Cancer Treatment Reviews 42 (2016) 47–55

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Lenvatinib: Role in thyroid cancer and other solid tumors

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ARTICLE INFO

Article history:
Received 20 March 2015
Received in revised form 3 November 2015
Accepted 12 November 2015

Keywords:
Refractory
Differentiated
Multikinase
Medullary
Survival
Advanced

ABSTRACT

Despite recent breakthroughs in treatment of advanced thyroid cancers, prognoses remain poor. Treatment of advanced, progressive disease remains challenging, with limited treatment options. Small-molecule tyrosine kinase inhibitors, including vandetanib, cabozantinib, sorafenib, and lenvatinib, which are now FDA-approved for thyroid cancer, have shown clinical benefit in advanced thyroid cancer. Lenvatinib is approved for treatment of locally recurrent or metastatic, progressive, radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC). It has been studied in phase II and III trials for treatment of advanced RAI-refractory DTC, and in a phase II trial for medullary thyroid cancer (MTC). Lenvatinib targets vascular endothelial growth factor receptors 1–3 (VEGFR1–3), fibroblast growth factor receptors 1–4 (FGFR-1–4), RET, c-kit, and platelet-derived growth factor receptor α (PDGFRα). Its antitumor activity may be due to antiangiogenic properties and direct antitumor effects. Lenvatinib has demonstrated antitumor activity in a variety of solid tumors, including MTC, in phase I and II clinical trials. In a phase II study in advanced RAI-refractory DTC, lenvatinib-treated patients achieved a 50% response rate (RR), with median progression-free survival (PFS) of 12.6 months. In a phase III trial in RAI-refractory DTC, median PFS in lenvatinib-treated patients was 18.3 months, with a 65% overall RR, versus 3.6 months in placebo-treated patients, with a 2% RR. Adverse events occurring in >50% of patients included hypertension, diarrhea, fatigue/asthenia, and decreased appetite. Lenvatinib is a promising new agent for treatment of patients with advanced thyroid cancer.

Introduction

The incidence of thyroid cancer is increasing in the United States [1]. Average annual percentage increases from 2006 to 2010 for thyroid cancers were 5.4% for men and 6.5% for women, some of the largest annual increases among cancers [1]. Thyroid cancer can be divided into 3 primary histologic types—differentiated, medullary, and anaplastic—and these histologic subtypes have different characteristics and prognoses. Differentiated thyroid cancers (DTCs) account for about 95% of all thyroid cancer cases and can be subdivided into 2 major histologic subtypes (papillary thyroid carcinoma and follicular thyroid carcinoma) [2]. Medullary thyroid cancers (MTCs) account for about 4% of all thyroid cancers [2–4]. Sporadic MTC usually presents in the 5th or 6th decade of life, and these make up approximately 80% of cases, while hereditary MTC typically presents in the 2nd–3rd decade of life [3–5]. Anaplastic thyroid cancers (ATCs) are the most aggressive form of the disease. Anaplastic thyroid cancers account for <2% of all thyroid cancers and typically occur in older patients, with a mean age of 71 years [2].

Across all thyroid cancers, 5-year relative survival rates are high at about 98%; however, about 30% of patients have disease recurrence [1,2]. Unfortunately, the prognosis remains poor for patients with unresectable, advanced, or refractory DTC and MTC, with median 10-year survival rates of 40–42%; survival rates are dismal for ATC patients, who often die within 1 year of diagnosis [2,4,6].

Currently, treatment of recurrent DTC and MTC may include surgical resection of cervical disease and localized therapies targeted at metastatic sites. Radioactive iodine (RAI) therapy is used in DTC; however, many patients are refractory to RAI, and alternative options for treatment remain limited [5].

Treatment with small molecule inhibitors or systemic therapy may be considered for thyroid cancer patients, in particular, those with progressive, clinically significant, or symptomatic disease which cannot be managed with other strategies [5]. Vandetanib and cabozantinib are FDA approved for patients with progressive, metastatic, or unresectable MTC. Sorafenib and lenvatinib are FDA approved for patients with RAI-refractory DTC.

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http://dx.doi.org/10.1016/j.ctrv.2015.11.003
0305-7372/

Limitations in the management of thyroid cancer beyond surgery

Although radioiodine ablation following thyroidectomy is standard treatment in patients with metastatic DTC, about 25–50% of patients with locally advanced or metastatic disease become refractory to RAI therapy [7,8]. Cytotoxic chemotherapy has a limited role in the management of DTC or MTC [8] and is associated with low response rates (RRs) and significant side effects. Cytotoxic chemotherapeutic agents have included doxorubicin, cisplatin, bleomycin, and etoposide [9]. Conventional cytotoxic chemotherapy has not been shown to prolong survival.

External beam radiation therapy (EBRT) has a limited role in patients with advanced DTC or MTC, and it is not commonly used [10]. Retrospective studies have reported variable findings, and the role of EBRT remains controversial. Current National Comprehensive Cancer Network (NCCN) and American Thyroid Association (ATA) guidelines suggest that EBRT should be considered for patients with unresectable locally advanced DTC or MTC to optimize locoregional control [5,11,12]. EBRT may also be considered for patients with distant metastases, which are painful or threatening vital structures, such as the brain and spinal cord. Treatment options are limited for those with progressive disease that cannot be managed with localized therapies such as radiation, which underscores the need for new treatment options in patients with advanced thyroid cancer. A comprehensive review of localized therapies for the management of metastatic, RAI-refractory DTC is beyond the scope of this review and can be found elsewhere [13].

Systemic therapy: rationale for targeting tyrosine kinases

There are a number of intracellular molecular pathways that contribute to the development of advanced thyroid cancer and cell surface receptors that modulate the growth of these tumors through those pathways (Fig. 1). The most common mutations in differentiated primary thyroid cancers are mutations along the Ras–Raf–MEK–ERK (MAPK), such as RAS and BRAF mutations. In papillary thyroid carcinomas, signaling differences between RAS-driven and $BRAF^{v600E}$-driven tumors have been observed, with $BRAF^{v600E}$-like tumors signaling preferentially through MAPK and RAS-like tumors signaling through both MAPK and phosphatidylinositol-3 kinase (PI-3K) [14]. Mutations along the PI-3K pathway are also more commonly seen in advanced differentiated, poorly differentiated, and anaplastic thyroid cancers. However, gene amplifications in several tyrosine kinase receptors have also been described. In medullary thyroid cancer, mutations in RET have been described in 88% of cases with inherited MTC types [5] and RAS mutations have been described in 69% of RET wild-type cases and 2.5% of RET-positive sporadic MTC cases [15]. Overexpression of HGF and its receptor, MET, has also been reported [16–21].

Papillary tumors with *BRAF* mutations are associated with significantly reduced expression of genes involved in the metabolism of iodine, including genes for the sodium/iodide symporter (NIS), apical iodide transporter (AIT-B), thyroglobulin (Tg), and thyroperoxidase (TPO). *BRAF*-mutated papillary tumors also exhibit higher glucose transporter type 1 (Glut-1) transcript levels [22]. These differences may play a role in tumor dedifferentiation and reduce the efficacy of radioiodine [22]. In patients undergoing total thyroidectomy for papillary tumors, *BRAF* mutations were associated with extrathyroidal extension, thyroid capsular invasion, lymph node metastasis, and increased disease persistence and recurrence [23]. *BRAF* mutations have also been associated with higher clinical stage, age at diagnosis, and tumor volume [24,25].

Although the MAPK pathway is activated in primary well-differentiated thyroid cancers as well as poorly differentiated and metastatic thyroid cancers, the PI3K pathway is preferentially activated in advanced thyroid cancers, supporting the development of advanced disease, as tumors may acquire additional mutations [18]. Inhibition of the MAPK pathway through MEK inhibition in tumors with various MAPK genotypes inhibits cell proliferation, induces cell cycle arrest, inhibits cancer cell invasion, and abolishes

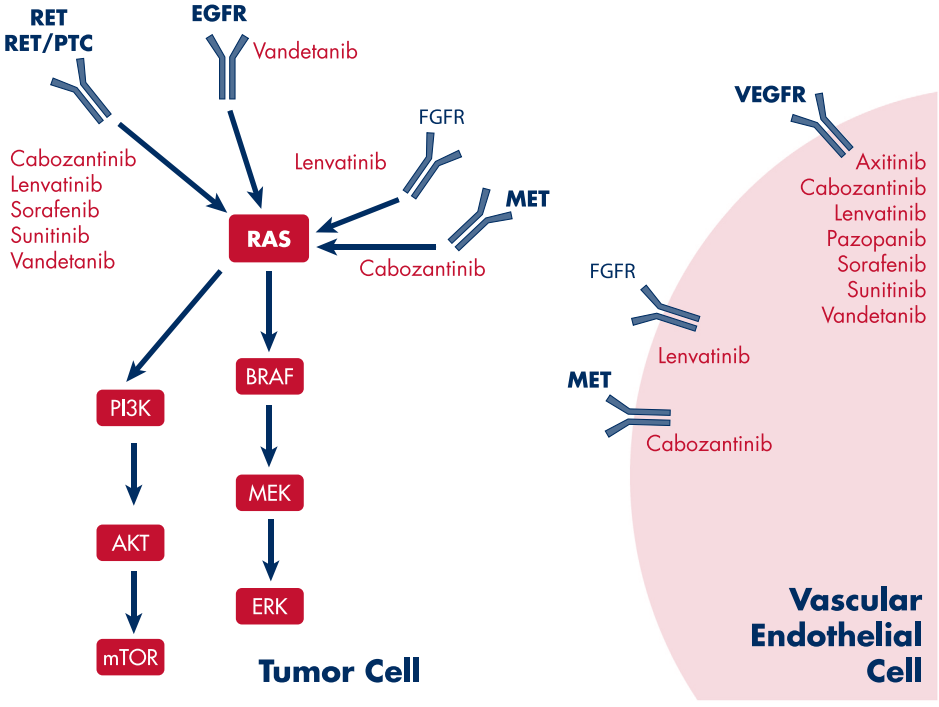

Fig. 1. Signaling pathways in thyroid cancer [18]. AKT = protein kinase B; EGFR = epidermal growth factor receptor; mTOR = mammalian target of rapamycin; PI3K = phosphatidylinositol-3 kinase; PTC = papillary thyroid carcinoma; RET = rearranged during transfection; VEGFR = vascular endothelial growth factor receptor. Adapted with permission Haugen and Sherman [18].

anchorage-independent growth [26,27]. Inhibition of the PI3K pathway through Akt inhibition also inhibits cell proliferation [26,28]. Inhibition of the MAPK and either the PI3K or NF-κB pathways synergistically inhibits cell proliferation [26,27]. MAPK and PI3K inhibition also synergistically induces non-apoptotic cell death [27].

VEGF is an important cytokine for the growth and proliferation of tumors and is associated with the formation of new blood vessels for tumors, increased tumor proliferation, and the growth of tumor cells [29,30]. The intracellular activity of the VEGF receptor is mediated by receptor tyrosine kinases [29]. Inhibition of the tyrosine kinase domain of the VEGF receptor leads to inhibition of tumor cell growth [30].

The fibroblast growth factor receptor (FGFR) pathway is an important signaling pathway for tumor proliferation in thyroid cancers, and inhibition of FGFR in mice with a xenograft of a human DTC cell line, R082-W-1, using a specific FGFR kinase inhibitor, led to significant antitumor activity [31]. Selective FGFR kinase inhibition also inhibited proliferation of human DTC cell lines *in vitro* [31]. When lenvatinib was tested, it inhibited FGFR signaling pathways in R082-W-1 cells *in vitro*, as measured by Western blotting [31]. Overall, these data suggest that both attenuation of an FGFR signaling pathway and antiangiogenesis through VEGFR may lead to antitumor effects [31].

The intracellular activities of signaling pathways important for development and growth of thyroid cancers, e.g., the MAPK, Pax8-PPAR, PI3K, and Akt pathways, are modulated by receptor tyrosine kinases associated with cell surface receptors such as VEGFR and EGFR (Fig. 1). Inhibition of VEGFR and other cellular receptors can lead to inhibition of these intracellular pathways. As an example of the importance of oncogenes and tyrosine kinases, alterations in *RET* associated with thyroid cancer lead to constitutive activation of ligand-independent kinases [32]. Inhibition of the *RET* oncogene by a tyrosine kinase inhibitor (TKI) prevented proliferation and tumorigenicity of thyroid cancer cells [32]. The importance of the RET receptor tyrosine kinase as a central mediator of the processes that lead to the development and progression of thyroid cancer provided the rationale for studying multikinase inhibitors (specifically, those which target RET) in MTC [5]. It is still unclear if targeting RET versus other cellular receptors, particularly VEGFR, is the primary mechanism by which multikinase inhibitors lead to clinical responses. While specific inhibitors, such as inhibitors of RAS, BRAF, MEK, PI3K, mTOR, and Akt, are potential therapies, these agents are not yet approved for use in this disease, and multikinase inhibition is the primary therapeutic approach [5,18].

Role of targeted therapies in thyroid cancer

Vandetanib and cabozantinib are approved by the FDA for treating advanced MTC. Sorafenib and lenvatinib are FDA approved for the treatment of RAI-refractory advanced DTC. The receptor targets and results from clinical trials of these drugs are summarized in Table 1. All 4 of them were approved based on statistically significant increases in progression-free survival (PFS), not increased overall survival [33–37].

The efficacy and safety of vandetanib were evaluated in an international, randomized, placebo-controlled, double-blind phase III trial (ZETA) in patients with locally advanced or metastatic MTC [38]. Progressive disease was not a requirement for study entry and patients were permitted to cross-over to the treatment arm if they were randomized to placebo at the time of progression. This trial randomized patients 2:1 to daily vandetanib or placebo, and it showed a median PFS of 19.3 months for patients receiving placebo and estimated PFS of 30.5 months for patients receiving vandetanib, with the median not being reached by the data cutoff (hazard ratio [HR] 0.46, $P < 0.001$) [38]. Grade 3 adverse effects occurring in >5% of patients receiving vandetanib included diarrhea, hypertension, QT interval prolongation, and fatigue [37,38].

The efficacy and safety of cabozantinib were determined in an international, double-blind, randomized, placebo-controlled phase III trial (EXAM) in patients with progressive metastatic or unresectable MTC, with PFS as the primary endpoint [39]. Cross-over to treatment was not permitted. The trial randomized patients to either cabozantinib or placebo, with a median PFS of 11.2 months in patients receiving cabozantinib versus 4.0 months in patients receiving placebo (HR 0.28, $P < 0.001$) [39]. The most frequent grade 3 or 4 adverse events in patients receiving cabozantinib were diarrhea, palmar-plantar erythrodysesthesia, and fatigue [39]. A recent subanalysis of cabozantinib in patients with *918 RET*-mutated tumors showed an overall survival advantage in this population [37,40].

The efficacy and safety of sorafenib in progressive metastatic, RAI-refractory, targeted therapy-naïve DTC were evaluated in a double-blind, multicenter phase III trial (DECISION) that randomized patients 1:1 to sorafenib or placebo, with PFS as the primary endpoint [34]. Patients receiving sorafenib had a median PFS of 10.8 months compared with 5.8 months for patients receiving placebo. The most common treatment-emergent adverse events of any grade occurring in >40% of patients receiving sorafenib were hand-foot skin reaction, diarrhea, alopecia, rash, fatigue, loss of weight, and hypertension [34,37].

The efficacy and safety of lenvatinib in progressive RAI-refractory DTC were evaluated in a double-blind, multicenter phase III trial (SELECT) that randomized patients 2:1 to lenvatinib or placebo, with PFS as the primary endpoint [37,41]. Patients previously treated with VEGF-based therapies were included in this trial. Results are summarized below (see "Clinical Trials with Lenvatinib in Thyroid Cancer").

Due to the importance of a range of tyrosine kinase families in thyroid cancer, other kinase inhibitors have been studied in several phase I and II clinical trials, and clinical trials with kinase inhibitors in DTC are summarized in Table 2 [37,42–49]. Most of these kinase

Table 1
FDA-approved multikinase inhibitors approved for patients with advanced MTC and DTC.

Drug	Indication	Primary targets for trial rationale	Phase	Total number of patients	PFS (months)
Vandetanib [38]	Symptomatic or progressive metastatic or unresectable locally advanced MTC	RET, VEGFR, BRK, TIE2, EPH, Src	III	331	30.5*
Cabozantinib [39]	Progressive, metastatic MTC	MET, VEGFR2, RET	III	330	11.2
Sorafenib [34]	Locally recurrent or metastatic progressive DTC	VEGFR1-3, RET, RAF, PDGFRβ	III	417	10.8
Lenvatinib [41]	Locally recurrent or metastatic, progressive, RAI-refractory DTC	VEGFR, FGFR, PDGFRα, RET, c-kit, SCFR	III	392	18.3

BRK = breast tumor kinase; c-kit = receptor for stem cell factor; DTC = differentiated thyroid cancer; EPH = ephrin receptor; FGFR = fibroblast growth factor cell surface receptor; MTC = medullary thyroid cancer; PDGFR = platelet-derived growth factor receptor; PFS = progression-free survival; RAI = radioactive iodine; RET = rearranged during transfection; SCFR = stem cell growth factor receptor; VEGFR = vascular endothelial growth factor receptor.
* Estimated PFS; PFS not reached by data cutoff.

Table 2
Kinase inhibitors in phase I and II clinical trials in patients with advanced DTC.*

Drug	Primary targets for trial rationale	Phase	Total number of patients	RR (%)	PFS (months)
Multikinase inhibitors					
Axitinib [42]	VEGFR, PDGFR, c-kit	II	60	30	18.1
Motesanib [43]	VEGFR, PDGFR, c-kit	II	93	14	9.3
Sunitinib [44]	PDGFR, FLT3, c-kit, VEGFR, RET	II	35	31	12.8
Pazopanib [45]	VEGFR, PDGFR, c-kit	II	37	49	11.7
Vandetanib [46]	RET, VEGFR, EGFR	II	145	8	11.1
Cabozantinib [47]	MET, VEGFR2, RET	I	15	53	ND
Selective BRAF inhibitors					
Dabrafenib [48]	BRAF	I	14	29	11.3
Vemurafenib [49]	BRAF	II	51	35	15.6

c-kit = receptor for stem cell factor; DTC = differentiated thyroid cancer; EGFR = epidermal growth factor receptor; FLT = FMS-like tyrosine kinase; ND = not determined; PDGFR = platelet-derived growth factor receptor; PFS = progression-free survival; RET = rearranged during transfection; RR = response rate; VEGFR = vascular endothelial growth factor receptor.
* This table is not for between-trial comparative purposes.

inhibitors have numerous targets, including VEGFR, platelet-derived growth factor receptor (PDGFR), c-kit, RET, and FLT3. The PFS in these trials ranged from 9.3 months to over 18 months.

Vemurafenib is a BRAF kinase inhibitor that was tested in an open-label, multicenter phase II clinical trial in patients with metastatic or unresectable papillary thyroid cancer with a *BRAF* V600 mutation that is resistant to RAI [49]. This trial enrolled 51 patients to receive 960 mg vemurafenib orally twice daily until disease progression or unacceptable toxicity. Patients were divided into 2 cohorts: TKI-naïve and previously treated patients. Of the 26 evaluable treatment-naïve patients, 9 (35%) experienced a partial response. Median PFS in this group was 15.6 months. In the previously treated cohort, 26% of the 25 evaluable patients achieved a partial response. Median PFS was only 7 months in the pretreated cohort [37]. Among 17 patients receiving vemurafenib outside a clinical trial, 47% had a partial response and 53% had stable disease [50]. This drug has also been evaluated in a small number of BRAF mutated ATC patients [51]. Of 7 patients reported, 2 obtained objective responses.

Dabrafenib, a BRAF kinase inhibitor, was studied in a phase I trial which included 14 patients with *BRAF*-mutated thyroid cancer. Four patients (29%) achieved a partial response [48]. This drug has also been studied in the context of redifferentiation of RAI-refractory disease [52]. Dabrafenib is being studied in thyroid cancer in a phase I trial in combination with lapatinib [53]. Patients enrolled in this trial will have a thyroid cancer resistant to RAI and a *BRAF* V600E mutation. Dabrafenib is also being studied in combination with trametinib in 2 phase II trials. One of these trials is studying dabrafenib with or without trametinib and is enrolling patients with DTC (NCT01723202) [54]. The other trial is enrolling patients with rare cancers with *BRAF* V600E mutations, including anaplastic thyroid cancer (NCT02034110) [55].

Lenvatinib mechanism of action

Because of the known role of tyrosine kinase pathways in the development of thyroid cancer, and following the encouraging results with multitargeted tyrosine kinase inhibition as a treatment, lenvatinib was developed. Lenvatinib targets VEGFR1-3, fibroblast growth factor receptors 1–4 (FGFR1–4), RET, c-kit, PDGFRα, and mast/stem cell growth factor receptor (SCFR) in a variety of preclinical tumor models [56–58], and one of its potential advantages may be its broad-spectrum antitumor activity. Lenvatinib is a potent inhibitor of FGFR1, which differentiates it from other currently available TKIs with angiogenesis properties, and has significant antiangiogenic effects via inhibition of VEGFR2, VEGFR3, and FGF1 [59]. The inhibitory profile of lenvatinib for various kinases is listed in Table 3 [58]. Lenvatinib inhibited the progression of 3 malignant pleural mesothelioma (MPM) cell lines, which were orthotopically implanted in severe combined immunodeficient (SCID) mouse models [59]. In these mouse models, treatment with lenvatinib inhibited VEGF-mediated angiogenesis, with significantly lower microvessel density in treated mice ($P < 0.01$). Treatment with lenvatinib prolonged survival of MPM cell-bearing mice ($P < 0.001$). In a small cell lung cancer xenograft mouse model, lenvatinib caused inhibition of tumor growth and regression of tumors via inhibition of SCF-induced and c-kit-induced angiogenesis [58]. In this mouse model, lenvatinib demonstrated more potent antitumor effects than imatinib, which slowed tumor growth but did not affect tumor regression. The investigators suggested that lenvatinib may inhibit angiogenesis by decreasing mature endothelial cells and the KDR-mediated and c-kit-mediated recruitment of circulating endothelial cells from bone marrow into the circulation.

Table 3
Kinase inhibitory profile of lenvatinib [58].

Kinase	IC_{50} (nM)
VEGFR1	22
VEGFR2	4.0
VEGFR3	5.2
FGFR1	46
PDGFRα	51
PDGFRβ	39
EGFR	6500
c-kit	100

c-kit = receptor for stem cell factor; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor cell surface receptor; IC_{50} = half maximal inhibitory concentration; PDGFR = platelet-derived growth factor receptor; VEGFR = vascular endothelial growth factor receptor.

Lenvatinib may also act via direct antitumor effects. *In vitro* studies using 2 human tumor cell lines demonstrated that lenvatinib inhibits tumor cell invasion and migration [60]. Cellular invasion was reduced by 45% at 1 μM lenvatinib and to 13% by 10 μM lenvatinib [60]. Inhibition of cellular migration by lenvatinib may occur via inhibition of FGFR1 and PDGFRα signaling, which was shown to be required for cellular migration. Cellular proliferation assays conducted using 6 different human tumor cell lines demonstrated that lenvatinib did not have an effect on cellular proliferation. Lenvatinib was evaluated in preclinical models of *RET* gene fusions, which are current transmembrane tyrosine kinase oncogenes. In cellular assays, lenvatinib inhibited the growth of 3 human cancer cell lines with *RET* gene fusions, i.e., *KIF5B-RET*, *CCDC6-RET*, and *NCOA4-RET* [56]. Lenvatinib suppressed the growth of CCDC6-RET human thyroid and lung cancer cell lines and anchorage-independent growth and tumorigenicity of *RET* gene

fusion-transformed NIH3T3 cells. In a *RET* gene fusion tumor mouse model, treatment with lenvatinib daily for 10 days suppressed the growth of tumors from NIH3T3/KIF5B-RET and significantly decreased microvessel density [56].

Lenvatinib is rapidly absorbed, extensively metabolized, and excreted in urine and feces [61]. In a pharmacokinetic and excretion study of a single oral 24 mg lenvatinib dose, peak plasma concentrations of lenvatinib were reached at 1.6 h after administration [61]. The terminal half-life of lenvatinib was 34.5 h. Lenvatinib undergoes extensive metabolism, with unchanged lenvatinib in urine and feces accounting for 2.5% of the dose. Lenvatinib is eliminated by multiple pathways including metabolism by cytochrome P450s and aldehyde oxidase and conjugation with glutathione [62]. Based on drug–drug interaction and metabolic studies, lenvatinib has a low possibility of drug-drug interactions [62,63]. Lenvatinib exposure is slightly increased by ketoconazole and by P-gp inhibition with rifampicin but is not likely clinically meaningful [63,64]. In patients with severe hepatic impairment, a dose reduction from 24 mg to 14 mg is warranted [65].

Lenvatinib clinical trials

Phase I dose-escalation and biomarker analysis

Several phase I studies have demonstrated a benefit of lenvatinib in patients with a variety of advanced solid tumors. In a phase I dose-escalation study with biomarker analysis, lenvatinib was evaluated in patients with advanced solid tumors resistant to standard therapy or for which no therapy was available, performance status of Eastern Cooperative Oncology Group (ECOG) < 2, and life expectancy of >3 months [66]. This was a sequential, dose-escalation, open-label phase I study. Lenvatinib was administered twice daily in a 2-week-on/1-week-off 28-day cycle. Dosing began at 0.5 mg twice daily. The primary endpoint of the study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicities of lenvatinib. The secondary endpoints included pharmacokinetics, safety, and tolerability of lenvatinib, antitumor response, and establishing a dose for use in phase II trials. Exploratory endpoints included biomarker analysis of antitumor activity. Plasma angiogenic proteins, circulating endothelial cells, and circulating progenitor cells were measured for biomarker analysis. Twenty-seven patients were included in the study. Dose-limiting toxicities included a grade 3 AST/ALT increase in 1 patient at the 16 mg twice-daily dose and a grade 3 platelet count decrease in 2 patients at 20 mg twice daily. Therefore, the MTD was determined to be 13 mg twice daily. Antitumor activity was observed in 22 patients. One patient had a partial response, and 84% of patients had stable disease as the best response. Biomarker analysis suggested that antiangiogenic activity correlated with therapeutic effect in this patient population. Baseline levels of SDF1, c-kit(+), circulating endothelial progenitor cell (CEP) number, and c-kit(+) ratio in circulating endothelial cells (CEC) were correlated with treatment duration. The investigators suggest that high levels of these biomarkers (as opposed to lower levels) at baseline may predict tumor resistance [66].

Phase I study of lenvatinib in patients with advanced solid tumors

The safety and tolerability of lenvatinib were evaluated in 82 patients with advanced solid tumors refractory to conventional treatments. The majority of patients had sarcoma, melanoma, and colorectal and renal cancers [67]. This was a single-arm, open-label, phase I, dose-escalation study. The primary endpoint was the determination of the MTD. Secondary endpoints included safety, pharmacokinetic profile, and efficacy. Lenvatinib was administered once daily, using a 28-day cycle and beginning with a 0.2 mg/day dose. The starting dose was based on preclinical toxicology studies and was increased with an accelerated design until the MTD was reached. The dose-limiting toxicity was grade 3 proteinuria at the 32 mg dose of lenvatinib. The MTD was determined to be 25 mg. The most common adverse events were hypertension (40%), proteinuria (26%), diarrhea (45%), nausea (37%), stomatitis (32%), and vomiting (23%). Antitumor activity included partial response in 9% of patients and stable disease in 46%.

Phase I study of lenvatinib combined with carboplatin and paclitaxel in patients with non-small cell lung cancer (NSCLC)

In this phase I study, 28 patients with advanced or metastatic NSCLC received lenvatinib twice daily with carboplatin every 3 weeks, beginning with a 6 mg dose twice daily [68]. Six patients were enrolled per dose level of lenvatinib. The primary endpoint was the MTD. When the MTD was reached, the patient cohort was expanded to 16 patients, and safety, pharmacokinetics, pharmacodynamics, and antitumor effects were evaluated. Dose-limiting toxicities, which included febrile neutropenia and gingival infection, occurred at the 6 mg twice-daily dose. The MTD was determined to be 4 mg twice daily. At the MTD for lenvatinib, the most common adverse events were thrombocytopenia (100%) and neutropenia, leukopenia, peripheral sensory neuropathy, arthralgia, and alopecia (95% each). Other common toxicities of any grade included proteinuria (77%), hypertension (73%), and nausea (82%). Gastrointestinal adverse events including diarrhea, constipation, decreased appetite each occurred in 77% of patients. The most common grade 3 or 4 toxicities were neutropenia (95%), leukopenia (50%), hypertension (36%), thrombocytopenia (27%), and febrile neutropenia (23%). The pharmacokinetics of lenvatinib were not altered by concomitant administration of carboplatin and paclitaxel. Biomarker analysis revealed that VEGF, interleukin 8 (IL-8), and SDF1α were increased from baseline during the first cycle of treatment. Lenvatinib showed promising antitumor activity, with the majority of patients experiencing tumor shrinkage. The overall RR was 68%, with a median duration of response of 7.9 months. The median PFS was 9.0 months. At the MTD, 1 patient experienced a complete response and 14 (64%) had a partial response.

Phase Ib trial of lenvatinib in combination with everolimus for metastatic renal cell carcinoma (RCC)

A total of 20 patients with advanced unresectable or metastatic RCC and ECOG performance status 0 to 1 were enrolled in a combination trial of lenvatinib and everolimus [69]. The starting dose of lenvatinib was 12 mg once daily with everolimus 5 mg once daily, administered in a 28-day cycle using a conventional 3 + 3 dose-escalation design. The MTD was determined to be once-daily lenvatinib 18 mg plus everolimus 5 mg. The most common treatment-related adverse events included fatigue (60%), mucosal inflammation (50%), proteinuria (15%), diarrhea (10%), vomiting (5%), hypertension (40%), and nausea (40%). Antitumor effects included partial responses in 33% of patients and stable disease in 50%.

Clinical trials with lenvatinib in thyroid cancer

Three clinical trials—2 phase II and 1 phase III—have evaluated lenvatinib in MTC and RAI-refractory DTC (Table 4) [41,70–75]. The phase II international trial of lenvatinib (NCT00784303) included 2 cohorts that were reported separately for progressive MTC and DTC. In the MTC cohort, the partial response rate was 36% and PFS was 9 months [74]. In patients with progressive DTC, the

Table 4
Clinical trials of lenvatinib in thyroid cancer.

Trial	Phase	Patient population	Study description	Primary endpoint	Secondary endpoint	Status of trial
NCT01321554/SELECT trial (study of E7080 lenvatinib in differentiated cancer of the thyroid) [70]	III	Advanced RAI-refractory DTC with documented evidence of disease progression	Multicenter, randomized, double-blind, placebo-controlled study comparing lenvatinib 24 mg by continuous once-daily dosing versus placebo	PFS	ORR	Completed/ results published [41]
NCT01728623 [71]	II	Advanced thyroid cancer	Study evaluating the safety, efficacy, and pharmacokinetics of lenvatinib given once daily	Number of patients with nonserious AEs and SAEs Change from baseline in hematology, blood biochemistry, urinalysis, vital signs, ECG, and physical exam	PFS OS	Closed/ results presented [73]
NCT00784303 [72]	II	MTC or RAI-refractory unresectable DTC	Study evaluating the safety and efficacy of lenvatinib	Objective tumor RR according to RECIST	AEs Laboratory assessments ECG PFS Duration of response Time to response OS Pharmacokinetics	Completed/ results published [74,75]

AEs = adverse events; DTC = differentiated thyroid cancer; ECG = electrocardiogram; MTC = medullary thyroid cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RAI = radioiodine; RECIST = response evaluation criteria in solid tumors; RR = response rate; SAEs = serious adverse events.

partial response rate was 50% and PFS was 12.6 months [75]. Forty-three patients with thyroid cancer, including ATC, were included in a phase II trial conducted in Japan [73]. Of 11 ATC patients, 3 (27%) obtained an objective response. Median progression-free and overall survival were 7.4 and 10.6 months, respectively.

The results of the phase III trial (SELECT) were recently published [41]; this randomized, double-blind, placebo-controlled study evaluated the efficacy of lenvatinib in 392 patients with RAI-refractory DTC with disease progression. Patients previously treated with 1 TKI were eligible for this study. The primary endpoint was PFS. Secondary endpoints included overall RR, overall survival, and safety. Treatment with lenvatinib ($n = 261$) significantly prolonged PFS compared with placebo ($n = 131$) (HR: 0.21; 99% CI: 0.14–0.31; $P < 0.001$). Median PFS in patients receiving lenvatinib was 18.3 months versus 3.6 months in those patients receiving placebo. A significant PFS advantage in the lenvatinib arm was also seen in patients who had received one prior TKI treatment. Lenvatinib also significantly improved overall RRs compared with placebo (odds ratio 28.87; 95% CI: 12.46–66.86; $P < 0.001$). The RR for lenvatinib was 64.8% versus 1.5% for placebo. In patients receiving lenvatinib, complete responses were observed in 1.5% and partial responses in 63.2% of patients. In both groups, the median overall survival has not been reached, possibly because of the crossover design between the 2 groups. However, in a recently reported subanalysis, overall survival was only reached in patients >65 years old and was significantly different in the older patients, favoring lenvatinib over placebo (HR 0.53; 95% CI 0.31–0.91; $P = 0.02$) [76].

In terms of treatment-related adverse events, hypertension (68%), diarrhea (59%), fatigue/asthenia (59%), and decreased appetite (50%) were the most common. Dose reductions were needed in 67.8% of patients, and 14.2% of patients discontinued treatment due to adverse events. A total of 71 deaths occurred in the lenvatinib group (27.2%), mostly due to disease progression (74.6%). Fatal adverse events developed in 20 patients (7.7%), 6 of which were treatment-related (pulmonary embolism, hemorrhagic stroke, general deterioration, and 3 cases not otherwise specified) [41].

Lenvatinib is also currently being investigated in a variety of other malignancies, including advanced lung cancers, hepatocellular carcinoma, advanced or metastatic melanoma, endometrial cancer, and metastatic RCCs [77–81].

Conclusions

Lenvatinib is a multikinase inhibitor with potent inhibitory activity for FGFR1. It has antiangiogenic properties through inhibition of VEGFR and FGFR as well as direct antitumor effects [56–59]. Lenvatinib was approved for RAI-refractory DTC based on its phase III trial results. The drug also has shown encouraging efficacy in the treatment of MTC and ATC. Further investigation of the efficacy of lenvatinib in ATC is needed. In phase I and II clinical trials, lenvatinib—either alone or in combination—showed antitumor activity in a variety of solid tumors including NSCLC, metastatic RCC, colorectal cancer, sarcoma, and melanoma [66–69].

The phase III trials for lenvatinib (SELECT) and sorafenib (DECISION) were both multicenter, international, randomized, double-blind, placebo-controlled studies in RAI-refractory DTC [34,41]. The primary endpoint in both studies was PFS. DECISION included only treatment naïve patients and SELECT included patients who were treatment naïve and those who had received 1 prior TKI. After a median follow-up of 17.1 months in the SELECT trial, the median PFS was 18.3 months for lenvatinib-treated patients compared to 3.6 months with placebo ($P < 0.001$). The objective response rate was 65% (complete and partial responses). In the DECISION trial, sorafenib-treated patients had a median PFS of 10.8 months compared to 5.8 months with placebo after a median of 16.2 months follow-up and the objective response rate (partial response only) was 12%. Most patients without a partial response achieved stable disease for 4 weeks or longer. Common treatment-related adverse events were similar with both TKIs and included hypertension, diarrhea, fatigue, decreased appetite, and weight loss. Hypertension was the most common adverse event in the SELECT trial, reported in 67.8% of patients, with more severe hypertension reported in 41.8% of patients. In the DECISION trial, hypertension was reported in 41% of patients, with severe hypertension reported

in only 9.7% of patients. Hand-foot skin reaction was the most common adverse event in the DECISION trial, reported in 76.3% of patients, whereas, in the SELECT trial, it was reported in only 32% of patients. Fatal, treatment-related adverse events occurred in 6 patients in the SELECT trial but in only 1 patient in DECISION. These fatal adverse events in SELECT were due in part to thrombotic events and renal failure. Whether hypertension could have contributed to these is unknown. The possibility that these could have been associated with poor control of hypertension plus the fact that hypertension was so prevalent in lenvatinib-treated patients, makes an argument for aggressive blood pressure monitoring and treatment. Unfortunately, a very important aspect for cancer patients, quality of life, was not evaluated in the SELECT trial. Further investigation in this area is warranted [34,41].

Due to the poor survival rates from unresectable, advanced, or refractory DTC and MTC, it is important to develop effective treatment approaches for these patients. In a study evaluating the efficacy of salvage therapy in DTC after first-line sorafenib, the median OS was 58.4 months after receiving another TKI as salvage therapy compared to 28.8 months in patients who received sorafenib only ($P = 0.013$) [82]. Another study evaluating the efficacy of sunitinib therapy in 3 patients after failure of first-line sorafenib found that patients responded to the second-line therapy and were able to achieve a partial response or stable disease with combined PFS of 25–31 months [83]. These results demonstrate that patients continue to respond to the second-line TKI and that switching to another agent after failure can be effective as salvage therapy. The long PFS seen in previously treated patients in the SELECT trial randomized to lenvatinib is important to note, although it is not clear if these patients had progressed on the previous TKI. However, the mechanism of action of lenvatinib may allow it to be another effective option for patients with thyroid cancer refractory to radioactive iodine as well as other TKIs. Further investigation regarding sequencing of the kinase inhibitors in thyroid cancer is needed.

Lenvatinib appears to have one of the highest RRs to date in DTC and is now approved in the US [36] and Japan for this indication. The drug has also been approved in Japan for all subtypes of thyroid cancer. It is yet unclear whether this higher RR is at the expense of higher toxicity. Nevertheless, as a multikinase inhibitor, lenvatinib is a promising new agent for the treatment of patients with advanced thyroid cancer.

Disclosure/conflict of interest statement

MEC has received research funds from and has been a paid consultant and advisory board member for Exelixis, has received research funds from and has been an advisory board member for Eisai Inc., has been a paid consultant for Astra-Zeneca, and has received research funds from Roche/Genentech.

MAH has received research funds/support from and has been invited to attend an advisory meeting (with honorarium) for Eisai Inc.

Role of the funding source

Eisai Inc. consulted with advisors on the design of this analysis and provided financial and material support for the analysis.

Acknowledgments

This review was funded by Eisai Inc. The authors thank Mary Ellen Shepard, PhD, consultant to MedVal Scientific Information Services, LLC, and Bass Global Inc for providing medical writing and editorial assistance. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: The GPP2 Guidelines."

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