Review

Onconephrology
What Should the Internist Know About Targeted Therapy in Solid Tumors?

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Advances in medical oncology has led cancer patients to live longer. Moreover, the field of molecular oncology is rapidly evolving, new therapies emerge, and drugs are approved quickly. This has led nephrologists to encounter new and partially unrecognized treatments of the targeted therapy agents with kidney adverse effects. These agents fall mainly into 2 categories affecting the vascular endothelial growth factor and endothelial growth factor pathways. This review covers the incidence of kidney disease induced by these agents, pathophysiologic mechanisms, and clinical presentation, and is the first to recommend an adequate management for each pathophysiology.

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INTRODUCTION

The prevalence of both cancer and kidney disease is high and requires oncologists and nephrologists awareness about new cancer treatments and their potential adverse effects on the kidney function. Effectively, multiple experts raised the need for the development of a new subspecialty field of *onconephrology*.[1] Targeted therapy is one of the major developments in cancer treatment and is being incorporated in most treatment regimens. Moreover, these drugs are usually marketed to healthcare providers and patients as indolent with mild adverse effects.[2]

The toxicity profile of these drugs is well different from that of the conventional chemotherapy. However, due to their accelerated approval, knowledge of their toxicity profiles is still missing and their upcoming use confronted clinicians to new or partially recognized adverse effects. This toxicity was attributed to co-expression of same target molecules by both normal and cancer cells. This article aims to review what the nephrologists should know about the two most common pathways for targeted therapies in solid cancer: vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF). The incidence of kidney disease induced by targeted agents, pathophysiologic mechanisms, clinical presentation, and adequate management are reviewed.

VASCULAR ENDOTHELIAL GROWTH FACTOR PATHWAY INHIBITORS

Overview

Vascular endothelial growth factor plays a major role in tumor growth and development of metastasis by increasing vascular permeability and endothelial cell migration, proliferation, and survival.[3] Renal epithelial cells produce VEGF that binds to peritubular capillaries, mesangium, and glomeruli. This local VEGF allows repair and normal functioning of these cells and maintains integrity of the filtration system. Because of these different roles, targeting VEGF raises the possibility of adverse effects.[3] Two different approaches have been developed to inhibit the VEGF pathway. The first group of agents binds to the VEGF or VEGF receptor (VEGFR) and inhibits their action, such as bevacizumab, ramucirumab, and aflibercept. The others use small tyrosine kinase inhibitors (TKI) that blocks the intracellular domain of the VEGFR. These include sunitinib, ponatinib, sorafenib, axitinib, pazopanib, cabozantinib, and vandetanib.

Pathophysiology and Management

Proteinuria and hypertension are two main clinical syndromes that are particularly associated with the VEGF pathway inhibitors. Their pathogenesis and management in this setting are not well elucidated (Table 1).

Proteinuria

Animal studies of mice injected with anti-VEGF revealed disruption of epithelial cell slit diaphragm, swelling and vacuolization of glomerular endothelial cells, and downregulation of nephrin.[17] In fact, it is not yet established whether proteinuria is an adverse effect or on-target effect.[18] Factors affecting its occurrence and severity are incompletely characterized. Predisposing factors include pre-existence of kidney disease, diagnosis of renal cell carcinoma, combination of the targeted agent with chemotherapy, and increased dosages.[19-23] Interestingly, duration of infusions do not seem to affect the development of proteinuria.[24] Differences in affinities to VEGFR dictates the injury type: the complex VEGF-A bevacizumab deposits in the kidneys whilst VEGF-A aflibercept complex remains in the circulation.[25,26]

The underlying pathogenesis for the development of kidney injury is not well elucidated. Of the few renal biopsies performed, pathology demonstrated glomerulopathies, thrombotic microangiopathy (TMA), and rarely, interstitial nephritis.[18,27] Literature also describes the occurrence of focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, acute interstitial nephritis, and minimal change disease.[3,28-30] Moreover, clinical trials reported development of renal insufficiency and diabetes insipidus in these patients, albeit absence of a proof of causality.[31,32]

Patients present clinically with asymptomatic proteinuria, nephrotic syndrome, or acute kidney failure. Monitoring for proteinuria in oncology practice is performed by either dipstick or calculation of the urine protein-creatinine ratio on spot urine samples.[17] There are no evidence-based guidelines established by neither the National Cancer Care Network nor the European Society of Medical Oncology for the management of proteinuria induced by VEGF TKI. Commonly, asymptomatic proteinuria autoresolves after discontinuation of treatment but can rarely progress to nephrotic

Table 1. Vascular Endothelial Growth Factor Pathway Inhibitors-related Nephrotoxicity*

Molecule	Target	Malignancies	Incidence of hypertension	Incidence of proteinuria	References
Pazopanib (Votrient)	TK, VEGFR	Advanced renal cell carcinoma and advanced soft tissue sarcoma	Any grade: 40% Grade 3/4: 4%	Any grade: < 10% Grade 3/4: < 1%	4
Regorafinib (Stivarga)	TK, VEGFR	Metastatic colorectal carcinoma	Any grade: 28% Grade 3/4: 7%	Any grade: 7% Grade 3/4: 7%	5
Cabozantinib (Cometriq)	TK, VEGFR	Metastatic medullary thyroid cancer	Any grade: 22% to 40% Grade 3/4: 4% to 12%	Any grade: < 10% Grade 3/4: < 1%	6,7
Sunitinib (Sutent)	VEGF	Metastatic renal cell carcinoma, gastrointestinal stromal tumor not responding to imatinib, or pancreatic euroendocrine tumors	Any grade: 22% to 24% Grade 3/4: 5% to 8%	NA	8,9
Sorafinib (Nexavar)	VEGF	Advanced renal cell carcinoma, hepatocellular carcinoma, thyroid cancer	Any grade: 17% to 19.5% Grade 3/4: 4%	NA	10,11
Ziv-aflibercept (Zaltrap)	VEGF	Metastatic colorectal carcinoma	Any grade: 41.4% Grade 3/4: 19.3%	Any grade: 62.2% Grade 3/4: 7.8%	12
Axitinib (Imlyta)	VEGF	Metastatic colorectal carcinoma	Any grade: 40% Grade 3/4: 16%	NA	13
Bevacizumab (Avastin)	VEGF	Glioblastoma, nonsmall cell lung cancer, metasatatic colorectal carcinoma and renal cell carcinoma	Any grade (7.5 mg/kg): 14.3% Grade 3/4 (7.5 mg/kg): 0.8% Any grade (15 mg/kg): 21.9% Grade 3/4 (15 mg/kg): 4.5%	Any grade (7.5 mg/kg): NA Grade 3/4 (7.5 mg/kg): 0.8% Any grade (15 mg/kg): NA Grade 3/4 (15 mg/kg): 2%	14,15
Vandetanib (Caprelsa)	TK, EGFR, VEGF,RET	Metastatic medullary thyroid cancer	Any grade: NA Grade 3/4: 34%	NA	16

*TK indicates tyrosine kinase; VEGFR, vascular endothelial growth factor receptor; VEGF, vascular endothelial growth factor; NA: not available; EGFR, epidermal growth factor receptor; and RET, rearranged during transfection.

syndrome.[33] In the latter situation, the drug should be permanently discontinued. On the other hand, often disregarded low levels of proteinuria reflect renal TMA and serious renal injury in 35% of patients; subsequently, withdrawal of the culprit drug is recommended.[34] Its reintroduction requires close monitoring and discontinuation in case of TMA recurrence. Withdrawal of anti-VEGF agents commonly reduces proteinuria; however, its persistence is possible.[35] Based on his case series, Izzedin suggested in 2014 to differentiate between renal TMA that necessitates drug withdrawal in contrary to minimal change disease or focal segmental glomerulosclerosis that responds to antihypertensive and antiproteinuric treatments.[30]

Hypertension

Hypertension is definitely one of the most prevalent comorbidities found in cancer patients and happens to be the most reported grade 3 event in patients with preexisting hypertension.[36,37] Its occurrence and severity depends on the type of drug, dose, schedule used, age, and coexistence of cardiac disease.[36] Cardiac ischemia and infarction and reversible posterior leukoencephalopathy syndrome are the possible secondary events reported with hypertension attributed to anti-VEGF agents.[10,38-40] Interestingly, hypertension predicts response to therapy, time to progression, and survival, and should encourage physicians to continue its use along with proper blood pressure control, and preferably, without dose reduction.[41,42]

Hypertension commonly occurs within the first year after drug initiation. New-onset hypertension in previously nonhypertensive patients may be due to different pathogenesis: renal TMA, glomerular lesions, and isolated drug-induced hypertension.[36] For the first two, management is identical to that of proteinuria. As for the latter, Izzedine and colleagues attribute isolated hypertension to an increased systemic vascular resistance since VEGF infusions decreases cardiac ejection fraction.[36,43] This increased systemic vascular resistance is explained by neurohormonal factors, microvascular rarefaction, and endothelial dysfunction.[44]

The optimal monitoring pattern of blood pressure is not elucidated yet. One method is 3 ambulatory measures at 5-minute intervals and 3 night measurements for 3 days per week.[45] Another acceptable method is 1 weekly measure for the 1st 6 weeks.[46] Medical literature does not advocate a management different from that of noncancer patients. Hence, hypertension is managed no differently from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommendations.[36] Lifestyle modifications would be the first approach by limiting saturated and unsaturated fat intake with salt restriction.[47] If ineffective, most patients respond to oral hypertensive treatments without dose reduction. The antihypertensive treatment is personalized according to the patient comorbidities. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are privileged in patients with proteinuria and chronic kidney disease. Dihydropyridine calcium channel blockers are preferred in elderly and black patients whereas nondihyopyridine calcium channel blockers are contraindicated in patients receiving CYP450 inhibitors.[36] If refractory hypertension occurs, management encloses temporary or permanent discontinuation of the offending agent.[46]

ENDOTHELIAL GROWTH FACTOR PATHWAY INHIBITORS

Overview

Endothelial growth factor is a tyrosine kinase receptor found on almost all cells except for hematopoetic cells.[48] It has been found responsible for the activation of cancer invasion, apoptosis, and angiogenesis.[49,50] Subsequently, it has been targeted for the treatment of multiple malignancies and has been proven efficient in numerous clinical trials.[51,52] Ligands to EGFR were shown to increase in response to acute tubular and renal injury and administration of EGF accelerated recovery from kidney injuries.[53-59] Two different approaches have been developed to inhibit the EGF pathway. The first binds to EGF receptor (EGFR) and inhibits its action, such as cetuximab and panitumumab. The latter uses TKI that blocks the intracellular domain of the EGFR, such as erlotinib, gefitinib, and afatinib.

Pathophysiology and Management

The EGF pathway has been shown to affect the kidney through various mechanisms. Experimental animal studies have demonstrated an important role of local growth factors in stimulating proliferation and differentiation of cells after acute

tubular necrosis.[60] This finding correlates with the delayed recovery in renal proximal tubule epithelial cells after experimental deletion of EGF.[61,62] Consequently, alterations disturbing the EGF pathway result in tubulopathy manifestations. Particularly, the basolateral membrane encompasses EGFR that is responsible in part to the reabsorption of magnesium in the distal convoluted tubule. Upon activation, EGFR stimulates the translocation of the cation channel transient receptor potential M6 into the apical membrane where the magnesium is reabsorbed.[63-65] Moreover, recent studies described a cross-talk between mineralocorticoid receptors and EGFR responsible for proliferation, fibrosis, and hypertrophy.[62] Subsequently, EGFR pathways inhibitors present with tubulopathies or glomerulopathies (Table 2).

Tubulopathy is often described in patients receiving ligands to EGFR. These drugs are known to induce a renal magnesium wasting syndrome because of their affinity to EGFR that is 10-fold greater than that of the natural ligan.[58,63-65] When measured rigorously, all patients receiving ligands to EGFR present a decline in magnesium concentration with 50% developing hypomagnesaemia.[63-65] Risk factors include older age, baseline magnesium concentration, drug-induced diarrhea, and duration of administration.[76]

Very few cases report a correlation between EGFR TKI and renal complications. These were attributed to baseline hepatic impairment, severe dehydaration secondary to diarrhea, and glomerulopathies. Erlotinib induces hepatorenal syndrome, acute renal failure, and pauci-immune crescentic glomerulonephritis secondary to leucocytoclastic vasculitis.[77-79] Moreover, gefitinib was also associated with leucocytoclastic vasculitic glomerulonephritis and manifesting with tubulointerstitial nephritis secondary to interstitial lymphoplasmacytic infiltration.[80-82]

Management of TKI nephrotoxicity is empiric and aims at treating the underlying pathogenesis. In the case of kidney dysfunction attributed only to glomerulopathies secondary to TKI, the drug was discontinued and kidney function was normalized.[83] On the other hand, EGFR ligands monitoring is clearly established. Its administration warrants serum potassium, magnesium, and calcium periodic monitoring during treatment and 8 weeks thereafter. For grade 1-2 hypomagnesaemia,

Table 2. Epidermal Growth Factor Pathway Inhibitors-related Nephrotoxicity*

Molecule	Target	Malignancies	Renal Effect All Grades	Renal Effect Grade 3/4	Diarrhea All Grades	Diarrhea Grade 3/4	References
Gefitinib (Iressa)	EGFR, TK	Advanced nonsmall cell lung cancer	NA	NA	15% to 46.6%	0.9% to 5%	66,67
Erlotinib (Tarceva)	EGFR, TK	Metastatc nonsmall cell lung cancer and pancreatic cancer	Renal toxicity: 8%	2%	18% to 55%	3% to 6%	68,69
Afatinib (Gilotrif)	EGFR, TK	Advanced lung adenocarcinoma	Hypokalemia: 9%	2%	87% to 95.2%	14.4% to 22%	70
Cetuximab (Erbitux)	EGFR	Squamous cell carcinoma of the head and neck or colorectal cancer	Hypokalemia: 25.8% to 54% Hypomagnesemia: 33.8% to 57% Hypocalcaemia: 18%	Hypokalemia: 4,5% to 7% Hypomagnesemia: 3.3% to 9% Hypocalcaemia: 3.2	22% to 81%	3% to 28.4%	71,72,73
Panitumumab (Vectibix)	EGFR	Metastatic colon cancer	Hypokalemia: NA Hypomagnesemia: 28%	Hypokalemia: 7% Hypomagnesemia: 3%	9% to 74%	1% to 24%	74,75

*EGF indicates epidermal growth factor; EGFR, epidermal growth factor receptor; TK, tyrosine kinase; and NA, not available.

electrolytes supplementation is administered as needed after early assessment and management of possible drug-induced diarrhea. In cases of grade 3-4 hypomagnesaemia, withdrawal of the offending drug is recommended for four to 8 weeks after which the magnesium wasting syndrome resolve.[84] The drug may then be reintroduced following reversal of hypomagnesaemia.[85]

CONCLUSIONS

In summary, this article reports on targeted therapy in solid cancer from an onconephrology point of view. It covers the incidence of kidney disease induced by targeted agents, pathophysiology mechanisms, clinical presentations, and adequate managements. This treatment modality is continuously being developed, incorporated in cancer treatment regimens, and used among patients with comorbid kidney disease. Subsequently, onconephrology is undoubtedly an essential field that requires close collaboration between oncologists and nephrologists. Physicians should get quickly involved in cancer biology and familiar with the clinical and laboratory manifestations of these drugs for them to provide the optimum management for their patients. As proven throughout this article, multicenter randomized clinical trials should be promoted to fill the gaps.

CONFLICT OF INTEREST

None declared.

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