

## Advances in Chemotherapy of Differentiated Epithelial and Medullary Thyroid Cancers

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**Context:** Systemic chemotherapies for advanced or metastatic thyroid carcinomas have been of only limited effectiveness. For patients with differentiated or medullary carcinomas unresponsive to conventional treatments, novel therapies are needed to improve disease outcomes.

**Evidence Acquisition:** The PubMed and Google Scholar search engines were used to identify publications and peer-reviewed meeting presentations addressing chemotherapy and targeted therapy for differentiated or medullary carcinoma.

**Evidence Synthesis:** Multiple novel therapies primarily targeting angiogenesis have entered clinical trials for metastatic thyroid carcinoma. Partial response rates up to 30% have been reported in single agent studies, but prolonged disease stabilization is more commonly seen. The most successful agents target the vascular endothelial growth factor receptors, with potential targets including the mutant kinases associated with papillary and medullary oncogenesis. Two drugs approved for other malignancies, sorafenib and sunitinib, have had promising preliminary results reported, and are being used selectively for patients who do not qualify for clinical trials. Randomized trials for several agents are underway that may lead to eventual drug approval for thyroid cancer.

**Conclusion:** Treatment for patients with metastatic or advanced thyroid carcinoma now emphasizes clinical trial opportunities for novel agents with considerable promise. Alternative options now exist for use of tyrosine kinase inhibitors that are well tolerated and may prove worthy of regulatory approval for this disease. (*J Clin Endocrinol Metab* 94: 1493–1499, 2009)

Cytotoxic systemic chemotherapies for advanced, metastatic thyroid carcinomas have limited effectiveness, with response rates typically 25% or less (1). With such poor outcomes, results from few clinical trials of new therapies for thyroid carcinomas were published during the latter half of the 20th century (2). Plaguing these early trials was the practice of lumping patients with all histologies of thyroid carcinoma (differentiated, medullary, and anaplastic), confounding interpretation of the results. The definitions of response used in these earlier studies varied as well, and none are comparable with the currently used standard RECIST methodology [for detailed description of RECIST, see Refs. 3, 4]. Thus, treatment with cytotoxic chemotherapy is generally limited to patients with symptomatic or rapidly progressive metastatic disease unresponsive to or unsuitable

for surgery, radioiodine (for tumors derived from differentiated carcinomas), and external beam radiotherapy.

During the past decade, biological discoveries sparked trials testing novel therapies for advanced thyroid carcinomas. Of prime importance has been recognition of key oncogenic mutations in papillary (PTC) and medullary (MTC) carcinomas. *BRAF* and *RAS* genes code for kinases that activate signaling through the MAPK pathway, regulating growth and function in many cells both normal and neoplastic. Evidence from various tumor models support the contention that most PTCs arise as a result of single activating somatic mutations in one of three genes: *BRAF*, *RAS*, and translocations producing *RET/PTC* oncogenes (5). The resultant *RET/PTC* proteins signal upstream from *RAS*, thus activating the same MAPK pathway. For MTC,

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Abbreviations: DTC, Differentiated thyroid carcinoma; EGF, epithelial growth factor; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

almost all familial forms of the disease arise due to inheritable germline activating mutations in *RET*, and identical somatic mutations occurring in C cells commonly cause sporadic disease. Activated *RET* mutant proteins also enhance MAPK signaling. Consistent with the oncogene addiction hypothesis, inhibition of these etiologic activating mutations leads to either tumor stabilization or regression. Therefore, interest arose in the therapeutic potential of kinase inhibitors for these diseases.

A second development was recognition of processes facilitating tumor growth, reflecting either normal (such as hypoxia inducible angiogenesis) or abnormal (such as epigenetic modifications of chromosomal DNA and histones) adaptations. Angiogenesis plays a critical role in tumor cell growth and metastasis, supplying nutrients and oxygen, removing waste products, and facilitating distant metastasis (6). Of the identified proangiogenic factors, vascular endothelial growth factor (VEGF) is key, binding to two receptor tyrosine kinases, VEGF receptor (VEGFR)-1 (fms-like tyrosine kinase-1) and VEGFR-2 (fetal liver kinase-1/kinase insert domain-containing receptor) that also trigger MAPK signaling (7). In PTC, the intensity of VEGF expression correlates with a higher risk of metastasis and recurrence, and a shorter disease-free survival (8, 9).

Third, the National Cancer Institute and pharmaceutical companies have recognized that effective treatment for advanced thyroid cancers remains an unmet need. Clinical trials for thyroid cancer have evolved as hypothesis-driven protocols extending *in vitro* observations identifying a rationale for a particular drug's use as well as from empiric observations in phase I trials that certain therapies yielded clinical benefit in patients with thyroid cancers. Consensus treatment guidelines emerged, explicitly recommending clinical trials (10, 11). This review will focus on findings from key studies that reflect this new paradigm for research-driven treatment (online databases that can be searched to identify clinical trials currently recruiting patients can be found at [www.thyroid.org](http://www.thyroid.org) and [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) (12).

Small molecule inhibitors targeting signaling kinases have been of keen interest, given the oncogenic roles of mutant *BRAF*, *RET*, and *RAS*, and the contributory roles of growth factor receptors such as VEGFR (5, 13, 14). These drugs partially inhibit multiple kinases at nanomolar concentrations and often affect multiple signaling pathways (Table 1). Orally administered, these agents have common side effects that include hypertension, diarrhea, skin lesions, and fatigue. Interest in thalidomide arose after reported responses in individual patients with anaplastic

thyroid carcinoma (15). Abnormalities of nuclear gene regulation that affect differentiated function stimulated interest in targeting DNA methylation, histone deacetylation, and nuclear receptors as means to reverse these dedifferentiating steps.

## Motesanib

Motesanib (AMG706) is an oral, tyrosine kinase inhibitor (TKI) targeting the VEGFRs 1, 2, and 3 (16). In both *in vitro* and cell-based assays, nanomolar concentrations of motesanib inhibited autophosphorylation of both wild-type and mutant *RET*; growth of xenografts of TT cells bearing the C634W *RET* mutation was effectively inhibited (17). In a phase I study, motesanib demonstrated antitumor activity in patients with advanced solid malignancies, including five patients with differentiated thyroid carcinoma (DTC) and one with MTC; three thyroid patients experienced greater than 30% reductions in tumor diameters, qualifying as partial responders (3, 18). The most common toxicities included fatigue, nausea, diarrhea, and hypertension, all typical of this class of drugs.

Based on this phase I experience, a multicenter, open-label phase II trial was initiated, testing the efficacy of motesanib in separate cohorts of patients with progressive DTC (19) and patients with progressive or symptomatic MTC (20), starting at 125 mg daily. The eligibility criterion of progression was based on serial radiographic imaging studies within the preceding 6 months, applying RECIST response assessment (3). Of 93 DTC patients who initiated therapy, one third were still on drug after 48 wk. Partial response was confirmed by subsequent imaging and independent radiological review in 14% of the DTC patients, and another 35% of these previously progressive disease patients maintained stable disease for at least 24 wk. The median progression-free survival was 40 wk. Although the drug does not inhibit *BRAF*, patients with *BRAF* mutation-bearing tumors were less likely to progress while on the drug, which may relate to higher dependence on VEGF-mediated angiogenesis in such tumors (21). Of 91 patients with progressive or symptomatic MTC who initiated therapy, only 2% had confirmed partial response but another 47% experienced stable disease for at least 24 wk (20). Unexpectedly, the maximum and trough plasma concentrations of the drug in MTC patients were lower than reported with other solid tumor patients, and these differing pharmacokinetics may have contributed to the lower response rate.

**TABLE 1.** Kinase inhibitors recently in clinical trials for advanced or metastatic thyroid carcinomas

Drug category/drug	VEGFR1 IC <sub>50</sub> (nM)	VEGFR2 IC <sub>50</sub> (nM)	VEGFR3 IC <sub>50</sub> (nM)	RET IC <sub>50</sub> (nM)	RET/PTC3 IC <sub>50</sub> (nM)	BRAF IC <sub>50</sub> (nM)	Other IC <sub>50</sub> (nM)	References
Axitinib	1.2	0.25	0.29				C-KIT 1.7	(23)
Gefitinib							EGFR 33	(57)
Imatinib		>10,000		3,700			BCR-ABL 25 C-KIT 150	(53)
Motesanib diphosphate	2	3	6	59			C-KIT 8	(16)
Sorafenib		90	20	47	50	22	C-KIT 68	(36)
Sunitinib	2	9	17	41	224			(46)
Vandetanib	1600	40	110	130	100		EGFR 500	(28,29)
XL184		0.035		4			C-MET 1.8	(61)

EGFR, EGF receptor.

Overall, the drug was well tolerated, with similar side effects as reported in the phase I trial. An unanticipated side effect of motesanib therapy was a 30% increase in the mean dosages of levothyroxine required to maintain TSH suppression or euthyroidism, respectively, in DTC and MTC cohorts, and 60–70% of patients experienced peak TSH concentrations out of the therapeutic ranges (22).

### Axitinib

Axitinib (AG-013736) is an oral TKI that effectively blocks VEGFRs at subnanomolar concentrations but notably not the RET kinase (23). In a phase I study of 36 patients with advanced solid malignancies, one of five thyroid cancer patients experienced tumor shrinkage, although none qualified as a partial response (24). A multicenter, open-label phase II study examined the efficacy of axitinib in advanced or metastatic thyroid carcinoma, starting at a dose of 5 mg twice daily (25). Of the 60 patients who started therapy, 50% had PTC, 25% had FTC (including Hurthle cell variants), and 18% had MTC. Although response assessment was not possible in 25% of the patients, confirmed partial response rate was 30% by intent-to-treat analysis (31% in DTC; 18% in MTC; one patient with anaplastic thyroid cancer). Responses were seen in patients despite previous treatments with a variety of chemotherapeutic regimens. Median progression-free survival was 18 months. Common adverse events included fatigue, stomatitis, proteinuria, diarrhea, hypertension, and nausea. Exploratory analyses of soluble biomarkers demonstrated increases in serum VEGF levels, a recognized phenomenon of effective angiogenesis inhibition (26).

Currently recruiting patients is a multicenter, open-label phase II study to determine the efficacy of axitinib in patients with metastatic DTC refractory to doxorubicin or for whom doxorubicin therapy is contraindicated.

### Vandetanib

Vandetanib (ZD 6474) is an oral, small-molecule TKI that targets VEGFRs 2 and 3, RET, and at higher concentrations, the epithelial growth factor (EGF) receptor (27, 28). One of the first small molecule inhibitors to be studied in thyroid cancer cell lines, vandetanib was shown to inhibit effectively *RET/PTC3* mutations found in some PTC and *M918T* RET mutations occurring in multiple endocrine neoplasia 2B-associated and some sporadic MTC (29). Growth of cell lines containing *RET/PTC1* or *RET/PTC3* was inhibited. However, the drug was not able to block RET when a hydrophobic amino acid substitution occurs at V804, as in some inherited forms of MTC (30). In a phase I trial in 77 patients with various solid carcinomas other than thyroid, doses up to 300 mg daily were tolerated with the most common dose-limiting side effects of diarrhea, hypertension, and skin rash (31).

On the basis of the preclinical demonstration that vandetanib inhibited most *RET* point mutations, a multicenter, open-label, phase II trial studied the efficacy of the drug in patients with metastatic familial forms of MTC (32). Thirty patients were en-

rolled, starting therapy with vandetanib, 300 mg daily. Confirmed partial response was reported in 17% of these patients, and stable disease lasting at least 24 wk was seen in another 33%. Calcitonin levels dropped by more than 50% in almost two thirds of the patients, but blocking RET may lead to a direct inhibition of calcitonin gene expression, independent of tumor volume changes (33). The most commonly reported side effects included rash (particularly photosensitivity), diarrhea, fatigue, and nausea, whereas the most severe toxicities included asymptomatic QT interval prolongation, rash, and diarrhea. A second phase II trial in familial MTC, starting at 100 mg daily, reported similar preliminary results (34). Ongoing studies with vandetanib include: 1) an open-label, phase II trial in patients under the age of 18 yr with familial MTC [with partial responses described in several patients (35)]; 2) a randomized, placebo-controlled, phase II trial in patients with metastatic DTC; and 3) a multicenter, randomized, placebo-controlled, phase II trial in patients with metastatic MTC, either sporadic or inherited.

### Sorafenib

Sorafenib (BAY 43-9006) is an oral, small-molecule TKI targeting VEGFRs 2 and 3, RET (including most mutant forms that have been examined), and the serine kinase BRAF (36). In preclinical studies, sorafenib prevented the growth of the TPC1 and TT cell lines, which contain the *RET/PTC1* and *C634W* RET mutations, respectively (37). In four phase I trials testing varying doses and administration schedules of sorafenib, the optimal therapeutic dose was found to be 400 mg twice daily (38). The most common or significant toxicities included hand-foot syndrome, rash, fatigue, diarrhea, and hypertension.

Although no thyroid cancer patients were reported in these phase I trials, tumor shrinkage was reported in one thyroid cancer patient included in a phase II trial for advanced solid tumors (39). Subsequently two phase II trials were performed specifically in patients with metastatic PTC. Sponsored by the National Cancer Institute, an open-label, phase II trial recruited 58 patients in a 10-month period (40). Of 36 evaluable patients, confirmed partial response was seen in 8%, and minor response (defined as 23–29% reduction in tumor diameters) was described in another 19%. In a smaller open-label, phase II study, unconfirmed partial responses were reported in four of 15 evaluable patients with PTC and three of seven with FTC (41). Median progression-free survival was 84 wk.

The anti-RET activity of sorafenib makes MTC a potential therapeutic target for this drug as well (14). In a small pilot study, five patients with metastatic MTC were treated with sorafenib, and responses were described in two (including one complete response) after 6 months of treatment, and symptomatic improvement was seen in all (42). A larger, open-label, phase II study has been initiated in patients with metastatic MTC. Partial responses were also reported in three of six MTC patients participating in a phase I study of the combination of sorafenib and the farnesyltransferase inhibitor tipifarnib (43).

Sorafenib is approved by the Food and Drug Administration as treatment for advanced renal cell carcinoma and unresectable

hepatocellular carcinoma. Although not specifically approved for thyroid carcinomas, sorafenib is being used in selected patients with progressive metastatic papillary thyroid carcinoma for whom clinical trials are not appropriate (11). Treatment with sorafenib yielded a marked response in a child whose lung metastases from PTC were progressing despite radioiodine therapy; as with other antiangiogenic therapies, pediatric usage may result in bony growth plate inhibition and growth abnormalities (44). As with any new medication, further experience with the drug is leading to identification of less common but significant toxicities, which for sorafenib includes keratoacanthomas and other malignant cutaneous squamous cell lesions (45). Thus, only physicians familiar with management of adverse events of such therapies should consider their use in thyroid cancer patients.

### Sunitinib

Sunitinib (SU11248) is an oral, small-molecule TKI of all three VEGFRs, RET, and RET/PTC subtypes 1 and 3 (46). Prolonged partial responses have been described in three patients (with PTC, FTC, and MTC, respectively) treated with sunitinib, 50 mg daily for 28 d followed by 14 d of no treatment per cycle (47, 48). <sup>18</sup>F-fluorodeoxyglucose uptake by positron emission tomography imaging was markedly reduced in the DTC patients. Preliminary results from an open-label, phase II trial in patients with progressive DTC or MTC reported partial response in 13% of 31 DTC patients and disease stabilization in 68% of DTC and 83% of MTC patients (49). Common or severe adverse events included fatigue, diarrhea, palmar-plantar erythrodysesthesia, neutropenia, and hypertension. Preliminary analysis from a second open-label, phase II trial reported partial responses or stable disease for greater than 12 wk in two of 12 DTC and three of eight MTC patients (50). Like sorafenib, sunitinib is approved for treatment of renal cell carcinoma and is therefore available for use in selected thyroid cancer patients with metastatic disease warranting therapy outside of clinical trials.

### Imatinib

Imatinib (STI571), an oral, small-molecule TKI of breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 and c-KIT, inhibits RET autophosphorylation and RET-mediated cell growth (51–53). Two small open-label, phase II studies that examined a total of 24 patients with metastatic MTC treated with imatinib, starting at 600 mg daily have been completed (54, 55). No objective tumor responses were reported, and a minority of patients achieved stable disease as their best tumor response. Toxicities included diarrhea, laryngeal edema, rash, and nausea; increased thyroid hormone dosage requirements were reported nine of 15 patients in the larger trial (55). No objective responses were seen in a phase I study of imatinib combined with dacarbazine and capecitabine that included seven patients with MTC (56).

### Gefitinib

Gefitinib (ZD1839), an oral, small-molecule inhibitor of the EGF receptor, was initially introduced for therapy of non-small-cell lung carcinoma (57, 58). Because many papillary and anaplastic thyroid carcinomas display activated EGF receptor signaling and inhibitors have had demonstrated efficacy in preclinical models, an open-label, phase II study was initiated, examining the effectiveness of gefitinib in a mixed cohort of thyroid cancer patients (59). The starting daily dose was 250 mg. Of 27 enrolled patients, 41% had PTC, 22% FTC, 19% anaplastic carcinoma, and 15% MTC. There were no complete or partial responses in the 25 evaluable patients, although eight had tumor reduction that did not qualify as partial response. One patient with anaplastic carcinoma had stable disease beyond 12 months of therapy, similar to that reported in a phase I trial of gefitinib and docetaxel (60). Overall, median progression-free survival was just less than 4 months and less than 3 months in the MTC cohort.

### XL184

XL184 is an oral, small-molecule inhibitor of VEGFRs 1 and 2, C-MET, RET, C-KIT, FLT3, and Tie-2 (61). The inhibitory activity against C-MET, the cognate receptor for the hepatocyte growth factor, may provide additional synergistic benefit in thyroid carcinomas, given the enhanced expression of the receptor seen in PTC and MTC (62–64). An ongoing phase I, dose-escalation study has examined the safety and pharmacokinetics of XL184 in patients with metastatic solid malignancies, with an expansion cohort limited to MTC (65). Twelve MTC patients (55%) had achieved partial responses, and the overall rate of partial responses and stable disease at least 3 months in duration was 84%. A phase III trial, comparing XL184 with placebo, is now underway.

### XL281

XL281, an oral small-molecule that inhibits wild-type and mutant BRAF kinases, is currently in phase I trial (66). Preliminary data described prolonged stable disease in five PTC patients, two of which were documented to bear V600E BRAF mutations.

### Thalidomide

Thalidomide was found to inhibit angiogenesis decades after it achieved notoriety as a teratogenic cause of neonatal dysmelia (67). However, the exact mechanism by which thalidomide exerts its antiangiogenic effects remains unknown. In the report that described the efficacy of paclitaxel for treatment of anaplastic thyroid carcinoma, one patient subsequently stabilized for at least 6 months while taking thalidomide (15). An open-label, phase II trial was initiated to examine the efficacy of thalidomide in patients with progressive, metastatic thyroid carci-

noma of varying histologies (68). Starting at 200 mg daily, the dose of drug was progressively increased as tolerated, with a median maximum daily dose of about 600 mg. Of 28 evaluable patients, 18% achieved a partial response and 32% had stable disease as their best response. Histology-specific partial response rates were not reported, but partial response or durable stable disease was seen in three PTC patients, two FTC patients, three Hurthle cell cancer patients, and one MTC patient along with four patients with either tall cell or insular variants. Toxicities were dose limiting in the majority of patients, and the most common adverse events included somnolence, peripheral neuropathy, constipation, dizziness, and infection. Given the suggested efficacy but high rate of adverse events with thalidomide, a subsequent phase II study was initiated using the presumably less toxic lenalidomide (69). Eligibility was limited to DTC patients whose measured tumor volumes had increased by at least 30% in the past year. Of 18 evaluable patients, seven (39%) were reported with partial responses measured by reductions in tumor volumes, with a median duration of 11 months, and another nine (50%) were stable. However, median overall survival was less than 11 months, and three patients experienced pulmonary emboli.

### Intranuclear targeting

The possible role of retinoid receptors to regulate iodine uptake by thyroid follicular cells was suggested by studies demonstrating that incubation of poorly differentiated thyroid cancer cells with 13 *cis*-retinoic acid could partially restore radioiodine uptake (70). Subsequent clinical trials yielded conflicting results (71). Recently a synthetic agonist of the retinoid X receptor, bexarotene, was tested in a phase II trial in patients with radioiodine-unresponsive metastatic disease (72). After 6 wk of therapy with bexarotene, 300 mg daily, radioiodine uptake was partially restored in eight of 11 patients, but a clinical response with measurable tumor reduction was lacking. A similar rationale was the basis of studies of the histone deacetylase inhibitor depsipeptide (73). In a phase II trial in patients with radioiodine-unresponsive metastatic DTC, one of 14 patients exhibited dramatic restoration of uptake permitting therapeutic radioiodine administration. Significant cardiac toxicities were seen, however, including sudden death in one patient. The peroxisomal proliferator-activated receptor- $\gamma$  agonist rosiglitazone was evaluated for the potential of restoring radioiodine uptake in 10 patients with unresponsive metastases (74). In four patients, radioiodine uptake was visualized after 8 wk of therapy with oral doses up to 8 mg daily, but clinical response was limited. The lack of major clinical effect of restoring radioiodine uptake may have multiple explanations, including the acquisition by tumor cells of radiation resistance.

The orally available histone deacetylase inhibitor suberoylanilide hydroxamic acid was studied in 16 patients; no objective responses were reported, and most patients discontinued therapy due to adverse events (75). In a phase I trial, combining valproic acid, a histone deacetylase inhibitor, with 5-azacytidine, a DNA methylation inhibitor, was well tolerated; two patients with met-

astatic PTC demonstrated prolonged stable disease but radioiodine uptake was not assessed (76).

### Summary

Compared with the dismal historical track record, the recent proliferation of clinical trials for thyroid cancer has been remarkable. Targeting angiogenesis (and specifically VEGFRs) has produced the most impressive clinical responses to date in both DTC and MTC. Although most small-molecule VEGFR antagonists also inhibit RET, the efficacy of axitinib to induce objective responses in the absence of any anti-RET activity suggests that RET may not be as important a target for therapy as VEGFR. Unfortunately, eventual progression despite antiangiogenic VEGFR blockade suggests emergence of alternate pathways to promote tumor growth and metastasis (including fibroblast growth factor receptor, C-MET, and angiopoietins) (77). Further studies are necessary to explore the value of effective inhibition of the MAPK pathway downstream from oncogenic mutations as well as other pathways stimulating tumor growth and metabolism such as phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin signaling. Studies of therapies targeting nuclear mechanisms of gene regulation indicate that reversal of epigenetic or nuclear receptor abnormalities can potentially reestablish the cellular capacity to take up radioiodine, but the clinical significance of such an effect appears limited.

Comparison of outcomes among these various phase II trials is limited by variations in patient eligibility and response assessment. Among studies requiring progressive disease for eligibility, varying definitions of progression were used. Some studies report RECIST assessments with confirmation of response (19, 20, 25, 32, 40), whereas others do not (41). Independent, blinded radiological review was rarely reported (19, 20), despite recommendations as critical to minimize bias (78). Nonstandard response criteria have also been used in some trials (68, 69).

The overall goal of developing new treatments is to extend the duration of life without unduly harming the quality of that life. Presently no novel treatment has been demonstrated to improve survival for thyroid cancer patients. Toxicities of many of these new therapies, although less life threatening than cytotoxic chemotherapies, are common and can be dose limiting, and clinicians must be familiar with recognizing and managing the side effects if they intend to use these agents. Finally, the low rate of partial response, absence of complete responses, and emergence of resistance in all of the various monotherapy trials identify the need either to develop more effective single agents or to identify rational combinations of therapeutic targets (including cytotoxic chemotherapies) that have synergistic effectiveness without enhanced cross-toxicities.

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