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Understanding the impact of antiangiogenic drug-induced proteinuria on kidney function in cancer patients

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Background and Aims: Proteinuria is a common adverse event associated with the use of vascular endothelial growth factor (VEGF) inhibitor drugs, which are widely employed in oncology for treating various tumors.

The incidence of proteinuria of all degrees ranges from 10% to 90%, with proteinuria in the nephrotic range occurring in 1-5% of cases.

VEGF plays a crucial role in maintaining the integrity of the glomerular capillary wall. Podocytes, constitutively express VEGF, and VEGF receptors are present on both the surface of glomerular capillary endothelial cells and podocytes. Any disruption in the podocyte-endothelial VEGF axis can lead to the loss of endothelial fenestrations in glomerular capillaries, proliferation of glomerular endothelial cells, loss of podocytes, and subsequent proteinuria. The most common pathological findings include focal segmental glomerulosclerosis and minimal change nephropathy, typically associated with tyrosine kinase inhibitors (TKIs), as well as thrombotic microangiopathy (TMA), more frequently observed in pts treated with anti VEGF.

Proteinuria is a recognized risk factor for progressive renal damage and end-stage renal disease. However, it's worth noting that the average treatment duration for patients on anti-angiogenic therapy is considerably shorter than the time indicated by clinical studies as necessary to induce renal damage from proteinuria in healthy individuals.

However, the long-term impact of drug-induced proteinuria on renal function remains uncertain.

The aim of the study is to investigate the association between proteinuria induced by anti-VEGF/VEGFR drugs and its long-term effects on renal function in cancer patients.

Method: A retrospective study was conducted on 124 patients undergoing anti-VEGF/VEGFR therapy for ≥6 months.

45% of the patients enrolled in the study were on TKI monotherapy, 36% received TKI plus immune checkpoint inhibitors (ICIs), 10% received anti- VEGF treatment, 7% received TKI + chemotherapy (CT), and 2% received anti-VEGF + ICIs. Among patients, 51% were undergoing treatment for kidney cancer, 25% for thyroid cancer, 14% for colon cancer, 7% for liver cancer, and 5% for lung cancer.

The study assessed the time course of estimated glomerular filtration rate (eGFR), the influence of baseline eGFR on subsequent variations, the association between proteinuria and renal function, and the identification of risk factors for proteinuria or renal failure. Proteinuria was quantified as proteinuria/24 h.

Results: Among the 124 patients, 53 developed proteinuria <1 g/24 h, 41 between 1-3 g/24 h, and 30 >3 g/24 h. Specific data are outlined in Table 1. A trend toward a reduction in eGFR of −5 ml/min/1.73 m^2 was observed in all patients after 2 years of treatment. The high proteinuria group exhibited a greater percentage change in eGFR compared to the other groups (−1.5% vs −8.5% vs −12.3%) as depicted in Fig. 1A, along with a time-dependent decrease in eGFR. There was no significant difference in the development of eGFR <30 ml/min/1.73 m^2 between groups, and no patients permanently discontinued treatment due to nephrotoxicity. No differences in eGFR reduction were noted among the three groups categorized by baseline eGFR (Fig. 1B). Importantly, renal function after the end of therapy was found to be reversible.

Conclusion: The study did not find a correlation between the degree of proteinuria secondary to anti-VEGF/VEGFR and significant reductions in renal function. Therefore, treatment can be continued irrespective of the degree of proteinuria. Clinical decisions regarding the continuation of therapy with these drugs should weigh the benefits in terms of survival against the potential risks of toxicity, including a modest reduction in renal glomerular filtration rate.