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Molecular Targeted Cancer Therapies and the Kidney

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Abstract

Novel, targeted anticancer therapies have increased survival rates in patients. However, the incidence, severity, and pattern of their toxicities are different from those of traditional chemotherapies. The high prevalence of chronic kidney disease in the general population and the increased incidence of cancer highlight the need for nephrology consultation regarding this issue. Here, we review the incidence, mechanisms, and management of adverse renal effects associated with major molecular, targeted cancer therapies. Early diagnosis and prompt intervention in case of adverse renal events are crucial for the proper management of patients with cancer treated with targeted agents.

Keywords: Cancer, CAR-T, kidney, nephrotoxicity, onconephrology, targeted therapy

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INTRODUCTION

With Rudolf Virchow's introduction of the microscope in 1863, studies commenced on the cellular origins of cancer, and the first hypothesis about metastatic disease came from Stephan Paget's findings in 1889. At the beginning of the 20th century, Paul Ehrlich developed chemicals that could be used to treat cancer and eventually coined the word "chemotherapy." In the 1950s, despite the use of surgical resection and radiation alone or in combination in cancer treatment, only two-thirds of all cancer types were being treated. By the mid-1960s, there was clear evidence that childhood leukemia and advanced Hodgkin's lymphoma in adults could be cured by combination chemotherapy (1). In 2006, Druker et al. (2) demonstrated the efficacy of imatinib as a drug targeting molecular abnormality specific to chronic myeloid leukemia. This study provided evidence for the principle that treatments targeting specific molecular abnormalities specific to certain cancers could turn them into manageable chronic diseases (2). After the successful administration of interleukin-2 for the treatment of melanoma, immunotherapy showed its ability to mediate cancer regression and play a role in cancer treatment (1). Targeted anticancer therapies have resulted in a significant improvement in the survival rates of patients. Nevertheless, the incidence, severity, and pattern of their toxicities may differ from those of cytotoxic chemotherapies. The nephrotoxicity of targeted therapies occurs through several complex mechanisms. Agents might damage various parts of the nephron, yielding various clinical outcomes ranging from asymptomatic urine abnormality to renal failure. Besides, in most of the clinical trials, patients with decreased renal function are not included although many oncologic patients have low glomerular filtration rate (GFR). This makes it difficult to use targeted therapies in this population. Herein, we review the adverse renal effects associated with targeted therapies that have been widely used in our country in recent years. Table 1 summarizes targets and indications of major targeted therapies. Renal adverse effects and dosing information of those molecules are given in Table 2.

Vascular Endothelial Growth Factor Signaling Pathway Blockers

Vascular endothelial growth factor (VEGF) is an essential regulator of vasculogenesis during embryogenesis and angiogenesis in an adult. In addition to its physiological

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importance, VEGF plays an important role in tumor growth, metastasis, and survival by increasing vascular permeability and endothelial cell migration in tumor cells. In the kidney, VEGF receptors (VEGFR) are found in peritubular capillaries, mesangium, and glomerular cells. VEGF is produced by podocytes and helps in maintaining the integrity of visceral epithelial cells, acts as a filtration barrier, and regulates vascular permeability and endothelium-dependent vasodilatation. Thus, inhibition of this pathway results in proteinuria, hypertension, and thrombotic microangiopathy (TMA) (Figure 1) (3, 4).

There are different ways to block the VEGF signaling pathway:
- VEGF ligand inhibitors (bevacizumab, ramucirumab, aflibercept) bind directly to VEGF to form a complex that cannot bind to VEGFRs, thereby inhibiting receptor activation.
- Small molecules, tyrosine kinase inhibitors (TKIs) (sunitinib, sorafenib, pazopanib, ponatinib, axitinib, cabozantinib, lenvatinib, regorafenib, vandetanib) act by blocking the intracellular domain of the VEGFR.

Proteinuria is the most common adverse event seen with anti-VEGF agents. The incidence of mild proteinuria in patients treated with bevacizumab ranged from 21% to 63%, whereas grade 3-4 proteinuria (4+ with a dipstick or ≥3.5g/dL or nephrotic syndrome) was detected in 2.2%. The severity of proteinuria appears to be related to the dose of the agent, pre-existing renal disease (hypertension, higher baseline proteinuria), and the type of cancer (renal cell carcinoma). Patients who develop proteinuria were more likely to become hypertensive (47.1% vs. 16.9%). Although proteinuria and hypertension resolve after the discontinuation of the anti-VEGF agent, proteinuria might persist (5).

In 54 normotensive patients who were treated with sorafenib, hypertension was detected in 93% of the patients on the 6th day of the treatment via 24-hour blood pressure monitoring. Additionally, the highest blood pressure measurement was observed in the first 24 hours of the treatment (6). In a retrospective meta-analysis, bevacizumab-related hypertension was found to be related to tumor regression in patients with metastatic colorectal carcinoma (7). It has been suggested that anti-VEGF-related hypertension is linked to a positive antitumor response.

Mechanisms of nephrotoxicity (8):
- Decreased nitric oxide.
- Decreased microvessel density in vascular beds (rarefaction).
- Decreased protection against oxidative stress.
- Increased intraglomerular pressure.
- Loss of endothelial fenestrations in the glomerular capillaries, proliferation of glomerular endothelial cells (endotheliosis), loss of podocytes.
- Decreased lymphangiogenesis.
- Decreased pressure natriuresis.

In biopsy-proven cases, histopathologic lesions were as follows: TMA, focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), mesangioproliferative glomerulonephritis, cryoglobulinemic glomerulonephritis, immune complex glomerulonephritis, glomerular endotheliosis, and acute interstitial nephritis (AIN). In all these cases there was glomerular endothelial cell swelling, loss of endothelial fenestrae, and effacement of foot processes as well (3). In a single-center observational study, Izzedine et al. (9) reported that there were 73 patients with TMA out of 100 patients with biopsy-proven kidney disease who received anti-VEGF therapy. In 27 patients, there were glomerulopathies such as MCD or FSGS in the biopsy. The most common pathologic lesion was TMA. While TMA was observed especially in patients who received VEGF ligand inhibitors, glomerulopathies were detected in patients who received TKIs. In this study, hypertension and proteinuria improved after discontinuation of anti-VEGF therapy and initiation of antihypertensive therapy, and there were no patients with serious kidney failure requiring dialysis. In patients who developed TMA, continuation or re-initiation of anti-VEGF therapy resulted in worsening or recurrence of TMA. In contrast with cytotoxic chemotherapy-related TMA (mitomycin C, gemcitabine, cisplatin), conservative treatment with blood pressure control and discontinuation of the responsible drug seemed enough to improve clinical consequences in patients treated with anti-VEGF agents (9).

TKIs have also been known to cause electrolyte disorders besides proteinuria, hypertension, or TMA. Sorafenib may cause hypophosphatemia and hypocalcemia related to pancreatic dysfunction and vitamin D malabsorption (10). Regorafenib and vandetanib are associated with mild or moderate hypophosphatemia, hyponatremia, hypokalemia, and hypocalcemia, which do not require treatment interruptions (11). Interestingly, there is evidence that imatinib is associated with improvement of immune-mediated kidney disease via decreasing fibrotic and inflammatory markers (12).

Main Points

- Onconephrology, focuses on renal effects of anticancer treatments including targeted therapies and immunotherapies, is an emerging subspecialty of nephrology.
- The incidence, severity, and toxicities of the novel anticancer treatments are different from those of traditional chemotherapies.
- Renal biopsy findings have a prominent importance in differential diagnosis of renal adverse of targeted therapies.
- There should be a collaboration between oncology and nephrology in order to guide the proper management of the cancer treatment and specific treatment for the renal events.
- While various renal adverse events related to treatments in cancer patients are increasing, incidence of cancer is increasing in chronic kidney disease patients, as well. More knowledge and experience is needed in this issue.

Table 1. Molecular targets and indications of targeted therapies [modified from references (11, 14)]

Generic name	Target	Clinical indications
VEGF inhibitors		
Bevacizumab	VEGFR	Cervical cancer, CRC, GBM, NSCLC, epithelial ovarian cancer, RCC, breast cancer, primary peritoneal carcinoma, endometrial carcinoma, malignant pleural mesothelioma, soft tissue sarcoma, angiosarcoma, age-related macular degeneration, diabetic macular edema, hereditary hemorrhagic telangiectasia
Aflibercept	VEGFR	CRC
Ramucirumab	VEGFR	CRC, gastric cancer, HCC, NSCLC
Ponatinib	BCR-ABL TKI	CML, ALL
Axitinib	Multitarget TKI	RCC, thyroid carcinoma, pancretaic cancer, CML
Sunitinib	Multitarget TKI	GIST, pancreatic neuroendocrine tumor, RCC, soft tissue sarcoma, thyroid carcinoma
Sorafenib	Multitarget TKI	HCC, RCC, thyroid carcinoma, angiosarcoma, GIST
Other TKIs		
Imatinib	BCR-ABL TKI	CML, GIST
Dasatinib	BCR-ABL TKI	CML
Nilotinib	BCR-ABL TKI	CML
Bosutinib	BCR-ABL TKI	CML
Ibrutinib	Bruton kinase TKI	CLL, mantle cell lymphoma
ICPis		
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, NSCLC, RCC, Hodgkin's lymphoma, SCC of the head and neck, urothelial carcinoma, CRC with MSI or MMR deficiency
Pembrolizumab	PD-1	Melanoma, NSCLC, RCC, Hodgkin's lymphoma, SCC of the head and neck, urothelial carcinoma, gastric cancer, CRC with MSI or MMR deficiency
Atezolizumab	PD-L1	NSCLC, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma
EGFR inhibitors		
Cetuximab	EGFR	CRC, SCC of head and neck cancer
Panitumumab	EGFR	CRC
Erlotinib	EGFR TKI	NSCLC, pancreatic cancer
Gefitinib	EGFR TKI	NSCLC
Afatinib	EGFR TKI	NSCLC
mTOR inhibitors		
Temsirolimus	mTOR	RCC, MCL
Everolimus	mTOR	RCC, pNET, breast cancer
ERBB-2 (HER-2) inhibitors		
Trastuzumab	HER-2	Breast cancer, gastric cancer
Pertuzumab	HER-2	Breast cancer
Lapatinib	HER-2 TKI	Breast cancer
T-DM1 (trastuzumab emtansine)	HER-2	Breast cancer
ALK inhibitors		
Crizotinib	ALK	NSCLC
B-raf inhibitors		
Dabrafenib	BRAF	Melanoma

Table 1. Molecular targets and indications of targeted therapies [modified from references (11, 14)] (continued)

Generic name	Target	Clinical indications
Vemurafenib	BRAF	Melanoma, thyroid cancer, CRC
MEK inhibitors		
Trametinib	MEK	Melanoma
CAR-T cell products		
Tisagenlecleucel	CD19	Diffuse large B-cell lymphoma, ALL
Axicabtagene ciloleucel	CD19	Diffuse large B-cell lymphoma

ALK: anaplastic lymphoma kinase; ALL: acute lymphocytic leukemia; BCR-ABL: breakpoint cluster region-abelson; CAR-T: chimeric antigen receptors T-cell; CD: cluster of differentiation; CLL: chronic lymphoid leukemia; CML: chronic myeloid leukemia; CRC: colorectal cancer; CTLA-4: cytotoxic T-lympocyte-associated 4; EGFR: epidermal growth factor receptor; GBM: glioblastoma multiforme; GIST: gastrointestinal stromal tumor; HCC: hepatocellular carcinoma; HER-2: human epidermal growth factor-2; ICPis: immune checkpoint inhibitors; MCL: mantle cell lymphoma; MEK: mitogen-activated protein kinase; MMR: mismatch-repair; MSI: microsatellite instability; mTOR: mammalian target of rapamycin; NSCLC: non-small-cell lung cancer; PD-1: programed cell death protein-1; PD-L1: programed cell death protein ligand 1; pNET: pancreatic neuroendocrine tumours; RCC: renal cell carcinoma; SCC: squamous-cell carcinoma; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

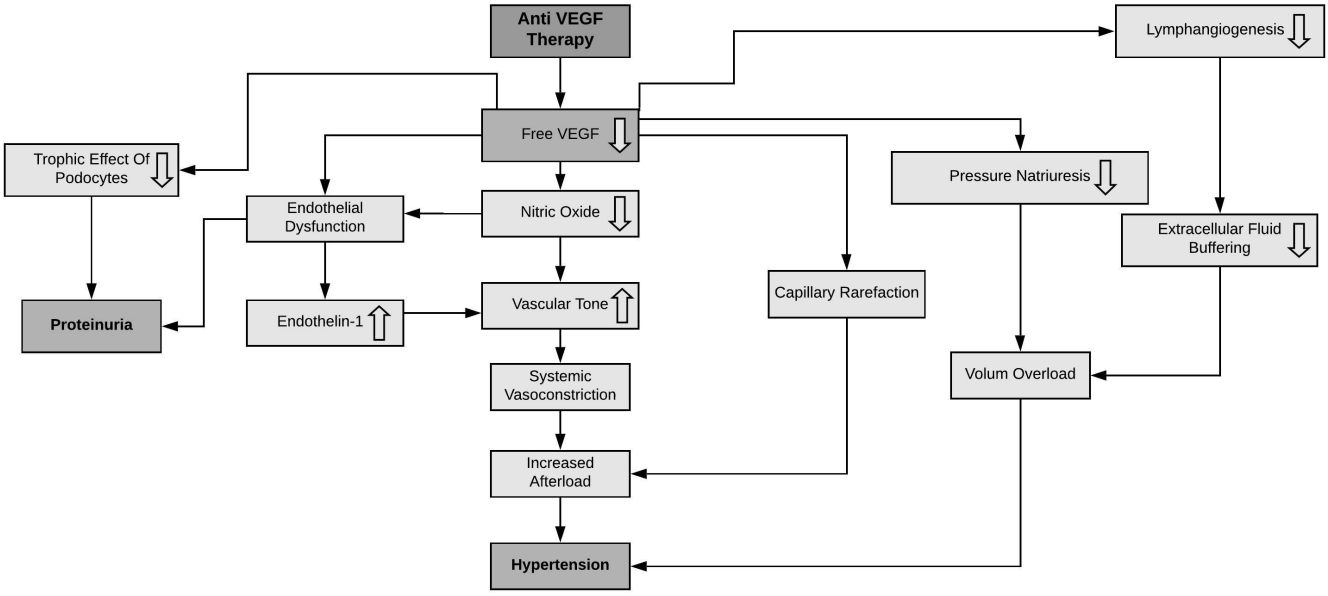

Figure 1. Pathogenesis of nephrotoxicity of anti-VEGF therapy [modified from reference (4)].

Clinicians should check for proteinuria (if possible, with a 24-hour urine sample) and renal functions before each cycle of the therapy. In case of development of non-nephrotic proteinuria, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin-receptor blockers (ARBs) may be used with caution. Nephrotic proteinuria is associated with renal damage and increased cardiovascular risk; therefore, anti-VEGF agents must be discontinued. Since oncological treatments might induce or worsen hypertension, pre-existing hypertension must be evaluated and adequately controlled. The most reliable method is via home blood pressure measurements, particularly at the beginning of the treatment (13). Vitamin D, phosphate, and calcium levels should be screened especially in patients who have received sorafenib. However, one should keep in mind that all electrolyte disorders might be seen with TKIs.

If hypertension is detected, standard antihypertensive treatment tailored to the individual should be administered. ACEIs or ARBs might be considered as first-line options and calcium channel blockers as a second choice. Diuretics should be used with caution because oncologic patients are prone to being hypovolemic. Nebivolol, because of its nitric oxide-mediated vasodilatory effects, might be a reasonable therapeutic option in this setting (11, 14).

The pharmacokinetics and toxic effects of anti-VEGF agents have turned out to be similar in patients with reduced kidney function compared with those observed in patients with normal renal function. Thus, no dose adjustment is recommended in patients with chronic kidney disease (CKD). Additionally, none of the drugs targeting VEGF are dialyzed; they may therefore be administered before or after dialysis sessions (15).

Table 2. Renal adverse events and dosing of targeted therapies [modified from reference (14)]

Drug	Renal excretion	Most-frequent renal AEs	Dose reduction required?		
			eGFR 30-60 mL/min/1.73 m^2	eGFR <30 mL/min/1.73 m^2	Dialysis
VEGF inhibitors					
Bevacizumab	No	HT, proteinuria, TMA	No	No (no data)	No
Aflibercept	No	HT, proteinuria	No	No (no data)	No
Sunitinib	16%	HT, proteinuria, MCD/FSGS, AIN	No	No (no data)	No
Pazopanib	<4%	HT, proteinuria	No	No (no data)	No
Axitinib	23%	HT, proteinuria	No	No (no data)	No
Sorafenib	19%	HT, proteinuria, hypophosphatemia, MCD/FSGS, AIN	No	No (no data)	No
Regorafenib	19%	HT, proteinuria, hypophosphatemia, hypocalcemia, AKI	No	No (no data)	No data
Vandetanib	25%	HT, proteinuria, AKI, hypokalemia, hypocalcemia	No	Yes	No data
Other TKIs					
Imatinib	13%	Renoprotective*, hypophosphatemia	No	No (no data)	No
Dasatinib	<5%	AKI, TMA, proteinuria	No	No (no data)	No data
Nilotinib	No	HT	No	No (No data)	No data
Bosutinib	No	Hypophosphatemia	Reduce dose to 300 mg/day	No (no data)	No data
Ibrutinib	No	AKI, edema, HT	No data	No data	No data
ICPis					
Ipilimumab	No	AIN, podocytopathy, hyponatremia	No	No (no data)	No (no data)
Nivolumab	No	AIN	No	No	No data
Pembrolizumab	No data	AIN	No	No	No
EGFR inhibitors					
Cetuximab	No	Hypomagnesemia, other electrolyte disorders	No	No (no data)	No
Panitumumab	No	Hypomagnesemia, other electrolyte disorders	No	No (no data)	No (no data)
Gefitinib	<4%	Electrolyte disorders	No	No (no data)	No
Erlotinib	<9%	Electrolyte disorders	No	No (no data)	No
Afatinib	<5%	Electrolyte disorders	No	No (no data)	No (no data)
mTOR inhibitors					
Everolimus	2%	Proteinuria, AKI, electrolyte disorders	No	No; suspend if AKI	No
Temsirolimus	4.6%	Proteinuria, AKI, electrolyte disorders	No	No; suspend if AKI	No
ERBB-2 (HER-2) inhibitors					
Trastuzumab	No	HT, AKI (with cisplatin)	No	No (no data)	No
Pertuzumab	No	No issues	No	No (no data)	No (no data)
Lapatinib	2%	No issues	No	No (no data)	No
Trastuzumab emtansine	<5%	Hypokalemia	No	No (no data)	No (no data)
ALK inhibitors					
Crizotinib	No	Reduction of eGFR (tubular necrosis?), renal cysts	Possible, with caution	Possible, with caution (no data)	No (no data)

Table 2. Renal adverse events and dosing of targeted therapies [modified from reference (14)] (continued)

Drug	Renal excretion	Most-frequent renal AEs	Dose reduction required?		
			eGFR 30-60 mL/min/1.73 m^2	eGFR <30 mL/min/1.73 m^2	Dialysis
B-raf inhibitors					
Vemurafenib	1%	AKI	No	No (no data)	Possible (risk of arrhytmia)
Dabrafenib	23%	Hypophosphatemia, (granulomatous nephritis?)	No	No (no data)	No (no data)
MEK inhibitors					
Trametinib	<20%	HT, hyponatremia (with dabrafenib)	No	No (no data)	No (no data)
CAR-T cell products					
Tisagenlecleucel	N/A	CRS, HLH	N/A	N/A	N/A
Axicabtagene ciloleucel	N/A	CRS, HLH	N/A	N/A	N/A

*Imatinib is associated with improvement of immune-mediated kidney disease via decreasing fibrotic and inflammatory markers (12).
AEs: adverse events; AIN: acute interstitial nephritis; ALK: anaplastic lymphoma kinase; AKI: acute kidney injury; CRS: cytokine-release syndrome; CAR-T: chimeric antigen receptors T-cell; EGFR: estimated glomerular filtration rate; HER-2: human epidermal growth factor-2; HLH: hemophagocytic lymphohistiocytosis; HT: hypertension; ICPis: immune checkpoint inhibitors; MCD/FSGS: minimal change disease/focal segmental glomerulosclerosis; MEK: mitogen-activating protein kinase; mTOR: mammalian target of rapamycin; N/A: not applicable; TKIs: tyrosine kinase inhibitors; TMA: trombothic microangiopathy; VEGF: vascular endothelial growth factor

Immune Checkpoint Inhibitors

T-cell-mediated immune response is regulated by a balance between co-stimulatory and inhibitory signals. Immune checkpoints are mechanisms for the immune system to control immune response, including self-tolerance. Immune checkpoint proteins cytotoxic T- lymphocyte-associated 4 (CTLA-4) and programmed cell death protein-1 (PD-1) are receptors that are expressed on cytotoxic T cells that interact with their ligands CD80/CD86 and programmed death-ligand 1/ programmed death-ligand 2 (PD-L1/PD-L2), respectively. When these co-stimulatory signals are activated, T cells become inactivated and tumor cells manage to evade the immune system. Immune checkpoint inhibitors (ICPis) prevent the receptor and the ligand from binding to each other, thereby allowing T cells to continue to attack tumor cells (11, 16).

There are three targets to inhibit the immune checkpoint pathway (17):

- Monoclonal antibodies against PD-1 (nivolumab, pembrolizumab).
- Monoclonal antibodies against PD-L1 (atezolizumab, avelumab, durvalumab).
- Monoclonal antibodies against CTLA-4 (ipilimumab).

The indications of ICPis are listed in Table 1.

With ICPis, there have been increased inflammatory findings such as colitis, pneumonitis, hepatitis, dermatitis, hypophysitis that are called immune-related adverse events (IRAEs). Robert et al. (18) reported that the incidence of acute kidney injury (AKI) was higher in the nivolumab-treated group than in the chemotherapy-treated group (13% vs. 9%).

Mechanisms of nephrotoxicity:

- Cell-mediated immunity leading to inflammatory cell infiltrates (granulomas may be seen).
- Cross reactions with tumor specific T cells.
- Increased serum cytokine/chemokine levels.
- Circulating immune complexes suggesting autoimmunity.

In biopsy-proven case series, AIN with or without granulomas is the most common pathologic lesion. Additionally, MCD, lupus-like nephritis with a membranous pattern, pauci-immune glomerulonephritis, IgA nephropathy, C3 nephropathy, FSGS, and TMA were reported as underlying pathologies of AKI and/or the nephrotic syndrome (19).

In one case report, a drug-specific lymphocyte test was positive to lansoprazole in a patient who developed AIN after initiating nivolumab therapy under long-term lansoprazole treatment. The authors think that ICPis may induce drug-specific T cells that normally permit renal tolerance of drugs known to be associated with AIN (20). In another case report of lupus-like nephritis secondary to the administration of ipilimumab, there were circulating antibodies for double-stranded DNA and antinuclear antigens which disappeared 3 months after the discontinuation of ipilimumab and initiation of corticosteroids (21). There is also evidence that the cause of renal damage may be related to increased serum cytokine and chemokine levels in patients who were treated with ipilimumab and nivolumab together (22).

Another problem that clinicians face with the treatment of ICPis is electrolyte disorder. Hyponatremia associated with hypoph-

ysitis is the most common and well-documented electrolyte disorder in this setting (23). Hypokalemia and hypocalcemia were also reported (24).

AKI appears usually in the 6- to 12-month period with PD-1 and PD-L1 inhibitors; however, it occurs in the first 3 months with CTLA-4 inhibitors. Thus, serum creatinine and urinalysis should be monitored regularly before the treatment and during follow-up. In patients with stage 1 AKI, other possible reasons for kidney injury should be checked first. In case of stage 2 or 3 AKI and/or non-nephrotic proteinuria, unless there is another reason for explaining AKI, renal biopsy should be considered. While waiting for the biopsy results, ICPis and possible related drugs must be discontinued. If biopsy reveals AIN or podocytopathy, corticosteroids (0.5-1 mg/kg/d prednisone) should be initiated and tapered down over a 1- to 3-month period. In patients with stage 1-2 AKI, after complete recovery with steroids, re-challenge with ICPis may be a reasonable option with close monitoring (11).

On the basis of findings from pharmacokinetic studies, no dose adjustment was required in patients with CKD (Table 2). The use of ICPis, especially ipilimumab, is not recommended because of the risk of rejection in transplant patients (14).

Epidermal Growth Factor Receptor Inhibitors

Epidermal growth factor receptor (EGFR) is an origin receptor of a key regulator of intracellular signaling pathways that are related to cancer-cell survival. Most of the EGFR is located in the thick ascending limb of Henle and distal tubule in kidney.

Two ways to block the EGFR signaling pathway include:
- Monoclonal antibodies that inhibit the receptor's function (cetuximab, panitumumab).
- Small-molecule TKIs (gefitinib, erlotinib, afatinib).

The indications of the EGFR inhibitors are given in Table 1.

Anti-EGFR agents are associated with hypomagnesemia, hypokalemia, AKI, and fluid retention (6.6% with gefitinib (25)). In two meta-analyses, incidences of grade 3-4 hypomagnesemia (grade 3, <0.9-0.7 mg/dL; grade 4, <0.7 mg/dL; life-threatening consequences) were found in 3.9% and 5.6% of the patients, respectively (26, 27). Incidences of hypomagnesemia and hypokalemia seem to be higher in combination therapies (chemotherapy or panitumumab). The main risk factors for hypomagnesemia are treatment duration, age, and baseline magnesium levels (11). Although hypomagnesemia is the most commonly reported toxicity with anti-EGFR agents in the literature, Jhaveri et al. (28) found a high degree of renal impairment with cetuximab (172 cases of AKI among the 467 renal events reported to the Food and Drug Administration [FDA]).

Mechanisms of nephrotoxicity (29, 30):
- Transepithelial magnesium transport impairment in distal convoluted tubules (TRPM6 and TRMP7 are regulated by EGF).
- Loss of regeneration capacity of tubular epithelial cells after acute tubular necrosis (ATN).

Magnesium levels should be checked before starting the treatment and monitored every 2-4 weeks. Concomitant medications, such as thiazide diuretics or proton pump inhibitors, should be overseen. Oral magnesium supplementation may be sufficient for grade 1 or 2 hypomagnesemia (grade 1, Mg level of < lower limit normal-1.2 mg/dL; grade 2, <1.2-0.9 mg/dL) whereas intravenous replacement is required for grade 3 or 4 hypomagnesemia. Diarrhea might occur in patients who receive oral magnesium supplementation.

Renal function has no impact on the drug metabolism of anti-EGFR agents according to pharmacokinetic analyses (14).

Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin (mTOR) is a protein that helps control several functions such as cell division, metabolic function, and protein synthesis. Everolimus and temsirolimus inhibit mTOR which leads to blocking of the tumor cell cycle, survival, and angiogenesis (31). The indications for the mTOR inhibitors are provided in Table 1.

Everolimus is also an immunosuppressive agent which is administered at a dose of 1.5 mg in solid-organ transplant recipients. When it is used as an anticancer agent, it is used at a dose of 10 mg. Proteinuria (may be at nephrotic range), hypertension, hypophosphatemia, AIN, and glomerulopathy have been reported to be associated with these agents.

Mechanisms of nephrotoxicity (32, 33):
- Immune-mediated tubular damage, interstitial infiltration.
- Podocyte damage due to the inhibition of VEGF expression.

In case of grade 3 renal toxic effects with these agents (creatinine >3× above baseline, proteinuria ≥3.5 g/d), treatment should be discontinued, and re-initiation should be considered upon renal recovery. In patients with additional risk factors (like diabetes), a close follow-up of renal functions is indicated. If ACEIs or ARBs are being used in the treatment of proteinuria in patients on temsirolimus, they should be followed up for angioneurotic edema carefully. No dose adjustments are required for mTOR inhibitors in patients with CKD (14).

ERBB-2 Inhibitors (HER-2)

Human epidermal growth factor-2 (HER-2) may be overexpressed in some forms of breast and gastric cancer cell membranes. With inhibition of this receptor, antibody-dependent cellular cytotoxic effects can be induced in tumor cells.

Agents blocking this pathway:
- Monoclonal antibodies that target the HER-2 receptor (trastuzumab, pertuzumab).
- Tyrosine kinase inhibitor (lapatinib).

· Monoclonal antibody linked to maytansinoid DM1 (trastuzumab, emtansine).

Trastuzumab alone has no known nephrotoxic effects; however, it can cause hypertension. Combination therapy with anastrozole and trastuzumab was associated with a higher incidence of hypertension as compared to treatment with anastrozole alone (34). On the other hand, pre-existing renal dysfunction (eGFR<78mL/min/1.73 m^2) has been shown to be a strong predictor of cardiotoxic effects (35). No published renal adverse events have been reported in patients treated with lapatinib and pertuzumab; however, a review of the analysis of FDA adverse events found renal adverse events up to 3.39% related to pertuzumab versus 5.8% related to lapatinib (28).

Mechanisms of nephrotoxicity remain unclear, although they are thought to be related to cardiotoxicity.

There is no dose adjustment for these drugs in patients with CKD. Caution is advised with regard to cardiotoxic effects when using these agents in patients who have stage 5 CKD or in those undergoing dialysis. There are a few case reports about trastuzumab and lapatinib in hemodialysis patients, and there were no toxic effects reported (36, 37).

Anaplastic Lymphoma Kinase Inhibitors

Anaplastic lymphoma kinase (ALK) activation results in inhibition of apoptosis and promotion of cell proliferation in tumor cells. Crizotinib is used for inhibiting the activity of the fusion protein of ALK and echinoderm microtubule-associated protein-like 4 (EML4) gene.

Drug-induced eGFR declines were reported with crizotinib. The mean reduction of eGFR was 23.9%, which was largely reversible. The cause of eGFR decline seems to be related to inhibition of creatinine secretion through a competitive mechanism (38). Renal cysts, usually complex and reversible, have been reported in 4% of patients treated with crizotinib. Progression of pre-existing renal cysts and local cystic invasion mimicking abscess formation were also detected (39). Hypophosphatemia, hyponatremia, and hypokalemia have also been reported (28).

No dosage adjustment is recommended for crizotinib in patients with CKD or for those receiving dialysis.

B-Raf Inhibitors and Mitogen-Activating Protein Kinase Inhibitors

Fibrosarcoma kinase B (B-raf) is a protein which is a member of the growth signal transduction protein kinase family of Raf. Mitogen-activating protein kinase (MEK) is a downstream signaling partner of this pathway. In patients with melanomas that contain the BRAF V-600 mutation, these agents change the disease course:

· B-Raf inhibitors (vemurafenib, dabrafenib).

· MEK inhibitor (trametinib in combination with dabrafenib).

Although during phase III trial of vemurafenib, there were no cases of AKI, but in a clinical setting, AIN, ATN, Fanconi syndrome, hyponatremia, proteinuria, and one case of granulomatous nephritis have been reported (40).

The mechanism of nephrotoxicity is unknown. Even though BRAF is normally expressed in the glomerulus, the reported adverse events were related to tubular cells (41).

Routine monitoring of renal functions, electrolytes, and eGFR is recommended. As there is some evidence of inhibition of the tubular secretion of creatinine with vemurafenib, clinicians should not rush to discontinue the treatment if it is effective (42).

No dose adjustment is necessary for mild-to-moderate renal impairment. However, in dialysis, dose reduction might be necessary because of the risk of arrhythmia (43).

Chimeric Antigen Receptors T-cell Therapy

Adoptive cellular therapy is a new treatment modality using genetically engineered T cells to redirect their cytotoxic effects toward tumor cells. T cells are generated to express chimeric antigen receptors (CAR) or T cell receptors in cell cultures. These CAR-T cells can selectively target cells expressing the tumor antigen (44).

CAR-T products that have been approved so far are CD-19-targeted tisagenlecleucel and axicabtagene ciloleucel.

CAR-T cell therapies have been largely used in acute lymphoblastic leukemia and non-Hodgkin's lymphoma. However, they are also being studied in glioblastoma multiforme, ovarian cancer, mesothelioma, and prostate cancer.

CAR-T cell therapies have their own toxicity profile that is distinct from those seen with traditional chemotherapies and other targeted therapies. The most common adverse events with CAR-T therapies are cytokine-release syndrome (CRS) and hemophagocytic lymphohistiocytosis (HLH).

CAR-T cell infusion can lead to cytokine release, and renal perfusion might be reduced by cytokine-mediated vasodilation, high fever, and low cardiac output. AKI may be prerenal and could be severe due to ATN (45).

CRS was reported in 40% of the patients who were treated with CAR-T therapies in different studies (46, 47). This syndrome is caused by high levels of circulating cytokines released from CAR-T cells or other immune cells activated by CAR-T cells, predominantly IL-6. Fever, hypotension, increased acute-phase reactant levels, and hypoxia may be seen associated with CRS. High fever that occurs on the 6^{th} or 7^{th} day after the therapy is

the initial finding seen with CRS. Multiorgan dysfunction is observed after the 14th day of the therapy (48). Increased fluid retention might occur as a part of this syndrome. Another contributing factor to renal damage is HLH caused by cytokines, such as IL-6 and IL-10. HLH is characterized by uncontrolled immune activation. Tumor lysis syndrome and electrolyte disorders have also been reported with CAR-T therapy (49).

These toxicities are manageable in most cases with supportive care. In serious cases, intensive care admission is necessary. In patients with HLH or CRS manifesting as hypotension and/or hypoxia, clinical findings are expected to improve after the antagonistic effect of IL-6 with tocilizumab (a human monoclonal antibody against IL-6 receptor). In refractory cases, methylprednisolone 1-2 mg/kg IV every 12 hours might help in CRS.

CONCLUSION

In oncology and hematology practices, renal toxic effects caused by the increasing use of targeted therapies are a growing concern for nephrologists. Some of the toxic events are ill-defined and hard to diagnose, and therefore, unnecessary treatment cessation or dose reductions may happen. Renal biopsy is an essential diagnostic tool for characterizing renal diseases. In patients with cancer and renal impairment, performing a renal biopsy is a challenging decision. However, it should be considered more frequently in patients treated with targeted therapies. On the other hand, before determining an oncological treatment as being responsible for an adverse renal event, other traditional possible causes should first be considered and excluded. Additionally, in most clinical trials, patients have normal renal functions which makes it difficult to interpret the effects of molecular targeted therapies in patients with CKD. Timely recognition of these toxicities and close collaboration of nephrology, oncology, and hematology departments can aid with the management of patients with cancer.

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