Clinical Thyroidology / Original Paper

European
Thyroid Journal

Eur Thyroid J 2018;7:308–312
DOI: 10.1159/000491387

Received: November 14, 2017
Accepted after revision: June 4, 2018
Published online: August 16, 2018

Anti VEGF-TKI Treatment and New Renal Adverse Events Not Reported in Phase III Trials

Luisa Paschke[a, e] Thomas Lincke[b] Katja Sibylle Mühlberg[c] Wolfram J. Jabs[d]
Tom H. Lindner[e] Ralf Paschke[f]

[a]Department of Endocrinology and Nephrology, Division of Endocrinology, University Clinic Leipzig, Leipzig, Germany; [b]Department of Radiology, Division of Nuclear Medicine, University Clinic Leipzig, Leipzig, Germany; [c]Department of Angiology, University Clinic Leipzig, Leipzig, Germany; [d]Department of Nephrology, Vivantes Clinics, Berlin, Germany; [e]Department of Endocrinology and Nephrology, Division of Nephrology, University Clinic Leipzig, Leipzig, Germany; [f]Division of Endocrinology, University of Calgary, Calgary, AB, Canada

What Is Known about This Topic?

- Both phase III trials of cabozantinib and lenvatinib reported that renal adverse events occurred in rare cases. The phase III study of carbozantinib reported no adverse events (AEs) regarding renal toxicity. In the lenvatinib phase III trial grade 3 (CTCAE), only proteinuria (urinary protein ≥3.5 g/24 h) was found in 10.0% of the lenvatinib and 0.0% of the placebo patients. No aggravation of known mild chronic renal insufficiency (KDOQI stage 2) under the treatment with lenvatinib and no concerning co-medications were reported.

What Does This Case Report Add?

- We report two severe AEs of anti-VEGF tyrosine kinase inhibitor treatment which were not reported in the phase III trials. Our case reports identify predisposing conditions like known mild chronic renal insufficiency with only mild proteinuria and with generalized atherosclerosis or precipitating co-medications like zolendronate infusion as important risk factors that need to be accounted for to prevent severe adverse renal events encountered in our patients. Compulsory registries for AEs not reported in phase III trials and national tumor boards like TUTYREF could help mitigate severe AEs to these rapidly evolving and expensive drugs.

Keywords
Medullary thyroid cancer · Differentiated thyroid cancer · Tyrosine kinase inhibitor · Lenvatinib · Cabozantinib · Renal adverse events · Chronic kidney failure

Abstract
Cabozantinib and lenvatinib have been approved for the treatment of progressive medullary thyroid cancer and radioiodine-resistant thyroid cancer, respectively. Both phase III trials of cabozantinib and lenvatinib reported that renal

KARGER

E-Mail karger@karger.com
www.karger.com/etj

Ralf Paschke, MD, PhD
Departments of Medicine, Oncology, Pathology, and Biochemistry and Molecular Biology and Arnie Charbonneau Cancer Institute, Cumming School of Medicine, University of Calgary, 382B Heritage Medical Research Building, 3330 Hospital Drive NW, Calgary, AB T2N 4N1 (Canada), E-Mail ralf.paschke@ucalgary.ca

adverse events (AEs) rarely occurred. The cabozantinib phase III study reported no AEs related to renal toxicity. In the lenvatinib phase III trial grade 3 (CTCAE), proteinuria (urinary protein ≥3.5 g/24 h) was found in 10.0% of the lenvatinib and 0.0% of the placebo patients. We report a 23-year-old patient with metastatic medullary thyroid cancer who was enrolled in the phase III trial, comparing cabozantinib to placebo and a 67-year-old patient with metastatic, papillary thyroid carcinoma who was undergoing treatment with lenvatinib during his enrollment in the phase III trial. The first patient had a normal kidney function initially, but developed end-stage chronic kidney disease unexpectedly on cabozantinib and additional zoledronate infusion. Whereas the second patient suffered from a dramatic aggravation of his known mild chronic renal insufficiency (KDOQI stage 2) due to long standing hypertension and atherosclerosis during the treatment with lenvatinib. These severe AEs due to anti-VEGF tyrosine kinase inhibitor treatment were unknown so far. In conclusion, these 2 cases argue for increased awareness for the possibility of renal failure as a consequence of anti-VEFG treatment. Predisposing conditions like known mild chronic renal insufficiency with only mild proteinuria and with atherosclerosis or precipitating co-medications like zoledronate infusion need to be accounted for to prevent these severe AEs.

Introduction

Tyrosine kinase inhibitors (TKIs) have been approved as an important therapeutic option for the treatment of progressive, metastatic medullary thyroid cancer (MTC) and radioiodine refractory differentiated thyroid cancer. For the treatment of MTC, cabozantinib was approved by the Food and Drug Administration in 2012 and by the European Medicines Agency in 2014. Lenvatinib was accepted for the treatment of radioiodine refractory differentiated thyroid cancer by the Food and Drug Administration and European Medicines Agency in 2015.

Adverse events (AEs) of all grades that were reported in ≥10.0% of the patients in a phase III study with cabozantinib included diarrhea (63.1%), plamar-plantar erythrodysesthesia (50.0%), decreased weight (47.7%), decreased appetite (45.8%), nausea (43.0%), and fatigue (40.7%). Rare but potentially life-threatening AEs including hemorrhage, gastrointestinal perforations, fistula development were also observed. In 16.0% of patients, AEs led to the discontinuation of treatment. No AEs related to renal toxicity have been reported [1].

The lenvatinib phase III study reported treatment-related AEs of any grade in ≥10.0% of the patients including: hypertension (67.8%), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), decreased weight (46.6%). AEs that led to treatment discontinuation were reported in 14.2% of patients receiving lenvatinib. Renal AEs were rare. However, renal failure, including acute renal failure of all grades, occurred in 4.2% of patients [2].

Both lenvatinib and cabozantinib are multikinase inhibitors with a strong VEGF signaling inhibition [3, 4]. Proteinuria is described as one of the most common renal side effects of other anti-VEGF drugs and frequently occurs with hypertension [5].

In the lenvatinib phase III trial grade 3 (CTCAE), proteinuria (urinary protein ≥3.5 g/24 h) was found in 10.0% of the lenvatinib and 0.0% of the placebo patients. A proteinuria screening with dose reductions or treatment discontinuation in case of an overt proteinuria was part of this trial [2]. Based on clinical trials with pazopanib for renal cell carcinoma, Carhill et al. [6] have previously recommended that baseline renal function and urine analysis in addition to periodic monitoring of renal function should be performed during the treatment with TKIs because of their potential to cause proteinuria.

Here, we report one patient with initially normal kidney function who unexpectedly developed chronic kidney disease under cabozantinib treatment and a second patient who suffered from a dramatic aggravation of his known mild chronic renal insufficiency (KDOQI stage 2) under lenvatinib. This study is aimed at determining how this previously unknown but severe side effect of anti-VEGF TKI treatment could be prevented in future.

First Patient

A 23-year-old patient with metastatic MTC was treated with 4.4 GBq Y-90-DOTATE 10 months after surgery because of progressive MTC. Five months following treatment with 4.4 GBq Y-90-DOTATE, the patient was enrolled in the phase III study comparing cabozantinib to placebo. He received blinded treatment for 3 weeks. His creatinine was normal (62 μmol/L 30 days before the treatment, 66 μmol/L on the first day of the treatment). Also, he showed a normal estimated glomerular filtration rate (eGFR) of 132.9 mL/min/1.73 m^2 on the first day of the study treatment. Due to bone metastasis, the patient received 4 mg zoledronate twice. Shortly after a third zoledronate infusion, the patient developed vomiting which did not occur with prior zoledronate infusions before the initiation of the study treatment with cabozantinib. Six-

teen days after his enrollment in the study and 11 days following the third zoledronate treatment, a creatinine of 150.4 μmol/L and a hypoproteinemia was detected. His eGFR was 52 mL/min/1.73 m^2. Subsequently, the patient developed hyperkalemia (6.3 mmol/L), LDH of 525 U/L, anemia, thrombocytopenia (76/nL) and nephrotic range proteinuria of up to 25,415 mg/24 h. Renal biopsy on day 30 revealed severe diffuse glomerular thrombotic microangiopathy of the VEGF-inhibitor associated type with podocyte damage. Although microangiopathic hemolytic anemia with thrombocytopenia ameliorated after 3 plasmapheresis treatments, his renal function showed no improvement. The patient was discontinued from study treatment. Unfortunately, 4 months after initiating study treatment, the patient received his first hemodialysis and died of progressive MTC 262 days after his enrollment in the study.

Second Patient

A 67-year-old patient with metastatic, papillary thyroid carcinoma was treated with total thyroidectomy, followed by 3 radioiodine therapies with a total activity of 20 GBq. Because of progressive radioiodine resistant disease 6 years after total thyroidectomy, the patient was enrolled in the double-blinded phase III study with lenvatinib versus placebo. Of note, the patient also suffered from long-term arterial hypertension and coronary heart disease with myocardial infarction 8 years before study inclusion. He presented a KDOQI stage 2 prior to the study introduction with an eGFR of 71.09 mL/min/1.73 m^2. There was spurious proteinuria assessed by a urine dip stix at study entry. Nevertheless, he fulfilled the study inclusion criteria and the criteria for the treatment with lenvatinib. During the study, instable angina led to coronarography with stenting. During this and further coronarographies, he received 140 mL of imeron 36 days after study entry and 46 mL of ultravist 370 on days 157 and 234 after study entry. Subsequently, the patient's creatinine rose to 143 μmol/L. Renal ultrasonography determined kidney lengths of 9.8 and 9.7 cm most likely due to chronic (formerly inadequately controlled) long-term arterial hypertension. His creatinine rose further to 218 μmol/L and his eGFR was 26.04 mL/min/1.73 m^2 on day 281 after study entry. Therefore, lenvatinib was discontinued 279 days after study initiation. Serum creatinine declined to 142 μmol/L. After further applications of 85 and 110 mL imeron for coronary angiography and femoral angioplasty 59 and 131 days after discontinuation of lenvatinib, respectively, his last creatinine was 177 μmol/L 264 days after discontinuation of lenvatinib. The patient died because of a cerebral infarction 708 days after his enrollment in the study.

Discussion

A review of proteinuria-related anti VEGF side effects concluded that the most common renal side effects of anti-VEGF drugs is proteinuria (range 21 up to 63%), which frequently occurs with hypertension [7]. Proteinuria has been described for several anti-VEGF agents [5, 7] and has also occurred during treatment with the recently approved TKI lenvatinib. Therefore, a drug class effect is highly likely.

To account for the known risk of renal AEs, proteinuria screening has been recommended for anti-VEGF drugs [6] and was part of the lenvatinib phase III trial [2]. Our first patient had a normal renal function at study entry (KDOQI: stage 1, eGFR 132.9 mL/min/1.73 m^2). Our second patient already presented with KDOQI stage 2 (eGFR of 71.09 mL/min/1.73 m^2). However, both developed chronic renal failure requiring dialysis and/or discontinuation of study treatment. Therefore, lack of sensitivity of dip stick proteinuria assessment and serum creatinine determination without the determination of the eGFR and protein differentiating analyses and other factors coprecipitating the renal damage in our 2 patients need to be considered before starting anti VEGF-TKI treatment. Patients with chronic kidney failure and planned TKI treatment are apparently at risk for further aggravation of renal failure.

Our first 23-year-old patient received 4 mg of zoledronate 5 days after his enrollment in the phase III study because of bone metastasis. The incidence of proteinuria in patients receiving concurrent bevacizumab and pamidronate was 33.9%, compared with 18.5% in patients without pamidronate in a phase III trial [8]. Moreover, zoledronate has been associated with both dose-dependent and infusion time-dependent acute and chronic renal failures [9]. To reduce the risk of renal damage, 100 mL of 4 mg zoledronate should be infused over no less than 15 min [10]. After the third infusion of 4 mg zoledronate, our first patient experienced vomiting, which did not occur with prior zoledronate infusions.

Bodmer et al. [9] reported a case of zoledronate-associated renal failure with focal segmental glomerulosclerosis in a myeloma patient. Focal segmental glomerulosclerosis has also been described during the treatment with pamidronate [11]. Other renal impairments attributable to zoledronate are zoledronate-associated toxic tubular necrosis, with the predominant pathological findings of tubular degenerative changes [10]. However, in our first patient the renal biopsy revealed severe diffuse glomerular thrombotic microangiopathy with podocyte damage. This histologic finding is not indicative of renal damage induced by zoledronate. However, severe diffuse glomerular thrombotic microangiopathy with podocyte damage has been described in 6 patients treated with bevacizumab [12] and is the pathognomonic histologic correlate in VEGF knock-out mice [12]. Therefore, this patient's renal damage is highly likely to be the consequence of the treat with an anti-VEGF agent. However, the only renal

AE in the cabozantinib phase III trial was proteinuria grade ≥3 in 0.9% and all grades in 1.9%. The only identifiable precipitating cofactor in this young patient without any preexisting renal impairment is vomiting after zoledronate infusion immediately prior to the onset of renal damage. This did not occur after the previous 2 zoledronate infusions. Therefore, this most likely indicates too fast infusion of zoledronate with possible blood pressure drop precipitating the anti-VEGF damage.

Our second patient already displayed initial signs of renal damage (KDOQI: stage 2, eGFR 71.09 mL/min/1.73 m^2) prior to anti-VEGF treatment with lenvatinib. He also had generalized atherosclerosis suggested by a myocardial infarction 8 years before study inclusion and femoral angioplasty and ischemic cerebral infarction. Formerly, inadequately controlled long-term arterial hypertension most likely was the major contributing factor for all of these pathologies. These findings strongly suggest an increased susceptibility for anti-VEGF adverse vascular events due to generalized atherosclerosis and chronic kidney disease which in this patient manifested as an drastic aggravation of his mild renal failure due to a chronic kidney disease of KDOQI of stage 4 (eGFR 26.78 mL/min/1.73 m^2). For this patient, the repeated angiographies must also be considered as a possible confounder or cofactor for the renal damage. However, diagnosis of contrast-induced nephropathy requires an absolute increase in serum creatinine by ≥26.5 μmol/L from baseline within 48 h after contrast media application, or a relative increase in serum creatinine levels by ≥50% from baseline, or a urine output reduced to ≤0.5 mL/kg/h for at least 6 h [13]. Thus, in our patients' case, the steady rise of serum creatinine 6 weeks after the last application of iodine-containing contrast media during treatment with lenvatinib is a strong indication of renal damage induced by a TKI (lenvatinib) with anti-VEGF receptor activity. However, it cannot be excluded that the concomitant application of imeron and ultravist together with lenvatinib could have led to an additive or cumulative nephrotoxic effect.

In conclusion, these 2 cases argue for increased awareness of the possibility that renal failure, as a consequence of anti-VEFG treatment, can occur in patients without proteinuria. Further predisposing or precipitating comedications or concomitant diseases like atherosclerosis need to be accounted for to prevent this AE as illustrated by these 2 case reports. Compulsory registries for AEs not reported in phase III trials and National Tumor Boards like TUTYREF [14] could help mitigate severe AEs to these rapidly evolving and expensive drugs.

Acknowledgement

We thank Prof. U. Helmchen, Department of Pathology, University Hospital Hamburg for his assessment of the renal biopsy of patient 1.

Disclosure Statement

R.P. has received honoraria for advisory board meetings and for lectures from Bayer and EISAI. The other coauthors do not have conflicts of interest.

References

1 Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, Niederle B, Cohen EE, Wirth LJ, Ali H, Hessel C, Yaron Y, Ball D, Nelkin B, Sherman SI: Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013;31:3639–3646.

2 Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI: Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372:621–630.

3 Cabanillas M, Habra MA: Lenvatinib: role in thyroid cancer and other solid tumors. Cancer Treat Rev 2016;42:47–55.

4 Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, Pfister DG, Cohen EE, Janisch L, Nauling F, Hong DS, Ng CS, Ye L, Gagel RF, Frye J, Muller T, Ratain MJ, Salgia R: Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J Clin Oncol 2011; 29:2660–2666.

5 Izzedine H, Rixe O, Billemont B, Baumelou A, Deray G: Angiogenesis inhibitor therapies: focus on kidney toxicity and hypertension. Am J Kidney Dis 2007;50:203–218.

6 Carhill A, Cabanillas ME, Jimenez C, Waguespack SG, Habra MA, Hu M, Ying A, Vassilopoulou-Sellin R, Gagel RF, Sherman SI, Busaidy NL: The noninvestigational use of tyrosine kinase inhibitors in thyroid cancer: establishing a standard for patient safety and monitoring. J Clin Endocrinol Metab 2013; 98:31–42.

7 Izzedine H, Massard C, Spano JP, Goldwasser F, Khayat D, Soria JC: VEGF signalling inhibition-induced proteinuria: mechanisms, significance and management. Eur J Cancer 2010;46:439–448.

8 Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V, Rugo HS: Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005;23:792–799.

9 Bodmer M, Amico P, Mihatsch MJ, Haschke M, Kummer O, Krähenbühl S, Mayr M: Focal segmental glomerulosclerosis associated with long-term treatment with zoledronate in a myeloma patient. Nephrol Dial Transplant 2007;22:2366–2370.

10 Berenson J, Hirschberg R: Safety and convenience of a 15-min infusion of zoledronic acid. Oncologist 2005;10:82–83.

11 Markowitz GS, Appel GB, Fine PL, Fenves AZ, Loon NR, Jagannath S, Kuhn JA, Dratch AD, D'Agati VD: Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am Soc Nephrol 2001;12:1164–1172.
12 Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, Richardson C, Kopp JB, Kabir MG, Backx PH, Gerber HP, Ferrara N, Barisoni L, Alpers CE, Quaggin SE: VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med 2008;358:1129–1136.
13 Lakhal K, Ehrmann S, Chaari A, Laissy JP, Régnier B, Wolff M, Pajot O: Acute Kidney Injury Network definition of contrast-induced nephropathy in the critically ill: incidence and outcome. J Crit Care 2011;26:593–599.
14 Massicotte MH, Brassard M, Claude-Desroches M, Borget I, Bonichon F, Giraudet AL, Do Cao C, Chougnet CN, Leboulleux S, Baudin E, Schlumberger M, de la Fouchardière C: Tyrosine kinase inhibitor treatments in patients with metastatic thyroid carcinomas: a retrospective study of the TUTHYREF network. Eur J Endocrinol 2014;170:575–582.