Lenvatinib Long-Term Responses in Refractory Thyroid Cancer: Our Mono-Institutional Real-Life Experience with the Multidisciplinary Approach and Review of Literature

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Keywords

Lenvatinib · Thyroid cancer · Toxicity management · Multidisciplinary approach

Abstract

Lenvatinib (LEN) is a multikinase inhibitor with antiangiogenic properties recently approved in radioactive iodine-refractory differentiated thyroid cancer, hepatocellular carcinoma, and renal cell carcinoma in combination with everolimus. LEN-treated patients frequently have adverse events (AEs) that generally require such dose modifications, including drug discontinuation. Hypertension, diarrhea, weight loss, proteinuria, fatigue, and palmar-plantar erythrodysesthesia are reported among the most frequent AEs, often leading to discontinuations or dose modifications. This paper reports a case series focusing on the role of the immediate multidisciplinary approach to manage AEs.

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Data Selection

Lenvatinib (LEN) is an oral tyrosine kinase inhibitor (TKI) that acts on vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor- α , and *RET* and *KIT* proto-oncogenes [1].

LEN was approved by the FDA for the treatment of locally recurrent or metastatic progressive radioactive iodine-refractory differentiated thyroid cancer (RR-DTC) in 2015.

The approval was based on the Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT). This was a randomized, double-blind phase III study that enrolled patients with histologically confirmed RR-DTC [2].

RR-DTC inclusion criteria were no radioactive iodine (RAI) uptake, disease progression within 12 months of RAI therapy despite RAI avidity at the time of treatment, and extensive (>600 mCi) cumulative RAI exposure.

Patients ($n = 392$) received LEN 24 mg/day ($n = 261$) or placebo ($n = 131$). The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), objective response rate, and safety. LEN improved the median PFS over placebo by almost 15 months and induced an objective response rate of 64.8%. In addition, 65% of the patients who received LEN had their tumor shrink [2].

Independently of the RR-DTC inclusion criteria, all patients reported a benefit, possibly because of a large overlap among patients fulfilling each criterion.

However, LEN is not easily manageable, and in the SELECT study, adverse events (AEs) occurred in almost all patients (97.3%).

The LEN safety profile is complex. LEN has a half-life of 28 h. The most common side effects in the study were hypertension, fatigue, diarrhea, articular and muscular pain, weight loss, nausea, loss of appetite, vomiting, proteinuria, abdominal pain, and voice changes. Less common serious AEs included heart failure, liver and renal damage, bowel perforation, and polycythemia [2].

In the SELECT study, hypertension occurred in approximately 68% of the patients receiving LEN and had a severity grade (G) 3 or greater in >40%. The median time to hypertension was 2.3 weeks (range: 1.4–5.0) in this study. Approximately one-third of the patients receiving LEN experienced proteinuria of any grade, and 10% had severe ($G \geq 3$) proteinuria.

Fatigue is reported in almost all patients, but its definition is very complex as it may depend on both cancer and elevated levels of thyroid-stimulating hormone (57% in SELECT study). Gastrointestinal AEs were common in the pivotal trial including about 64, 41, and 28% of the patients with diarrhea, nausea, and vomiting, respectively.

Stomatitis and palmar-plantar erythrodysesthesia occurred in 20% of the patients. In the SELECT study, 35% of the LEN-treated patients experienced hemorrhagic events of any grade. In the SELECT study, thrombocytopenia occurred in 8.8% of the LEN-treated patients and was of severity G3 or worse in 1.5% [2].

Toxicity is higher in the elderly. In 2017, Brose et al. [3] published a prespecified subanalysis to investigate the effect of age on the efficacy and safety of LEN. The authors reported LEN benefit in both age groups, although higher toxicity was observed in older patients. PFS benefit was maintained with LEN versus placebo in the younger and older age groups, with a median PFS of 20.2 versus 3.2 months (hazard ratio [HR], 0.19; 95% confidence interval [CI], 0.13–0.27; $p < 0.001$) and 16.7 versus 3.7 months (HR, 0.27; 95% CI, 0.17–0.43; $p < 0.001$), re-

spectively. PFS did not differ with age in either treatment arm. OS was improved in the older LEN-treated patients versus placebo (HR, 0.53; 95% CI, 0.31–0.91; $p = 0.020$). The younger LEN-treated patients showed significantly higher overall response rate (72 vs. 55%; $p = 0.0038$), a longer time to the first dose reduction (3.7 vs. 1.5 months), and a lower proportion of $G \geq 3$ treatment-related AEs (67 vs. 89%; $p < 0.001$) compared with older patients.

Real Life: Literature Experience

A French multi-institutional report on 88 patients revealed that the initial treatment dose was 24 mg in 54 patients and was lower in the other 21 patients. The median follow-up was 7 months, with a median duration of treatment of 6 months (0.3–15). Median (PFS) was 10 months. Among the 65 patients with evaluation of tumor response during treatment, best tumor response was a partial response (PR) in 23 patients (31%) and stable disease (SD) in 38 (51%). Eleven patients (14.7%) discontinued LEN because of disease progression. Forty-four (59%) and 23 (31%) patients had dose reductions or discontinuation of LEN for AEs. The most frequent AEs related to treatment were fatigue, hypertension, weight loss, diarrhea, and anorexia. Eleven deaths occurred during the study (one was considered to be drug related). Pneumothorax occurred in 2 patients with lung metastases [4].

Masaki et al. [5] presented a single-institution experience at the 41st Annual Meeting of ETA. In their Japanese report, they indicate three factors related to OS (poor general status, size of target lesion, and tumor doubling time). The outcomes were PR, SD, and progressive disease (PD) in 29 (69%), 8 (19%), and 8 (19%) patients, respectively.

Matrone et al. [6] present their widest Italian experience from Pisa University. They participated to the registrative SELECT study. Of the 15 patients, 3 had longer response (patients still on treatment), 6 patients (40%) died after a period of PR/SD while taking the drug, and 1 withdrew the consent for the severe AEs. The remaining 5 patients showed PD after a period of SD, 4/15 (26.6%) patients died because of PD while 1 started another TKI.

In an “expanded” and “compassionate use of the drug,” Matrone et al. [6] treated 36 patients, reporting a disease control rate of 78% (PR 42% and SD 36%), with PD in 14% and death before the first evaluation in 8%. Response was confirmed at 2 years of follow-up. Serious AEs were

Table 1. Patient characteristics and responses

Patient	Sex	Histology	RR-DTC	Treatment start	PFS, months	R 3 months	R 6 months	R 12 months
1	M	follicular	>600 mCi	July 2015	44+	PR	PR	PR
2	F	papillary	no RAI uptake	May 2015	46+	PR	PR	PR
3	M	papillary	>600 mCi	February 2017	8	PR	PD*	–
4	F	papillary	no RAI uptake	July 2017	6	PR	PD*	–
5	M	papillary	no RAI uptake	March 2018	13+	PR	PR	PR
6	M	papillary	>600 mCi	February 2018	13+	PR	PR	PR

M, male; F, female; RR-DTC, radioactive iodine-refractory differentiated thyroid cancer; RAI, radioactive iodine; R, response. * For toxicity.

described in 3/15 (2 gastrointestinal tract perforations, 1 esophageal fistula) [6].

Nervo et al. [7], after a median follow-up of 13.3 months, reported on 12 patients with 6- and 12-month PFS rates of 63.6 and 54.6%, respectively. OS at 6 and 12 months was 83.3 and 75.0%, respectively. Responses were as follows: PR, SD and PD in 5, 2 and 4 patients, respectively. All patients experienced at least one AE, including systemic and gastrointestinal toxicity, high blood pressure, and hand-foot syndrome. To manage toxicity, transient drug discontinuation and dose reduction were required in 80 and 66% of the cases, respectively.

Suyama et al. [8] demonstrated no difference in toxicities between the younger and elderly groups of 19 Japanese patients, with the exception of the median maximum systolic blood pressure (158 mm Hg in the younger group vs. 173 mm Hg in the elderly group; $p = 0.042$). The authors conclude that LEN should be introduced carefully to elderly patients, as they tend to present with hypertension during treatment.

Multidisciplinary Approach

Over the past 15 years, the multidisciplinary team management of many medical conditions, especially cancers, has increasingly taken a prominent role in patient management in many hospitals and medical centers in developed countries. Multidisciplinary teams involved in thyroid treatment should include endocrinologists, surgeons specializing in neck surgery and lymph node dissection, radiologists, nuclear physicians, oncologists, and radiotherapists. In our group, other physicians such as dieticians, cardiologists, and thoracic surgeons are requested on demand.

The aim of this paper was to describe our clinical experience with LEN and to evaluate its efficacy and tolerability in patients with RR-DTC treated with a multidisciplinary team approach.

Real Life: Results from the Cuneo Hospital Case Series

All patients with RR-DTC treated in our institution were considered for outcome. All patients with suspected thyroid cancer are evaluated by our multidisciplinary team before and after surgery. Patients with RR-DTC start treatment with TKIs. During the treatment, patients undergo regular clinical examinations by endocrinologists and nutritionists. Fatigue is treated in a program of physical activity by a team of physiotherapists. PFS was defined as the time from the date of the first assumption to the date of the first documentation of disease progression or death, whichever occurred first.

We report the results of 6 patients (4 males and 2 females) treated with LEN for RR-DTC. All patients were treated at least 3 times with RAI therapy; moreover, 3 had no RAI avidity anymore. Median PFS was 13 months (range: 6–46 months).

The Morisky scale was used to assess patient compliance to treatment. All patients candidate to LEN have a negative response to at least 3 questions. All patients candidate to treatment had progressive disease (no indolent or minimally metastatic disease), whereas patients with small (<1.5 cm) metastatic lymph nodes, multiple (sub) centimeter lung lesions, or asymptomatic stable bone metastases were candidate for active surveillance with serum thyroglobulin analyses every 3 months and imaging evaluation every 6 months. Patient characteristics and responses are described in Table 1.

Table 2. Adverse events

Patient	1st dose reduction	2nd dose reduction	Discontinuation	WL	Fatigue	Thyroid disorders	MDT assessment	Rehab
1	20 mg ^a	14 mg ^b	–	G1	G1	N	Y	Y
2	20 mg ^c	14 mg ^d	–	G1	G1	Y	Y	Y
3	20 mg ^c	14 mg ^e	at 5 months	G1	G1	N	Y	Y
4	20 mg ^c	14 mg ^e	–	G1	G1	N	Y	Y
5	20 mg ^c	–	–	G1	G1	N	Y	Y
6	20 mg	–	–	G1	G1	N	Y	Y

N, no; Y, yes; WL, weight loss; MDT, multidisciplinary team; rehab, rehabilitation (including physical exercise program and counseling). ^aReduction after 18 months; ^breduction after 40 months; ^creduction after 1 month; ^dreduction after 6 months; ^ereduction after 3 months.

Table 3. Morisky scale

1	Have you ever forgotten to take the drug?	Y/N
2	Do you take your drugs on time?	Y/N
3	When you feel well, do you stop taking the drug?	Y/N
4	Sometimes when you feel bad, do you stop taking the drug?	Y/N

Patients who answered yes to more than two of these questions were not included. Y, yes; N, no.

After 48 months of follow-up, overall response rate of 50% (95% CI, 37–63) with only PRs were reported. The median time to response was 3.6 months, the median response duration was 12.7 months, and the median PFS was 12.6 months (95% CI, 9.9–16.1).

Patients underwent weekly clinical visits for the first 2 months and monthly clinical visits thereafter. Strategies for managing AEs in the clinic include supportive care, dose modifications, and, if necessary, discontinuation of LEN therapy.

Table 2 summarizes AEs in our population. We tried to encourage patients to communicate earlier than possible signs and symptoms of AEs, we provided a diary for blood pressure and weight, a dietetic visit was programmed every month, a dietary program was provided, and endocrinology visits were performed monthly. Compliance of patients was evaluated with the Morisky test (Table 3).

Hypertension occurred in all patients (<G3 in 4/6; G3 in 2/6 patients). The diagnosis occurred after 2 weeks of treatment in all patients. We suppose that this early diagnosis avoided serious complications and allowed patients to stay on treatment. Three out of 6 patients received a

Table 4. Brief Fatigue Inventory median values

Items	Pt1	Pt2	Pt3	Pt4	Pt5	Pt6
Fatigue right now	2	6	4	4	4	3
Fatigue after 24 h	2	7	5	4	5	3
Worst fatigue	3	8	5	6	5	4
Interference with GA	0	6	3	4	5	3
Mood	0	2	4	2	4	3
Walking ability	0	4	3	4	4	3
Normal work	0	6	3	5	4	3
Relationship	0	0	3	2	3	2
Enjoyment of life	0	0	3	2	3	2

Pt, patient; GA, general activity.

combination of antihypertensive drugs and were followed by a cardiologist.

Proteinuria was reported in 3 patients (1 G2 and 2 G1). Urinalysis and protein-to-creatinine ratio were measured at baseline and every cycle throughout treatment.

Patients received the Brief Fatigue Inventory – Short Form; the data collected reported fatigue ranging from 2 to 6, with average interference of 4 with general activity and normal work (Table 4).

Fatigue was treated with exercise (in particular, a project on Nordic Walking was proposed) and other stress-reducing techniques (writing activity, groups activity, and so on).

In our small case series, gastrointestinal AEs were the most common, with all patients experiencing G2 diarrhea, and 3/6 patients experiencing nausea. We managed these AEs with the introduction of probiotics throughout treatment. Probiotic bacteria favorably alter the intestinal

microflora to promote digestion, enhance immune response, and inhibit the growth of harmful bacteria.

We prescribed probiotics with 5 core species that are widely available: *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus brevis*, *Bifidobacterium lactis*, and *Bifidobacterium longum*. We recommended a high number of species as each strain has different digestive and immune properties. Two patients also received rifaximine 400 mg b.i.d./day for 1 month, and all our patients received loperamide if the number of defecations or stool consistency was altered.

Other strategies included diet modification and rehydration management. To prevent stomatitis and to reduce dysgeusia, we suggested mouth rinses with water and bicarbonate. Palmar-plantar erythrodysesthesia G2 was reported in 2/6 of our patients and was treated with moisturizing creams and keratolytic agents. We did not encounter any significant hemorrhagic events or thrombocytopenia.

We report a severely complicated history of a patient (Patient 6) with cardiovascular disease (2012 cardiac valve replacement; atrial fibrillation, treatment with anticoagulant warfarin since 2015). The patient underwent biweekly cardiac clinical examination, electrocardiography and monthly echocardiography. Blood samples to check coagulation and electrolytes were also drawn every 2 weeks.

Patient 5 continued therapy while being on a direct-acting oral anticoagulant, without any AEs.

Conclusions

Early clinical intervention, in our experience, helps maintain the therapeutic program and has the advantage of asserting a good quality of life throughout treatment with LEN. As we reported all patients treated with LEN since July 2015, we believe that these long-term responses depend on the adequate management of side effects rather than the selection of patients.

This is the first study in which a multidisciplinary team approach is described not only in the diagnostic flow chart but also during the treatment of RR-DTC.

Statement of Ethics

Patient's informed consent was obtained for therapies and biological samples at the beginning of the treatment in the Oncology Day Hospital.

Disclosure Statement

None of the authors have public or private financial relationships with organizations or institutions that could be relevant for the results presented.

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