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ORIGINAL ARTICLE

Effectiveness and safety of lenvatinib in a series of advanced well-differentiated thyroid carcinomas from a single tertiary cancer center and literature review

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ABSTRACT

BACKGROUND: Treatment of advanced differentiated thyroid carcinoma (DTC) remains a challenge as 25-50% of patients with locally invasive or distant metastatic disease become refractory to radioiodine (RAI) therapy. Tyrosine kinase inhibitors (TKI) are increasingly used in this setting. The SELECT trial demonstrated that lenvatinib, a multikinase inhibitor, significantly improved progression free survival (PFS) compared to placebo. Our aim was to report the effectiveness and safety of lenvatinib in our series of patients with advanced DTC.

METHODS: A total of 25 patients with advanced DTC followed at a single tertiary center from January of 2016 to January of 2022 were retrospectively reviewed.

RESULTS: Patients were treated with a mean daily dose of lenvatinib of 16.9 mg for a mean of 9.1 months. Median estimated PFS was 31.3 months. One patient achieved complete response. The objective response rate (ORR) was 40% and the disease control rate was 84%. The mean change in summed longest diameter of target lesions from baseline to nadir was -36.9%. Lenvatinib prolonged the tumor volume doubling time in 86.7% patients. Interestingly, we found that patients treated with a lower dose of lenvatinib (<16.9 mg daily) had a significantly higher PFS and ORR than patients treated with higher dosages (>16.9 mg). Adverse events were frequently reported.

CONCLUSIONS: Our results confirm the effectiveness of lenvatinib in the management of patients with advanced DTC and support the need to adjust the dosage of lenvatinib to patient´s performance status and comorbidities.

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KEY WORDS: Thyroid neoplasms; Lenvatinib; Tyrosine kinase inhibitor.

Differentiated thyroid cancer (DTC) comprises the majority (>90%) of all thyroid malignancies and its incidence is increasing.[1] Well DTC (WDTC) can be divided in two main subtypes: papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) which, to-

gether, represent 87-90% of thyroid cancers. Total thyroidectomy followed by radioiodine (RAI) therapy in selected cases is the standard treatment modality for the majority of DTC patients. However, treatment of advanced DTC remains a challenge as 25-50% of patients with locally invasive or distant metastatic disease become refractory to RAI therapy.[2-4] Surgery remains one of the main tools regarding locally recurrent disease. External beam radiation therapy (EBRT) may also be considered for patients with loco-regionally recurrent disease[1] or with distant metastases that cause pain (such as bone metastases) or threat vital organs.[5, 6] Other localized treatments such as thermal or ethanol ablation and chemo-embolization may also be pursued in patients with single or oligo-metastatic disease.[7-9] Nevertheless, in a significant percentage of patients with advanced DTC, systemic therapy is needed. The role of cytotoxic chemotherapy is limited in this context, as it is associated with significant side effects without prolonging survival.[2, 10, 11] Given the established role of tyrosine kinase (TK) activation in the development of advanced thyroid cancer, tyrosine kinase inhibitors (TKI) are being increasingly used among patients with rapidly progressive and/or symptomatic RAI-refractory disease that cannot be managed with local therapies.[1, 12, 13]

Three phase 3, multicenter randomized clinical trials demonstrated a significant improvement in progression free survival (PFS) in patients treated with sorafenib,[14] lenvatinib[15] or cabozantinib[16] compared to placebo. Based on these results, these TKIs have been approved in the United States and in Europe for patients with advanced RAI-refractory DTC. Our aim was to report the effectiveness and safety of lenvatinib in our series of patients with advanced WDTC.

Materials and methods

Study design

We retrospectively reviewed the clinical records of 25 patients with advanced WDTC who started treatment with lenvatinib at the Instituto Português de Oncologia de Lisboa between January 2016 and January 2022. Patients with poorly differentiated or anaplastic thyroid carcinomas were excluded.

This study was conducted in compliance with the Helsinki Declaration and was approved by the Ethics Committee of our Institution.

Patients

Inclusion criteria: Patients with ≥18 years of age with the diagnosis of WDTC (as confirmed by histological analysis of thyroidectomy specimens or by cytological findings in the case of one patient who did not undergo surgery) who had disease progression in the 12 months before initiation of lenvatinib.

RAI-refractory disease was defined as: disease with at least one lesion without RAI uptake on whole-body scintigraphy, documented disease progression within a year after RAI treatment despite RAI avidity, or persistent disease after a cumulative activity ≥600 mCi of RAI.

Imaging and biochemical assessment

Serum levels of TSH, T3, TSH-suppressed thyroglobulin (Tg) and antithyroglobulin antibodies (TgAB) were measured at 3-month intervals. Imaging evaluation was also carried out every 3 months after starting treatment with lenvatinib. Computed tomography (CT) and neck ultrasound were the imaging techniques most frequently used throughout the follow-up to define disease status. Fluorodeoxyglucose positron emission tomography (PET-FDG) or magnetic resonance imaging was also performed in some patients.

Effectiveness

Effectiveness measures included best overall response (BOR) evaluation according to the RECIST v. 1.1 criteria: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Overall objective response rate (ORR) was defined as CR+PR; Disease-control rate (DCR) was defined as CR+PR+SD and Clinical Benefit Rate (CBR) was defined as CR+PR + sustained SD >23 weeks.

Progression free survival (PFS) and median overall survival (OS) were also calculated.

PFS was defined as the time from initiation of lenvatinib therapy to PD, death from thyroid cancer or last day of follow-up. OS was defined as the time from initiation of lenvatinib therapy until death or last day of follow-up.

To calculate the change in the sum of target lesions' greatest diameters from baseline to nadir and to estimate tumor volume doubling times (TVDT), we excluded patients with non-measurable disease (lesions smaller than 5 mm, lesions that were not clearly demarcated at diagnosis or follow-up and lung miliary lesions, in which it was not possible to trace a specific nodule over time).

TVDT pre and post-therapy with lenvatinib were calculated by a method used in the Kuma Hospital (http://www.kuma-h.or.jp/english/about/doubling-time-progression-calculator/).http://www-kuma-h.or.jp/english/about/doubling-time-progression-calculator/).[11]

Safety

Severity of adverse effects (AE) was assessed according to the National Cancer Institute Common Terminology for Adverse Effects (CTCAE) v5.0.

Statistical analysis

Categorical variables are presented as absolute numbers and percentages. Continuous data are presented as mean and standard deviations or median and interquartile ranges (IQR). Qualitative data is described as percentage. Normal distribution was checked using Shapiro-Wilk Test or skewness and kurtosis.

The differences among groups were estimated with the Pearson's Chi-square Test and Fisher's Exact Test as appropriate for the categorical variables and with the Mann-Whitney U Test for continuous variables. Median PFS and median OS were calculated with the Kaplan-Meier method.

All analyses were performed using SPSS software v. 25. A P value of ≤0.05 was considered statistically significant.

Results

Background characteristics

The baseline characteristics of the 25 patients are summarized in Table I. Median age at initiation of lenvatinib was 67.6±1.8 years and 64% patients were females. Twenty-four patients underwent total thyroidectomy and RAI treatment with a mean cumulative activity of 332.5±56.9 mCi. The remaining patient was considered to have unresectable disease and had only cytological confirmation of PTC.

TABLE I.—*Baseline characteristics of the patients.*

Characteristics	Value	N. patients
Age (years)		25
At diagnosis	59.5±8.9	
At lenvatinib initiation	67.6±9.2	
Gender		25
Female	16 (64%)	
Male	9 (36%)	
Histological subtype		24
Papillary	19 (79.2%)	
Classic	5 (20.8%)	
Follicular	5 (20.8%)	
Solid/trabecular	2 (8.3%)	
Classic and follicular	2 (8.3%)	
Classic and solid/trabecular	2 (8.3%)	
Classic, follicular and solid/trabecular	1 (4.2%)	
Follicular	5 (20.8%)	
Tumor characteristics		23
Multifocality	15 (65.2%)	19
Vascular invasion	18 (94.7%)	19
Microscopic extrathyroid extension	13 (68.4%)	25
T		23
T1b	2 (8.7%)	
T2	5 (21.7%)	
T3a	7 (30.4%)	
T3b	3 (13%)	
T4a	4 (17.4%)	
T4b	2 (8.7%)	
N		25
N0	8 (32%)	
N1a	7 (28%)	
N1b	10 (40%)	
M		25
M0	1 (4%)	
Lung	22 (88%)	
Bone	15 (60%)	
Other	7 (28%)	
AJCC 8ª Editions		25
II	4 (16%)	
IV b	21 (84%)	
Previous treatments		25
RAI therapy	24 (96%)	
Mean cumulative activity (mCi)	332.5±56.9	
Radiotherapy (RT)	13 (52%)	
Bone	12 (48%)	
Neck	4 (16%)	
Lung	1 (4%)	
Chemotherapy (CT)	2 (8%)	
Gemcitabin + oxiplatin	1 (4%)	
Doxorrubicin + docetaxel	1 (4%)	
Tyrosine kinase inhibitors (TKI)	8 (32%)	
Sorafenib	6 (24%)	
Sorafenib + sunitinib	2 (8%)	
Eligibility for inclusion in SELECT	10 (40%)	25

Of the 24 patients who had a thyroidectomy, 19 (79.2%) had a diagnosis of PTC, with classic and follicular subtypes being the most common (20.8% each). The remaining 5 patients (20.8%) had FTC. The majority of tumors were multifocal (65.2%), had vascular invasion (94.7%) and microscopic extrathyroidal extension (68.4%). BRAFV600E mutation status was assessed in 13 patients and was negative in 11. In the two patients with tumors harboring BRAFV600E mutation, this analysis was performed after lenvatinib progression in order to look for targetable mutations.

Sixteen patients (69.5%) had T3 or T4 disease and 17 (68%) had neck nodal metastasis. Among the 24 patients with distant metastasis (M1), 62.5% had M1 disease in two or more tissues. The most frequent sites of metastasis were lung (91.7%), bone (62.5%) and mediastinal lymph nodes (41.7%).

Regarding prior treatments: 24 (96%) patients underwent RAI therapy with a mean cumulative activity of 332.5±56.9 mCi; 13 (52%) patients received EBRT and eight (32%) patients received other TKI therapy previously to lenvatinib.

Only 10 (40%) patients would have been eligible to be included in the SELECT trial. The main reasons for exclusion would be: Eastern Cooperative Oncology Group (ECOG) performance status >2 in six patients; inadequately controlled blood pressure (>150/90 mmHg) in three patients; diagnosis of other within in the 24 months prior to lenvatinib initiation in one patient; anticancer treatment in the previous 21 days in three patients (TKIs in two patients, RT in one patient) and prior treatment with two different TKIs in two patients.

Treatment course

In our population, the median follow-up time was 14.5 months (IQR: 5-28) and the median duration of lenvatinib treatment was 9.1 (IQR: 3.9-18.7) months. Lenvatinib was started with a median daily dose of 20 mg (IQR 14-24), and dose was adjusted to patient performance status and comorbidities. The mean daily dose was 16.9±3.3 mg. The median daily dose at the end of treatment was 14 mg (IQR: 14-18). Lenvatinib was started at a mean of 4.7±2.4 months after demonstration of progression.

Effectiveness measures

Effectiveness measures are summarized in Table II.

Median estimated PFS was 31.3 months (95% CI: 15.7-46.9) and median estimated OS was 29.6 (25-34.1). Plotted PFS and OS are displayed in Kaplan-Meier curves in Figures 1 and 2, respectively. A brief analysis comparing TKI-naïve patients (N.=17) vs patients treated with one or more TKI before lenvatinib (N.=8) has been performed but no statistical significant differences in respect of PFS and OS between these two groups was find.

BOR could be evaluated in 22 patients: one (4%) patient achieved CR during 7 months after 2 months of therapy. PR was reported in nine (36%) patients with a median duration of 12 months (IQR: 10.4) and SD was reported in 11 (44%) patients with a median duration of 4 months (IQR: 10). One (4%) patient showed PD as BOR after 2 months of treatment. At the end of the observation period, five more patients had PD, after a mean of 18.8±17.9 months under len-

TABLE II.—*Effectiveness measures.*

Measures	Value
PFS	
Estimated median (95% CI), months	31.3 (15.7-46.9)
Estimated mean (95% CI), months	28.5 (20.2-36.9)
PFS rate (95% CI)	
6 months	79.5%
12 months	71.1%
18 months	65.6%
24 months	49.2%
OS	
Estimated median (95% CI), months	29.6 (25-34.1)
Estimated mean (95% CI), months	29.4 (21.1-37.7)
OS rate (95% CI)	
6 months	79.5%
12 months	71.1%
18 months	71.1%
24 months	35.5%
BOR	
CR	1 (4%)
PR	9 (36%)
SD	11 (44%)
PD	1 (4%)
Not estimable	3 (12%)
ORR	10 (40%)
DCR	21 (84%)
CBR	13 (52%)
PD at the end of follow-up	6 (24%)
Overall deaths	10 (40%)
Disease related deaths	7 (28%)
Treatment related deaths	1 (4%)
Unknown	2 (8%)

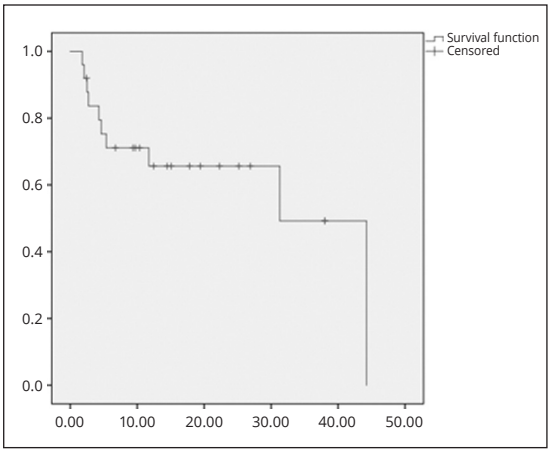

Figure 1.—Survival Function. Kaplan-Meier analysis of progression free survival.

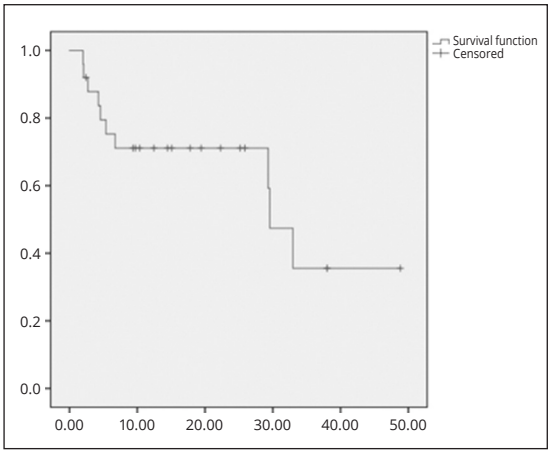

Figure 2.—Survival function: Kaplan-Meier analysis of median overall survival.

vatinib therapy. ORR was 40%, DCR was 84% and CBR was 52%.

It was possible to determine the evolution of target lesions in 16 patients (Figure 3). At baseline, the median sum of target lesions was 45 mm (IQR:89) and tumor shrinkage was observed in 15 (93.8%) patients. The mean change in summed longest diameter of target lesions from baseline to nadir was -36.9±27.8%.

TVDT was determined in 15 patients and tumor shrinkage was observed in 14 (93.3%) patients. The median TVDTs before and at best lenvatinib response were 9 months (IQR: 3-12.3) and -3.7 months (IQR: -7 to -2.2), respectively.

Figure 4 depicts the change in TVDT of target lesions: before the initiation of lenvatinib, 12 patients (80%) had TVDT ≤1 year and three (20%) had TVDT 1-3 years. After a mean of 14.5±12.4 months of therapy with lenvatinib, one patient (6.7%) had TVDT ≤ 1 year, one (6.7%) patient had TVDT 1-3 years and 13 (86.7%) patients had TVDT ≥3 years.

Therapy with lenvatinib prolonged the TVDT of 13 (86.7%) patients, from which 12 (80%) had TVDT≤1 year before treatment. From the 12 patients with TVDT pre-lenvatinib ≤1 year, 11 (91.7%) showed a prolongation of TVDT to ≥3 years.

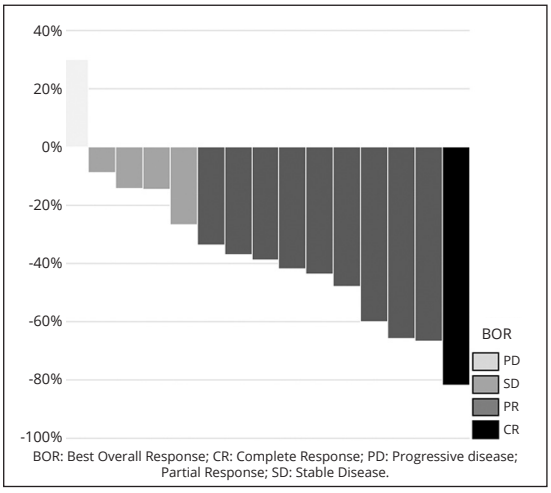

Figure 3.—Waterfall plot of percentage change in summed longest diameter of target lesions from baseline to nadir.

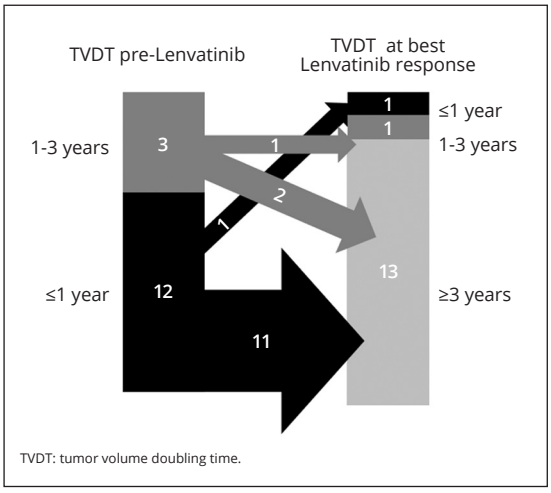

Figure 4.—Change in tumor volume doubling times of target lesions.

TABLE III.—*Most prevalent adverse events.*

Adverse events	Grade 1-2	Grade 3	All grades
High blood pressure	14 (56%)	7 (28%)	21 (84%)
Asthenia	11 (44%)	6 (24%)	17 (68%)
Proteinuria	16 (64%)	1 (4%)	17 (68%)
Diarrhea	5 (20%)	9 (36%)	14 (56%)
Decreased appetite	8 (32%)	4 (16%)	12 (48%)
Blood loss	8 (32%)	0 (0%)	8 (32%)
Arthralgias	3 (12%)	2 (8%)	5 (28%)
Weight loss	1 (4%)	2 (8%)	3 (12%)
Vomiting	4 (16%)	3 (12%)	7 (28%)
Hyponatremia	7 (28%)	0 (0%)	7 (28%)
Palmar-plantar erythrodysesthesia	3 (12%)	3 (12%)	6 (24%)
Mucositis	3 (12%)	1 (4%)	4 (16%)
Thrombocytopenia	4 (16%)	0 (0%)	4 (16%)
Hypocalcemia	4 (16%)	0 (0%)	4 (16%)
Dysphonia	3 (12%)	0 (0%)	3 (12%)
Hepatotoxicity	3 (12%)	0 (0%)	3 (12%)
Rash	1 (4%)	1 (4%)	2 (8%)

Safety

In our cohort, 24 (96%) patients reported adverse events (AE). The single patient who did not report any AE was under therapy with lenvatinib for just 2.4 months.

Fifteen patients (52%) experienced a dose reduction due to AE and 17 patients (68%) had a transient treatment discontinuation. Additionally, five patients (20%) required definitive lenvatinib discontinuation due to AE.

Table III shows the most prevalent AE. High blood pressure was reported in 21 patients (84%) and was the most frequent AE. It was also the first reported AE in 14 patients (56%). Despite its frequency, it was reasonably well managed in all patients with initiation and/or titration of antihypertensive drugs. Other common AE included asthenia and proteinuria, both in 17 (68%) patients, diarrhea in 14 (56%) patients and anorexia in 12 (48%) patients.

Diarrhea was the most common grade 3 AE, requiring drug discontinuation in five patients (20%) and dose reduction in eight patients (32%). Diet modifications (with increasing water and low-fiber foods, avoidance of caffeine and alcohol) and antidiarrheal agents such as loperamide were used in all cases. However, these measures were rarely effective and dose reductions were frequently needed.

Nine grade 4 AE were reported: a pleural fistula in one patient; pneumonia in two patients, cholecystitis due to gallbladder stones in one patient; ulceration of a metastatic lesion in two patients; ulceration of a non-metastatic pre-existing lesion in 1 patient; acute myocardial infarction in one patient and asymptomatic aortic dissection in 1 patient. Of note, this last patient had poor compliance to anti-hypertensive medication.

There was one grade 5 AE: rectovaginal fistula followed by sepsis. This patient as well as the patient that presented an ulceration of a metastatic lesion in the manubrium had received radiotherapy in the affected areas.

Group analysis based on median daily dose

Patients were divided in two groups according to mean daily dose of lenvatinib: group 1 consisted of 12 patients (48%) who were treated with a mean daily dose of lenvatinib >16.9 mg and group 2 included 13 patients (52%) treated with a mean daily dose of lenvatinib <16.9 mg. These two groups were compared for several parameters, as shown in Table IV.

We found that patients from group 1 were significantly younger and received more often radiotherapy than patients from group 2. Also, significantly more patients from group 2 had metastasis only in the lungs. Although not significant, there was a trend for higher rates of bone metastasis in group 1.

The median estimated PFS was significantly higher in group 2 (P=0.018) despite the fact that they were treated with a lower mean daily dose (Figure 5). Also, RR and the median reduction in summed diameters of target lesions from baseline to nadir were significantly higher in group 2 (P=0.004 and P=0.032, respectively). While more patients from group 1 achieved SD (P=0.01), more patients from group 2 achieved PR (P=0.01). Of note, patients treated with higher lenvatinib doses had a tendency for having target lesions with greater dimensions compared to patients treated with lower doses (61.5 *vs.* 43 cm, P=0.713). There were no differences between the two groups regarding the occurrence of grade 4-5 AE, frequency of drug discontinuation or dose reduction due to AE.

Figure 6 shows patients' treatment timelines

TABLE IV.—*Comparison between group 1 (mean daily dose >16.9 mg) and group 2 (mean daily dose <16.9 mg).*

Parameter	Group 1 (mean daily dose >16.9 mg) N.=12	Group 2 (mean daily dose <16.9 mg) N.=13	P value
Age at lenvatinib initiation, months	63.5 (12.75)	73 (8)	0.014
Duration of therapy with lenvatinib, months	5.6 (23.2)	9 (11.3)	0.470
Previous CT	1 (8.3%)	1 (7.7%)	1
Previous TKI	4 (33.3%)	3 (23%)	0.450
Previous irradiation	9 (75%)	4 (30.8%)	0.027
≥T3	8 (66.7%)	8 (61.5%)	1
≥N1	7 (58.3)	10 (76.9%)	0.400
Bone metastases	9 (75%)	6 (46.2%)	0.220
Lung metastases only	1 (8.3%)	6 (46.2%)	0.046
Metastasis in ≥2 organs	9 (75%)	10 (76.9%)	1
Eligible to be included in SELECT	5 (41.7%)	5 (38.5%)	1
Median estimated PFS (95% CI), months	4.6 (0-16.2)	NE	0.018
Median estimated OS (95% CI), months	29.3 (0.0-75.5)	NE	0.063
BOR (available in 22 patients)	N.=10	N.=12	
CR	0 (0%)	1 (8.3%)	1
PR	1 (10%)	8 (66.7%)	0.011
SD	8 (80%)	3 (25%)	0.010
PD	1 (10%)	0 (0%)	1
ORR	1 (10%)	9 (75%)	0.004
DCR	8 (80%)	12 (100%)	0.195
CBR	5 (50%)	8 (66.7%)	0.361
Death during lenvatinib treatment	7 (58.3%)	3 (30%)	0.082
Prolongation of TVDT (available in 15 patients)	4 (66.7%) Total of 6 patients	9 (100%) 9 patients	0.143
Sum of target lesions, cm (available in 16 patients)	61.5 (76.35) Total of 6 patients	43 (93) Total of 10 patients	0.713
Mean change in summed longest diameter of target lesions from baseline to nadir (available in 16 patients)	-11.36±27.8%	-49.7±17.8%	0.032
Grade 4-5 AE	3 (25%)	6 (46%)	0.400
Interruption due to AE	9 (75%)	8 (61.5%)	0.673
Dose reduction due to AE	7 (58.3)	6 (46%)	0.848
Withdrawal due to AE	1 (8.3%)	4 (30.7%)	0.322

Data presented as number (percentage), median (95% CI), or median (interquartile range).
AE: adverse events; BOR: best overall response; CBR: clinical benefit rate; CI: confidence interval; CT: chemotherapy; CR: complete response; ORR: overall response rate; PD: progressive disease; PR: partial response; TKI: tyrosine kinase inhibitors; TVDT: tumor volume doubling time; NE: not estimable.

and evolution and emphasizes the possibility of achieving durable PR and even a CR in patients treated with lower mean doses.

Discussion

Lenvatinib is a multikinase inhibitor with anti-angiogenic properties and direct antitumor effects. Its targets include vascular endothelial growth factor receptor (VEGFR 1-3), fibroblast growth factor receptors (FGFR) 1-4, rearranged during transfection (RET), c-kit, platelet-derived growth factor receptor (PDGFR) α and mast cell/stem cell growth factor receptor (SCFR).[2] The SELECT trial demonstrated that lenvatinib significantly improved PFS compared to placebo

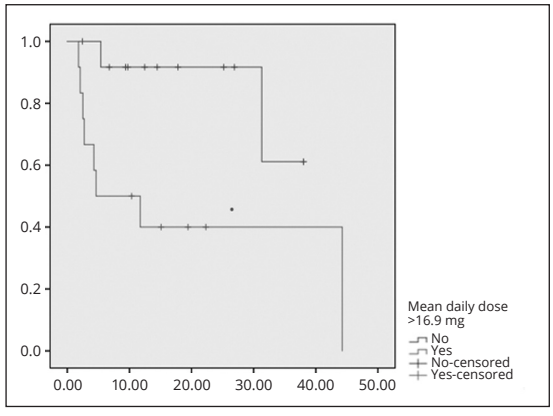

Figure 5.—Survival function: Kaplan-Meier analysis of progression free survival in patients treated with a mean daily dose >16.9 mg *versus* patients treated with a mean daily dose <16.9 mg.

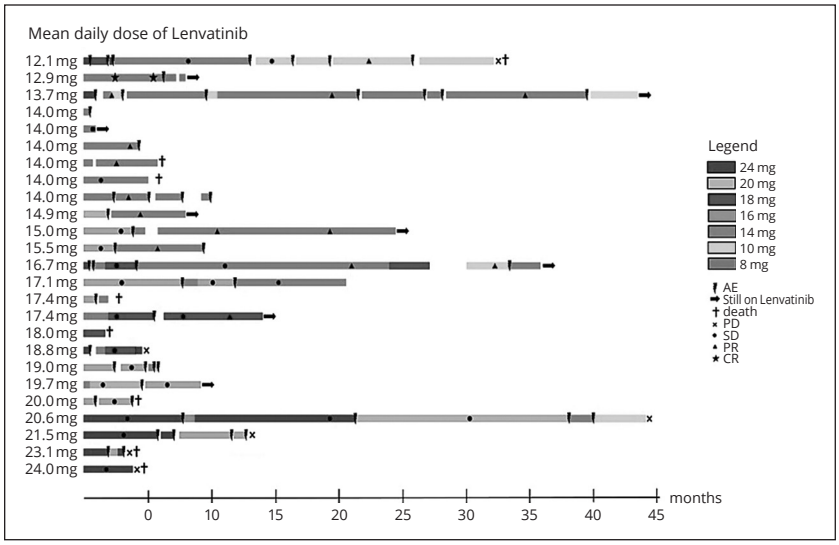

Figure 6.—Patient treatment timelines and evolution.

(median 18.3 *vs.* 3.6 months, P<0.001) both in TKI-naive patients and in patients who received one prior TKI treatment. This beneficial effect was also observed in terms of ORR (64.8% *vs.* 1.5%).[5] As with other clinical trials, SELECT only included patients with minimal co-morbidities and with only one prior TKI treatment.[5]

Since its approval in 2015, several authors documented their experience with the use of lenvatinib in patients with advanced and RAI-refractory DTC in real-world (RW) settings with different results (Supplementary Digital Material 1: Supplementary Table I).[17-28]

Median follow up time among RW studies was 15.4 months and ranged from seven[17] to 34.6 months.[29] Median treatment duration was 6.8 months and ranged from five[18] to 27 months.[29] Median PFS was 13.7 and ranged from 7.2[18] to 31.3 months (our study). Median ORR was 38% and ranged from 9%[29] to 69%[19] and median DCR was 77% and ranged from 25%[29] to 100%.[20]

Interestingly, in our study, when we compared by univariate analysis, outcomes of two groups according to the mean daily dose (<16.9 and >16.9 mg daily), we found out that patients treated with a lower dose had a better response to lenvatinib. However, the toxicity profile was similar to the high dose group. One possible explanation is the trend to more aggressive disease in group 1. Indeed, there was a trend to higher bone metastization rates and larger target lesions in the group treated with higher doses and significantly greater proportion of patients with metastasis only in lungs in the group treated with lower dose, which usually respond better to TKIs than bone lesions.[29]

The effectiveness of lower doses has also been shown in other RW studies.[17, 21, 30]

On the other hand, Rendl *et al.*[29] report, in their cohort of 43 patients, that a daily dose of lenvatinib ≤10 mg (N.=17) was associated with a lower OS rate compared to patients treated with daily dose ≥14 mg (N.=26) (63% *vs.* 82% at 24 months respectively, P=0.048). However, neither baseline characteristics of the patients nor treatment modalities of the two groups were presented.[29]

Also, a multicenter phase-2 trial showed that a starting dose of 18 mg/day of lenvatinib did not demonstrate noninferiority compared to the standard 24 mg/day.[31]

In our cohort, tumor shrinkage with lenvatinib was observed in 93.3% patients with a median TVDT of -3.7 months, similar to the findings of Song *et al.*,[12] who reported a 90.7% rate of tumor shrinkage and median TVDT of -6.2 months. In addition, the analysis of TVDT in our cases confirmed that lenvatinib had greater benefit in more rapidly progressive disease. This finding is in line with the study of Sabra *et al.*,[12] which included 122 patients with lung metastasis from DTC treated with one or more

molecular target therapies that included lenvatinib, among other TKIs.

Regarding AEs, 96% of the patients in our series had AE that motivated drug interruption, dose reduction and permanent withdrawal in 68%, 52% and 20% of patients, respectively. These results are in line with other RW studies, in which drug interruption and dose reduction occurred with a median of 60.9% and 59%, respectively. Permanent discontinuation of lenvatinib due to AE occurred in a median of 16.4% in RW studies. When group analysis based on mean daily dose was performed in our cohort, we did not find a significant difference between groups regarding rates of interruption, dose reduction or withdrawal due to AE, probably because lower lenvatinib doses were used upfront in elderly patients. Additionally, as one can see in Figure 6, even the patient treated with the lowest median dose had various treatment interruptions due to AE. These findings may suggest that, to some extent, the occurrence of AE may also be related to an individual susceptibility, yet to be clarified.

Limitations of the study

This study has some limitations related to its retrospective nature and small size of the sample. In addition, we did not include patients with poorly differentiated thyroid carcinomas, as in the SELECT trial, but we had a greater burden of previous therapies (32% *vs.* 25.3%) and a higher prevalence of bone metastases (62.5% *vs.* 39.8%), which are postulated to be associated with poor survival in DTC.[11] Also, in our series, only 40% of the patients fulfilled inclusion criteria for the SELECT. However, we have a homogeneous population of patients with WDTC who were followed in a single center with the same protocol.

Conclusions

Our results confirm the effectiveness of lenvatinib in the management of patients with advanced DTC and support the idea that, when there is a clinical concern about serious adverse events, lower dosages of lenvatinib are still effective in achieving durable responses. Hence, lenvatinib dosage should be adjusted to achieve an optimal balance between efficacy and toxicity.

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Conflicts of interest

Sara Donato and Tiago Silva received honoraria for lectures from EISAI. Valeriano Leite is the president of Associação de Endocrinologia Oncológica, a Portuguese association dedicated to promote post-graduate courses and research projects in the field of Endocrine Oncology, which has received funding from EISAI. The remaining authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Inês L. Damásio has given substantial contributions to study conception, data acquisition, manuscript writing and editing, Ana Figueiredo to data acquisition and manuscript writing, Joana Maciel to manuscript writing and editing, Mariana Horta to data acquisition and radiological analysis, Joana Simões-Pereira to statistical analysis and manuscript writing, Tiago Silva, Sara Donato, and Valeriano Leite to manuscript revision. All authors read and approved the final version of the manuscript.

History

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SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Table I.—Comparison of our data with SELECT and other real-world studies.

Study	N. (%)	SELECT Inclusion criteria (%)	Single center	M1 bone (%)	Previous TKI (%)	Daily median/mean dose (mg)	Median duration of treatment (month)	Median OS (months)	Median PFS (months)	ORR (%)	DCR (%)
SELECT	261, 10% PDTC	100	No	39.8	25.3	NA/17.2	13.8	NR	18.3	64.8	87.7
Jasim *et al.* (2017)[23]	25, 28% PDTC	NA	Yes	NA	32	NA/NA	Mean 6.5	NR	NR	50	40
Balmelli *et al.* (2018)[18]	13	NA	No	69	76.9	NA/NA	5	22.7	7.2	31	62
Berdelou *et al.* (2018)[17]	75, 25% PDTC	23	No	60	9.3	20/NA	6	NR	10	30.7	81.3
Kim *et al.* (2018)[24]	23, 8.6% PDTC	NA	Yes	39.1	0%	NA/NA	NA	NA	NA	NA	NA
Nervo *et al.* (2018)[25]	12, 50% PDTC	NA	Yes	41.7	66.7	NA/18.2	NA	NA	NA	41.7	58.4
Locati *et al.* (2019)[20]	94	57.4	No	NA	87.6	19.2/NA	5.9	23.8	10.8	36	77
Aydemirli *et al.* (2020)[26]	39, all WDTC	31	No	74	77	NA/18.6	6.1	18.3	9.7	38	74
Masaki *et al.* (2020)[27]	42, all WDTC	45	Yes	48	10	NA/ 11.6	14.9	NR	NR	62	86
Song *et al*. (2020)[21]	43, 13.9% PDTC	NA	No	58.1	74.4	10/NA	14	NR	21.8	64.7	98
Jerkovich *et al.* (2020)[22]	22, 4.5% PDTC	57.1	No	45.5	59.1	NA/ 16.1	7.1	NR	13.7	31.8	63.3
De Leo *et al.* (2021)[19]	13, 15.4% PDTC	NA	Yes	23.1	0	11/NA	NA	NA	22	69	100
Rendl *et al.* (2020)[29]	43, 9% PDTC; 7% ATC	NA	No	35	19	14/14	27	NR	NR	9	25
Jiang *et al.* (2021)[28]	65, all WDTC	NA	No	38.5	21.5	10/NA	NA	NR	26.1	24.6	89.2
Damasio *et al.* (2022)	25, all WDTC	40	Yes	60	32	16.7/16.9	9.1	29.6	31.3	40	84
RW STUDIES Median (min-max)	32 (12-94)	42.5 (23.1-57.4)	---	46.8 (23.1-74)	32 (0-87.6)	14 (10-20) / 16.5 (11.6-18.6)	6.8 (5-27)	23.2 (12-94)	13.7 (7.2-31.3)	38 (9-69)	77 (25-100)