Lenvatinib in Advanced, Radioactive Iodine-Refractory, Differentiated Thyroid Carcinoma

Kay T. Yeung1 and Ezra E.W. Cohen2

Abstract

Management options are limited for patients with radioactive iodine refractory, locally advanced, or metastatic differentiated thyroid carcinoma. Prior to 2015, sorafenib, a multtargeted tyrosine kinase inhibitor, was the only approved treatment and was associated with a median progression-free survival (PFS) of 11 months and overall response rate (ORR) of 12% in a phase III trial. Lenvatinib, a multitargeted inhibitor with high potency against VEGFR and FGFR demonstrated encouraging results in phase II trials. Recently, the pivotal SELECT trial provided the basis for the FDA approval of lenvatinib as a second targeted therapy for these patients. Median PFS of 18.3 months in the lenvatinib group was significantly improved from 3.6 months in the placebo group, with an HR of 0.21 (95% confidence interval, 0.4–0.31; P<0.0001). ORR was also significantly increased in the lenvatinib arm (64.7%) compared with placebo (1.5%). In this article, we will review the molecular mechanisms of lenvatinib, the data from preclinical studies to the recent phase III clinical trial, and the biomarkers being studied to further guide patient selection and predict treatment response. Clin Cancer Res; 21(24); 5420–6. ©2015 AACR.

Introduction

Thyroid carcinoma is the most common endocrine malignancy, with an estimated incidence rate of 1.35 per 100,000 people per year and a prevalence of approximately 600,000 people in the United States (1). Differentiated thyroid carcinoma (DTC) is a heterogeneous group which includes papillary (PTC), follicular, Hurthle cell, and poorly differentiated histologies. Despite generally good prognosis and cure rates of DTC with surgery, radioactive iodine (RAI) therapy, and thyroid stimulating hormone suppressive therapy, 10% to 20% of patients will develop recurrent or metastatic disease. Those who respond to RAI have excellent 10-year survival, but a minority will have poor survival of less than 5 years due to RAI-refractory, metastatic, aggressive disease. This review will focus on the recent approval of lenvatinib for the patient subset with locally recurrent or metastatic, RAI refractory DTC. The molecular pathways involved in tumorigenesis of DTC will be briefly reviewed. Other selected targeted therapies will also be mentioned for historical comparison.

Aberrant Molecular Pathways

Cancers evolve through a multistep tumorigenic process with alterations in crucial signaling pathways. Thyroid carcinoma is no exception. In fact, almost all (>96%) PTCs have at least one driver genomic alteration found in The Cancer Genome Atlas (TCGA; ref. 2). Thyroid cancer has a low density of somatic mutations and most aberrances involve the MAPK and the PI3K–mTOR pathways (reviewed in ref. 3). The signals ultimately converge in the nucleus, influencing transcription of oncogenic proteins including, but not limited to, NF-kB, hypoxia-induced factor 1 alpha unit (HIF1α), TGFβ, VEGF, and FGF. This leads to enhanced tumor proliferation, differentiation, survival, angiogenesis, invasion, and metastasis (Fig. 1). Genetic alterations in this pathway are usually mutually exclusive and thus supporting their dominant role of tumorigenesis.

Binding of growth factors to transmembrane receptor tyrosine kinase (RTK) such as ret proto-oncogene (RET), platelet-derived growth factor receptor (PDGFR), EGFR, stem cell factor receptor (SCFR), or also known as cKIT, FGFR, or VEGFR results in receptor dimerization and autophosphorylation. Through a series of adaptor proteins, ret sarcoma (RAS) is activated and B-Raf proto-oncogene serine threonine kinase (BRAF) is recruited and activated at the plasma membrane. Activated BRAF then phosphorylates MAPK/extracellular regulated MAPK (ERK) kinase (MEK) which in turn phosphorylates and activates ERK. ERK translocates into nucleus where it stimulates transcription of genes involved in cell proliferation, differentiation, and survival.

The PI3K–mTOR pathway is a parallel signaling pathway with cross talk with the MAPK pathway. PI3K can be activated by either RTK or RAS. Activated PI3K then activates alpha serine/threonine protein kinase (AKT) which activates mTOR. mTOR then translocates into the nucleus and affects transcription of genes related to cell growth, angiogenesis, cell motility, and invasion.

On the basis of the recently published TCGA data on more than 400 PTCs, genomic alterations can be divided into two major clusters that are dominated by either BRAF V600E or RAS mutations. BRAF V600E–like PTCs (BVL-PTCs) carry aberrancies including BRAF V600E, or fusions of BRAF or RET, and anaplastic lymphoma kinase (ALK). They represent a heterogeneous subset, enriched for classical and less differentiated tall cell histologic subtype of PTC, with advanced stage and higher recurrence risk, and predominately activating MAPK signaling. BVL-PTCs is associated with high levels of expression of genes downstream of MAPK and reduced expression of proteins involved in iodine...
metabolism which may explain the mechanism for high RAI resistance (2). On the other hand, the RAS-like mutation subgroups (RL-PTC) are more homogenous, enriched for highly differentiated follicular tumors, lower risk of recurrence and RAI refractoriness, and with activation of both the MAPK and PI3K–mTOR pathways.

Tumor angiogenesis also plays a key role in tumor growth, survival, and development of metastasis. VEGF binds to VEGFR which activates both the MAPK and PI3K–mTOR pathways. Overexpression of VEGF is prevalent in DTCs and is associated with increased tumor size, extrathyroidal extension, and BRAF mutations (4, 5). It was found that VEGF may signal in an autocrine loop in DTCs and blockade of either VEGF or its receptors with neutralizing antibodies may significantly increases apoptosis in VEGFR-positive thyroid cancer cell lines (6). VEGF immunohistochemistry (IHC) was shown as a marker for metastasis spread in PTC where metastatic papillary carcinoma had a higher IHC staining than nonmetastatic papillary cancer.

Figure 1. Two receptor pathways involved in pathogenesis of DTC. Activation of RTK such as RET, PDGFR, EGFR, FGFR, and VEGFR by growth factors leads to downstream effectors mainly through the MAPK (left) or PI3K–mTOR (right) signal transduction pathways to increase tumor proliferation, survival, angiogenesis, and metastasis. Selective kinase inhibitors being studied in differentiated thyroid cancer are illustrated. Lenvatinib, along with sorafenib, axitinib, pazopanib, sunitinib, and vandetanib, exert inhibitory action at the tyrosine receptor level. BRAF can be inhibited by vemurafenib and sorafenib, whereas MEK can be inhibited by selumetinib. Finally, everolimus, an mTOR inhibitor, is also being studied.
<table>
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<tr>
<th>Drug</th>
<th>Molecular targets</th>
<th>Number of patients</th>
<th>Dose</th>
<th>Phase III trials</th>
<th>Phase II trials</th>
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</thead>
<tbody>
<tr>
<td>Sorafenib (Nexavar; Bayer)</td>
<td>RET VEGFR1 VEGFR2 VEGFR3 BRAF Other</td>
<td>417</td>
<td>400 mg twice daily</td>
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<td>Lenvatinib (Lenvima; Eisai)</td>
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<td>32</td>
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<td>Everolimus (Afinitor; Novartis)</td>
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<td>X X X X</td>
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<tr>
<td>Everolimus + sorafenib</td>
<td>RET VEGFR1 VEGFR2 VEGFR3 BRAF Other</td>
<td>19 DTC</td>
<td>5 mg daily, 400 mg twice daily</td>
<td>X X X X</td>
<td>mTOR</td>
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<tr>
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Abbreviations: CR, complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.
mice (8). Macroglobin FGFR-4 inhibition resulted in proliferation arrest of expressed in aggressive rapidly proliferating tumor types. Pharoehorst well-differentiated tumor types, whereas FGFR-4 was be involved in thyroid cancer. FGFR-1 and -3 were expressed in follicular thyroid carcinoma-derived cell growth in xenograft mice (8).

**Multitargeted Kinase Inhibitors**

Development of oral kinase inhibitors to directly inactivate the driving tumorigenic pathways with manageable toxicity profiles has changed the treatment landscape for patients with refractory DTC. Table 1 summarizes the current clinical trials evaluating various targeted therapies for the treatment of DTC.

Sorafenib was among the first MKI to demonstrate efficacy and was approved for use in locally recurrent or metastatic progressive DTC refractory to RAI in November 2013. Sorafenib targets RET/PTC, VEGFR 1–3, and BRAF. Two phase II trials at a dose of 400 mg twice daily showed partial response (PR) rates of 15% to 23% (9, 10). Median PFS from the two studies were between 15 and 20 months (9, 10). A subsequent phase III, double-blinded, randomized controlled trial (RCT) showed improvement in the primary endpoint of median PFS of 10.8 months with sorafenib compared with 5.8 months on placebo (HR, 0.59; 95% confidence interval [CI], 0.45–0.76; ref. 11). This study included 417 patients with locally advanced or metastatic DTC progressing within the past 14 months of study entry. Subgroup analysis reported similar treatment response regardless of BRAF or RAS mutation status. Adverse events (AE) occurred in 98% of the patients with most frequent events requiring treatment which included palmar–plantar erythrodysesthesia, diarrhea, alopecia, and skin rash or desquamation. These events led to dose interruption in 66% of patients, dose reduction in 64%, and discontinuation in 18%.

Sunitinib inhibits RET/PTC subtypes 1/3 and VEGFR 1–3. It was studied in an open label phase II trial in 31 patients with progressive DTC at 50 mg daily, 4 weeks on and 2 weeks off. Preliminary reports demonstrated a PR in 13% of patients and stable disease (SD) in 68% with response duration of more than 12 weeks in 17% of patients (12). In another phase II trial using sunitinib 37.5 mg daily in 35 patients with FDG-PET avid, RAI refractory, metastatic DTC (28/35) and MTC, overall response rate (ORR) was 31% with complete response (CR) in 3% of the patients, PR in 28%, and SD in 46% (13).

Pazopanib inhibits VEGFR, FGFR, and PDGFR. In a phase II trial of 37 patients with refractory, progressive metastatic DTC, PR was achieved in 49% with pazopanib 800 mg daily (14). PFS at 1 year was 47% and the median PFS was 11.7 months. The median overall survival (OS) at 1 year was 81%. Interestingly, serum levels of pazopanib were higher in patients who obtained PR than in those who did not. Major AEs include fatigue, skin hypopigmentation, diarrhea, and nausea and 43% of patients required dose reduction. Of note, the FDA placed a black box warning on this medication due to severe and fatal hepatotoxicity observed in renal cell carcinoma patients.

Axitinib inhibits VEGFR 1–3. In a multicenter phase II study with 45 patients with advanced or metastatic DTC, PR was achieved in 31% and SD in 38% with axitinib 5 mg twice daily (15). Median PFS was 18 months with median follow-up of 16.6 months. The most common AEs were hypertension, stomatitis, fatigue, and diarrhea. Only 13% of patients discontinued axitinib due to AEs. In a second phase II trial, the overall ORR was 35% with (18 PR) and 18 patients with stable disease for more than 16 weeks with same dose of axitinib. Median PFS was 16.1 months with median OS of 27.2 months. Most common AEs were similar—fatigue, dyspnea, diarrhea, decrease weight, pain in extremity, hypertension, decreased appetite, palmar–plantar erythrodysesthesia, hypocalcemia, and myalgia. Quality of life was maintained during treatment with axitinib without any deterioration or interference in daily life caused by symptoms (16).

Vandetanib inhibits VEGFR2, RET/PTC subtype 1 and 3, and FGFR. In a phase II trial of 145 patients with locally advanced or metastatic DTC, vandetanib 300 mg daily led to improvement in PFS from 5.8 months in placebo group to 11.1 months in vandetanib group (17). ORR and OS were higher in the vandetanib arm but did not reach statistical significance. Subgroup analysis showed those with papillary thyroid cancer had the best response, whereas those with follicular or poorly differentiated carcinoma had the worst response. The most common toxicities were QT prolongation, diarrhea, asthenia, and fatigue. A large phase III RCT is currently ongoing.

**Selective BRAF Inhibitors**

Vemurafenib is a selective inhibitor of BRAF V600E mutant. In a phase II trial of 51 patients with progressive RAI-refractory BRAF V600–mutant PTC, half of the enrolled patients were previously treated with antiangiogenic kinase inhibitors such as sorafenib. Preliminary results showed PR of 35% in the TKI treatment–naïve group with median PFS of 15.6 months compared with PR of 29% and PFS of 6.3 months in the group previously treated with TKI (ref. 18, NC101286753, NO25530). AEs included rash, weight loss, fatigue, and hyperbilirubinemia.

Dabrafenib is another BRAF-specific inhibitor and was effective in 14 patients with BRAF V600E–mutant thyroid carcinoma refractory to RAI in a phase I study (19). PR achieved in 29% of patients and SD in 50%. A phase II study comparing dabrafenib versus dabrafenib plus MEK inhibitor trametinib is ongoing.

**Other Targeted Therapies**

Sелуметиниб, a selective MEK 1/2 inhibitor, was shown to have radiosensitizing activity in patients with previously RAI-refractory PTC achieving increased RAI uptake after selumetinib in a small pilot phase I study (20). In a phase II trial of 32 RAI-refractory patients administering selumetinib 100 mg twice daily, PR was achieved in 3% of patients and SD in 66% (21).

Everolimus, an inhibitor of mTOR, had poor efficacy as monotherapy in a phase II study at 10 mg daily with PR in 4% of 25 enrolled patients and PFS of 43 weeks (22). However, a second trial investigating the combination of everolimus and sorafenib is ongoing and preliminary results showed synergistic effect with PR

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achieved in 58% of patients and SD in 37% when a combination of everolimus 5 mg daily and sorafenib 400 mg twice daily was given (23).

**Lenvatinib**

**Preclinical data**

Lenvatinib has *in vitro* kinase inhibitory activity strongly against VEGFR 1–3, FGFR 1–3, RET, and cKIT with half maximal inhibitory concentration (IC₅₀) of 2.3–4.7 nmol/L, 27–61 nmol/L, 12 nmol/L, and 6.4 nmol/L, respectively (24). This is in contrast to sorafenib which has weaker inhibitory activity against VEGFR 1–2 (IC₅₀ = 16–21 nmol/L) and FGFRs (IC₅₀ = 150–340 nmol/L). *In vitro*, lenvatinib was shown to inhibit VEGF- and FGFR2-driven proliferation and tube formation of HUVECs via angiogenesis. However, lenvatinib did not show potent *in vitro* antiproliferative activity for 9 of 11 human thyroid cancer cell lines, except in the RO82-W-1 thyroid cancer cell line which highly overexpressed FGFR1. Lenvatinib was also shown to significantly inhibit the growth of KP-1/VEGF tumor cell line which was enhanced by VEGF-driven angiogenesis. Despite the *in vitro* studies, lenvatinib showed significant antitumor activity in five DTC xenograft nude mouse models (25). This supports the notion that lenvatinib specifically targets the microvascular environment dependent on angiogenic VEGFR and FGFR signaling pathways rather than tumor proliferation pathways or cell cycle. Expectedly, antitumor activity of lenvatinib was shown to be highly associated with vascular score in a panel of 19 human tumor xenograft models consisting of different cancer types.

**Clinical trials**

In a phase II trial, 58 patients with advanced, RAI refractory, DTCs who had disease progression during the previous 12 months received lenvatinib 24 mg daily until disease progression, toxicity, withdrawal, or death. After more than 14 months of follow-up, ORR was 50% (95% CI, 37%–63%) with only PR but median response duration of 12.7 months. PFS was 12.6 months (95% CI, 9.9–16.1 months; ref. 26).

The promising phase II findings prompted a follow-up phase III study of lenvatinib in differentiated cancer of the thyroid (SELECT trial) (2). As a result of this pivotal study demonstrating dramatic efficacy and manageable side effects of lenvatinib compared with placebo, FDA expedited approval of lenvatinib for the treatment of patients with locally recurrent or metastatic RAI-refractory DTCs. This is the second drug approved for the patient population.

The SELECT trial was a randomized, double-blinded, placebo controlled study with 392 patients from 21 different countries with progressive refractory DTCs. These patients had proven disease progression within the previous 13 months by independent radiology review based on the RECIST v1.1 criteria, were refractory to RAI treatment, and had up to one prior antiangiogenic therapy. A majority of patients (96%) had good performance status with ECOG of 0–1 and did not have prior antiangiogenic therapies (75%). Almost all of the patients with metastatic disease had pulmonary involvement (99%). Patients were randomized in 2:1 fashion, after stratification by geographic region (Europe, North America, or other), age (≥65 years old or >65 years old), and prior antiangiogenic therapy, into the lenvatinib arm receiving lenvatinib 24 mg daily (261 patients) and the placebo arm (131 patients). Crossover from placebo to open label lenvatinib was allowed based upon disease progression.

The SELECT trial met its primary endpoint of an improvement in PFS assessed on the basis of the RECIST v1.1 criteria. Median PFS improved significantly from 3.6 months in placebo group to 18.3 months in lenvatinib group with an HR of 0.21 (95% CI, 0.4–0.31; P < 0.0001; ref. 2). Improvement in PFS was seen in all of the predefined subgroups. ORR was seen in 64.8% patients treated with lenvatinib; 1.5% of the study subjects achieved complete response, whereas 63% achieved PR. The median time to response was 2 months (95% CI, 1.9–3.5 months). Response for lenvatinib was long lasting with 75% of responders having an objective response duration of more than 9.4 months. The median OS has not been reached. Most common grade 3 or more AEs were hypertension (42%), proteinuria (10%), weight loss (10%), and diarrhea (8%). Other less common but serious AEs include heart failure, thromboembolism, hepatic and renal failure, bowel perforation, and QT prolongation. Dose interruption was necessary in 82% of the patients, dose reduction in 67%, and discontinuation in 14%.

In a subgroup analysis, a numeric trend towards improved PFS for patients receiving lenvatinib first-line, as compared with those receiving it after a prior VEGF-targeted therapy. Sorafenib was the most commonly used prior anti-VEGF therapy (77%), then sunitinib (9%) and pazopanib (5%). Among lenvatinib-treated patients, anti–VEGF-naive patients demonstrated a comparable PFS benefit to that of prior anti–VEGF–treated patients. In anti–VEGF-naive patients, a median PFS of 18.7 months was seen in the lenvatinib group versus 3.6 months in placebo group. In anti–VEGF-treated patients, a median PFS of 15.1 months was seen in the lenvatinib group versus 3.6 months in the placebo group. The ORR was also similar between both groups, with 65.6% in the anti–VEGF-naive patients compared with 62.1% in the anti–VEGF-treated patients. Median times-to-response were also similar with 1.9 months and 2.0 months in anti–VEGF-naive and prior anti–VEGF-treated patients, respectively.

**Biomarkers**

Biomarkers have been gathering interest in early prediction of treatment efficacy, toxicities, and resistance in DTC. In particular, circulating angiogenic factors (CAF) have been under heavy investigations. Vascular damage or elevated tumor hypoxia during treatment are thought to elicit an acquired compensatory mechanism of upregulation of alternative proangiogenic factors and downregulation of angiogenic inhibitors to maintain vascular integrity. Therefore, levels of proangiogenic factors such as VEGF and stromal cell-derived factor 1 alpha (SDF1A) from tumor tissues increases in the presence of efficacious VEGF inhibition. On the contrary, level of circulating angiogenetic inhibitors such as angiopeptin-2 (ANG-2) decrease.

In a phase I study with biomarkers, in the presence of lenvatinib, proangiogenic SDF1A and VEGF levels significantly increased and correlated with treatment response (27). For the SELECT trial, blood samples were collected at baseline, cycle 1 day 15, and day 1 of subsequent cycles. VEGF level was again found to be increased and correlated with tumor shrinkage. On the other hand, levels of two inhibitory CAFs—ANG-2 and angiopoietin receptor (TIE-2)—decrease with treatment and are inversely correlated with tumor shrinkage (2). PFS HR of lenvatinib to placebo for patients with low ANG-2 (HR, 0.08; 95% CI, 0.04–0.17) was less than those with high ANG-2 (HR, 0.24; 95% CI, 0.18–0.33).
regardless of baseline CAF levels or BRAF/RAS mutational status. Finally, among lenvatinib-treated patients with disease response, almost all patients had a decrease in levels of ANG-2, and TIE-2 at cycle 2 compared with baseline. An increase in levels of ANG-2, and TIE-2 was observed to be an early indication for disease progression. Further analyses using these biomarkers may identify those with most likely will benefit from lenvatinib.

Circulating tumor or epithelial cells (CEC) have been implicated as prognostic biomarker in metastatic breast, prostate, and colorectal cancer (28–30). This is based on the idea that disseminated tumor cells can represent a real time reflection of tumor activity and the ability for dissemination in the body. An improved therapeutic effect of lenvatinib was correlated with the number of CECs with expression of cKIT, a factor important in survival of disseminated tumor cells in new host environment (31). In a phase 1 dose escalation study with 27 patients with DTCs, lenvatinib led to a significantly decreased number of CKIT (+) CECs but not CKIT(−) CECs (31). Patients with excellent response to lenvatinib had a significant change from baseline cKIT (+) CECs within 14 days suggesting that antiangiogenic activity correlated with antitumor activity in DTC.

Conclusion and Future Directions

RAI-refractory recurrent DTCs is a heterogeneous group of thyroid cancer with diverse histology, disease progression, and genomic alterations. Overall survival is usually poor for those with aggressive metastatic disease due to limited treatment options. Management of this unique group of patients is improving with better understanding of the genomic landscape of somatic aberrations and development of targeted therapies. The most recent example is the impressive result from the SELECT trial demonstrating improved ORR and PFS in subjects who received lenvatinib. The timely approval of lenvatinib now offers patients another chance at disease control and survival. Ongoing phase II or III trials using other targeted therapies will hopefully continue to expand the treatment options beyond the two currently approved drugs. At this time, there are no head-to-head comparisons between sorafenib and lenvatinib in the first-line setting. However, it appears that lenvatinib is quite promising with PFS of 18.3 months and HR of 0.21 compared with sorafenib which had PFS 10.8 months with HR 0.59. Toxicity profiles of the two medications are slightly different and may be the deciding factor for some patients.

Many questions remain to be addressed to optimize outcome. First, the specific subset of patients who may most benefit from treatment initiation needs to be better defined. For example, will early treatment benefit patients with asymptomatic low volume disease despite potential treatment adverse events? Development of clinical prognostication using tumor molecular signatures using next generation sequencing to differentiate those with aggressive disease may help guide these pretreatment decisions. Second, the appropriate sequence and combination of various targeted therapies to achieve superior response and survival without significant toxicity remains to be determined. As many more targeted agents actively under investigations and potential wide repertoire of available options, identification of the driver somatic alterations may guide the precise choice of therapy targeting the appropriate components of the MAPK or mTOR pathway. Biomarkers such as CEC or CAF may further predict treatment response. In summary, lenvatinib represents an important stride made against RAI-refractory DTCs. Further research in the molecular mechanisms of thyroid cancer continues to be crucial in addressing challenges of maximizing clinical benefits and limiting toxicities in these patients.

Disclosure of Potential Conflicts of Interest

E.E.W. Cohen reports receiving speakers bureau honoraria from Eisai. No potential conflicts of interest were disclosed by the other author.

Authors’ Contributions

Conception and design: E.E.W. Cohen
Development of methodology: E.E.W. Cohen
Writing, review, and/or revision of the manuscript: K.T. Yeung, E.E.W. Cohen

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References


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