.gov/clinicaltrials; both accessed May 16, 2007).

Because of this influx of new information, health care providers caring for patients with aggressive thyroid cancer must have a good understanding of the molecular pathogenesis of thyroid cancer to understand the potential actions of new targeted agents and to help patients identify specific clinical trials for which they may be eligible. This review focuses on the specific molecular pathways that are most likely to be targeted in upcoming clinical trials without trying to review the wide range of molecular abnormalities involved in the initiation, progression, or metastatic spread of differentiated thyroid cancer.

Potential Molecular Targets
Recent work has revealed that mutations in one of several genes involved in the receptor tyrosine kinase mitogen-activated protein kinase (MAPK) pathway can be detected in up to 80% of well-differentiated thyroid cancers (Figure 1). In adults, mutations in ret/PTC are found in 5% to 30%, ras mutations in 10%, and BRAF mutations in nearly 40% of well-differentiated thyroid cancer samples.12,13

The importance of this pathway is further underscored by the demonstration that, within an individual tumor, activations of ret/PTC, ras, or BRAF are mutually exclusive, non-overlapping activating events.14 As seen in Figure 1, activation of the transmembrane tyrosine kinase receptors (e.g., vascular endothelial growth factor [VEGF], endothelial growth factor receptors [EGFR], RET, c-MET), results in signal transduction through both the MAPK pathway (ras, BRAF, ERK, and MEK) and the phosphoinositides-3 (PI3) kinase pathway (AKT, mTOR), resulting in transcriptional effects within the cell nucleus. Although the MAPK kinase and PI3 kinase pathways are shown as independent linear pathways, new data are emerging that considerable cross talk occurs between these 2 major pathways at several levels. Furthermore, activation of the RET oncogene is central to the pathophysiology of medullary thyroid cancer and is therefore a prime target for therapy.15,16

In addition to the mutations associated with activation of the tyrosine kinase pathways, several investigators have shown abnormalities in DNA methylation and histone deacetylation that are important regulators of transcription in several of the thyroid-specific genes in non-medullary thyroid cancer.17,18 These epigenetic modifications appear to decrease the expression of sodium iodine symporter (NIS) and could therefore serve as a potential target to upregulate NIS expression in thyroid cancer, thereby restoring the sensitivity to RAI. More recent studies have shown that activation of the receptor tyrosine kinases, signaling through MAPK or PI3 kinase, also decrease NIS expression.

Yet other investigators have explored agents that could initiate or enhance apoptosis in thyroid cancer cells by increasing tumor necrosis factor – related apoptosis-inducing ligand or inhibition of phosphorylated Bcl-2.19

Targeting the MAPK Pathway
Because activating mutations in the MAPK pathway are present in most differentiated thyroid cancers, inhibition of this pathway may result in a decrease in thyroid cancer growth and proliferation. Fortunately,
activating mutations in the MAPK pathway are also common in other solid tumors, resulting in widespread interest in developing safe, effective, targeted inhibition of the MAPK pathway for a wide variety of malignancies. Both cell culture data and preclinical studies suggest that inhibition of one of the many steps in the MAPK pathway can cause significant growth inhibition in thyroid cancer models.

Inhibition of the MAPK activation could be achieved with the use of selective inhibitors of any number of steps in the pathway. One strategy is to use specific antibodies to target either the specific tyrosine kinase ligand or its transmembrane tyrosine kinase receptor to interfere with the normal ligand-receptor interactions. Ligand-specific antibodies have been developed against VEGF (bevacizumab, VEGF trap), and receptor-specific antibodies to EGRF receptors are being used in treating other solid tumors (trastuzumab, cetuximab).

In addition to antibody-mediated inhibition of the interaction between the tyrosine kinase ligands and the tyrosine kinase receptors, a wide variety of new compounds have been developed that specifically inhibit activation of the tyrosine kinase receptor by interfering with adenosine 5'-triphosphate (ATP) binding to the receptor (Table 1). These agents are often multikinase inhibitors, inhibiting several tyrosine kinases to varying degrees. Because of the importance of VEGF and EGRF in solid tumors, researchers have shown significant interest in the available agents known to inhibit various steps in the MAPK pathway. Recent work has focused on inhibition of downstream targets in the MAPK pathway, including BRAF and MEK. At least 2 potent MEK inhibitors are entering clinical trials. Although sorafenib proved to be a weak inhibitor of BRAF, other more potent BRAF inhibitors are currently in development. The complex nature of these signaling pathways was underscored by the recent demonstration that cells with activating BRAF mutations were exquisitely sensitive to MEK inhibition, while cell lines bearing RAS mutations showed a lower and more variable sensitivity to MEK inhibitors.

Although most studies to date have explored single-agent therapy, the complex, interactive nature of these molecular pathways will probably require combination therapies directed at multiple targets within a single pathway or in different pathways or a combination of cytotoxic chemotherapy or radiation therapy with targeted therapy to achieve optimal tumoricidal effects.

### Table 1 Potential Targets Within the MAPK Pathway

<table>
<thead>
<tr>
<th>Specific Target</th>
<th>Mechanism</th>
<th>Selected Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>TK ligand</td>
<td>Antibody against ligand</td>
<td>VEGF trap (VEGF ligand) bevacizumab (VEGF ligand)</td>
</tr>
<tr>
<td>TK receptor</td>
<td>Antibody against TK receptor</td>
<td>Trastuzumab (EGFR) cetuximab (EGFR)</td>
</tr>
<tr>
<td></td>
<td>Inhibit ATP binding to TK receptor</td>
<td>Vandetanib (anti-VEGF, EGFR, and RET) motesanib (anti-VEGF, PDGF, KIT, and RET)</td>
</tr>
<tr>
<td></td>
<td>Inhibit TK receptor phosphorylation or activation</td>
<td>Vatalanib (VEGFR) gefitinib (EGFR) sunitinib (VEGFR and others) sorafenib (also Raf inhibitor)</td>
</tr>
<tr>
<td>Downstream targets</td>
<td>Ras inhibition</td>
<td>Ras antisense compounds</td>
</tr>
<tr>
<td></td>
<td>Raf inhibition</td>
<td>sorafenib (also VEGF inhibitor)</td>
</tr>
<tr>
<td>MEK inhibition</td>
<td>PD 98059, AZD6244</td>
<td></td>
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Abbreviations: ATP, adenosine triphosphate; EGRF, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; TK, tyrosine kinase; VEGF, vascular endothelial growth factor.

### Targeting Epigenetic Modifiers

Agents targeting both the methylation status and the histone acetylation status have been shown in cell culture to redifferentiate thyroid cancer cells, often restoring the function of the NIS protein and increasing the cellular uptake of RAI. In addition, the histone deacetylase inhibitors also appear to have significant effects on cell cycle regulation, which suggests more than one mechanism of action. Clinical trials are ongoing using agents that inhibit DNA methylation and histone deacetylase inhibitors (Table 2).

Other important determinants of the differentiation status of thyroid cells, particularly the expression of NIS, include nuclear retinoic acid receptors and retinoid X receptors. In preclinical studies and in a
small number of patients with thyroid cancer, retinoic acids have increased NIS expression and uptake of RAI in poorly differentiated thyroid cancer. Interestingly, a combination of retinoic acid and peroxisome proliferator-activated receptor (e.g., thiazolidinediones) resulted in a more substantial decrease in cellular proliferation than either agent alone.8

Other Potential Targets

In addition to the anti-angiogenic effects that may be expected by targeting the VEGF-VEGFR-MAPK pathway, other agents with a more direct effect on the vascular endothelium are being evaluated in clinical trials. Thalidomide appears to have weak anti-angiogenic effects in the established tumor vasculature, but combretastatin has shown more promising results, including a dramatic response in a patient with anaplastic thyroid cancer.24

Other agents that have a wide variety of potential molecular actions and are currently being evaluated in clinical trials include cyclo-oxygenase (COX-2) inhibitors, heat shock protein 90 (Hsp-90) inhibitors, and proteosome inhibitors.7,19

Finally, gene therapy approaches are being evaluated in an effort to restore NIS expression in poorly differentiated thyroid cancers, restore p53 expression in anaplastic thyroid cancer, or produce cytotoxic effects with suicide gene therapy.25

Effect of Targeted Therapy in Thyroid Cancer Patients

With the rapid increase in the number of specific agents to inhibit many potential targets, the quantity of literature now available detailing the impact of these agents in a variety of preclinical models is not surprising. Although many of these novel agents are proceeding to clinical trials or have had preliminary results reported in abstract form at various meetings, peer reviewed publications are available on only a small number of these agents.

A recent report of celecoxib (a COX-2 inhibitor) in 32 patients with progressive metastatic-differentiated thyroid cancer showed a partial response in 1 patient and 12-month progression-free survival in another patient.26 Several small studies have shown an increase
in RAI avidity in 20% to 40% of patients with differentiated thyroid cancer treated with retinoids before RAI therapy.\textsuperscript{13,27} A phase II trial of rosiglitazone (PPAR-\(\gamma\) agonist) improved RAI uptake in 4 of 10 patients with RAI-refractory metastatic thyroid cancer.\textsuperscript{28} The effect of long-acting somatostatin-receptor analogue therapy in RAI-negative, somatostatin receptor--positive metastatic thyroid cancer is occasionally effective, but it usually does not produce long-term stabilization.\textsuperscript{29,30}

Interesting results are often obtained in phase I toxicity studies. For example, a dramatic complete response was shown in a single patient with anaplastic thyroid cancer treated on a phase I trial of combretastatin A-4 phosphate (anti-angiogenic factor), and disease stabilization was seen in another single patient with metastatic medullary thyroid cancer.\textsuperscript{31} In a phase I study of sorafenib (VEGF and BRAF inhibitor), one partial response was seen in a patient with metastatic papillary thyroid cancer.\textsuperscript{32} Recently, a partial response was seen in 1 patient with anaplastic thyroid cancer in a phase I trial of gefitinib (EGFR receptor inhibitor) and docetaxel (taxane).\textsuperscript{33}

**Target Selection**

With an increasing number of clinical trials either currently underway or soon to be opened, clinicians are now faced for the first time with having to help patients decide which of the several available clinical trials is likely to be most beneficial. Unfortunately, currently available data do not allow us to identify the single best target or agent to use. Therefore, patients usually select a trial based on potential or known side effects and the time and travel requirements for trial participation. Patients often prefer oral over intravenous agents for convenience and sometimes under the mistaken impression that oral drugs are safer than intravenous medications. Until more data are available, selecting a specific trial for an individual patient will depend heavily on the side effect profile, route of administration, intensity of follow up, and practical logistical issues.

**Patient Selection**

Because clinical trials have a small but definite risk of morbidity and mortality, proper patient selection is critical.\textsuperscript{7} Furthermore, because trial outcomes are usually based on disease stabilization rather than dramatic reduction in tumor size, patients must have structurally progressive, measurable disease before entering a clinical trial. As noted, many patients with non-RAI–avid metastatic thyroid cancer have very slowly progressive disease that may appear stable in a 6- to 12-month trial.

Additionally, clinical trials are usually considered only after the clinical utility of surgery, RAI, and external beam irradiation is exhausted.\textsuperscript{10} Most patients enrolled in clinical trials will have RAI refractory, unresectable, structurally progressive, FDG-PET–positive metastatic thyroid cancer. Furthermore, because entry into a clinical trial usually requires an index lesion at least 1 cm to allow accurate measurements, patients with progressive thyroid cancer manifested only by serum thyroglobulin elevations, without structural evidence of disease, will not qualify for most available trials.

However, because traditional chemotherapies have disappointing response rates, patients should not have to wait until chemotherapy fails before being offered participation in clinical trials. This is explicitly stated in both the NCCN and ATA guidelines.\textsuperscript{10,11}

As physicians gain more experience using targeted therapies in RAI-refractory thyroid cancer, they can expect to offer these therapies to patients with less-aggressive thyroid cancer and using less-rigorous requirements for documented structural progression. Until a better understanding of both the true effectiveness of these agents and possible side effects is achieved, however, phase II clinical trials should be reserved for patients with progressive disease that is likely to cause life-threatening complications within the next few years.

**Summary**

Although most patients with differentiated thyroid cancer have excellent response to initial surgery and RAI therapy, a small subset of thyroid cancer patients develop life-threatening RAI-refractory, progressive metastatic disease. Previously used systemic therapies for these patients have largely been disappointing. However, major advances in understanding the pathophysiology and molecular biology of thyroid cancer, coupled with the new availability of molecular targeted therapies, suggests the promise of a major therapeutic breakthrough in the next few years. Critically, patients with progressive thyroid cancer must be informed about ongoing clinical trials and offered participation...
when appropriate. Only through well designed, properly controlled, clinical trials can researchers identify which of the many potential novel agents (or combinations) is most likely to be effective for treating these patients.

References