REVIEW

Kidney injury during VEGF inhibitor therapy

E.S.G. den Deurwaarder[1]*, I.M.E. Desar[2], E.J. Steenbergen[3], P.F. Mulders[4], J. F.M. Wetzels[5],
C.M.L. van Herpen[2]

[1]Department of Internal Medicine, Medisch Spectrum Twente, Enschede, the Netherlands,
Departments of [2]Medical Oncology, [3]Pathology, [4]Urology and [5]Nephrology, Radboud University
Nijmegen Medical Center, Nijmegen, the Netherlands, *corresponding author: tel: 0534872420;
fax: 0534872412; e-mail: E.denDeurwaarder@mst.nl

ABSTRACT

Antiangiogenic therapy targeting vascular endothelial growth factor (VEGF) or its receptor (VEGFR) has proven its effect in the treatment of several types of cancer, including renal cell carcinoma (RCC). However, treatment can be accompanied by notable adverse effects. Mild proteinuria and hypertension are often seen, but sometimes nephrotic range proteinuria and/or renal insufficiency develop. In recent years insight into the toxic effects of anti-VEGF therapy in the kidney has increased. A few biopsies have been done and thrombotic microangiopathy is reported in the majority of cases. However, other patterns of kidney injury have been described as illustrated by the case of a 62-year-old patient who presented two years after initiation of the VEGFR inhibitor cediranib with a nephrotic syndrome and acute renal failure. Kidney biopsy disclosed focal segmental glomerulosclerosis (FSGS) and interstitial nephritis. Partial remission was achieved after stopping the cediranib and a short course of prednisone. We review the different forms of kidney injury that could be caused by anti-VEGF therapy.

KEYWORDS

Kidney toxicity, anti-VEGF therapy, FSGS, cediranib

INTRODUCTION

Vascular endothelial growth factor (VEGF) is an important signalling protein involved in angiogenesis, a key process in cancer growth and dissemination. Thus, inhibition of VEGF signalling has become a target for antitumour therapy and many new drugs are being developed. Based on their mechanism of action, three classes of agents can be discerned: 1) antibodies against VEGF (e.g. bevacizumab); 2) soluble receptors (VEGF Trap) that bind and inactivate VEGF; and 3) VEGF receptor tyrosine kinase inhibitors (e.g. sorafenib, sunitinib).[1] Inhibitors of the VEGF pathway, angiogenesis inhibitors, have been effective in reducing tumour growth and improving patient survival in several types of cancer, especially metastatic renal cell carcinoma (RCC). In the past few years it has become evident that angiogenesis inhibitors may cause renal and vascular damage. These adverse events may be more common than previously thought and the long-term effects of antiangiogenic treatments are largely unknown.[2] Also insight into the pathophysiological mechanisms involved in these side effects has increased, although many questions remain to be answered.

We describe a patient who developed a severe nephrotic syndrome and acute renal failure after prolonged use of cediranib (AZD2171), a tyrosine kinase inhibitor that selectively blocks all three known VEGF receptors, VEGFR-1, -2 and -3. We summarise literature data on anti-VEGF-induced proteinuria.

The patient, a 62-year-old male, was admitted because of progressive kidney failure and hypercalcaemia. Three years before he underwent a nephrectomy because of clear cell RCC. One year after the nephrectomy and two years before admission cediranib (AZD2171) 30 mg once daily was started within a phase II trial because of progression of para-aortic lymph nodes and development of multiple lung metastases. At the start of therapy he had no proteinuria and a normal glomerular filtration rate. The patient experienced the frequently occurring adverse events of mild diarrhoea and hypertension, which was well controlled with enalapril 5 mg once daily.

Six weeks before presentation pravastatin was started because of hypercholesterolaemia, but he had stopped this drug after four weeks because of general malaise.

At presentation he complained of apathy, loss of appetite and aggravated diarrhoea. The blood pressure was 120/80 mmHg, the pulse 68 beats/min. There was slight pitting oedema at the ankles. Laboratory results were as follows: serum creatinine 235 µmol/l (2.7 mg/dl), urea 41.2 mmol/l, albumin 23 g/l, calcium 3.0 mmol/l (corrected for low albumin), and total cholesterol 8 mmol/l. Urine microscopy demonstrated 1 to 4 erythrocytes (20% dysmorphic) per high power field; no red cell casts were seen. A 24-hour collection of urine contained 11.3 g protein. Thus the patient was diagnosed with a nephrotic syndrome and acute kidney failure. Cediranib was discontinued and the hypercalcaemia was corrected with intravenous fluids. Two weeks after discontinuing the cediranib, the creatinine was still elevated at 268 µmol/l and the patient complained of fluid retention. Furosemide was initiated and a kidney biopsy was performed: on light microscopy the tip variant of focal segmental glomerulosclerosis (FSGS) was demonstrated. There was global interstitial fibrosis with tubular atrophy and a diffuse interstitial infiltrate with monocytes, plasma cells and eosinophils. No signs of thrombotic microangiopathy were seen. Immunofluorescence showed no specific findings. Electron microscopy revealed some swollen endothelial cells and also partial podocyte foot process effacement. There were no electrondense depositions (*figure 1*).

It was concluded that FSGS, caused by cediranib, was the cause of the proteinuria, whereas the renal insufficiency was more related to the interstitial nephritis. The latter may have been caused by pravastatin, a drug recently introduced in our patient. Statins are a known cause of tubulo-interstitial nephritis.[3] In view of the severity and persistence of the renal failure and the cellular infiltrate,

we decided to treat our patient with prednisone (80 mg/day starting dose, with rapid tapering and stopped at three months) and cediranib was stopped indefinitely. The serum creatinine decreased and also his oedema disappeared.

One year after discontinuation of the cediranib, the serum creatinine was 110 µmol/l and urine protein excretion was 0.73 g/24 hours.
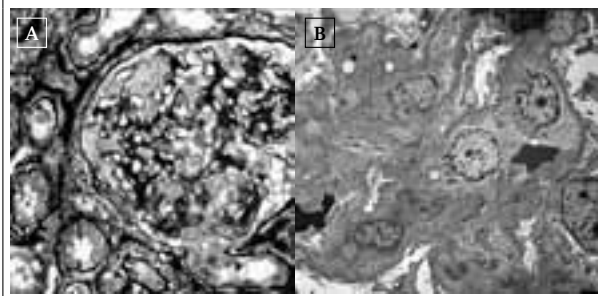
VEGF INHIBITORS AND KIDNEY TOXICITY

Proteinuria as well as hypertension are well-known dose-dependent adverse events of angiogenesis inhibitors. A meta-analysis demonstrated that treatment with bevacizumab, a recombinant humanised monoclonal antibody against VEGF, resulted in overt proteinuria (>0.5 g/day) in 21 to 41% of the patients with low-dose bevacizumab and up to 64% in the high-dose group.[2] The relative risks for hypertension were 3.0 and 7.5, respectively. Although less well studied, the small tyrosine kinase inhibitors and VEGF Trap can also cause hypertension and proteinuria.[4-8] One phase I study in Japanese patients demonstrated proteinuria in 27/40 (68%) and hypertension in 32/40 (80%) patients receiving cediranib. The proteinuria was not quantified and different doses were used.[9]

Usually, proteinuria induced by inhibitors of VEGF signalling is not severe and resolves when the drug is discontinued, although nephrotic range proteinuria (>3.5 g/day) has been described in up to 6.5% of patients treated with bevacizumab for metastatic renal cancer.[10] Less often acute renal failure evolves. *Table 1* shows the biopsy-proven cases of (mostly severe) proteinuria and/or renal failure linked to anti-VEGF(R) therapy.[11-27]

From *table 1* it is evident that in all these patients there was an indication for renal biopsy, most patients presenting with nephrotic proteinuria (13/20) and/or severe renal failure. Causative agents belonged to all three different classes of VEGF-signalling directed therapy. Various patterns of renal injury were observed, the most common being thrombotic microangiopathy in 13 of 22 patients. An FSGS pattern of injury was seen in five patients, a tubulo-interstitial nephritis in three. In most patients studied by electron microscopy there was evidence of swollen endothelial cells and foot process effacement. In two of the patients with FSGS lesions there was evidence of a collapsing FSGS, which might have been the consequence of the simultaneously used pamidronate. Pamidronate is a well-known cause of collapsing FSGS. Of note, the incidence of proteinuria was higher with bevacizumab and pamidronate when compared with bevacizumab without pamidronate (33.9 *vs* 18.5%,

Figure 1. *(A) Glomerulus with FSGS tip lesion. Near the urinary pole (bottom) there is a glomerular segment with collapse and also a few endocapillary mononuclear inflammatory cells and foam cells. Surrounding this segment mild epithelial hyperplasia can be seen. Podocytes globally appear swollen. (B) Electron microscopy. A glomerular segment is shown with wrinkling of the glomerular basement membrane (collapse). Podocytes show extensive foot process effacement. There is swelling of the endothelial cells*

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p<0.05).[14] Our patient did not receive pamidronate for the treatment of hypercalcaemia.

The literature data do not provide details on follow-up in all patients; in general withdrawal of anti-VEGF treatment resulted in a decrease of proteinuria.

PATHOPHYSIOLOGY

In recent years the role of VEGF in the kidney has been clarified. VEGF is produced by the glomerular podocytes and to a lesser extent in the (proximal) tubular epithelial cells. Seven different subtypes of VEGF have been described of which VEGF-A is the most predominant in angiogenesis. Three VEGF-receptors types are known: VEGFR-1 or Flt-1, VEGFR-2 or Flk-1/KDR and VEGFR-3 or Flt-4. In the kidney VEGFR-2 predominates and is mainly found in the mesangium and in endothelial cells and tubular capillaries. Interaction of the podocytes and endothelial cells by VEGF expression appears to be vital for the development and maintenance of the glomerular filtration function by inducing endothelial fenestrations and maintaining glomerular permeability.

Specific knockout of VEGF in podocytes in mice resulted in nephrotic range proteinuria, endotheliosis, loss of podocytes and hyaline deposits, as seen in kidney biopsies of patients with preeclampsia.[9] Pharmacological inhibition or targeted heterozygotic deletion of VEGF-A in mice resulted in a reduction of endothelial fenestrations in the glomerulus as well as downregulation of the key endothelial protein nephrin, resulting in glomerular cell detachment and swelling and therefore malfunction of the glomerular filtration apparatus.[28,29] Moreover, overexpression of soluble Flt-1 seems to be an important cause of preeclampsia. By neutralising VEGF, endothelial dysfunction is induced. This underscores the importance of VEGF for the endothelium.

In contrast, in a mouse model, upregulation of VEGF-A resulted in collapsing glomerulopathy.[28]

In our patient, histology demonstrated FSGS (tip variant) accompanied by a chronic active tubulo-interstitial nephritis. Based on the findings in animal models, one might have expected a thrombotic microangiopathy rather than FSGS in our patient. Still, more cases of FSGS and interstitial nephritis linked to anti-VEGF therapy have been published. What could be the explanation? We

Table 1. *Kidney biopsies of proven kidney lesions attributed to anti-VEGF(R) therapy*

Ref	Anti-VEGF	Disease	Age	Sex	Onset	Proteinuria	Creatinine (μmol/l)[b]	Histology
11	Bevacizumab	HC	59	M	9 months	3.4 g[a]	N/A	TMA
11	Bevacizumab	HC	74	M	3 months	2.7 g[a]	N/A	TMA
11	Bevacizumab	BC	56	M	9 months	0.16 g/24 h	274	TMA
11	Bevacizumab	SCLC	62	M	3 months	0.5 g	504	TMA
11	Bevacizumab	PC	61	M	5 months	4.6 g/24 h	230	TMA
11	Bevacizumab	Ovarian	59	F	9 months	0.8 g/24 h	80	TMA
12	Bevacizumab/ sunitinib	RCC	70	M	2 weeks	5.3 g/10 mmol[a]	N/A*	TMA
13	Bevacizumab	NSCLC	N/A	N/A	N/A	Nephrotic	N/A	Cryoglobulin GN
14	Bevacizumab	Breast	N/A	F	N/A	Nephrotic	N/A	Collapsing FSGS
15	Bevacizumab	PC	71	M	1 month	9.6 g/24 h	97	ICGN
16	VEGT TRAP	Ovarian	59	F	1 week	16.6 g/l	71	TMA
17	Bevacizumab	RCC	59	M	9 months	Nephrotic	141	TMA/IgA deposits
18	Bevacizumab	Breast	59	F	3 months	3.6 g/24 h	282	TMA/collapsing FSGS
19	Bevacizumab	LM	26	M	2 weeks	N/A	414	AIN
20	Sunitinib	MM	50	M	1 month	3.2 g/24 h	651	ATN
21	Sunitinib	SH	44	F	4 weeks	1.1 g/24 h	64	TMA
22	Bevacizumab	NSCLC	67	M	6 weeks	9.5 g/24 h	461	MPGN
23	Sunitinib	RCC	66	M	10 months	5.4 g/24 h	167	TMA/FSGS
24	Sunitinib	RCC	66	M	10 days	0.7 g/24 h	400	AIN
25	Sunitinib	RCC	61	M	9 months	1.1 g/10 mmol[a]	583	FSGS/AIN
26	Sunitinib	GIST	72	M	6 months	10.1 g/24 h	170	FSGS/TMA
27	Bevacizumab	SCLC	67	M	15 months	5.7 g/24 h	478	Crescentic GN

AIN = acute interstitial nephritis; ATN = acute tubular necrosis; BC = bronchoalveolar carcinoma; FSGS = focal segmental glomerulosclerosis; GIST = malignant gastrointestinal stromal tumour; GN = glomerulonephritis; HC = hepatocellular carcinoma; ICGN = immunocomplex glomerulonephritis; LM = leiomyosarcoma; MPGN = membranoproliferative glomerulonephritis; N/A = not available; NSCLC = non-small cell lung cancer; PC = pancreatic cancer; RCC = renal cell carcinoma; SCLC = small cell lung cancer; TMA = thrombotic microangiopathy; *GFR 23 ml/min; [a]protein/creatinine ratio; [b]for mg/dl divide by 88.

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can only speculate. As mentioned above inhibition of VEGF not only results in endothelial damage, but also causes loss of nephrin. Congenital loss of nephrin is associated with the development of a congenital nephrotic syndrome and FSGS. Thus, in our patient the phase of thrombotic microangiopathy might have been skipped (possibly due to adequate antihypertensive therapy) and FSGS may have been the consequence of long-term inhibition of nephrin. Alternatively, development of FSGS in this case may be governed by the nephrectomy three years before. After nephrectomy adaptive hyperfiltration occurs. In animal models of nephron reduction VEGF is necessary for compensatory glomerular and tubular hypertrophy. Later in the process VEGF levels decrease paralleled by development of glomerulosclerosis and tubular atrophy.[30] Possibly, this process was influenced by the use of cediranib.

Few cases of biopsy proven anti-VEGF associated kidney injury have been published, given the frequency of proteinuria. In recent years new light has been shed on the paracrine and autocrine (on the podocyte) roles of VEGF. In many patients no biopsy is done because of decreasing proteinuria or improvement of kidney function after withdrawal of the offending agent or simply because one is reluctant to do a biopsy in a single kidney. We expect that more cases of FSGS would be found if biopsies were performed.

The clinical experience with long-term treatment with VEGFR inhibitors in cancer patients is limited. The most commonly used VEGFR inhibitors, sunitinib and sorafenib, were already approved after the successful phase II studies. The dose-defining phase I studies were based on dose escalation, in which dose-limiting toxicity was determined in only short periods (usually three to four weeks). The frequently occurring mild proteinuria that has been described originates from these phase I and II studies. Insights into the development of proteinuria during prolonged use of VEGFR inhibitors are lacking.

Registered treatment strategies for metastatic RCC are the VEGFR inhibitors sunitinib, sorafenib and pazopanib, mTOR inhibitors temsirolimus and everolimus and the combination of the VEGF-antibody bevacizumab with interferon-alpha. Proteinuria is a class effect of all VEGF(R) targeting agents.[31] Unfortunately, mTOR inhibitors are also associated with the development of proteinuria, although this association seems less severe.[32] Knowledge about the effects of sequential use of different VEGF-targeting therapy or sequential use of VEGFR inhibitors and mTOR inhibitors on the clinical course of proteinuria is not available. Therefore, we decided to wait for as long as possible to restart anticancer therapy.

In conclusion, angiogenesis inhibitors can induce a nephrotic syndrome and possibly acute failure. Awareness of these, although infrequent, adverse events is mandatory. Development of these adverse events should lead to prompt discontinuation of the medication or lowering the dose. In most cases this will lead to (partial) remission of proteinuria. Further insight into the development of renal injury by angiogenesis inhibitors will require increased use of renal biopsies in patients who develop proteinuria and/or renal insufficiency during treatment with these agents.

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