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Case report

MANAGEMENT OF LENVATINIB-INDUCED PROTEINURIA WITH DAPAGLIFLOZIN

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Abstract

Proteinuria is an adverse event described in 30% of thyroid cancer patients treated with lenvatinib, a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors. Management of proteinuria is challenging, involving control of arterial hypertension. We describe the case of a patient with advanced radioiodine refractory thyroid cancer treated with lenvatinib who developed late-onset grade 3 proteinuria, despite adequate blood pressure control. He was treated with dapagliflozin 10 mg/day, which promptly improved proteinuria to grade 1. Treatment with lenvatinib was subsequently restarted, with good control of proteinuria. Dapagliflozin is a sodium-glucose co-transporter type 2 (SGLT2) inhibitor that acts in the proximal convoluted tubule, improving renal function in diabetic and non-diabetic patients. SGLT2 inhibitors may have a role in the management of lenvatinib-induced proteinuria, however further study is needed.

Key words: proteinuria, multikinase inhibitors, lenvatinib, dapagliflozin, thyroid cancer

Resumen

Manejo de la proteinuria inducida por lenvatinib con dapagliflozina

La proteinuria es un evento adverso descrito en 30% de los pacientes con carcinoma de tiroides tratados con lenvatinib, un inhibidor de tirosina quinasa que actúa sobre el receptor del factor de crecimiento vascular endotelial. El manejo de la proteinuria es complejo e incluye el control de la hipertensión arterial. Describimos el caso de un paciente con carcinoma diferenciado de tiroides avanzado yodo refractario tratado con lenvatinib que desarrolló proteinuria grado 3 tardíamente, pese al control adecuado de la tensión arterial. Fue tratado con dapagliflozina 10 mg/día, con rápida mejoría de la proteinuria a grado 1. Se reinició posteriormente el tratamiento con lenvatinib con buen control de proteinuria. La dapagliflozina es un inhibidor del cotransporte de sodio y glucosa tipo 2 (SGLT2) que actúa en el túbulo contorneado proximal, mejorando la función renal en pacientes diabéticos y no diabéticos. Los inhibidores de SGLT2 podrían tener un rol en el manejo de la proteinuria inducida por lenvatinib, sin embargo, se requieren más estudios para confirmarlo.

Palabras clave: proteinuria, inhibidores multiquinasas, lenvatinib, dapagliflozina, cáncer de tiroides

The standard treatment for differentiated thyroid carcinoma (DTC) consists of surgery followed by radioactive iodine administration in selected cases. However, a percentage (10–15%) of patients with advanced disease do not respond to radioactive iodine therapy. This group of patients is considered radioactive iodine-refractory DTC (RAIR DTC), and this condition has a poor prognosis[1].

Tyrosine kinase inhibitors (TKIs) such as lenvatinib and sorafenib are first-line therapies for advanced RAIR-DTC, while cabozantinib is reserved for second-line treatment[2]. Lenvatinib is a TKI that targets vascular endothelial growth factor receptors (VEGFR), fibroblast growth factor receptors (FGFR), and platelet-derived growth factor receptor α (PDGFRα)[3]. The SELECT trial showed a marked improvement in response rates with lenvatinib versus placebo in patients with RAIR DTC (65% vs 1.5%; $p < 0.001$). Of note, adverse events (AEs) were reported in 97.3% of patients receiving lenvatinib, with grade ≥3 events occurring in 76%. The most frequent AEs were hypertension (67.8%), diarrhea (59.4%), and fatigue or asthenia (59.0%). Proteinuria was reported in 31% of cases[4].

Proteinuria is a recognized class effect of antiangiogenic therapy, initially identified with the anti VEGF antibody bevacizumab[5], but also common to most TKIs, and is a direct indicator of nephrotoxicity.

Compared to other TKIs, lenvatinib has shown a trend toward a higher incidence of proteinuria (24–34%) in several studies[5,6] Management of proteinuria consists of preventing dehydration, discontinuing the use of potentially nephrotoxic medications, and controlling blood pressure. In grade 3 or 4 the dose of the TKI should be withdrawn and restarted when proteinuria resolves to grade < 1[7]. TKI-induced proteinuria is usually reversible[6].

Sodium-glucose co-transporter type 2 (SGLT2) inhibitors are drugs used for the treatment of diabetes. These drugs decrease albuminuria and reduce the risk of kidney disease progression even in non-diabetic patients[8]. Dapagliflozin, a SGLT2 inhibitor, can limit podocyte damage in non-diabetic proteinuric nephropathy[8,9].

Given the limited evidence supporting the utility of SGLT2 inhibitors in this setting, we report a case of lenvatinib-induced proteinuria unresponsive to standard treatment that improved with dapagliflozin therapy.

Clinical case

We describe the case of a 49-year-old man with RAIR DTC with symptomatic advanced disease. He had a personal history of hypercholesterolemia (treated with 10 mg/day of atorvastatin). The patient was normotensive, with a body mass index of 22 kg/m², a non-smoker, and had no significant personal or family medical history.

In 2019, he had undergone a total thyroidectomy with cervical lymphadenectomy for a 6 cm widely invasive oncocytic cell thyroid cancer with lateral lymph node metastases. Afterwards, he received a radioiodine dose of 150 mCi with cervical uptake in the thyroid bed. Two months later, due to diplopia, he was diagnosed with a skull base lytic bone metastasis. A subsequent ^{18}FDG PET CT scan confirmed hypermetabolic foci of disease in the skull base, lungs and cervical lymph nodes. He underwent external beam radiotherapy (3000 cGy) to the skull base. After a normal electrocardiogram and echocardiogram, lenvatinib was started at a dose of 24 mg/day in March of 2020. He developed grade 2 hypertension, which was treated with losartan 50 mg/d and amlodipine 5 mg/d. Grade 2 proteinuria (1.39 g/24 h) was also noted after five months of treatment. It was resolved after increasing losartan dose to 100 mg/d and reducing lenvatinib dose to 20 mg/d. Stable disease was found on subsequent imaging studies.

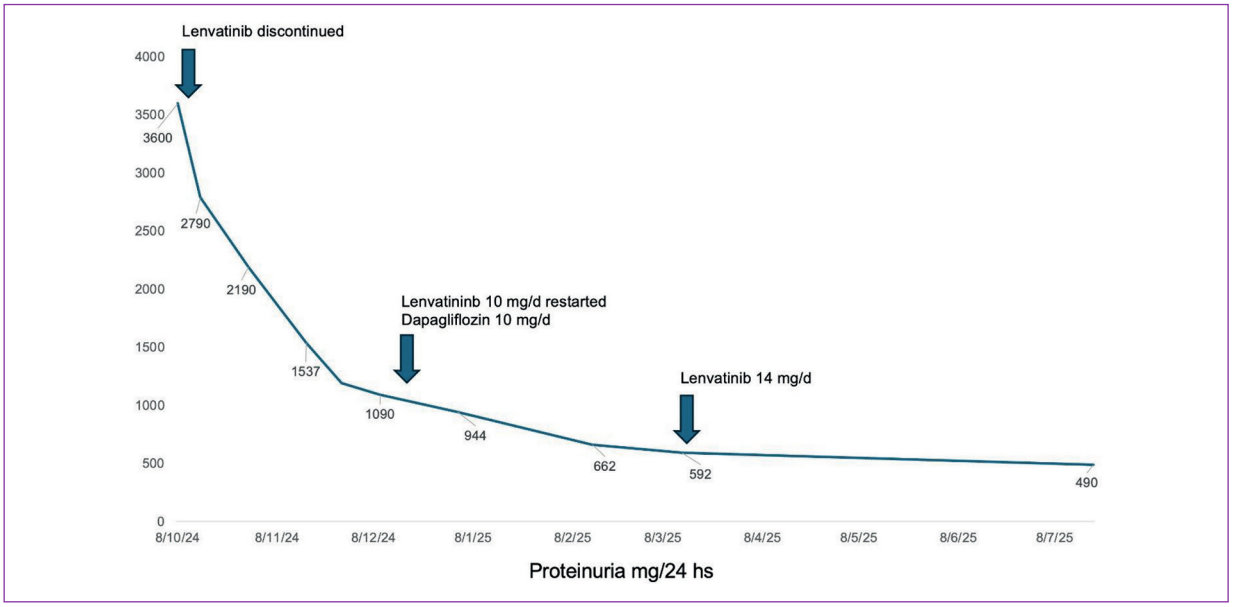
In June of 2022, the patient presented with unstable angina, prompting the temporary discontinuation of lenvatinib therapy. Subsequent evaluation revealed multivessel coronary artery disease, requiring angioplasty. Atorvastatin dose was increased to 40 mg/day, bisoprolol, clopidogrel and aspirin were added. A molecular interrogation was negative for *BRAF* mutations and *NTRK* fusions (the only targeted therapies available in the country at the time). After multidisciplinary tumor board discussion, lenvatinib was reinitiated at a reduced dose of 14 mg/day four months later, following cardiology approval. Stable disease persisted, without other relevant toxicities until October of 2024. At this time, while normotensive, he had an estimated glomerular filtration rate (GFR) of 67.4 mL/min/1.73 m² he developed nephrotic range proteinuria (3.5 g/24 h). Lenvatinib was discontinued. Proteinuria improved but persisted after a month. Dapagliflozin was initiated at 10 mg/day, resulting in improvement of proteinuria to grade 1, which allowed lenvatinib to be restarted at a reduced dose of 10 mg/day (Fig. 1). Nine months after reinitiating lenvatinib, proteinuria remained detectable at 0.490 mg/24 h (grade 1) with a GFR of 83 mL/min/1.73 m². The patient maintained stable disease at last assessment.

The patient provided written informed consent for the publication of the case.

Discussion

The frequency of proteinuria during TKI treatment ranges from 6 to 34% for all grades, and from 1 to 10% for grade ≥3[6]. In the SELECT trial,

Figure 1 | Evolution of proteinuria. The arrows show the discontinuation of lenvatinib, the start of dapagliflozin and restart of lenvatinib



proteinuria related to lenvatinib was detected in 31% (10% of grade ≥3)[4]. Proteinuria typically occurs early during TKI therapy, with median time to onset of 6.1 weeks[10].

Several mechanisms of TKI-related proteinuria were proposed, most of them related to the inhibition of VEGF and nephrin production leading to dysregulation of renal repair processes and the interruption of glomerular filtration barrier[6]. Hypertension, another side effect of TKIs, also contributes to the development of proteinuria, through the inhibition of nitric oxide production leading to an increase in vascular resistance. Pre-existing comorbidities and concomitant drugs should be evaluated when considering TKI therapy.

Management of TKI-induced proteinuria is currently based on expert recommendations, as clinical trials specifically addressing optimal management strategies are lacking. All patients should have a baseline urinalysis with proteinuria and frequent monitoring throughout treatment[7]. The assessment of proteinuria is according to Common Terminology Criteria for Adverse Events v5.0 (CTCAE)[11]. The management differs according to the grade of proteinuria. Observation is indicated in grade 1, discontinuation in grade 2 (>1.0–3.5 g/24 h) and grade 3 (>3.5 g/24 h) until proteinuria resolves to ≤2.0 g/24 h. Treatment with angiotensin-convertase enzyme inhibitors or angiotensin II receptor blockers may be considered in these stages. Finally, permanent discontinuation is indicated in cases of grade 4 proteinuria[7].

SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin) were initially developed for the management of hyperglycemia in patients with type 2 diabetes mellitus. Their primary mechanism of action involves the inhibition of glucose and sodium reabsorption at the level of the proximal convoluted tubule. In the DAPA-CKD trial it was demonstrated that SGLT2 inhibitors can improve renal outcomes even in non-diabetic chronic kidney disease[8]. Specifically, a sub-analysis of the DAPA-CKD trial that included 1,398 non-diabetic patients showed a significant reduction in proteinuria levels in this population (22.9%)[12]. Patients with an estimated GFR of 25–75 mL/min/1.73 m² and macroalbuminuria, regardless of the etiology of kidney disease, showed improved renal outcomes when randomized to receive SGLT2 inhibitors, similar to our patient who had deteriorating kidney function and proteinuria[8].

The 2024 KDIGO Guidelines recommend treating adults with chronic kidney disease with

a SGLT2 inhibitors in the case of GFR ≥20 mL/min/1.73 m² with urinary albumin-to-creatinine ratio ≥ 200 mg/g and recommend SGLT2 inhibitors in non-diabetic patients with albuminuria[13].

These findings have prompted investigations into additional mechanisms contributing to their renoprotective properties. In a study conducted by Cassis et al., the authors highlight several pleiotropic effects of SGLT2 inhibitors. Firstly, they observed that dapagliflozin reduces podocyte dysfunction and apoptosis within the glomerulus. Proteinuria-induced podocyte stress leads to the loss of β1-integrin expression and reorganization of F-actin and α-actinin-4 cytoskeletal filaments, events associated with podocyte detachment and injury. Dapagliflozin appears to counteract these changes, thereby enhancing podocyte survival. Secondly, the reduction in podocyte loss was associated with an increased expression of SGLT2 in surviving podocytes, potentially enhancing pharmacological responsiveness to the drug. Lastly, the authors propose that dapagliflozin attenuates cytoskeletal remodeling induced by proteinuria through inhibition of NF-κB, a nuclear transcription factor that plays a central role in inflammatory activation and cell injury pathways[9]. Additionally, SGLT2 inhibitors have shown to improve outcomes in proteinuria of non-diabetic origin[8,12,13].

Grade 3 proteinuria is a reason for discontinuing treatment in up to 10% of patients receiving lenvatinib for RAIR DTC, therefore optimizing its management is crucial. Often, antihypertensive agents are not sufficient for its management, as evidenced in our case[7]. Therefore, new therapeutic strategies are needed to manage this toxicity.

Collective evidence of the benefit of SGLT2 inhibitors in proteinuria of diverse etiologies suggests these agents may have a role in TKI-induced proteinuria. Additionally, preclinical studies in mouse models indicate a potential beneficial role of SGLT2 inhibitors in TKI-induced proteinuria[14].

Recently, Fages et al reported a patient with RAIR DTC treated with lenvatinib who developed nephrotic-range proteinuria and was successfully treated with dapagliflozin[15]. Similar results were observed in our patient, in whom proteinuria remained detectable but was controlled below 1 g/24 hours without further deterioration of renal function. These findings should be interpreted with caution given the limited experience. Nonetheless, the role of SGLT2 inhibitors in the therapeutic management of TKI-induced proteinuria warrants further investigation.

Conflict of interest: None to declare

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