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Lenvatinib in Advanced Radioiodine-refractory Thyroid Cancer: A Snapshot of Real-life Clinical Practice

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Abstract. *Background: We retrospectively analyzed the efficacy and safety of lenvatinib in 12 patients with advanced radioiodine-refractory thyroid cancer in the setting of daily clinical practice. Patients and Methods: The starting daily dose of lenvatinib was 24 mg, tapered in the case of adverse events. Disease status was periodically evaluated by a single radiologist and safety assessment was regularly performed. Results: After a median follow-up of 13.3 months, 6- and 12-month progression-free survival rates were 63.6% and 54.6%, respectively. Overall survival at 6 and 12 months was 83.3% and 75.0%. Partial response was observed in five patients, while two showed stable disease as their best response. Conversely, progressive disease at first radiological assessment was detected in four patients. All patients experienced at least one adverse event, including systemic and gastrointestinal toxicity, high blood pressure and hand–foot syndrome. In order to manage toxicity, transient drug interruption and dose reduction were required in 10 and 9 cases, respectively. Conclusion: Our data confirm lenvatinib efficacy in patients with advanced thyroid cancer, despite an important toxic profile.*

Thyroid cancer represents the most common endocrine malignancy. Differentiated thyroid carcinoma (DTC), arising from thyroid follicular epithelial cells, accounts for the vast majority of thyroid cancers; among DTCs, papillary cancer (PTC) comprises about 85% of cases, followed by follicular cancer. Fewer than 3% of thyroid carcinomas are poorly differentiated thyroid tumours (PDTC) (1).

Worldwide, the incidence of thyroid cancer has been increasing in the past few decades, more rapidly than that of any other cancer type. This increase seems to be partially attributable to a greater awareness of the disease that leads to earlier diagnoses of micro PTC or otherwise indolent disease subtypes. However, despite the potential 'overdiagnosis' of indolent DTC, a slight increase in mortality has also been observed (2, 3).

Ten-year survival rates in patients with DTC are usually considered excellent, ranging from 80% to 95%, after surgery followed by radioiodine ablation therapy (RAI), if necessary, and levothyroxine treatment. However, a small subgroup of patients (<10%) develop distant metastases and are inherently insensitive or acquire insensitivity to RAI, with a significant worsening in survival rates (4, 5).

Until the last decade, therapeutic options had been limited in patients with RAI-refractory DTC. Traditional chemotherapy and external beam radiotherapy (EBRT) produced disappointing results: both had marked toxicity with low and transient efficacy, mainly playing a palliative role (1, 3, 6).

In recent years, better knowledge of the aberrant molecular signalling pathways implicated in human tumorigenesis has led to the development of several molecular-targeted agents. The use of tyrosine kinase inhibitors (TKIs) is now suggested for patients with RAI-refractory DTC with metastatic, rapidly progressive, symptomatic, or imminently threatening disease not otherwise amenable to local control using other approaches (1).

Among the TKIs, sorafenib and lenvatinib were recently approved for the treatment of advanced RAI refractory DTC (6). Lenvatinib is an oral, multitargeted TKI of vascular endothelial growth factor receptor (VEGFR) 1-3, fibroblast growth factor receptor (FGFR) 1-4, platelet-derived growth factor receptor (PDGFR) α, rearranged-during-trasfection (RET) and KIT proto-oncogenes (7).

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The encouraging results observed in a phase 2 study (8) were confirmed in the SELECT study (7), a phase 3, randomized, double-blind, placebo-controlled, multicentre study. In the SELECT trial, lenvatinib treatment led to a prolongation of the progression-free survival (PFS) in comparison to placebo in patients with RAI-refractory DTC, both in naïve patients and in those who had received a prior TKI treatment (median PFS: 18.3 months in TKI-naïve patients and 15.1 months in pre-treated patients *vs*. 3.6 months with placebo). Moreover, lenvatinib was associated with an improvement in the response rate (64.8% *vs*. 1.5% with placebo). However, almost all patients treated with lenvatinib experienced adverse events (AEs), and a large proportion of them required dose reduction or drug interruption, while treatment discontinuation was necessary in order to manage complications in a few cases (7).

The aim of our retrospective study was to analyse efficacy and safety of lenvatinib in a single cohort of patients with advanced RAI-refractory thyroid cancer consecutively treated at a tertiary centre in the setting of daily clinical practice.

Patients and Methods

Our analysis included all eligible patients with advanced RAI-refractory DTC who started lenvatinib, through compassionate use, between May 2015 and May 2016; patients were switched to the commercially available drug after June 2016.

Advanced RAI-refractory DTC was defined as progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) (9), with no further indication for RAI treatment, because of a partial or complete lack of RAI uptake, or evidence of progression despite RAI avidity at the time of treatment or after receiving cumulative RAI activity ≥600 mCi (10).

All of the following inclusion criteria for treatment had to be fulfilled: i) age ≥18 years (pregnant or lactating women were excluded); ii) at least one measurable lesion by computed tomographic (CT) scan or magnetic resonance imaging (MRI), and evidence of progression within the past 12 months, according to RECIST 1.1 criteria; iii) Eastern Cooperative Oncology Group (ECOG) performance status ≤2; iv) adequate bone marrow, blood coagulation, renal, and liver function; v) blood pressure (BP) levels ≤150/90 mmHg, with or without antihypertensive therapy.

Patients were excluded if they had prolongation of QTc interval, congestive heart failure greater than New York Heart Association class II, myocardial infarction, unstable angina, or stroke within 6 months. Patients who had previously been treated with traditional chemotherapy, EBRT, or sorafenib were considered eligible for treatment.

All patients provided written informed consent for therapy with lenvatinib and for entering data in our database; the Ethics Committee of our Institution approved the use of lenvatinib for the treatment of these patients from May 2015 (n°2015/43398, 2015/69251, 2015/67500, 2015/31703, 2016/34354).

The daily starting dose of lenvatinib was 24 mg, with reduction or brief transient interruption of therapy in case of AEs, and definite discontinuation when unacceptable toxicity or clinically significant progressive disease (PD) was observed.

The study aimed to evaluate the efficacy and safety of lenvatinib. In order to assess efficacy, we calculated PFS, overall survival (OS), and the disease control rate, defined as complete response (CR) plus partial response (PR) plus stable disease (SD). A CT scan evaluation was performed approximately at 3, 6, and 12 months after initiation of therapy and then at 6-month intervals. All CT images were evaluated by a single radiologist assessing the radiological response to therapy according to RECIST criteria.

Safety evaluation, based on physical examination and laboratory testing (including blood cell count, liver and renal function, electrolyte levels, and proteinuria), was performed during monthly follow-up visits. Serum thyrotropin-stimulating hormone (TSH), free-thyroxine (fT4), thyroglobulin (Tg), and Tg antibody levels were determined every month together with safety parameters.

Potential drug-induced cardiac toxicity was monitored by electrocardiogram (including QTc interval calculation) and *N*-terminal pro-brain natriuretic peptide (NT-proBNP) dosage every 3 months.

Any AE recorded during treatment was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (11). We considered the occurrence of any grade AE and of severe AEs (grade 3-4), together with the need for dose reduction, drug interruption or discontinuation.

Statistical analysis. Baseline characteristics of patients included in the analysis are summarized descriptively using median and interquartile range (IQR) or number and percentages. OS was estimated by Kaplan–Meier method. The observation period for the OS was defined as the time from the starting date of treatment to the date of death from any cause (failure) or until the last follow-up visit (censoring). PFS was also estimated: the observation period started from the beginning of treatment until death or the date of progression (failures), whichever occurred first, or until the last follow-up visit (censoring). Statistical analyses were performed using Stata 13.1 software (StataCorp LP, College Station, TX, USA).

Results

Twelve consecutive patients with advanced RAI-refractory DTC were included in the analysis.

Baseline characteristics of patients are summarized in Table I. Median age at diagnosis was 61.1 years (IQR=51.5-68.0 years). The male to female ratio was 1:4. Six patients had a histological diagnosis of PDTC, four of PTC, and two of follicular thyroid cancer.

Treatment with lenvatinib was started after a median of 3.1 years from initial diagnosis (IQR=1.9-5.7 years). All patients had undergone total thyroidectomy followed by 131I ablation and TSH-suppressive treatment with levothyroxine. Eight of them had been re-submitted to surgery for locoregional recurrence or distant metastases, five had been treated with EBRT, and one with conventional chemotherapy. Furthermore, the majority of patients (8/12, 66.7%) had previously received sorafenib until evidence of PD or unmanageable toxicity.

Before starting lenvatinib, all patients presented distant disease: baseline lung lesions were detected in 9/12 (75%) cases, while 5/12 (41.6%) of the patients had bone metastases.

Table I. *Patient characteristics at baseline.*

Characteristic	N (%)
Gender	
Female	9 (75.0)
Male	3 (25.0)
Histology	
Poorly differentiated	6 (50.0)
Papillary	4 (33.3)
Follicular	2 (16.7)
Metastasis	
Locoregional	10 (83.3)
Distal	12 (100.0)
Lymph nodes	11 (91.7)
Lung	9 (75.0)
Bone	5 (41.7)
Liver	2 (16.7)
Treatment*	
Sorafenib	8 (66.7)
Surgery	8 (66.7)
EBRT	5 (41.7)
Conventional chemotherapy	1 (8.3)

EBRT: External beam radiotherapy. *After initial surgery and ^{131}I therapy.

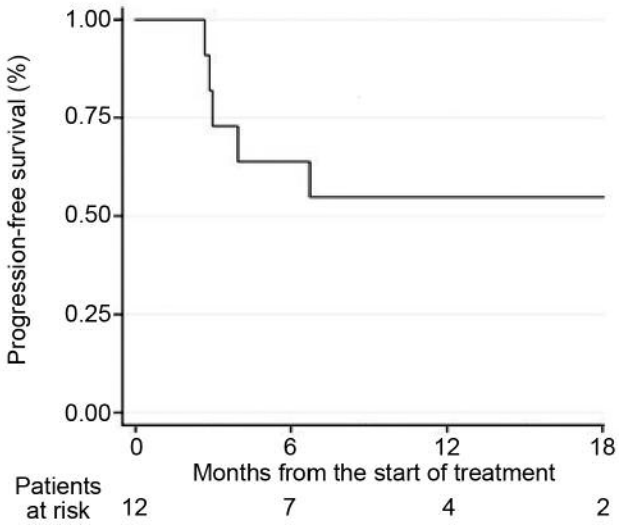

Figure 1. *Progression-free survival from the date of the first lenvatinib dose (N=12).*

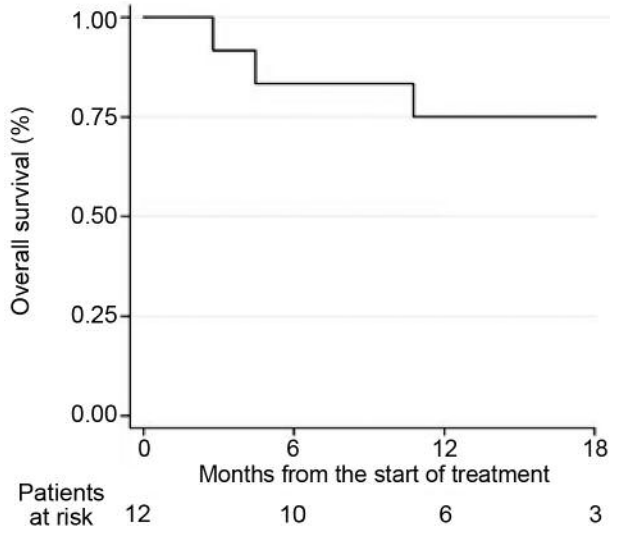

Figure 2. *Overall survival from the date of the first lenvatinib dose (N=12).*

Prior to treatment, Tg levels were markedly increased in all but one patient, with a median baseline value of 3,777 ng/ml (IQR=507-15,030 ng/ml).

Efficacy. At the end of our observation (30th April 2017), the median follow-up was 13.3 months (IQR=10.9 to 19.3 months). During treatment with lenvatinib, 6- and 12-month PFS rates were 63.6% [95% confidence interval (CI)=29.7-84.5%] and 54.6% (95% CI=22.9-78.0%), respectively (Figure 1); OS at 6 and 12 months were 83.3% (95% CI=48.2-95.6%) and 75.0% (95% CI=40.8-91.2%), as displayed in Figure 2.

One patient died due to tumour progression within 3 months, before the first CT evaluation.

PR was observed in five patients, with a median time to response of 3.7 months (IQR=3.1-4 months); four of them maintained SD at last follow-up visit, while one patient showed progression 4.1 months after previous evidence of PR and died soon thereafter.

Two out of twelve patients showed SD as their best response, which lasted for 22 months in one case and was confirmed at the last CT scan in the other patient. The disease control rate was 58.3%.

Conversely, PD was detected at first radiological assessment in four patients (36.4%). One of them died within 1 month due to further tumour progression, while the other three patients continued treatment with lenvatinib and showed subsequent SD, still detected at last radiological assessment. Maximum percentage change from baseline in target lesion sum is displayed in Figure 3.

After 3 months of therapy, Tg levels had significantly decreased in all patients with detectable Tg before treatment (median 500 ng/ml; IQR=50-2,065 ng/ml; p=0.003). Nevertheless, no significant association between Tg fluctuations and radiological response was observed (data not shown).

Table II. *Treatment-related adverse events experienced on therapy with lenvatinib.*

	Any grade[a] N (%)	Grade 3 or more[b] N (%)
Any adverse event	12 (100.0)	10 (83.3)
Decreased weight	11 (91.7)	2 (16.7)
Hand–foot syndrome	11 (91.7)	2 (16.7)
High blood pressure	9 (75.0)	5 (41.7)
Nausea	9 (75.0)	1 (8.3)
Diarrhoea	8 (66.7)	5 (41.7)
Fatigue	7 (58.3)	1 (8.3)
Oral mucositis	7 (58.3)	1 (8.3)
Hyporexia	7 (58.3)	0
Myalgia	7 (58.3)	0
Arthralgia	6 (50.0)	1 (8.3)
Vomiting	4 (33.3)	1 (8.3)
Dysphonia	3 (25.0)	0
Abdominal pain	2 (16.7)	0
Cutaneous infection	2 (16.7)	0

[a]In ≥10% of patients; [b]in ≥5% of patients.

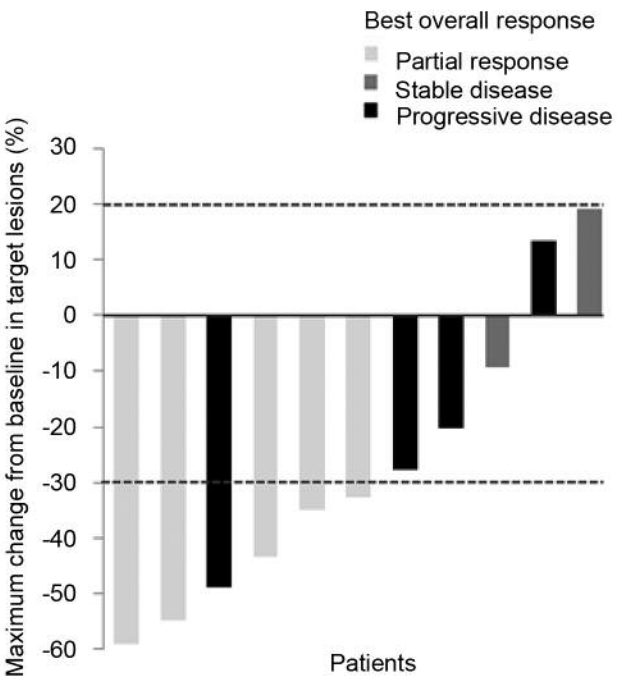

Figure 3. *Maximum percentage change in target lesion sum from baseline during treatment with lenvatinib.*

Safety and tolerability. During treatment with lenvatinib all patients experienced at least one AE, mostly of grade 1-2 severity, although 10/12 (83.3%) patients reported at least one AE of grade 3 or more. The most common AEs included systemic toxicity (decreased weight, fatigue, hyporexia, arthralgia, myalgia), high blood pressure, hand–foot syndrome, and gastrointestinal symptoms (nausea, vomiting, diarrhoea, oral mucositis), as shown in Table II.

The incidence of AEs was higher in the first months of therapy and decreased during treatment. No significant difference was found according to patient age, neither for the time of onset nor in the severity of toxicity. No fatal AEs occurred during treatment and all deaths were attributable to underlying tumour progression.

Proteinuria, increased liver enzyme levels, and elevated NT-proBNP were identified in two, eight, and two patients, respectively. Levothyroxine dose adjustment due to alteration in TSH level was required in 8/12 (66.7%) of patients. Neither bone marrow toxicity nor corrected QTc prolongation beyond the upper normal limit were detected during observation.

In order to manage AEs, 10 out of 12 patients (83.3%) required at least one transient drug interruption, while dose reduction was needed in nine (75%), resulting in a mean dose of 18.2 mg per day. The first dose reduction occurred after a median of 4.2 months (IQR=2.2-5.2 months). At the end of our observation, seven patients were still on therapy with lenvatinib, while treatment was discontinued for clinically significant PD or unmanageable toxicity in one and two patients, respectively.

Discussion

After the publication of the SELECT trial (7) and due to approval by both Food and Drug Administration and European Medicines Agency, and subsequently by other national regulatory agencies, lenvatinib is considered the first-line systemic treatment for patients with RAI-refractory DTC (1).

The efficacy of lenvatinib in this setting was firstly evaluated in open-label, non comparative, phase 2 study (12) and subsequently in the phase 3, randomized, double-blind, sponsored multicentre clinical trial SELECT (7).

Observational studies aiming to confirm these results in the setting of daily clinical practice and to describe the real-life management of patients treated with lenvatinib are still scarce, paying attention mainly to effectiveness outcomes (13) or focusing specifically on AEs (14). Recently, Berdelou et al. evaluated both the efficacy and the toxicity of lenvatinib in the context of real-life practice in 75 patients followed at 27 different French centres: their results substantially confirm the clinical benefit of lenvatinib, but the median follow-up of their study was only 7 months (15).

Although our study analysed a smaller sample, the length of follow-up was longer (13.3 months) and all patients were managed uniformly by the specialists of a single tertiary referral centre.

Comparing our results to SELECT data, as far as baseline characteristics are concerned, the median age at lenvatinib treatment, sites of metastases and rate of previous treatment with another TKI were similar, whereas the male/female ratio and the distribution of histological subtypes were quite different. In particular, in our study about half of the included patients were affected by a PDTC (*vs.* 10.7% in the SELECT population): therefore, it could be argued that our patients might have a worse prognosis than those of the SELECT trial, as commonly seen in daily clinical practice observational studies versus clinical trials.

Our data substantially confirm that lenvatinib can slow down the disease progression of patients with RAI-refractory DTC and are consistent with the currently available evidence (6). In our cohort, we found 6- and 12-month PFS rates of 63.6% and 54.6%, respectively, quite similar to the rates of the SELECT trial (77.5% and 63%). No solid comparison can be made between the 6- and 12-month OS observed in our cohort and those reported in the SELECT trial, considering the crossover design of that study which potentially misrepresents the effect of lenvatinib on the SELECT population (16). Our results confirm previous data retrospectively reported outside the context of clinical trials (15).

The disease control rate in our study was quite lower than that reported in the SELECT study (58.3% *vs.* 87.7%) and we did not observe any CR. Besides the small size of our cohort, a possible explanation for this result could be that some of our patients received lenvatinib in a more advanced phase of disease. Moreover, it should be underlined that the maximum percentage change during treatment showed tumour reduction in nearly all patients, consistent with available sub-analysis conducted on the SELECT population (7, 16). At present, a head-to-head comparison between lenvatinib and sorafenib, the first TKI approved for patients with advanced DTC, has not been published, to the best of our knowledge. An indirect comparison between these two treatments, considering the results previously obtained with sorafenib at our centre (17), shows similar OS and PFS rates at 12 months; conversely, 6-month PFS was lower during treatment with lenvatinib (63.6% *vs.* 81.4%). It must be underlined that patients treated with sorafenib in our cohort were TKI-naïve, similar to the population of the DECISION trial (18). By contrast, lenvatinib represented second-line TKI therapy in our study for two-thirds of patients. Therefore, a discrepancy in survival rates could reflect the different characteristics of patients.

As reported in previous studies (13, 19), the median Tg level also significantly dropped within the first weeks of treatment in our cohort. A clear association between Tg oscillations and radiological response was not observed in our population, perhaps as a consequence of the small number of patients. Another possible explanation could be that transient Tg fluctuations might reflect a change in cancer metabolic activity during treatment, not necessarily translating into a clinical tumour response (19).

With regard to side-effects, lenvatinib had a significant toxicity profile, substantially consistent with previously reported studies (15, 16, 20, 21). AE management was almost always achieved either by supportive care and by dose reduction or transient drug interruption, while lenvatinib discontinuation was required in only a very few cases. All of our patients experienced at least one AE, of severe degree in most cases. In agreement with previous studies, the frequency of AEs was higher in the first months of therapy and declined over the course of treatment.

In a sub-analysis of SELECT data (16), older patients experienced more severe treatment-related AEs and required shorter time to the first dose reduction; in contrast, a recent retrospective study found no significant differences in toxicity between patients aged <75 years and those aged 75 years or more (14). In our population, patient age seemed not to influence the time of onset and the severity of AEs.

Differently from the SELECT trial, hand–foot syndrome was a frequent AE in our population, occurring in almost all patients, but it was well controlled with local treatment and dose reduction.

Hypertension was confirmed to be very common; BP management was quite difficult even from the first month of treatment, especially in those with previously known high blood pressure levels. Differently from data reported in the SELECT trial, no patient experienced severe or life-threatening consequences. In any case, it is mandatory for clinicians to take into account and adequately control pre-existing conditions that could worsen during TKI administration.

In the SELECT study, the main causes of dose reduction or transient drug interruption were diarrhoea, hypertension and proteinuria, whereas in our cohort, systemic toxicity, even though of mild degree, led to the need for dose modulation. Finally, as previously reported, treatment with lenvatinib caused a variation in levothyroxine requirement, frequently leading to dose modulation.

The main limitations of our study are its retrospective nature without a control group and the small sample size, which reduces the statistical power of analyses. Safety was evaluated only on the basis of the clinician assessment and did not include self-perceived quality of life, since we included a validated quality of life questionnaire in clinical routine only recently.

Despite these limitations, our study describes the use of lenvatinib in the setting of everyday clinical practice, allowing comparison of these data with the results of clinical trials.

In conclusion, our findings confirm lenvatinib efficacy in advanced RAI-refractory DTC. The real meaning of Tg variations during treatment with lenvatinib is still unclear.

Thus, further larger studies are required to investigate the utility of monitoring Tg levels during treatment with lenvatinib.

Despite an important toxicity profile in many cases, treatment is usually well manageable by dose modification or drug interruption, as well as by supportive care. Therefore, as recently underlined (22), a careful selection of candidates for treatment is mandatory, including only patients showing both rapid PD with high tumour burden and acceptable basal performance status, in order to balance clinical benefits and harms of lenvatinib administration.

At present, the management of patients with advanced DTC after failure of lenvatinib, or in the case of unacceptable toxicity during treatment, still remains a matter of debate and needs to be fully evaluated in prospective randomized studies.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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