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The Newest Targeted Therapeutics for Thyroid Cancer: Development of Sorafenib and Lenvatinib

Mark Steven Cohen*

Department of Surgery, Section of General Surgery, Division of Endocrine Surgery University of Michigan Comprehensive Cancer Center, 2920K Taubman Center,1500 East Medical Center Drive, SPC 5331 Ann Arbor, Michigan, USA

***Corresponding author:** Mark Steven Cohen, Department of Surgery, Section of General Surgery, Division of Endocrine Surgery University of Michigan Comprehensive Cancer Center, 2920K Taubman Center,1500 East Medical Center Drive, SPC 5331 Ann Arbor, Michigan, USA, Tel: 734 - 615-4741; E-mail: cohenmar@umich.edu

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Abstract

Sorafenib was specifically developed using high-throughput screening and structure-activity relationships to target important pathogenic pathways in thyroid cancer. Initially developed to target rapidly accelerated fibrosarcoma (RAF) kinase, it was also found to inhibit several key receptor tyrosine kinases (RTKs) within the mitogen-activated protein kinase (MAPK) pathway. Preclinical and clinical studies demonstrated significant efficacy in differentiated thyroid cancer (DTC), and following the phase III DECISION trial comparing sorafenib to placebo in DTC, it received Food and Drug Administration (FDA) approval in November 2013 for treatment of advanced, radioactive iodine-refractory DTC. Sorafenib is shown to significantly improve progression free survival (PFS) an average of 10.8 months (hazard ratio [HR] 0.59, 95% CI, 0.45-0.76; P<0.0001), although an overall survival (OS) benefit has yet to be proven. An additional targeted RTK inhibitor, lenvatinib, was recently approved by the FDA in February 2015 for advanced, RAI-refractory DTC following the phase III SELECT trial. While lenvatinib has a higher average PFS of 18.3 months (HR 0.21; 99% CI, 0.14-0.31; P<0.001), as well as higher complete and partial response rates, it too has yet to prove an OS benefit. While there is clear evidence of the clinical benefit for both sorafenib and lenvatinib treatment in advanced RAI refractory patients, it is unclear which may be superior. However, each has a different side effect profile that may help guide initial treatment decisions in an individualized approach. Additionally, because lenvatinib demonstrated a similar increase in PFS for those who were previously treated with RTK inhibitors like sorafenib, lenvatinib is a powerful addition to the treatment of advanced DTC and creates another option for either initial therapy or secondary therapy following disease progression.

Keywords: Differentiated thyroid cancer; Sorafenib; Lenvatinib; Thyroid cancer; Thyroid cancer treatment; Tyrosine kinase inhibitor

Introduction

Differentiated thyroid cancer (DTC) includes papillary, follicular and Hürthle cell variants and has an overall excellent prognosis with 5-year overall survival (OS) approaching 98% [1]. Definitive standard treatments depend on disease stage, and include radioactive iodine (RAI) ablation, surgical resection and thyroid-stimulating hormone (TSH) suppression [2]. Despite optimal therapy, up to 25% of patients will have recurrent disease, with 7% distant recurrence, and importantly over 30% of this distant metastasis will be RAI-non-avid [3]. With over 600,000 people in the US affected by thyroid cancer, and 62,500 cases projected for 2015 [1], this highlights the need for additional therapies to treat this important group of patients that cannot undergo RAI ablation. Advances in our understanding of thyroid cancer pathogenesis has highlighted key receptor tyrosine kinases (RTKs) and protein kinases within the mitogen-activated protein kinase (MAPK) pathway, which have enabled the discovery of targeted therapies such as sorafenib. Through a multi-faceted approach using combinatorial chemistry, high-throughput screening and structure activity relationships, lead molecules targeting target rapidly accelerated fibrosarcoma (RAF) kinase were identified, and then further refined using a mechanistic immunoprecipitation assay to detect inhibitory activity against BRAF-1[4]. Through pre-clinical studies, sorafenib was found to not only inhibit BRAF-1, but also the BRAF V600E mutation and additional RTKs, including vascular endothelial growth factor receptor 1-3 (VEGFR1-3), platelet derived growth factor receptor (PDGFR), FMS-like tyrosine kinase 3 (FLT3), and ret proto-oncogene (RET). This inhibition decreases the downstream oncogenic effects of MAPK and mechanistic target of rapamycin (mTOR) on cellular growth, proliferation, angiogenesis and survival. Following initial phase I and II trials, the pivotal multi-center, randomized, double-blind phase III DECISION trial demonstrated a significant clinical effect of sorafenib (400 mg twice daily) compared to placebo. Sorafenib treatment resulted in a 12.2% (n=25) partial response rate versus 0.5% (n=1) for placebo, and doubled progression free survival (PFS) from 5.8 months for placebo to 10.8 months in the treatment arm (hazard ratio [HR] 0.59, 95% CI, 0.45-0.76; P<0.0001) [4]. When phase II trials are included, the partial response rate overall was 20.7% (95% CI, 14.1-27.2) and the average PFS increased to 16.1 months (95% CI, 13.3-18.8) [5]. Although there was no demonstrable overall survival (OS) benefit, the significant increase in PFS lead to Food and Drug Administration (FDA) approval for sorafenib in November 2013 for the treatment of advanced, RAI refractory DTC.

Recently, in February 2015 the small-molecule RTK inhibitor lenvatinib was also FDA approved for treatment of progressive, RAI refractory DTC [6]. Lenvatinib inhibits multiple RTKs including VEGFR1-3, fibroblast growth factor receptor 1- 4 (FGFR1-4), PDGFR-alpha, RET and KIT, which similar to sorafenib, leads to downstream inhibition of cellular proliferation, angiogenesis and survival. The key multi-center, randomized, double-blind, placebo-controlled phase III

SELECT trial (24 mg daily lenvatinib, 28-day cycle) demonstrated a significant 18.3 month PFS compared to 3.6 months for placebo (HR for progression or death 0.21; 99% CI, 0.14 - 0.31; P<0.001), with a 1.5% (n=4) complete response rate and 64.8% (n=169) partial response rate, versus 0% (n=0) and 1.5% (n=2) for placebo, respectively [7]. Unfortunately, there was no improvement in OS (HR 0.62), though both the DECISION and SELECT trials included patient cross-over from placebo, which complicates this outcome.

	Decision	**Select**
	Brose et al. 2014 [4]	[7]
	Response Rate	
Number of DTC Patients Evaluated	n=196	n=261
Complete Response	0	0.015
Partial Response Rate	0.122	0.648
Stable Disease	0.418	0.23
Progressive Disease	0.46	0.069
Median PFS - Months (95% CI)	10.8 (HR 0.59)	18.3 (HR 0.21)
	Overall Incidence Of Adverse Events (Grade 3/4)	
Number of Patients	**n=207**	**n=261**
Hand-Foot Skin Reaction	76% (20%)	32% (3%)
Diarrhea	69% (6%)	59% (8%)
Alopecia	67% (0%)	11% (0%)
Rash/Derm Other	50% (5%)	16% (0.4%)
Fatigue	50% (6%)	59% (9%)
Weight Loss	47% (6%)	46% (10%)
Nausea	43% (0%)	41% (2%)
Hypertension	41% (10%)	68% (42%)
Anorexia	32% (2%)	50% (5%)
Arthralgia/Myalgias	14% (0.5%)	18% (0%)
Hypocalcemia	19% (6%)	7% (3%)
Mucositis/Stomatitis	23% (1%)	36% (4%)
Overall Deaths	6% (n=12)	7.7% (n=20)
Treatment Related	0.5% (n=1)	2.3% (n=6)

Table 1: Comparison of overall response rates and adverse events of sorefenib and lenvatinib phase iii trials.

Compared to the sorafenib DECISION trial (Table 1), lenvatinib demonstrated an increased PFS length (18.3 months vs 10.8 months) as well as a higher complete (1.5% vs 0%) and partial response rate (64.8% vs 12.2%). While these results make lenvatinib an exciting new DTC therapy, it is not without its own drawbacks. When looking at the adverse effect profile of lenvatinib, 97.3% of patients had at least one treatment-related adverse effect, while 75.9% had adverse effects grade 3 or higher. The most common adverse effects with lenvatinib were hypertension (68%, 42% grade ≥ 3), diarrhea (59%, 8% grade ≥ 3), fatigue/asthenia (59%, 9% grade ≥ 3), decreased appetite (50%, 5% grade ≥ 3), decreased weight (46%, 10% grade ≥ 3) and nausea (41%, 2% grade ≥ 3). Additionally, there were a total of 20 deaths (7.7%), of which 6 were determined to be treatment related (2.3% overall) [7]. It is important to note that this adverse effect profile of lenvatinib differs from sorafenib (Table 1). In the DECISION trial, although 98.6% of patients taking sorafenib had an adverse event, only 37.2% had one or more severe events (grade ≥ 3) compared to 75.9% for lenvatinib. The most common side effects were hand-foot skin reaction (76%, 20% grade ≥ 3), diarrhea (69%, 6% grade ≥ 3), alopecia (67%, 0% grade ≥ 3), rash or desquamation (50%, 5% grade ≥ 3), fatigue (50%, 6% grade ≥ 3) and decreased weight (47%, 6% grade ≥ 3). There were also fewer overall deaths (n=12, 5.8%), of which only 1 was deemed to be treatment related (0.5% overall) [4].

There are several important considerations with lenvatinib use that where highlighted by the FDA during their New Drug Application review [8]. Lenvatinib demonstrated similar treatment effects on PFS for those who did [[HR 0.22 (95% CI 0.12, 0.41)] and did not [HR 0.20 (95% CI 0.14, 0.27)] receive prior anti-VEGF therapy, such as sorafenib, and was given priority review in part due to this effect because disease progression for those with prior-VEGF therapy represents an unmet medical need. Additionally, the SELECT trial is the lone phase III randomized, controlled trial with lenvatinib in DTC, however, the FDA granted approval without the need for additional trials due to the large, consistent PFS effect with very low chance of type I error across multiple subsets of treated patients. A third consideration was whether 24 mg daily dosing was the optimal dose from a risk-benefit standpoint, as 68% of patients required dose reduction due to an adverse event. Although 27 patients who crossed over from placebo were treated with 20 mg lenvatinib daily, there were too few to provide conclusions. Therefore, the FDA is requiring the developer (Eisai Inc) to perform a post-marketing clinical trial in order to investigate the anti-tumor treatment effect of lower doses in relation to frequency of severe adverse reactions [8].

Conclusion

Looking at the primary outcomes between sorafenib and lenvatinib, it appears that lenvatinib in DTC may have a more robust tumor response and PFS despite neither treatment demonstrating an improvement in OS. However, without a head-to-head randomized trial this comparative finding can only be deemed as speculative. While both drugs are efficacious in this disease, there are several major differences. First, lenvatinib was shown to provide a significant PFS effect for patients who had already been treated with anti-VEGF therapy (such as sorafenib), whereas sorafenib has not been significantly studied in this population. Secondly, there are significant differences between these drugs' toxicity profiles. Lenvatinib had an overall higher severe adverse effect rate compared to sorafenib, but the effects were effectively managed with supportive care or dose modification as only 14.2% of patients discontinued treatment, whereas 18.8% discontinued treatment with sorafenib. Also, lenvatinib had higher rates of hypertension, decreased appetite and nausea, whereas sorafenib treatment resulted in higher rates of hand-foot skin reaction, alopecia and rash. Diarrhoea and fatigue were common among both treatments. Lastly, there remains some uncertainty

regarding the optimal dosing of lenvatinib to provide the greatest risk-benefit profile, and an additional clinical trial is expected to clarify optimal dose.

When discussing the risk-benefit stratification with patients who have advanced, RAI refractory DCT, an individualized approach is warranted. Comparing risk profiles for differences in adverse effects between these two drugs may help guide the initial treatment regimen, in addition to considerations of each individual patient's disease burden, symptoms, comorbidities, prognosis, cost of treatment and prior therapies. What is clear is that the approval of lenvatinib gives a powerful new option when treating these patients regardless of initial treatment. As multiple other therapies, including RTK inhibitors, BRAF inhibitors, mTOR inhibitors and re-differentiation agents, progress in clinical trials [9] and new, efficacious targeted agents are being developed pre-clinically; patients will have expanded treatment options available in the event of disease progression that may provide additional benefit to the course of their disease.

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