Lenvatinib: an investigational agent for the treatment of differentiated thyroid cancer

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Abstract

Introduction Differentiated thyroid cancer (DTC; >90% of all TCs) derives from follicular cells. Surgery is the main therapeutic strategy, and radioiodine (RAI) is administered after thyroidectomy. When DTC progresses, it does not respond to RAI and TSH-suppressive thyroid hormone treatment, and other therapies (i.e. surgery, external beam radiation therapy and chemotherapy) do not lead to a better survival. Thanks to the understanding of the molecular pathways involved in TC progression, important advances have been done. Lenvatinib is a multitargeted tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT signaling networks implicated in tumor angiogenesis, approved in locally recurrent or metastatic, progressive, RAI-refractory DTC. Unmet needs regarding the patient clinical therapy responsiveness in aggressive RAI-refractory DTC still remain.

Areas covered We provide an overview from the literature of *in vitro*, *in vivo* and real-life studies regarding lenvatinib as an investigational agent for the treatment of aggressive TC.

Expert opinion According to the SELECT trial, the treatment should be initiated with a dosage of 24 mg/**day**, subsequently decreasing it in relation to the side effects. The decision making process in patients with aggressive RAI-refractory DTC should be personalized and the potential toxicity should be properly managed.

Keywords: aggressive radioiodine-refractory differentiated thyroid cancer, lenvatinib, thyroid cancer, tyrosine kinase inhibitors.

1. Introduction

Thyroid cancer (TC) is the 8th most commonly diagnosed cancer in the world and its incidence has been increasing in the last 20 years. In the United States, from 2006 to 2010, the mean annual percentage increase was 6.5% for women and 5.4% for men [1], and in 2017 there were an estimated 859,838 people living with TC [2]. The most important increment has been shown in South Korea (in 1993–1997, 12.2 cases per 100,000 subjects; in 2003–2007, 59.9 cases per 100,000 subjects) [3]. Its increased incidence appears to be also associated with the widespread use of neck ultrasound (US) and fine-needle aspiration (FNA), that permit to detect small, low-risk tumors [4].

Differentiated thyroid cancer (DTC) derives from follicular cells and it accounts for >90% of all TCs. DTCs are papillary TC (PTC; ~90%), follicular TC (FTC; ~10%), and Hurthle cells TC (3-5%) [5,6]. Medullary TC (MTC) comes from thyroid parafollicular C cells, and it can be sporadic, or it has a hereditary component (~25% of cases) [7]. Anaplastic TC (ATC) is rare (~1% of TC), and it has an aggressive behaviour, causing 15–40% of TC death [8-15]. Poorly differentiated thyroid carcinoma (PDTC) is a follicular cancer that shows morphological and behavioural characteristics between DTC (FTC and PTC) and ATC [16]. PDTC is frequently radioactive iodine (RAI)-resistant, and it has a 5-year overall survival rate of 60–85% [17,18].

More than 90% of patients with DTC has a normal life expectancy [19]. Approximately 5% of DTC patients have distant metastases at the diagnosis, and ~15% of them develop recurrences, with a decrease in the survival from 70% to 50% at 10 years [20]. ATC is classified as Stage IV TC by the American Joint Committee on Cancer, independently from tumor size or presence of lymphnode or distant metastases [21], with a median survival of 6-10 months.

Surgery is the main therapeutic strategy for MTC and DTC patients; after thyroidectomy, RAI is used to ablate residual normal thyroidal tissue, and/or treat metastatic TC [22]. Neck US, baseline and thyroglobulin (Tg) after thyroid-stimulating hormone (TSH) stimulation are used in the follow up to detect persistent/recurrent disease every 3-6 months for the first year, and then at different intervals according to the initial risk assessment [23]. If DTC progresses, thyrocytes become

refractory to RAI, and prognosis is poorer [20]. When metastatic DTC does not respond to RAI and L-thyroxine TSH-suppressive (TH) treatment [24], other therapies [including surgery, chemotherapy and external beam radiation therapy (EBRT)], alone or in combination, are not associated with a significant prolongation of survival and have a palliative role [25].

The standard treatment of ATC includes surgical debulking, accelerated hyperfractionated EBRT, and chemotherapy. Doxorubicin, docetaxel/paclitaxel and platins are endorsed by American Thyroid Association (ATA) guidelines in ATC, but with no significant improvement of the survival [26].

Given the scarcity of effective treatment options, novel therapeutic strategies are needed for advanced DTC patients.

Lenvatinib received the approval by Food and Drug Administration (FDA) and European Medicines Agency (EMA) in February and March 2015 in patients with locally recurrent or metastatic, progressive, RAI-refractory DTC [27,28].

In this paper, we review the scientific literature regarding lenvatinib as an investigational agent for the treatment of aggressive TC, and the data arisen from clinical studies that aimed to assess its efficacy and safety.

2. Overview of the molecular pathways and targets in aggressive RAI-refractory DTC

It is still arduous to predict the patient clinical therapy responsiveness in aggressive RAI-refractory DTC. Thanks to the understanding of the molecular pathways that take part in TC progression, important advances have been done. Drugs inhibitor that target the intracellular tyrosine kinases (TKs) linked to different receptors [including c-Met, Vascular Endothelial Growth Factor Receptor (VEGFR)1-3, RET, Platelet-Derived Growth Factor Receptor (PDGFR), KIT, fibroblast growth factor receptors (FGFR), epidermal growth factor receptor (EGFR), and Tie2] have been developed [5,27,29,30].

2.1 Molecular pathways and targets in aggressive RAI-refractory DTC

The most frequent genetic mutations reported in DTC are alterations in rat sarcoma (RAS), rearranged-during-transfection (RET)/PTC rearrangements, and murine sarcoma viral oncogene homolog B (BRAF); tumor protein p53 (TP53) mutations are frequently observed in PDTC. These genetic alterations affect mainly phosphoinositide-3-kinase (PI3K) signaling and mitogen-activated protein kinase (MAPK) [31,32]. Dysregulation of multiple signaling pathways, including MAPK, PI3K, and Wingless/Integrated (WNT), are at the basis of the pathogenesis of TC [33].

In PTC, one of the predominant mutations (18–87%) is BRAFV600E, and it is also present in PDTC, and Hurthle cells TC [34]. It is correlated to tumor aggressiveness and poor prognosis and is characterized by the substitution valine-glutamate, that activates the BRAF kinase phosphorylating various targets, including mitogen activated protein kinase (MEK) and extracellular signal-regulated kinase (ERK) [35,36].

RAS mutations have been detected in 30–50% FTC, 30–45% follicular-variant of PTC, 15% Hurthle cells TC, 20–40% PDTC, and occasionally in classical PTC patients [32]. The most frequent RAS mutations occur at codons 12, 13, and 61, on the three RAS genes (HRAS, KRAS, and NRAS), and NRAS61 is the main RAS mutation in TC [37].

BRAF and RAS alterations are mutually exclusive genetic mutations [38].

Mutations, and epigenetic alterations of the tumor suppressor gene Phosphatase and tensin homolog (PTEN), which lead to its loss of expression, have been reported in DTC, PDTC, and Hurthle cells TC [33,39]. Its methylation appears to be involved in the trasformation from benign thyroid adenomas into aggressive ATC. Other genetic alterations are induced by PTEN expression, involved in the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway, as RAS and Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA) [5].

Sporadic PTC patients have RET/PTC rearrangements in ~40% of cases [5,32], that are reported in benign thyroid lesions and microcarcinomas, too. The Nuclear Receptor Coactivator 4 (NCOA4)-RET (RET/PTC3) and Coiled Coil Containing 6 (CCDC6)-RET (RET/PTC1) fusions constitute

~90% of RET/PTC rearrangements. CCDC6-RET are frequent more than twice vs. NCOA4-RET fusions in sporadic TC, whereas NCOA4-RET have a similar prevalence than CCDC6-RET fusions in PTC induced by radiation [5]. The RET/PTC1 rearrangement is observed in childhood TC after the Chernobyl nuclear power accident [40], and RET fusions are present in ~50% of atomic bomb survivors with PTC after an elevated radiation exposure [41].

Paired Box 8/Peroxisome Proliferator Activated Receptor γ (PAX8/PPARγ) rearrangements are observed in ~35% FTC and <5% Hurthle cell TC, with a good prognosis. About 2–10% follicular adenomas and ~0–1% PTC have PAX8/PPARγ rearrangements [5,32]. PAX8/PPARγ acts as a dominant negative activator of PPARγ and as a transcriptional activator of certain PPARγ-inducible genes explicating its oncogenic effects [32]. In FTC, tumors with PAX8/PPARγ rearrangements do not have RAS alterations, suggesting that RAS oncogenic activation or PAX8/PPARγ translocation take part differently in this type of tumors [42].

Neurotrophic receptor tyrosine kinase (NTRK) rearrangements are receptor TKs encoded by the NTRK1-3 genes [43]. NTRK fusions have been shown in ~2% of patients with sporadic PTC [44], in particular the ETS Variant Transcription Factor 6 (ETV6)-NTRK3 was reported in 14.5% of post-Chernobyl PTC [45].

The ALK gene fusions are detected in particular in ATC and PDTC, but with a low frequency also in PTC (~1–3%), especially Striatin (STRN)-ALK, and activate the MAPK and PI3K pathways [5].

Telomerase reverse transcriptase (TERT) promoter mutations have been reported in PDTC (40%), ATC (40–70%), an aggressive form of Hurthle cells TC (32%), FTC (20%) and PTC (10%) [32].

3. Introduction to the compound: Chemistry; Pharmacodynamics; Pharmacokinetics and metabolism

Lenvatinib is a multitargeted, oral TK inhibitor (TKI) of VEGFR1-3, FGFR1-4, PDGFRα, RET, and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) signaling networks

that take part in tumor angiogenesis. It is used in form of the mesylate salt (CAS number 857890-39-2), for the treatment of aggressive RAI-refractory DTC [27].

Lenvatinib is rapidly absorbed in the gut and it attains its maximal blood level between 1-4 hours after oral ingestion in healthy subjects or patients with solid tumors; its bioavailability in capsule form is 85-90%, and its half-life is 28 hours [27,46].

Lenvatinib has been approved for the treatment of advanced RAI-refractory DTC following the results of the Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) trial, demonstrating a significant amelioration in progression-free survival (PFS) and an elevated response rate (RR) in these patients, with a Response Evaluation Criteria in Solid Tumors (RECIST) objective response rate >60% and ~80% decrease in the risk of disease progression. Considering the results obtained in the SELECT trial, the recommendation is to begin the treatment with 24 mg daily and to diminish the doses in relation to the adverse events (AE) [47,48].

3.1 Preclinical studies in aggressive RAI-refractory DTC

***In vitro* studies have shown the antineoplastic activity of lenvatinib in aggressive DTC, mainly because of its antiangiogenetic effects.**

A study evaluated the antitumor activity of lenvatinib in human TC xenograft models in nude mice. Lenvatinib had an antitumor activity in xenograft models of 5 DTC, 5 ATC, and 1 MTC xenograft models, and it showed an antiangiogenetic effect in 5 DTC and 5 ATC xenografts, whereas the antiproliferative action was detected *in vitro* in 2/11 TC cell lines (RO82-W-1 and TT cells). The data demonstrated that lenvatinib has antitumor activity mainly via angiogenesis in preclinical human TC models [49].

Most cancers have intrinsic or evasive resistance to VEGF inhibitors (through different mechanisms). Serum angiopoietin-2 (Ang2) and its receptor Tie2 are considered as potential biomarkers of VEGF inhibitor response in different cancers. A study evaluated a novel strategy to bypass the resistance combining lenvatinib and golvatinib (E7050, c-Met, Tie2, and EphB4

inhibitor). Tie2 identifies a highly pro-angiogenic subset of macrophages, called “Tie2-Expressing Macrophages” (TEM), and Ang2-Tie2 have a crucial role in pericyte-mediated vessel stabilization. Golvatinib, in combination with lenvatinib, inhibited *in vitro* the stabilization of pericytes and TEM differentiation. In K1 DTC cell line xenograft models, golvatinib plus lenvatinib inhibited pericyte development and TEM infiltration, leading to perfusion disorder and apoptosis. These preclinical studies suggested the combination of TKIs can sensitize cancer to VEGF inhibitors [50].

A study investigated a novel treatment protocol in refractory TC (SoLAT), with alternative sorafenib and lenvatinib [51]. Aggressive PTC cell lines obtained from patients with biochemical and histologically proven aggressive RAI-refractory PTC were treated alternatively with sorafenib and lenvatinib. Human TC cell xenografts were obtained in female BALB/c nude mice, and tumor-bearing mice received alternatively sorafenib and lenvatinib. SoLAT inhibited PTC progression by inducing cell cycle arrest, more effectively than individual treatment with sorafenib or lenvatinib [51].

The antitumoral effect of combining lenvatinib and radiation (CTLR) for DTC was evaluated, by using the human DTC cell lines, K1 (a PTC cell line) and FTC-133 (a FTC cell line) [52]. *In vitro* CTLR synergistically inhibited cell replication and colony formation, inducing also apoptosis and G2/M phase cell cycle arrest. Moreover, it inhibited tumor growth in nude mice with no toxicity and the expression of the proliferation marker Ki-67. Upon 48h from irradiation, the intracellular uptake of lenvatinib was increased significantly, suggesting that the elevated irradiation-induced membrane permeability increases the intracellular level of lenvatinib, in this way contributing to the synergistic effect. This combination therapy could be a good novel therapeutic strategy in advanced TC with fewer AE [52].

4. Clinical efficacy

4.1 *In vivo* clinical studies in aggressive RAI-refractory DTC

Phase I, phase II, and phase III studies in patients with aggressive RAI-refractory DTC have demonstrated that lenvatinib is linked to an improvement in PFS vs. placebo (18.2 vs. 3.6 months), even though AE of any grade occur in more than 40% of cases [27].

Fifty-eight patients with aggressive RAI-refractory DTC were enrolled in a phase II study, who showed a disease progression in the earlier 12 months, and received lenvatinib (24 mg once daily) in 28-day cycles. The circulating levels of angiogenic factors and 51 cytokines were evaluated [53]. Objective response rate (ORR) was the primary endpoint; secondary endpoints included PFS and safety. Upon 14 months of follow up, ORR was of 50% (for the 17 patients who received previously VEGF therapy was 59%), and only partial response (PR) was reported. Median Time to Response (TTR) was 3.6 months, median response duration 12.7 months, and median PFS 12.6 months. Lower baseline levels of angiopoietin-2 were linked to the tumor response and longer PFS. In 72% of patients grade 3 and 4 AE were reported (weight loss, 12%; hypertension, 10%; proteinuria,10%; diarrhea,10%). The encouraging data led to the need of further investigations in a phase III trial [53].

A randomized, double-blind, phase III study was conducted in patients with progressive RAI-refractoy TC, 261 of whom received lenvatinib (24 mg daily in a 28-day cycle) and 131 placebo [48]. DTC patients treated with placebo could receive open-label lenvatinib, at the time of disease progression. The primary endpoint was PFS, and secondary endpoints were RR, overall survival (OS), and safety. The median PFS was 18.3 months and 3.6 months ($P<0.001$), and the RR was 64.8% and 1.5% ($P<0.001$), in the lenvatinib group vs. the placebo group, respectively. In patients treated with lenvatinib, 4 complete responses (CR) and 165 PRs were reported. OS was not reached in both groups. More than 40% of patients administered with lenvatinib had AE of any grade: nausea (41.0%), decreased weight (46.4%), decreased appetite (50.2%), asthenia or fatigue (59.0%), diarrhea (59.4%), and hypertension (67.8%). The study was discontinued by 37 lenvatinib-treated patients (14.2%) and 3 patients receiving placebo (2.3%) owing to AE, and 6/20 deaths in the

lenvatinib group were drug-related. In patients with aggressive RAI-refractory TC, lenvatinib led to significant improvements in PFS and RR [48].

A subanalysis investigated the safety and efficacy of lenvatinib in Japanese patients (10 receiving placebo and 30 lenvatinib) who took part in the SELECT study and the results were evaluated in relation to the SELECT population (131 treated with placebo, and 261 with lenvatinib) [54]. Median PFS in lenvatinib-treated patients was 16.5 months, and in those receiving placebo was 3.7 months (P=0.067). Overall response rate was 63.3% for lenvatinib and 0% for placebo, and OS was not significantly different. In the evaluated patients the lenvatinib safety profile was similar to that of the overall SELECT population, even if with a higher incidence of hypertension (any grade: Japanese, 87 %; overall, 68 %; grade ≥ 3: Japanese, 80 %; overall, 42 %). More dose reductions (overall, 67.8%; Japanese, 90%), but fewer discontinuations due to AE (overall, 14.2%; Japanese, 3.3%) were present in Japanese patients. Overall, clinical data similar to those from the SELECT population were reported in these RAI-refractory DTC patients [54].

Another paper investigated the changes in tumoral size associated with the lenvatinib treatment, in the SELECT Phase III, randomized, multicenter, double-blind study [55]. Patients reporting CR or PR (n=169) were considered responders to the therapy. Among nonresponders, 76/92 had at least one postbaseline tumor evaluation and were included in the study. The median maximum percentage change in tumor size in patients treated with lenvatinib (-51.9%, responders; -20.2%, nonresponders) was -42.9%. At the first evaluation the decrease of tumor size was higher (median, -24.7% at 8 weeks after randomization); subsequently the rate of decrease was slower even though continuous (-1.3% / month). The percentage change in tumor size at the first evaluation was a moderately significant positive predictor for PFS in a multivariate model. The reported data suggest that lenvatinib-associated tumor size changes consist of a first rapid decline, followed by a slow, continuous shrinkage [55].

A subanalysis evaluation evaluated the effect of age on the safety and effectiveness of lenvatinib in RAI-refractory DTC patients of the SELECT trial, treated with lenvatinib 24 mg/day or placebo

[56]. In both treatment arms, median ages were 71 years (older group) and 56 (younger group), and PFS was not significantly different in either treatment arm. This subanalysis reported an improved PFS in lenvatinib-treated patients (vs. placebo) in both age groups, even if a higher toxicity was shown in older subjects [56].

A phase II study evaluated the efficacy and safety of lenvatinib (24 mg, once daily) in 51 Japanese patients with RAI-refractory DTC, ATC or MTC patients. The primary end point was safety. For RAI-refractory DTC patients, RR was 68%, and median PFS 25.8 months. Lenvatinib demonstrated a manageable safety profile and antitumor activity in RAI-refractory DTC patients [57].

Since some patients with DTC may need an initial low dose of lenvatinib, a cross-sectional study reviewed retrospectively records of 36 DTC patients treated with lenvatinib, subdivided into 2 groups according to the first dose of lenvatinib: 30 treated with an initial full dose (FD) of 24mg/d and 6 with an initial low dose (LD) of less than 24mg/d [58]. The RR was 33% and 43% in the LD and FD groups, respectively. The median PFS duration was 696 days in the FD group, while it was not reached in the LD group (P=0.293). No significant differences in the incidence of common AE were present between the 2 groups, but also the LD group needed frequently dose reduction or interruption. It was concluded that a large number of cases and long-term observations were necessary to clarify whether an initial LD is effective in DTC patients in poor general conditions [58].

4.2 Real-life studies in aggressive RAI-refractory DTC

In the registration study SELECT, lenvatinib (24 mg) had a clinical benefit as confirmed in patients by PFS and radiological response. PFS was 18.3 vs. 3.6 months in the placebo group (P<0.001) and 64.7% of patients had a PR or CR in comparison to 1.5% in the placebo group, according to the RECIST criteria [48]. An analysis of the efficacy of lenvatinib in the SELECT trial demonstrated a median PFS of 19.4 months in comparison to 3.7 months in patients receiving placebo, with a median PFS of 33.1 months, considering data from the responsive patients [59]. Real-life studies

agreed with the drug effectiveness, even if lower than that reported by the SELECT study, with PFS <15 months. This is probably caused by a more advanced tumor stage, the more common pretreatment of patients with other TKIs, the presence of comorbidities, that would have not permitted to enroll them in the SELECT trial. Concerns are reported regarding the reliability of clinical trials data in real world, and EMA has confirmed the use of real-life studies considering their determinant role to monitor drugs, and supporting the data derived from randomized clinical trials [60].

A monocentric study was conducted in 13 patients with progressive, locally advanced or metastatic, RAI-refractory DTC treated with lenvatinib. Median PFS was 22 months with PR in 69% and stable disease (SD) in 31% of patients. Among all published real-life studies, PFS was the longest, with the most elevated rate of PR and one of the lowest drug discontinuation rate owing to AE [61].

In another real-life study, 22 patients were treated for about 7.1 months with lenvatinib, 13 of whom had previously received one or more TKI. Best overall response was CR in one patient (4.5%), PR in 7 (31.8%), SD in 7 (31.8%), and progressive disease (PD) in 6 (27.3%). Median PFS was 13.7 months. PFS and the tumor response were similar to those of other real-life studies, but inferior to those of the SELECT trial, probably because of a higher number of patients with prior TKI therapy, comorbidities, and poor performance status [62].

The efficacy of lenvatinib was also evaluated retrospectively in 42 RAI-refractory DTC patients. The best overall response were PR of 62%, SD of 24%, and PD of 14%. OS and PFS rates were 51.0% and 32.4%, respectively. Twenty-three (55%) patients did not match the inclusion criteria of the SELECT trial. Moreover, PD-experienced patients individually decided whether to continue lenvatinib, and 41% made the decision themselves; these patients had a 3-year OS of 43.0% and post-progression survival of 13.3 months. The data reported an equivalent efficacy of lenvatinib as in the SELECT study, proving the efficacy of lenvatinib in a real-world setting [63].

A retrospective multicenter study analyzed OS and PFS and tolerability in 43 patients with RAI-refractory TC with metastases to the brain (12%), liver (16%), bone (35%), lymph nodes (74%),

and lungs (86%), treated with lenvatinib. After 24 months PFS was 71% and OS 74%, respectively. Lenvatinib had a sustained clinical efficacy in these patients and the effects were similar to the registration trial, although patients had a higher median age and more common dose reductions [64].

A multisite, retrospective chart review of US RAI-refractory DTC patients, who had started lenvatinib as first-line therapy, was conducted. Patients were subdivided in 2 cohorts: cohort 1, patients still receiving lenvatinib as first-line therapy; and cohort 2, patients who had started second-line therapy prior to data cutoff [65]. A total of 252 patients with PTC and lung metastases were enrolled: 71 in cohort 1 and 181 in cohort 2. In cohort 2, median PFS from first-line lenvatinib initiation was 14.0 months. Second-line treatments were sorafenib (49.7%), cabozantinib (19.3%), and other targeted/chemotherapy/immune-oncology agents. The data indicated that first-line lenvatinib followed by another second-line agent could have a clinical benefit, permitting different second-line options following first-line lenvatinib for RAI-refractory DTC patients [65].

5. Safety and tolerability

AE of any grade can occur in >40% of patients receiving lenvatinib, including hypertension, asthenia or fatigue, nausea, decreased appetite, proteinuria, diarrhea, decreased weight, palmar-plantar erythrodysesthesia. Discontinuations of the therapy because of AE are present in ~14% of patients, and even drug-related deaths [27,66].

Hypertension is an established AE of VEGFR inhibition. In the SELECT trial, hypertension was the most frequent AE of lenvatinib. An exploratory analysis assessed treatment-emergent hypertension and its relation with lenvatinib efficacy and safety in SELECT [67]. Seventy-three% of patients treated with lenvatinib and 15% with placebo experienced treatment-emergent hypertension. The median PFS was 18.8 and 12.9 months for lenvatinib-treated patients with and without hypertension, respectively (P=0.0085). In patients receiving lenvatinib, the ORR was 69% with treatment-emergent hypertension and 56% without. The median change in tumor size for patients

without and with hypertension was -40% and -45%, respectively (P=0.2). Treatment-emergent hypertension correlated significantly with improved outcomes in patients with RAI-refractory DTC, suggesting that hypertension could predict the lenvatinib efficacy in these patients [67].

VEGFR inhibitors could induce hypertension through different mechanisms: the interruption of endothelial cell survival signaling, leading to apoptosis and capillary rarefaction [68]; the inhibition of endothelial production of nitric oxide, leading to constriction of vascular smooth muscle cells [69] and activation of the endothelin-1 pathway [70]. Moreover, it has been hypothesized that angiotensin receptor blockers and angiotensin converting enzyme (ACE) inhibitors could have some antitumor effects [71].

An exploratory post hoc analysis evaluated the effect of dose interruption on lenvatinib efficacy in the SELECT study. Dose changes were necessary for grade 3 or intolerable grade 2 AE. Patients treated with lenvatinib were dichotomised according to the duration of dose interruption with respect to total treatment duration: shorter dose interruption (<10% of total treatment duration) and longer dose interruption (≥10%). In patients with RAI-refractory DTC, lenvatinib improved efficacy vs. placebo, independently from the duration of dose interruption, even if those with shorter dose interruptions had a higher benefit vs. those with longer interruptions. The obtained data suggest the importance of timely management of lenvatinib toxicity to maximise lenvatinib efficacy in these patients [72].

A literature review was conducted to develop consensus-based guidance in order to manage lenvatinib-associated AE [73]. Blood pressure (BP) should be evaluated once a day in patients who already had hypertension, or starting 1 week upon the beginning of lenvatinib and once a week in the first two months. In patients with systolic BP ≥135 mmHg to <160 mmHg or diastolic BP ≥85 mmHg to <100 mmHg, an antihypertensive treatment should be initiated, or increased. In patients who are still hypertensive, a treatment interruption can be evaluated. For grade 1/2 diarrhoea, loperamide could be used first with a one week therapy interruption if diarrhoea goes on; if diarrhoea occurs again once restarted the treatment, a reduction of the dosage should attempted.

Patients should have a healthy lifestyle, and the appearance of anorexia and/or a 10% weight loss with respect to basal body weight could be managed interrupting the therapy once a week. Considering proteinuria, patients with grade 2 can continue lenvatinib, but an angiotensin II receptor blocker or ACE inhibitor could be suggested. If proteinuria is >grade 3, lenvatinib could be interrupted until proteinuria returns to grade 1, while to stop the therapy is necessary for chronic proteinuria. Regularly repeated monitoring and symptomatic management with appropriate short treatment breaks, or dose reductions for persistent AE, are recommended to permit patients to remain on the optimal dose regimen [73].

Recently a study evaluated retrospectively the clinical records of 37 patients with RAI-resistant DTC treated with lenvatinib, in order to investigate the incidence of treatment-related late toxicities [74]. Among patients, 65% had ≥65 years and 68% were female; 30 patients were treated with lenvatinib for more than 12 months. The frequency of late AE was 80% and cardiovascular toxicity was the most common (57%; in particular arterial hypertension, 23%), with no difference in their incidence considering younger/older subjects. Among the 13 patients with an age <65 years, 77% had at least one new late treatment-related AE (proteinuria, hypertension, diarrhea, thrombosis and pulmonary thromboembolic). Among the 17 patients over 65 years, 82% developed a late treatment-related AE: 7 new cardiotoxic event other than hypertension (QTc prolongation and Q-wave, rhythm disturbances), new hypertension, weight loss and acalculous cholecystitis. This study shows that the burden of late treatment-related AE is not negligible (80%) and it underlines the importance of maintaining a close follow-up also in patients on prolonged treatment. The findings reported a higher frequency of cardiovascular AE other than hypertension, overall in patients with an age ≥65 years. In the SELECT trial, QT prolongation occurred in 8% of patients, and in this study in 7% of patients only as a late treatment-related AE, suggesting the importance of a periodic ECG monitoring also in case of long-term exposure to lenvatinib [74]. Intestinal toxicity with diarrhea was the second most common late treatment-related AE in younger patients. Acalculous cholecystitis is an uncommon complication [75]. The mechanism at the basis appears to involve

microthrombi formation and microvascular ischemia, comparable with what described with other TKIs [75]. When symptoms (such as abdominal pain, nausea, and diarrhea) can not be managed by symptomatic treatment, colechystectomy should be considered, unless lenvatinib discontinuation, in order to continue the treatment [74].

6. Conclusion

Lenvatinib is a multitargeted, oral TKI of VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT signaling networks implicated in tumor angiogenesis, approved in patients with locally recurrent or metastatic, progressive, RAI-refractory DTC.

In vitro studies have shown the antineoplastic effect of lenvatinib in DTC, overall because of its antiangiogenetic effects.

In vivo studies in patients with aggressive RAI-refractory DTC have shown that lenvatinib administration was linked to a significant PFS improvement in comparison to placebo (18.2 vs. 3.6 months), even if OS was not significantly different.

AE of any grade occur in >40% of patients receiving lenvatinib.

Real-life studies confirmed the drug effectiveness, even if lower than that reported by the SELECT study, with PFS <15 months.

The decision making process in patients with aggressive RAI-refractory DTC should be personalized for each patient and the potential toxicity should be evaluated and properly managed.

7. Expert Opinion

Approximately 5% of DTC patients have distant metastases at the diagnosis, and ~15% of them develop recurrences. At 10 years, survival decreases from 70 to 50% [20].

If DTC progresses, thyrocytes become refractory to RAI, and prognosis is poorer [20]. When metastatic DTC does not respond to RAI and TSH-suppressive TH treatment [24], different

therapeutical options (including surgery, chemotherapy and EBRT), alone or in combination, are not associated with a significant prolongation of survival and have a palliative role [25].

Unmet needs regarding the patient clinical therapy responsiveness in aggressive RAI-refractory DTC still remain. Thanks to the understanding of the molecular pathways that take part in TC progression, important advances have been done, and small molecule inhibitors able to target the intracellular TKs linked to different receptors have been developed [5,27,29,30].

Lenvatinib is a multitargeted TKI of VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT signaling networks implicated in tumor angiogenesis, and it was approved by FDA and EMA in February and March 2015 in patients with locally recurrent or metastatic, progressive, RAI-refractory DTC [27,28].

Considering the results obtained in the SELECT study, the recommendation is to begin the treatment with 24 mg daily and to decrease the dose in relation to side effects [47,48,76]. It could be rational to interrupt treatment upon disease progression, but an acceleration in disease progression upon TKIs discontinuation has been demonstrated [77]. However, it cannot be ignored that therapy continuation could result in a clinical benefit.

The antineoplastic effect of lenvatinib on the reduction of tumor lesions is different from one patient to another one. Sometimes even with lenvatinib 10 mg/day important unexpected reduction of the tumor lesion has been reported and the regression in some cases is associated with the appearance of important side effects, such as bleeding or perforation of infiltrated organs (i.e., the trachea). For this reason some Authors prefer to start the treatment with a suboptimal dose of lenvatinib, overall in patients with infiltration of vital organs, with periodical evaluation of the changes of the tumor mass.

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.

Recently, a phase II, open-label, single-arm study in patients with TC was conducted (including ATC, RAI-refractory DTC, and MTC), who took lenvatinib 24 mg daily until disease progression

or development of intolerable toxicities. At data cutoff, 17 ATC patients were enrolled. All had ≥1 AE. The median PFS was 7.4 months, the median OS 10.6 months, and the ORR 24%. Lenvatinib showed a manageable toxicity with dose adjustments and clinical activity in ATC patients [78].

Moreover, another study evaluated 32 patients with stage IVC ATC, among whom 16 received lenvatinib. The other 16 patients were treated with palliative therapy, of whom 7 received weekly paclitaxel, 2 external radiation for tumor reduction 5 days per week until treatment completion, and 2 underwent tracheostomy. A significant survival improvement was observed in patients receiving lenvatinib vs. the others (P=0.00298). Lenvatinib treatment had a median survival improvement of ~2 months in comparison to the other therapies in stage IVC ATC, even if an appropriate lenvatinib dose reduction could be necessary, owing to the reported AE [79].

Lenvatinib has one of the highest RR in DTC and to date for example it has been approved in Japan for treating patients with all histological subtypes of unresectable TC, even if it is not completely clear whether this higher RR is at the expense of a higher toxicity. However, lenvatinib is a promising novel agent for the treatment of patients with advanced TC, and recently its effects in combination therapy also with mmune checkpoint inhibitors have been evaluated.

Mechanisms of resistance to lenvatinib can be of intrinsic or acquired origin; as regard the acquired resistance, it can be due to the upregulation of FGFR, therefore anti-FGFR agents may have application in this setting [80].

Recently it has been shown the interaction between the immune system cells and TC cells can be altered by immune checkpoints (PD1, PDL-1, CTLA-4) and it has been shown that the expression of PDL-1 in TC was related to tumor recurrence and poor survival [81,82]. However, some studies revealed a relatively poor response to immunotherapy with checkpoint inhibitors in DTC [83,84].

A new strategy is to combine lenvatinib with immunotherapy. Several studies are evaluating lenvatinib and pembrolizumab in RAI-refractory DTC patients [85]. Moreover, other clinical

trials for radioiodine-refractory TC are ongoing (such as for Metastatic DTC: NCT03732495, Lenvatinib + Denosumab).

According to the above mentioned data, the decision making process in patients with aggressive RAI-refractory DTC should be personalized for each patient and the potential toxicity should be evaluated and properly managed.

To obtain more stringent results the enrollment of subject with RAI-refractory TC in clinical trials should be encouraged to better evaluate the clinical outcomes, and effects on the quality of life of patients with TC treated with lenvatinib alone or in combination with other chemoterapeutics.

Financial and competing interests disclosure

The authors report no conflicts of interest

Article highlights box

1. When DTC progresses, it does not respond to RAI and TSH-suppressive thyroid hormone treatment, and other therapies (i.e. surgery, external beam radiation therapy and chemotherapy) do not lead to a better survival. Thanks to the understanding of the molecular pathways involved in TC progression, important advances have been done for the therapy

2. Lenvatinib is a multitargeted tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT signaling networks implicated in tumor angiogenesis, approved in locally recurrent or metastatic, progressive, RAI-refractory DTC

3. According to the results deriving from the SELECT trial, the treatment with lenvatinib should be initiated with a dosage of 24 mg/die, subsequently decreasing the dose in relation to the side effects

4. AE of any grade can occur in >40% of patients receiving lenvatinib, including hypertension, asthenia or fatigue, nausea, decreased appetite, proteinuria, diarrhea, decreased weight, palmar-plantar erythrodysesthesia

5. The decision making process in patients with aggressive RAI-refractory DTC should be personalized and the potential toxicity should be evaluated and properly managed

Drug Summary Box

Drug name (generic)	E7080 or Lenvatinib
Phase (for indication under discussion)	Phase I, phase II, and phase III studies
Indication (specific to discussion)	Locally recurrent or metastatic, progressive, RAI-refractory DTC
Pharmacology description/mechanism of action	Lenvatinib is a multitargeted tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT signaling networks implicated in tumor angiogenesis
Route of administration	Oral TKI
Chemical structure	$C_{21}H_{19}ClN_4O_4$
Pivotal trial(s)- please include references	[48,53]

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