Review article

Current trends of anti-cancer molecular targeted therapies: a narrative review focusing on renal complications and their histological features

Running title: Renal injury of molecular targeted drug

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Abstract

Among the recent advancements in cancer treatment, the emergence of novel drugs targeting a specific molecule has considerably modulated the therapeutic strategies. Despite the efficacy, the associated renal complications distinct from conventional chemotherapeutic drugs have been reported. Targeted therapy drugs include monoclonal antibodies and small molecule agents. Bevacizumab is one of the monoclonal antibodies that targets vascular endothelial growth factor (VEGF) and blocks tumor angiogenesis. This anti-angiogenic effect causes endothelial injury, resulting in “thrombotic microangiopathy-like lesion” confined to the glomerulus. Segmental hyalinosis of the glomerular tuft is also observed. The small molecular agents, including tyrosine kinase inhibitors (TKIs), such as pazopanib, can cause endothelial injury and podocytopathy through blocking VEGF receptors and their downstream signaling. Minimal change nephrotic syndrome and focal segmental glomerulosclerosis are associated with TKIs-induced renal complications. Immune checkpoint inhibitors (ICIs), such as PD-1, CTLA-4 and PD-L1, are a novel form of immunotherapy against cancer, which modulates immune checkpoints. Owing to its unique function, ICIs cause inflammatory side effects referred to as immune-related adverse events (irAEs). irAEs in the kidney commonly include acute tubulointerstitial nephritis and tubulitis, occasionally accompanied by granuloma formation. The occurrence of vasculitis, thrombotic microangiopathy, and glomerulonephritis is also reported. Renal toxicity associated with other molecular drugs such as protease inhibitors and mammalian target of rapamycin inhibitors has also been documented. In this article, we review the clinico-histopathological aspects of renal complications associated with molecular targeted therapies, focusing on anti-VEGF agents and immune checkpoint inhibitors from the pathologists’ viewpoint.

Keywords
Onconephrology/ Targeted therapy / anti-VEGF / immune checkpoint inhibitors / histopathology
Introduction

Cancer treatment includes surgery, anti-cancer drugs, and radiotherapy. For advanced cancer patients, cytotoxic chemotherapy drugs, such as alkylating agents or antimetabolite, have been administered conventionally despite strong side effects, including cellular toxicity in cancer as well as non-cancer cells, being a major issue to be resolved. Based on our understanding of cancer genomics or pathogenesis progression, molecular targeted therapies have emerged recently as one of the most potential cancer treatments\(^1\). Molecular targeted therapy involves identifying and destroying cancer cells through blocking specific molecules involved in the tumor growth, such as receptor tyrosine kinase, or through activating the immune cells programmed to target cancer cells. Due to tumor specificity, molecular targeted therapy rarely exerts lethal side effects compared to traditional chemotherapy. However, distinct side effects affecting the systemic organs have been reported, some of which are yet to be unveiled owing to the limited number of cases. In this article, we review and discuss the clinico-histopathological aspects of renal complications associated with molecular targeted therapy, including anti-vascular endothelial growth factor (VEGF) drugs and immune check point inhibitors, to update our knowledge for regular clinical practice while treating cancer patients.

Drug-induced renal complications

Due to the function of excreting waste from the body, the kidney is highly susceptible to extrinsic insults. Renal complications can potentially be elicited by a variety of therapeutic agents, including antimicrobial agents, analgesics, immunosuppressive agents, and chemotherapeutic agents \(^2\). Clinically, drug-induced renal injury is classified into 4 types as follows: acute kidney injury (AKI), tubular dysfunction, glomerular disease, and nephrolithiasis \(^3\). From the histological viewpoint, AKI and glomerular injury are more likely associated with morphological changes. AKI is characterized by acute tubular necrosis and acute tubulointerstitial nephritis, and the glomerular lesions include podocytopathy and glomerulonephritis. Although both chemotherapy drugs and molecular targeted
agents both can cause nephrotoxicity, the pattern of injury is different 4. Chemotherapy drugs, such as cisplatin and ifosfamide, an alkylating agent, commonly affect tubules, leading to acute tubular necrosis or injury 5. Conversely, molecular targeted agents tend to cause glomerulopathy characterized by podocytopathy or thrombotic microangiopathy5,6,7 (Table 1). We will address the histological variations of renal injury associated with each type of molecular targeted drugs as follows.

Renal complications of molecular targeted drugs (Table 2)

Targeted therapy drugs include monoclonal antibodies and small molecular agents8. Monoclonal antibodies are proteins that bind to specific targets on cancer cells. They include various types of antibodies, such as rituximab (anti-CD20 antibody), nivolumab (anti-programmed cell death-1(PD-1) antibody), and bevacizumab (anti-vascular endothelial growth factor (VEGF) antibody). Small molecular agents include low molecular weight compounds that enter the cells to modify the cell signaling cascade. The currently employed small molecular agents are represented by tyrosine kinase inhibitors (TKIs), including anti-epidermal growth factor receptor (EGFR) (gefitinib), and anti-breakpoint cluter region-Abelson (BCR/ABL) (imatinib). Conversely, a recent analysis conducted using the Food and Drug Administration Adverse Event Reporting System found that small molecular protein kinase inhibitors, such as entrectinib, sirolimus, and cobimetinib, are strongly associated with the occurrence of AKI9. In the following sections, we will address the histopathological features of renal injury induced by anti-VEGF drugs and other types of TKIs. Nephrotoxicity induced by immune checkpoint inhibitors (ICIs) will also be discussed.

Anti-VEGF drugs and other types of tyrosine kinase inhibitors

1. Classification of anti-VEGF drugs

Anti-VEGF drugs include a monoclonal antibody, VEGF trap, and TKIs 10, 11 (Fig 1). Furthermore, monoclonal antibody drugs include anti-VEGF and anti-VEGFR2 antibodies. VEGF trap,
commercially recognized as aflibercept, is a recombinant fusion protein comprising the VEGFR1 and VEGFR2 extracellular domains and acts as a soluble decoy receptor of VEGF. \(^{12,13}\)

2. Endothelial injury associated with inhibition of VEGF and its receptors

VEGF and its receptor (VEGFR) are the principal drivers of angiogenesis and lymphangiogenesis, and they are also important for the maintenance of the vascular network. \(^{14}\) VEGF induces endothelial cell proliferation, migration, and promotes the permeability of vessel walls. \(^{15}\) In the kidney, the integrity of glomerular capillaries is preserved by VEGF through promoting transmembrane communication between podocytes and endothelium. \(^{16}\) VEGF, produced by podocytes, binds to VEGF receptors on endothelial cell to exert its effect while VEGF elicits an autocrine effect on podocytes. Anti-VEGF drugs can impair the function of glomerular capillary walls through blocking the communication between endothelial cells and podocytes via VEGF. \(^{17}\) Proteinuria and hypertension are the two major adverse effects associated with anti-VEGF drugs. \(^{18}\)

While patients with acute thrombotic microangiopathy (TMA) usually presented with thrombocytopenia and fragmented erythrocytes, the typical bevacizumab-induced lesions are a renal limited disease, histologically characterized by duplication of glomerular basement membrane, microaneurysm, and rare thrombi formation (Fig 2 A, B). \(^{19}\) Once the endothelium is damaged, the subendothelial spaces are filled with proteineous fluid, causing microaneurysms. Over time, plasma insudations solidify to form segmental hyalinosis that can be described as “pseudo-thrombi” (Fig 2 C, D). Because of these unique findings, the term “glomerular microangiopathy” was proposed for the bevacizumab-induced lesions. \(^{19,20}\) It remains uncertain why anti-VEGF drugs induce renal-limited TMA, not systemic acute TMA. We postulate that it may be due to the unique nature of glomerular endothelial cells distinct from other vessels. The integrity of glomerular endothelial cells is maintained by communication between endothelial cells and podocytes over GBM. Once this integrity is destroyed, glomerular endothelial cells suddenly become vulnerable, resulting in renal-limited TMA. These are our speculation, and this issue needs to be further resolved.
microscopical observation revealed that this microaneurysmal space is filled with materials with different intensity. By contrast, the segmental hyalinosis exhibits the structure consisting of homogeneous osmiophilic material \(^\text{19}\). In mass spectrometry, C4b-binding protein alpha chain is the major protein occupying a bevacizumab-induced microaneurysm, whereas fibrin is a major constituent in other types of TMA-like lesions such as transplant glomerulopathy\(^{20}\).

A recent study reported that intravitreal injection of bevacizumab triggers TMA-like lesions in glomeruli, causing proteinuria\(^{21,22,23}\). From these findings, clinicians should be aware that even the local use of bevacizumab, such as via intravitreal injection, can lead to a systemic side effect, although the possibility is supposedly negligible.

Ramucirumab is a monoclonal antibody against VEGF receptor 2, which causes renal limited TMA-like lesions \(^{24,25}\). We had patients developing nephrotic syndrome soon after switching from bevacizumab to ramucirumab \(^{24}\). Renal biopsy showed the presence of chronic phase of TMA-like lesions, represented by duplicated glomerular basement membrane (GBM) and segmental hyalinosis. It appeared to us that the chronicity of the renal injury is not correlated with the rapid onset of nephrotic syndrome after the use of ramucirumab; however, it is speculated that the use of bevacizumab might have already predisposed the glomeruli to develop nephrotic syndrome, which was triggered by the use of ramucirumab\(^{25}\). In addition to these chronic changes, the infiltration of foamy macrophages was noted in some of the glomerular capillaries. We thus postulated that these changes are associated with hyperlipidemia as all patients exhibited a high cholesterol level. Similar finding has also been reported in a setting of bevacizumab-induced glomerular microangiopathy, although the underlying etiology is under debate\(^{19}\).

3. Podocytopathy in anti-VEGF drugs

Podocytopathy, characterized by minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS), is another manifestation of renal complications in anti-VEGF drugs (Fig 3A). In particular, TKIs can preferentially cause podocytopathy by blocking several receptors,
including VEGFR and its downstream signaling, resulting in suppression of endothelial proliferation and maintenance \(^\text{15}\). This process is hypothetically mediated by two intra-cellular proteins, c-mip and RelA, which regulate cell integrity based on the observation that there is a decrease and an increase in the expression of RelA and c-mip, respectively, in the podocytes of patients treated with TKIs \(^\text{13,26,27,28}\). This finding was further confirmed through an in vitro study demonstrating that RelA blocking can induce an overexpression of c-mip, leading to podocyte injury\(^\text{28,29}\). In addition to podocytopathy, TMA-like lesions are also reported in patients treated with TKIs \(^\text{30,31}\) (Fig 3B). In these patients, both podocytopathy and TMA-like lesions occurred at the same time. These diverse histological changes are attributed to the co-occurrence of podocytopathy, possibly via mechanism involving c-mip and RelA, and endothelial cell injury by TKIs. We observed similar histological changes in the nephrectomy specimen resected after neoadjuvant therapy using TKIs for renal cell carcinoma. Although the degree of proteinuria was not prominent in these patients, the rapid onset right after the use of TKIs suggested that the glomerular injury might have been induced upon the drug administration (our unpublished data). This finding suggests that we should carefully monitor renal function during anti-VEGF drug therapy regardless of the clinical conditions.

4. Renal injury in other types of tyrosine kinase inhibitors

Renal complications are reported in other types of tyrosine kinase inhibitors \(^\text{9,32}\). An EGFR tyrosine kinase inhibitor, gefitinib, which is originally used for non-small cell carcinoma of the lung, has been suggested to rarely cause renal disease. Recent reports, however, suggest that gefitinib can trigger diverse renal disease, MCNS, tubulointerstitial nephritis, membranous nephropathy, and IgA nephropathy, although the underlying mechanisms are yet to be clarified\(^\text{33,34,35}\). Conversely, an anti-EGFR antibody, such as cetuximab, has been associated with hypomagnesaemia due to inhibition of EGFR-mediated Mg\(^{2+}\) re-absorption from urine in renal tubules\(^\text{36}\). Recently, renal toxicity due to Bruton’s tyrosine kinase (BTK) inhibitor, ibrutinib, has been documented\(^\text{37,38}\). BTK plays an important role in the regulation of immune-system, including B-cell
development, and production of inflammatory mediators and cytokines. Therefore, ibrutinib has been used to treat patients with chronic lymphocytic leukemia or mantle cell lymphoma. A recent study reported several cases of acute tubular injury or tubulointerstitial nephritis with elevated serum creatinine levels induced on ibrutinib administration. Although the mechanisms of these lesions remained unclear, an association with endothelial injury is suspected.

**Immune checkpoint inhibitors (ICIs)**

A novel treatment strategy against cancer using ICIs is a form of immunotherapy. This therapy involves the modulation of immune checkpoints that are key regulators of the cancer immunity.

1. **Cancer immune cycle**

Fig 4 depicts a cancer immune cycle. The currently approved ICIs target the immune checkpoint molecules, such as PD-1, cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and PD-L1. In cancer immune cycle, a CD8+ T cell plays a major role of recognizing and destroying cancer cells. However, some cancer cells can evade this host immune system through taking advantage of peripheral tolerance mediated via CTLA-4- or PD-1-dependent pathways. In lymph nodes, antigens from degraded cancer cells are processed and presented to naïve CD8+ T cells by antigen presenting cells (APCs) (priming phase). Subsequently, the activated CD8+ T cells are recruited as cytotoxic T cells to the cancer microenvironment to destroy the target cells (effector phase). To escape from the immunological attack, cancer cells mute T cells by limiting the binding of the ligand PD-L1, expressed on the cancer cell, to its receptor PD-1 on the T cells.

2. **Characteristics and associated complications of ICIs**

Anti-PD-1/PD-L1 antibody can disrupt the inhibitory effect of the immune checkpoint molecule and recover the cytotoxic effect of T cells. Anti-CTLA-4 antibody can also stimulate the cytotoxic T cells
by blocking the association between T cells and APCs via CTLA-4. Ipilimumab, an anti-CTLA-4 antibody, was the first administrated ICIs in the world, followed by anti-PD-1 antibodies, including nivolumab and pembrolizumab.

ICIs are different from other types of anti-cancer drugs in many ways, and more specifically, they cause inflammatory side effects referred to as immune-related adverse events (irAEs). irAEs might occur due to the overactivation of the immune system, affecting multiple organs such as skin, gastrointestinal tract, and endocrine organs, among others. The common irAEs includes hypophysitis, colitis, hepatitis, pneumonitis, and skin rash. Some patients develop irAEs resembling to those of autoimmune disease such as arthritis, myositis and polymyalgia-like syndromes. Anti-CTLA-4 drugs are more likely to be associated with the occurrence of irAEs than with anti-PD-1. It is considered that the inhibition of CTLA-4 leads to diffused and non-specific T-cell activation during the priming phase, while blocking of PD-1/PD-L1 activates effector T cells that are already engaged in cancer immunity. For the kidney, irAEs were believed to be less common. However, the incidence of renal toxicity by irAEs increased from 2% to 16.5% for the last 4 years. Combination therapy using anti-PD-1 and anti-CTLA-4 antibodies might be attributed for inducing more renal irAEs than monotherapy affecting both priming and effector phases involving dysregulation of Treg.

Another unique hallmark of ICIs-related renal disease is the duration between the exposure to the drug and the onset of renal irAEs, ranging from a few weeks to 2 years. The most common clinical feature of renal irAEs is AKI. Upon nivolumab and pembrolizumab administration, AKI appears much later than in case of anti-CTLA-4 antibody after the drug initiation. For example, pembrolizumab-associated renal disease occurs at a median time of 9 months, whereas AKI in anti-CTLA-4 antibody manifests within 3 months. However, the onset of ICIs-related symptom is unpredictable as there is one reported case of malignant melanoma treated with nivolumab, who developed systemic vasculitis within 1 week after the first drug infusion.
The diverse duration time between the drug exposure and the onset of AKI suggests a distinct mechanism for renal irAEs, and currently two theories are proposed\textsuperscript{5,56}. One suggests the development of autoimmunity to renal self-antigens due to blockage of the CTLA-4 or PD-1 pathway. Immune checkpoint molecules are involved in the regulation of the peripheral tolerance, which can be impaired by ICIs, leading to the overactivation of T cells. The other theory suggests the loss of tolerance to drug-specific effector T cells\textsuperscript{53}. Interestingly, a significant proportion of patients with AKI due to the administration of ICIs used nephrotoxic agents, such as proton pump inhibitor (PPIs) and non-steroid anti-inflammatory drugs, long before the initiation of ICIs. Inhibition of immune checkpoint signaling by ICIs can re-activate the T cells that have been primed during the previous exposure to these nephritogenic drugs.

3. Histological findings of renal injury by ICIs

Since the invention of ICIs, the incidence of drug-related renal diseases has increasingly been reported worldwide, illustrating various types of kidney injury. Common clinical features of renal irAEs include elevated serum creatinine levels with mild proteinuria, occasionally accompanied by sterile pyuria and microhematuria\textsuperscript{52}. In these conditions, the renal dysfunction is mostly due to acute tubulointerstitial nephritis (ATIN) alone or in combination with other kidney lesions such as glomerular disease\textsuperscript{53}. The histopathological features of ATIN induced by ICIs include massive infiltration of inflammatory cells, such as lymphocytes, a few eosinophils and neutrophils into the tubulointerstitium (Fig 5A, B). Although the T cells are predominant among the infiltrates, CD4/CD8 ratios are reported varyingly\textsuperscript{55,58,59,60}. Granuloma is observed sometimes\textsuperscript{49,59} (Fig 5C). These observations collectively indicate that the histological feature of renal irAEs cannot be readily distinguished from conventional acute ATIN. A recent article by Cassol et al demonstrated focal staining of PD-L1 along the cell membranes of tubular epithelial cells within the areas of interstitial inflammation in anti-PD-1 antibody-treated patients, suggesting that PD-L1 staining might be
useful in differentiating renal irAEs from other types of ATIN\textsuperscript{61}. More future studies are needed to confirm their findings.

Other histological features of renal irAEs include acute tubular injury\textsuperscript{60}, vasculitis\textsuperscript{64}, thrombotic microangiopathy\textsuperscript{50}, immune complex glomerulonephritis\textsuperscript{62}, and podocytopathy\textsuperscript{63}. Mamlouk et al. described 16 patients of ICIs-related nephrotoxicity, of which 14 exhibited some kinds of glomerular lesions, such as pauci-immune glomerulonephritis and C3 glomerulonephritis\textsuperscript{55}. Izzedine et al. reported 12 cases of pembrolizumab-related renal toxicity\textsuperscript{51} wherein AKI was the most common clinical manifestation, followed by nephrotic syndrome. The histological characteristics involved ATIN, Acute tubular necrosis(ATN), and Minimal change disease(MCD) \textsuperscript{51}. Distal tubular acidosis after the use of anti-PD-1 drugs for several months has been reported\textsuperscript{64}. Renal biopsy revealed interstitial edematofibrosis and mild lymphocytic infiltration around distal tubules and collecting ducts (Fig 5D). IrAEs associated with anti-PD-L1 antibody has been reported in a small number of cases showing ATIN, as also seen in cases with anti-PD-1\textsuperscript{65}.

**Renal impairment with other molecular targeted agents.**

Besides anti-VEGF drugs and ICIs, some molecular targeted agents have been shown to exert nephrotoxic effects. Protease inhibitors (PIs), bortezomib and carfilzomib, have been used for the treatment of hematologic disorders such as multiple myeloma and mantle cell lymphoma but can sometimes trigger TMA\textsuperscript{66,67}. Yui et al reported PIs-related renal TMA in 11 patients with clinical features of thrombocytopenia and microangiopathic hemolytic anemia\textsuperscript{68}. In two of these patients, renal biopsy confirmed histological changes suggestive of TMA. Moore and Romeril postulated that autoantibodies against ADAMTS13, produced during the inflammatory process, might have triggered renal TMA in PIs-treated patients\textsuperscript{69}. As impairment of ADAMTS13 was not found in all PIs-related TMA, the presence of other mechanisms has been suggested\textsuperscript{68}.

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase involved in many intracellular pathways responsible for cellular proliferation, and tumor growth in some cancer types.
mTOR inhibitors, everolimus and temsirolimus, were shown to decrease cancer cell growth by suppressing mTOR activity\(^70\). Renal impairment including proteinuria and AKI can sometimes occur in patients treated with mTOR inhibitors although the incidence rate is low\(^71,72\). Histologically, renal dysfunction in mTOR inhibitors manifests as acute tubular necrosis, and FSGS is reported in some patients\(^72\). The underlying mechanism remains unclear, but the disruption of the VEGF pathway is strongly suggested\(^73\).

**Conclusion**

In this article, we reviewed renal side effects associated with recent anti-cancer drugs, including molecular targeted agents and ICIs with an emphasis on histopathological aspects. As a new drug is invented one after another, their side effects are newly reported. Some of the drugs are administered as part of multi-drug therapy by combining conventional anti-cancer drugs and molecular targeted agents, complexifying clinical manifestations of side effects. Renal biopsy is one of the most reliable methods to evaluate the renal damage and help elucidate the etiology. To correctly grasp a patient’s condition and provide an optimal treatment, not only the clinicians but also the pathologists must understand pathogenesis of nephrotoxicity in each anti-cancer agent, and a close communication between pathologists and clinicians including oncologists and nephrologists is requisite.

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**Conflicts of Interests**

The authors declare that there are no conflicts of interests.
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Vascular endothelial growth factor (VEGF) is released by podocytes and binds to VEGF receptors of endothelial cells, thus leading to the initiation of signal transduction pathways. Anti-VEGF drugs comprises anti-VEGF antibody, VEGF trap, anti-VEGFR2 antibody, and tyrosine kinase inhibitors. Anti-VEGF and anti-VEGFR2 antibodies block VEGF function at the extracellular sites. VEGF trap is a recombinant fusion protein composed of the VEGFR1 and VEGFR2 extracellular domains and acts as a soluble decoy receptor of VEGF. Tyrosine kinase inhibitors are small molecules that enter endothelial cells to inhibit downstream signals.
Figure 2. Characteristic findings of anti-VEGF drug-induced thrombotic microangiopathy (TMA)

A-C. Bevacizumab-induced renal lesions (A-C. PAM stain). Within glomerular capillaries, the dilatation of subendothelial spaces is noted (A. arrows). Over time, the subendothelial spaces are becoming wider (B. arrows), developing microaneurysms (C. arrows). Insudative materials within the dilated subendothelial space around narrowed capillary lumina (C. arrowheads) solidify to form segmental hyalinosis.

D. Schematic diagram of anti-VEGF drug-induced TMA in glomeruli. Endothelial injury causes dilation of the subendothelial space whereas original capillary lumen collapses, subsequently developing a microaneurysm filled with proteineous fluid. Over time, the plasma insudations solidified, forming segmental hyalinosis. Although these lesions are unique, it is sometimes difficult
to distinguish between widened subendothelial spaces and the dilated capillary lumina, when endothelial cells are severely damaged and are accompanied by insudative change.
Figure 3. Glomerular findings associated with pazopanib (tyrosine kinase inhibitor)(A,B).

Focal segmental glomerular sclerosis with hypertrophy of overlying epithelial cells (A. PAM stain).

Segmental hyalinosis (arrow) within the glomerular capillaries, referred to as “TMA-like lesion” (B. PAS stain).
Cancer antigens released by the degenerated cancer cells are trapped and processed by antigen presenting cells and are presented on the surface of naïve CD8 T cells (priming phase). Then naïve T cells become activated T cells, and infiltrate into cancer microenvironment to recognize and destroy cancer cells (effector phase). Some type of cancer can survive through escaping from this immunity cycle via CTLA4 and/or PD-1/PD-L1-dependent mechanisms. CTLA4 and PD-1 / PD-L1 have the function of suppressing T cells in the signal transduction of APCs or cancer cells and T cells, respectively. Anti-CTLA-4 / PD-1 / PD-L1 antibodies activate T cells by blocking their inhibitory signals and contribute to attacking cancer cells.
Figure 5. Histological findings of immune checkpoint inhibitor-related renal disease (A–D. PAS stain).

Acute tubulointerstitial nephritis due to anti-PD-1 antibody (A, B. Pembrolizumab). The presence of extra-tubular deposition of cast (A. arrow) suggests a significant tubular injury. Some tubules are infiltrated by inflammatory cells, showing the features of tubulitis (B). Acute tubulointerstitial nephritis forming granuloma (C) due to combination therapy of anti-CTLA-4 antibody (ipilimumab) and anti-PD-L1 antibody (durvalumab). Anti-PD-1 therapy (nivolumab) can induce distal tubular acidosis, characterized by focal lymphocytic infiltration around distal tubules and collecting ducts (D. asterisks).
| Tubules | Glomeruli |
|---------|-----------|
| ATIN | ATI | Podocytopathy | TMA-like lesion | Immune complex-mediated glomerulonephritis | Others |
| Cisplatin | +++ | | | | Fanconi syndrome |
| Ifosfamide | +++ | | | | Fanconi syndrome |
| Gemcitabine | + | | | +++ | |
| Bevacizumab (anti-VEGF antibody) | | | +++ | | |
| Ramucirumab (anti-VEGFR2 antibody) | | | +++ | | |
| Tyrosine kinase inhibitors | + | ++ | ++ | | |
| Immune check point inhibitor | +++ | + | + | + | |
| EGFR inhibitors | + | + | + | | |
| mTOR inhibitors | +++ | + | + | | cast |
| Proteosome inhibitors | | | | + | |

Table 1. Common histological variations of drug-induced renal injury.

Abbreviations: ATIN, Acute tubulo-interstitial nephritis; ATI, Acute tubular injury; TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; EGFR, epidermal growth factor receptor; mTOR, mechanistic target of rapamycin.
| Target | Name of the drugs |
|--------|-------------------|
| CD20   | Rituximab         |
| VEGF   | Bevacizumab       |
| VEGFR2 | Ramucirumab       |
| PD-1   | Nivolumab, Pembrolizumab |
| PD-L1  | Durvalumab, Atezolizumab, Avelumab |
| CTLA-4 | Ipilimumab        |
| VEGF   | Pazopanib         |
| EGFR   | Gefitinib         |
| BCR/ABL| Imatinib          |
| ROS1/TRK| Entrectinib      |
| Bruton's TK | Ibrutinib |
| protease inhibitor | Bortezomib, Carfilzomib |
| mTOR inhibitor | Everolimus, Sirolimus, Temsirolimus |
| VEGF trap | Aflibercept |
| MEK inhibitor | Cobimetinib |

Table 2. Targeted agents described in this review

Abbreviations: VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; BCR/ABL, breakpoint cluter region·Abelson; ROS1/TRK, ROS proto-oncogene 1/tropomyosin receptor kinase; Bruton’s TK, Bruton’s tyrosine kinase; mTOR, Mammalian target of rapamycin.