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Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

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To cite this article: Stefano Cavalieri, Laura Cosmai, Augusto Genderini, Manuela Nebuloni, Antonella Tosoni, Federica Favales, Paola Pistillo, Cristiana Bergamini, Paolo Bossi, Lisa Licitra, Laura D. Locati & Salvatore Alfieri (2018): Lenvatinib-induced renal failure: two first-time case reports and review of literature, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1080/17425255.2018.1461839

To link to this article: https://doi.org/10.1080/17425255.2018.1461839

Accepted author version posted online: 04 Apr 2018.

Publisher: Taylor & Francis

Journal: *Expert Opinion on Drug Metabolism & Toxicology*

DOI: 10.1080/17425255.2018.1461839

Lenvatinib-induced renal failure: two first-time case reports and review of literature

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Funding:
This paper was not funded.

Declaration of Interest: L Licitra reports grants and personal fees from Eisai, Merck Sharp & Dohme, Boehringer Ingelheim, Novartis, Astrazeneca, Roche; personal fees from Bristol-Myers Squibb; grants, personal fees and other (travel expenses) from Merck-Serono, Bayer, Debiopharm, Sobi. L Locati reports honoraria from Eisai. P Bossi reports honoraria or consultation fees from Roche, Merck Serono, Mundipharma, Kyowa Kyrin and Astra Zeneca.

Aknowledgment: The Authors dedicate this work to dr. Augusto Genderini, who passed away before the completion of this manuscript. Without his essential contribution this work could not be realized.

Authorship: Laura D. Locati (reported as second to last Author) and Salvatore Alfieri (reported as last Author) equally contributed to this paper.

Abstract

Introduction:

Lenvatinib (LEN) is a multi-kinase anti-angiogenic drug recently approved in several cancers. LEN is not easily manageable due to its complex safety profile. Proteinuria and renal failure (RF) were reported among the most frequent LEN-induced adverse events (AEs), often leading to discontinuations or dose modifications. Understanding the pathogenesis of these AEs could ameliorate the management of LEN-induced renal toxicity.

Areas covered:

We present two cases of LEN-induced renal failure (LIRF) with different pathogenesis. 1) LIRF with severe proteinuria in a man treated for a metastatic papillary thyroid carcinoma. Kidney biopsy showed a glomerular damage secondary to LEN, having excluded other causes of RF. 2) LIRF without proteinuria in a woman with metastatic adenoid cystic carcinoma of minor salivary gland. A tubulointerstitial nephropathy was supposed by clinical evaluation and laboratory tests. Effective management was obtained by oral steroids without interrupting LEN.

Expert opinion:

The case 1 presented for the first time the histological picture of LIRF with a classical glomerular damage leading to secondary proteinuria and tubular failure. Case 2 showed an alternative LIRF pattern of likely tubulointerstitial injury without proteinuria. These reports reflect two sides of the same coin, both to be considered in case of LIRF.

KEYWORDS:

Antiangiogenic, lenvatinib, nephropathy, proteinuria, renal failure, salivary gland cancer, thyroid cancer, toxicity, VEGF, VEGFR

Article Highlights:

1. Proteinuria is recognized as a class side effect among antiangiogenic drugs, such as lenvatinib
2. Proteinuria often leads to lenvatinib interruptions and/or dose modifications
3. Lenvatinib-induced renal failure (LIRF) might be associated with glomerular damage, with secondary proteinuria and tubular injury
4. A primary tubulointerstitial injury may be identified as alternative pattern of LIRF without proteinuria development
5. Low-dose steroids can be used to manage the primary non-glomerular lenvatinib-induced damage without requiring lenvatinib interruption or discontinuation

1. INTRODUCTION

Lenvatinib (Lenvima®, LEN) is an orally bioavailable multitarget tyrosine kinase inhibitor (TKI), acting on VEGFR, FGFR, PDGFR-α, KIT and RET. [1]

To date, LEN is licensed for advanced progressive radioactive-iodine (RAI) refractory differentiated thyroid cancer (DTC) patients [2] . It has also been approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA), in combination with everolimus, as second-line in advanced renal cell carcinoma (RCC)[3]. Recently, FDA has recently approved LEN as first-line therapy in advanced hepatocellular carcinoma (HCC) considering the results of non-inferiority (versus sorafenib) phase III trial (REFLECT) [4]. Moreover, LEN has already been studied as monotherapy [5] and in combination with immunotherapy (pembrolizumab) [6] in renal cell carcinoma, in metastatic or recurrent endometrial cancer (EC) [5] and in anaplastic thyroid cancer (ATC) [7]. The results of a single-Institution phase II study with LEN in advanced adenoid cystic carcinoma (ACC) of salivary glands will be published in the near future since recruitment has already been completed [8]. Table 1 summarized all ongoing clinical trials evaluating LEN in several other malignancies.

In brief, in the era of targeted therapies, LEN is is one of the most promising targeted agents with multiple opportunities of application in the clinical practice.

2. CASE REPORTS

Here, we report two cases of LEN-induced renal failure (LIRF).

These two reports gave us the opportunity to review, understand and discuss pathogenesis of LIRF in order to better manage this toxicity. Both cases were reported to the Italian network of pharmacovigilance [9]. Informed consent forms were collected.

2.1 CASE 1

2.1.1 CLINICAL HISTORY

In 1998 a papillary thyroid carcinoma was diagnosed in a 44-year-old man, with arterial hypertension (AH) as only comorbidity (AH managed by doxazosin 2 mg, atenolol 25 mg and chlorthalidone 6.25 mg per day). He underwent total thyroidectomy (stage pT2a, cN0 cM0 according to seventh edition of AJCC TNM), post-

operative thyroid stimulating hormone (TSH) suppression by oral levothyroxine and one course (80 mCi) of RAI. During follow-up (2004), despite a negative whole body ^{131}RAI scan (^{131}RAI -WBS), serum thyroglobulin progressively increased, suggesting the presence of micrometastatic dissemination, so a new course of ^{131}RAI (200 mCi) was administered. In 2007 a right selective neck dissection was performed due to locoregional relapse (3 out of 30 lymph nodes were metastatic). Two years later (2009), ^{131}RAI-WBS was negative while both ^{18}FluoroDesoxyGlucose (FDG)-Positron Emission Tomography (PET) and ^{68}Ga DOTATOC [^{68}gallium bound to DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and octreotide] PET showed a locoregional and distant (mediastinal lymph nodes and right lung) disease recurrence. Based on these characteristics, disease was considered as RAI-resistant and four cycles of ^{68}Ga-DOTATOC were administered (cumulative dose 403 mCi) with substantial stable disease (SD). Due to progression of disease (PD) with concomitant negative ^{68}Ga DOTATOC PET scan, patient was treated with sorafenib from September 2010 until PD in August 2011. Further surgery (left selective neck dissection) was performed in December 2011 due to lymph nodal progression. In April 2012 FDG-PET showed bilateral pulmonary PD, confirmed by a chest CT scan. Therefore, in September 2012 patient, aged 58 years, was referred to our Institution for a second-line systemic therapy. Patient was enrolled within SELECT trial [2] and received LEN at daily dose of 24 mg. At baseline, patient performance status (PS) was good (Eastern Cooperative Oncology Group, ECOG PS 1) and blood pressure was well balanced by his usual anti-hypertensive therapy. Pre-treatment laboratory (lab) tests showed mild [grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE) 4.03] abnormalities of serum creatinine (1.65 mg/dl, range 0.10-1.20) and proteinuria (1+ at urine dipstick). Proteinuria was managed as per protocol: if proteinuria was ≥2+ at urine dipstick, a 24-hour proteinuria was evaluated within 72 hours without LEN interruption; in case of proteinuria lower than 1 g/24h (≤ grade 1 CTCAE) the drug was continued, otherwise LEN was discontinued until toxicity was resolved to grade 0-1 or baseline and reduced at lower level dose when resumed. Figure 1 summarized a time-dependent overview of LEN management (e.g. all temporary discontinuations and dose reductions to 20, 14 and 10 mg/day at 6th, 10th and 36th treatment month, respectively) based on the evolution of serum creatinine and proteinuria. Concomitantly, a persistent disease control was achieved after a partial remission, occurred as best response at 2nd month of LEN course. Considering this significant clinical benefit and that baseline proteinuria was abnormal (grade 1) remaining stable (2+ at urine dipstick) for one year of treatment (with no further AEs), an agreement with study Sponsor (Eisai) was established. This consisted of performing 24-hour proteinuria only in case of 3+ at urine dipstick. At the fourth year of LEN, proteinuria worsened (G3, >3.5g/24h according to CTCAE), with significant increase of AH (G3, 160/80 mmHg) and serum creatinine (G1, 1.9 mg/dl), so LEN was interrupted and patient was hospitalized. Due to the persistence of lab tests abnormalities after 10 days of LEN discontinuation (half-life of LEN is approximately 28 hours), a kidney biopsy was performed in order to exclude all possible other causes of renal failure (RF). So, a complex pattern of drug-related glomerular, tubulointerstitial, and vascular renal

injury was diagnosed (Figures 2 and 3). Histological details will be reported in the next paragraph. After the start of angiotensin converting enzyme (ACE) inhibitor, blood pressure values were normalized while proteinuria (G1) and serum creatinine significantly decreased (G1, 1.68 mg/dl) within further 4 weeks.

LEN was definitively stopped and patient went on clinical and radiological follow-up every 4-6 months. Following lab tests showed chronic kidney damage (serum creatinine ranging from 1.4 to 1.6 mg/dl and proteinuria 1+ to 2+ at urine dipstick).

2.1.2 HISTOLOGICAL FINDINGS

For the histological analysis, kidney biopsy was fixed in 10% buffered formalin and embedded in paraffin. Specific staining for renal tissue was performed. A second specimen was snap-frozen and used for immune-fluorescence analysis. A third sample (5 mm) was fixed in 2.5% glutaraldehyde, embedded in resin and reserved for electron microscopy. Semi-thin and thin sections were cut and stained using conventional methods. Tissues were then examined by transmission electron microscopy (Zeiss EM109 electron microscope).

Light microscopy examination revealed a huge number (n=24) of glomeruli, whose 45% (n=11) were globally sclerotic. The remaining glomeruli (n=13) showed mesangial hypercellularity and increase of mesangial matrix. In one glomerulus, segmental features of mesangiolysis were observed. Capillary basal membranes were thickened with double contours (Figure 2). Moreover, endothelial ipertrophy and swelling, intimal edema and focal sub-endothelial necrosis characterized the arteriolar narrowing. No inflammatory reaction was detected in the vessels wall. The interstitial component showed fibrosis and tubular atrophy.

Immune-fluorescence analysis revealed weak focal and segmental staining for immunoglobulins and complement along the capillary basal membrane.

Ultrastructural examination (Figure 3) showed focal glomerular sclerosis, focal podocyte foot process effacement and rare electron dense deposits with subendothelial and intramembranous localization.

The diagnosis concluded for a drug-induced renal damage characterized by tubulointerstitial vascular necrotic injury and endothelial alterations suggesting for a thrombotic microangiopathy (TMA)-like pattern with ultrastructural evidence of podocytes foot process effacement.

2.2 CASE 2

2.2.1 CLINICAL HISTORY

In 2015 a 59-year-old woman, without significant cardiologic or pneumologic comorbidities (no conocomitant medications at baseline), started her clinical history suffering of steroid-resistant mild dyspnea. A fiber optic bronchoscopy showed a subtotal occlusion of the medium third part of the trachea

by neoplastic nodules protruding from the anterior and right lateral walls, which widely infiltrated the carina. Laser photocoagulative treatment and endoscopic excision of the tumor lesions allowed a prompt airways recanalization. The histopathological exam showed an adenoid cystic carcinoma (ACC) with cribriform and solid features, originating from the minor salivary glands of the trachea.

A whole body computed tomography (CT) scan showed enlarged mediastinal (upper carinal and pre-carinal regions) lymph nodes obstructing the trachea from its anterior wall. Multiple liver metastases (maximum diameter 35 mm) were observed as well.

Two courses of palliative chemotherapy with cisplatin and doxorubicin was administered every 3 weeks from May to June 2015. Endoscopic assessments showed stable disease at the tracheal level and a multidisciplinary team consultation excluded the feasibility of a local irradiation. However, a CT scan revealed disease progression in the liver. Therefore, chemotherapy was discontinued and patient was referred to our Institution for enrollment within a phase II trial with LEN in recurrent and/or metastatic ACC[8]. On July 2015, patient with ECOG PS 0, no symptoms and normal baseline blood/urinary analyses, received the first course of LEN at 24 mg daily. After only one month, LEN was temporarily discontinued for 15 days and then resumed at 20 mg daily due to G3 gastrointestinal toxicity. During LEN trial, disease revaluations (whole body CT scan and bronchoscopy) performed one every 8 weeks showed a SD both at local and distant sites.

In October 2016 (15 months from the LEN start), lab tests showed a progressive impairment in renal function tests: serum creatinine values increased from 0.95 mg/dl (range: 0.1-0.9 mg/dl) to 1.34 mg/dl in November 2016 until a maximum value of 2.81 mg/dl in December 2016, when blood urea nitrogen (BUN) was 155 mg/dl (range: 15-45 mg/dl) and no associated blood electrolytes imbalances were observed. In December 2016, urine exams (including creatinine clearance/24 hours) excluded any grade of proteinuria. This acute RF improved very rapidly (after only 2 LEN days off, creatinine was 1.27 mg/dl and BUN 53 mg/dl) thanks to intravenous hydration and temporary LEN interruption (lasting for 10 days). After one month of LEN, which was resumed at reduced daily dose of 14 mg, a new increase of serum creatinine (1.63 mg/dl) and BUN (91 mg/dl) occurred, without any other laboratory abnormalities. Primary glomerular damage was excluded because proteinuria and albuminuria were lower than 1 g/24h and 20 mg in spot urinalysis, respectively. At urine exam amorphous sediment and no cylindruria were also observed. Normal blood count, coagulation tests, lactate dehydrogenase and haptoglobin excluded hemolytic uremic syndrome and other thrombotic microangiopathies. Therefore, a nephrologic consultation supposed the clinical diagnosis of a tubulointerstitial LEN-induced nephropathy without proteinuria. Patient never stopped/reduced LEN since December 2016 and concomitantly received corticosteroids (starting dose of prednisone was 40 mg/day), with progressive tapering according to renal function tests (serum creatinine and BUN). After one month of steroid dose adjustment, patient carried on fixed daily dose of prednisone 12.5 mg/day with stabilization (within grade 1 or 2) of renal function in the following six months. On August

2017, a CT-scan showed a PD in the liver according to RECIST 1.1 and LEN plus prednisone were definitely stopped. Because of persistent good performance status, chemo-refractory and slow-growing disease (with most tumor burden in the liver), two cycles of Trans-Arterial Chemo-Embolization (TACE) on the largest liver metastases were performed (in October and December 2017).Patient is still alive without any disease-related symptoms and creatinine increase is still within grade 1.

3 REVIEW

3.1 LENVATINIB-INDUCED RENAL FAILURE (LIRF) AND PROTEINURIA

Data coming from the only LEN pivotal trials already published as full-papers [2] [3] showed a complex safety profile for this drug. As illustrated in Table 2, in both trials almost 100% and 75% of patients experienced at least one any-grade (AG) and grade 3 (G3) treatment-related adverse events (TRAE), respectively. This led to frequent drug discontinuations and/or dose reductions, thus impairing the LEN exposition and potentially patient outcomes. Indeed, a clear-cut relationship between drug exposure and anticancer activity has already been well described for multikinase inhibitors Sunitinib and Sorafenib. [10, 11].

In the pivotal trial of LEN in RAI-refractory metastatic and progressive DTC (SELECT study) [2], proteinuria was one of the most frequent TRAEs, resulting as the second one (10%) among ≥G3 TRAEs (after AH, 41.8%) and the third cause (18.8%) of drug interruptions and/or reductions after diarrhea (22.6%) and AH (19.9%). In a subgroup analysis of SELECT trial, including elderly patients (> 65 years) [11], a higher incidence of G3 TRAEs, especially including AH and proteinuria, was reported in elderly (88.7%) versus younger (≤ 65 years) DTC patients (67.1%), thus leading to a shorter time (1.5 vs 3.7 months, respectively) elapsed before the first dose reduction.

Proteinuria was the most frequent G3 TRAE when LEN has been studied as monotherapy in RCC patients (19%), compared to combination of LEN plus everolimus (4%) and everolimuns alone (2%) [3].

In the phase II trial of LEN in HCC [12], proteinuria was the most frequent cause of study drug withdrawal (11%).

Table 3 reported the incidence of AG and G3 LEN-induced renal failure (LIRF) and proteinuria in all studies actually published as full-papers.

The percentage of ≥G3 proteinuria (10%) of overall SELECT population approximately doubled analyzing only Japanese patients (20%) included in the same study [13] or considering different cancer settings, such as HCC (19.6%) [12] and RCC (19%) [3].

The subgroup analysis of elderly (> 65 years) in SELECT trial [11] confirmed this trend for G3 proteinuria (13.2%) when compared to that observed (7.7%) in younger patients (≤ 65 years).

In addition to age, further pre-existing risk factors of RF induction were identified: AH, stage≥3 chronic kidney disease (CKD), TMA, and all grade proteinuria [14].

3.2 PATHOGENESIS

3.2.1 HYPERTENSION AND PROTEINURIA

Isolated AH is the most common adverse event observed with agents targeting the VEGF/VEGFRs. This side effect can be mediated by several mechanisms: reduction of cell renewal, apoptosis of endothelial cells, rarefaction of capillaries and arterioles, reduced production of vasodilators (e.g. nitric oxide and prostacyclin), direct vasoconstriction leading to peripheral resistance increase, and reduction of sodium renal excretion [15].

On the other hand, proteinuria has a controversial pathogenesis. Taking into account that VEGF-A is expressed on podocytes, glomeruli and tubular cells, while VEGFRs on endothelial, mesangial and peritubular capillary cells, different mechanisms of proteinuria can be hypothesized [15]: dysregulation in repairing the early renal damage thus enhancing glomerulosclerosis; loss of selective glomerular permeability; increased intraglomerular pressure. The latter could also be secondary to AH. However, although there is a frequent association between proteinuria and AH, it is not clear whether one is secondary to the other or both are independently caused by VEGF blockade. Proteinuria and AH are likely associated since patients with proteinuria develop hypertension more frequently. In contrast, AH does not seem to play a role in the pathogenesis of proteinuria, since the glomerular damage induced by reduced VEGF expression on podocytes has been demonstrated before the development of AH in animal knockout models [16].

Starting from a phase I study, Keizer et al. structured a pharmacokinetic–pharmacodynamic model for AH and proteinuria. In this work they showed that both lenvatinib plasma concentration and an increased diastolic blood pressure have a separate effect on the development of proteinuria. [17]

3.2.2 FGF/FGFR PATHWAY INHIBITION

Other molecular targets could also explain LIRF. Among them, the FGF/FGFRs pathway blockade has to be cited, though controversial evidences are available; indeed, in vitro, FGF23 proved to exert divergent effects on fibroblast activation in cells derived from normal and obstructed kidneys. While FGF23 failed to stimulate fibrogenesis in normal fibroblasts, in those primed by injury, FGF23 induced pro-fibrotic signaling cascades via activation of TGF-β pathways. Tubule-derived FGF23 may thus amplify myofibroblast activation in acute renal injury, leading to renal fibrosis and injury [18].

Having said that, because FGF/FGFR is not targeted by other antiangiogenic drugs, VEGF/VEGFR axis inhibition has to be considered the key mechanism in inducing RF.

4. CONCLUSION

We described two cases of LIRF with alternative clinical and pathogenetic patterns.

In both reports, further causes of renal damage, such as concomitant nephrotoxic medications, co-existing autoimmune syndromes, infections and any other renal disorder, were excluded.

In case 1, a glomerular drug injury with secondary proteinuria and indirect tubulointerstitial damage was observed and histologically characterized. Potentially, this represented a spurious (with only kidney disease) TMA-like pattern induced byVEGF/VEGFRs pathway inhibition.

In case 2, the kidney damage was mainly based on a direct tubular failure, without proteinuria and glomerular involvement. A possible tubulointerstitial nephritis was clinically diagnosed. This hypothesis was also supported by the ex juvantibus effect yielded using corticosteroids.

The putative pathogenetic mechanism presented in case 2 could open the way to a completely different diagnostic and therapeutic approach, based on chronic low-dose steroids use.

5. EXPERT OPINION

Acute or chronic renal function deficiency, regardless of its drug-related pathogenesis is based on a damage of renal tubuli. That is the reason why any primary glomerular injury, with secondary proteinuria, is rarely linked to RF, as it needs longer time to induce tubular alterations. This is the classical way throughout the most part of antiangiogenic agents, as LEN, might lead to renal disorders. Therefore, tubulointerstitial RF is underestimated compared to proteinuria [15]. Notably, in case 1, proteinuria needed almost four years to induce an acute RF. Moreover, in the literature [8], Brose et al also described renal toxicities as the most frequent LEN AEs (after AH) among elderly (> 65 years) thyroid cancer patients.

The renal side effects from TKIs have already been described, and the first multicentric experiences of LIRF in DTC as well [2]. However, to the best of our knowledge, this work reports the histological features of LIRF for the first time.

In case 1, mesangiolysis is very rare and usually lacking in primary glomerular nephropaties, except for those observed in diabetes and hemolytic uremic syndrome (both excluded in our patient) or in case of some cytotoxic chemotherapy-induced kidney injury (e.g. Mitomycin-C) [19]. Concomitantly, LEN-induced endothelial alterations, notably hypertrophy, determine severe vascular injury, configuring a TMA-like pattern, similarly to that observed in the kidney injury caused by other antiangiogenics.

In this drugs class, the classical histopathological picture is characterized by glomerular endotheliosis, focal segmental glomerulosclerosis (sometimes collapsing), various glomerulopathies, and most commonly TMA [20], with few cases of acute interstitial nephritis.

With regards to the medical treatment of TKIs induced proteinuria, no standardized guidelines are available. Nevertheless, many papers reported the activity of ACE inhibitors in this setting [21]. In fact, the rationale to use this drugs class is the prevention of both AH and cardiovascular events [22].In case 2, a direct tubulointerstitial damage, without glomerular involvement and proteinuria development, was hypothesized. This type of injury was described for almost all antiangiogenics (e.g. Bevacizumab, Sorafenib, Sunitinib [23]), but it has never been reported with LEN.

The time needed to be elapsed before LIRF induction was significantly shorter in case 2 (14 months) than what observed in case 1 (42 months) due to the intrinsic LIRF mechanisms explained. However, in both reports, timing remains as one of the most important variables, together with the presence or not of proteinuria, to differentiate these two models of LIRF.

The weakness of case 2 was the lack of the histological confirmation: all conclusions were based only on the clinical results (blood and urinary tests) and no kidney biopsy was performed to avoid patient an invasive diagnostic approach. Moreover, apart from interstitial nephritis, a relevant number of glomerular abnormalities, like glomerulosclerosis, can respond to corticosteroid therapy. Our diagnosis of interstitial nephritis may be also less consistent due to the absence of both eosinophiluria and eosinophilia in our patient. With these caveats, in case of LIRF without proteinuria, low doses of steroids shoud be considered in order to avoid kidney biopsy and carry on with an active anti-tumor agent. In fact, an inflammatory component is very likely in TKI-induced renal damage.

Regardless of these limitations, the identification of different pathogenetic LIRF mechanisms could have a key relevance in optimizing the diagnostic and therapeutic strategies. Indeed, for example in case of a LIRF pattern characterized by G2 proteinuria (24-hour urine), such as in case 1, one could speculate to temporarily stop and reduce LEN after recovery from toxicity. This could be suggested because proteinuria tends to resolve with drug withdrawal. For this reason, proteinuria should be always assessed in patients under treatment with LEN and the management of LEN-induced proteinuria could be the same of that caused by bevacizumab [24].

On the other hand, an acute kidney injury secondary to a possible interstitial nephritis could often lead to treatment discontinuation due to its trend to a rapid relapse, as demonstrated in case 2. In this alternative LIRF model, patients can benefit of chronic low-dose steroids without any drug interruption and/or dose reduction. The latter aspect is particularly relevant to optimize drug exposition.

Therefore, it is intuitive that better understanding LIRF mechanisms may lead to a such promptness in discovering or preventing RF, thus improving drug efficacy and safety. Notably, saving toxicities deserves to be considered in long-term survivor cancer patients, like those here reported.

Abbreviation	Meaning
ACC	Adenoid Cystic Carcinoma
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AH	Arterial Hypertension
AJCC	American Joint Committee on Cancer
ATC	Anaplastic Thyroid Cancer
BUN	Blood Urea Nitrogen
CKD	Chronic Kidney Disease
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Event
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTATOC	DOTA-octreotide
DTC	Differentiated Thyroid Cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDG	Fluoro-Deoxy-Glucose
FGF	Fibroblast Growth Factor
FGFR	Fibroblast Growth Factor Receptor
G1-G2-G3-G4-G5	Grade 1 - Grade 2 - Grade 3 - Grade 4 - Grade 5
HCC	HepatoCellular Carcinoma
KIT	KIT proto-oncogene
LEN	Lenvatinib
LIRF	Lenvatinib-Induced Renal Failure
PD	Progression of Disease
PDGFR-α	Platelet Derived Growth Factor Receptor Alpha
PET	Positron Emission Tomography
PS	Performance Status
RAI	RadioActive Iodine
RCC	Renal Cell Carcinoma
RET	RET proto-oncogene
RF	Renal Failure
SD	Stable Disease
TACE	Trans-Arterial Chemo-Embolization
TKI	Tyrosine Kinase Inhibitor
TMA	Thrombotic MicroAngiopathy
TNM	Tumor Node Metastasis staging system
TRAE	Treatment Related Adverse Event
TSH	Thyroid Stimulating Hormone

VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBS	Whole Body Scan

List of abbreviations used in the text

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* A single-Institution phase II trial (to date completed recruitment) in which the case 2 of this article was enrolled. The study proposal was monotherapy with lenvatinib in advanced adenoid cystic carcinoma (ACC) patients.

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Figure Legends:

Figure 1 – Overview of case 1 time dependent values of serum creatinine (mg/dl; black line), proteinuria at urine dipstick (semiquantitative measurements: 1+, 2+, 3+; grey columns), 24-hour proteinuria (g/24h; green triangles), and lenvatinib daily dose (mg; blue lines. White spaces correspond to drug interruptions).

Figure 2 – PAS staining of a glomerulus with segmental mesangiolysis (*) and rare double contours (arrow) in capillary wall. PAS staining, OM 40x.

Figure 3 – Electron microscopy of a glomerulus: podocyte foot process effacement (**) and subendothelial/intramembranous deposits (*). Electron microscopy, x12000

Recruitment	Disease	Phase	Title	NCT number
Recruiting	Thyroid cancer	2	Phase II Study Assessing the Efficacy and Safety of Lenvatinib for Anaplastic Thyroid Cancer	NCT02726503
		3	A Trial of Lenvatinib (E7080) in Radioiodine (131 I)-Refractory Differentiated Thyroid Cancer in China	NCT02966093
		4	Post-marketing Surveillance of Lenvatinib Mesylate (Lenvima Capsule) in Patients With Unresectable Thyroid Cancer (Study LEN01T)	NCT02430714
		2	A Phase 2 Trial of Lenvatinib (E7080) in Subjects With Iodine-131 Refractory Differentiated Thyroid Cancer to Evaluate Whether an Oral Starting Dose of 18 mg Daily Will Provide Comparable Efficacy to a 24 mg Starting Dose, But Have a Better Safety Profile	NCT02702388
		2	UPCC 36315 A Phase II Study Of Everolimus (RAD001) And Lenvatinib (E7080) In Patients With Metastatic Differentiated Thyroid Cancer Who Have Progressed on Lenvatinib Alone	NCT03139747
		4	Post-Marketing Surveillance of Lenvima in Korean Patients	NCT02764554
	Recurrent Endometrial or Ovarian Cancer	1	Lenvatinib and Weekly Paclitaxel for Patients With Recurrent Endometrial or Ovarian Cancer	NCT02788708
	GastroEsophageal Cancer	2	A Study of Lenvatinib, a Multi-targeted Tyrosine Kinase Inhibitor, Combined With Pembrolizumab (PD-1 Inhibitor) for the Treatment of Metastatic Gastroesophageal Cancer Patients Who Have Progressed on First or Subsequent Line Therapies	NCT03321630
	Hepatocellular Carcinoma	1	A Trial of Lenvatinib Plus Pembrolizumab in Subjects With Hepatocellular Carcinoma	NCT03006926
	Osteosarcoma	1/2	Study of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults With Osteosarcoma	NCT02432274
	Solid tumors	2	Eribulin and Lenvatinib in Advanced Solid Tumors	NCT02640508
		1/2	Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors	NCT02501096
	Renal Cell Carcinoma	2	Trial to Assess Safety and Efficacy of Lenvatinib in Combination With Everolimus in Participants With RCC	NCT03173560
		3	Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone as Treatment of Advanced RCC	NCT02811861
	Non Clear Cell Renal Cell Carcinoma (nccRCC)	2	A Phase 2 Trial to Evaluate Efficacy and Safety of Lenvatinib in Combination With Everolimus in Subjects With Unresectable Advanced or Metastatic Non Clear Cell Renal Cell Carcinoma (nccRCC) Who Have Not Received Any Chemotherapy for Advanced Disease	NCT02915783
	Rectal Cancer	1	Capecitabine and Lenvatinib With External Radiation in Rectal Adenocarcinoma	NCT02935309
	Advanced Pheochromocytoma	2	Lenvatinib in Treating Patients With Metastatic or Advanced Pheochromocytoma or Paraganglioma That Cannot Be Removed by Surgery	NCT03008369
	Neuroendocrine Tumors	2	Lenvatinib Efficacy in Metastatic Neuroendocrine Tumors	NCT02678780
	Breast Cancer	2	Phase II Study of Single Agent Lenvatinib	NCT03168074
		1/2	Neoadjuvant Lenvatinib Combined With Letrozole in Hormone Receptor Positive Breast Cancer	NCT02562118
Not yet recruiting	Solid tumors	1	Pharmacokinetic Study of E7080/Lenvatinib in Chinese Subjects With Solid Tumor	NCT03009292
		1/2	Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including Central Nervous System Tumors	NCT03245151
		1	Pharmacokinetic Study of E7080/Lenvatinib in Chinese Subjects With Solid Tumor	NCT03009292
		2	Study of Lenvatinib in Patients With Advanced Cancer and Aberrations in FGF/FGFR Signaling	NCT02846766
	Renal Cell Carcinoma	2	Lenvatinib and Everolimus in Renal Cell Carcinoma (RCC)	NCT03324373
	Differentiated Thyroid Carcinoma	2	Pembrolizumab and Lenvatinib in Treating Metastatic or Recurrent Differentiated Thyroid Cancer That Cannot Be Removed by Surgery	NCT02973997

Table 1 – Summary of ongoing (recruiting and not yet recruiting patients) clinical trials evaluating lenvatinib in Oncology

	Schlumberger, NEJM 2015 N = 261	**Motzer, Lancet Oncol 2015 N = 52**
Any-grade TRAE (%)	97.3	94
≥ G3 TRAE (%)	75.9	73
Drug interruption (%)	82.4	25
Dose reduction (%)	67.8	62

TRAE, treatment-related adverse events

Table 2 – Safety of lenvatinib in pivotal trials for advanced thyroid and renal cell cancers

Disease	Reference	N pts	Initial daily dose of lenvatinib	Proteinuria		Renal failure	
				Any grade	*Grade≥3*	*Any grade*	*Grade≥3*
RAI-DTC	Schlumberger, NEJM 2015	261	24 mg	32.2%	10%	4.2%	1.9%
	Brose, JCO 2017	106	24 mg	27.7% (≤65y) vs 35.8% (>65y)	7.7% (≤65y) vs 13.2% (>65y)	0% (≤65y) vs 0.9% (> 65y)	NS
	Kiyota, Cancer Sci 2015	30	24 mg	63%	20%	NS	NS
	Berdelou, Thyroid 2017	88	24 mg	NS*	NS*	NS*	NS*
ATC	Tahara, Front Oncol 2017	17	24 mg	59%	6%	NS	NS
RCC	Motzer, Lancet Oncol 2015	52	24 mg	31%	19%	NS	NS
HCC	Ikeda, J Gastroenterol 2017	46	12 mg	60.9%	19.6%	NS	NS

Table 3 – Incidence of any CTCAE grade and grade≥3 Lenvatinib-induced renal failure and proteinuria in Medical Oncology

*Underestimated because of urine analysis was not done as routine test in study patients.

Abbreviations (in alphabetical order):

ATC, Anaplastic Thyroid Cancer. HCC, Hepatocellular Carcinoma. N pts, number of patients treated with lenvatinib. NS, Not Specified. RAI-DTC, Iodine-131 Refractory Differentiated Thyroid Cancer. RCC, Renal Cell Carcinoma. y, years.

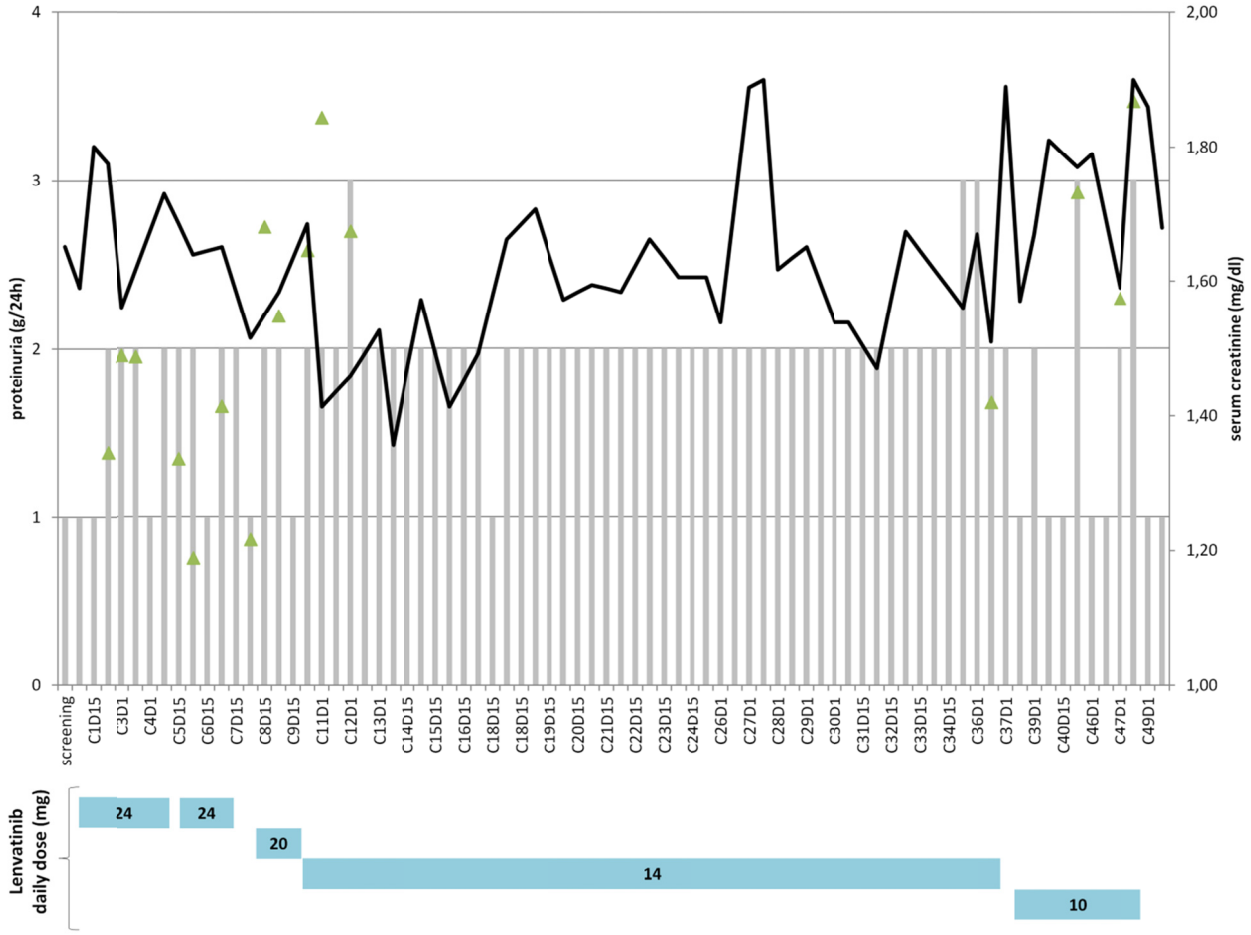

Figure 1

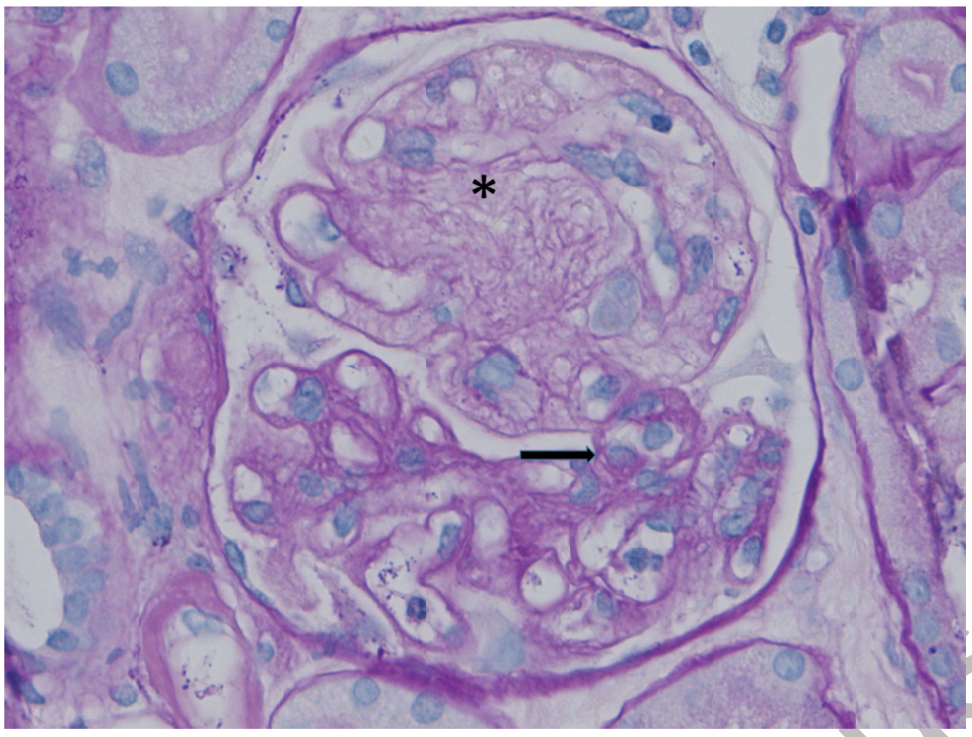

Figure 2

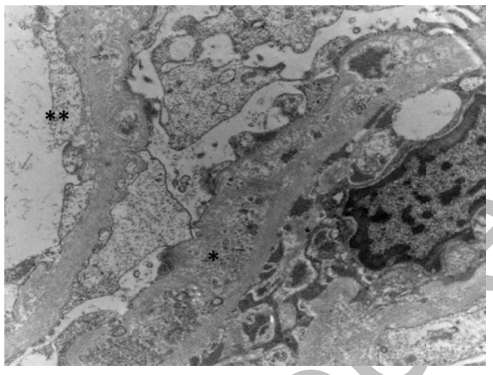

Figure 3