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Nephrotoxicity in Cancer Treatment: An Update

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Abstract

It has been estimated that nearly 80% of anticancer drug-treated patients receive potentially nephrotoxic drugs, while the kidneys play a central role in the excretion of anticancer drugs. Nephrotoxicity has long been a serious complication that hampers the effectiveness of cancer treatment and continues to influence both mortality and length of hospitalization among cancer patients exposed to either conventional cytotoxic agents or targeted therapies. Kidney injury arising from anticancer drugs tends to be associated with preexisting comorbidities, advanced cancer stage, and the use of concomitant non-chemotherapeutic nephrotoxic drugs. Despite the prevalence and impact of kidney injury on therapeutic outcomes, the field is sorely lacking in an understanding of the mechanisms driving cancer drug-induced renal pathophysiology, resulting in quite limited and largely ineffective management of anticancer drug-induced nephrotoxicity. Consequently, there is a clear imperative for understanding the basis for nephrotoxic manifestations of anticancer agents for the successful management of kidney injury by these drugs. This article provides an overview of current preclinical research on the nephrotoxicity of cancer treatments and highlights prospective approaches to mitigate cancer therapy-related renal toxicity.

Keywords

Chemotherapy; targeted cancer therapy; kidney toxicity; risk factor; immune checkpoint; non-coding RNAs; sphingolipids

Introduction

The kidneys represent one of the major sites for the elimination of anticancer drugs. Approximately 80 percent of cancer patients are administered anticancer drugs that potentially have nephrotoxic effects (Launay-Vacher et al., 2007). The nephrotoxicity of anticancer drugs remains a serious complication of cancer therapy, leading to delayed treatment, the lengthening of hospital stays, as well as increased mortality rates for cancer patients (A. Kitchlu et al., 2019; Lameire, Flombaum, Moreau, & Ronco, 2005). Therefore, anticancer drug-induced renal toxicity is increasingly regarded as a principal factor that limits the efficacy of cancer treatments.

Nephrotoxicity is defined as the loss of the kidneys' ability to filtrate, detoxify and/or excrete harmful metabolites due to anticancer drugs-induced injuries to renal structure and/or function. Drug-induced renal toxicity can affect different cell types in the kidneys including glomerular, tubular, interstitial or vascular cells. Both conventional chemotherapy and targeted agents can cause a diversity of renal complications such as proteinuria, electrolyte imbalance, glomerulopathy, hypertension, interstitial nephritis, and tubulointerstitial damage. Consequently, in many cases, anticancer drugs require dose modification or discontinuation in the setting of renal impairment (Naughton, 2008).

It is also of critical importance to identify risk factors and associated pathogenic mechanisms for nonchemotherapeutic nephrotoxic therapies that could potentially contribute to the deterioration of renal function in cancer patients. In addition to radiation therapy-induced kidney injury (Klaus, Niyazi, & Lange-Sperandio, 2021), concomitant use of analgesics, bisphosphonates, or other chronic disease mediations are common factors leading to renal dysfunction, which need to be taken into consideration (Abhijat Kitchlu et al., 2018; Lameire et al., 2005). Moreover, cancer patients with underlying compromised renal function are prone to develop acute kidney injury (AKI) and subsequent long-term chronic kidney disease (CKD) during anticancer therapy (A. Kitchlu et al., 2019). Unfortunately, the biochemical, physiological and molecular mechanisms underlying anticancer drug-induced renal toxicities remain poorly understood. As nephrological management for most anticancer drugs largely depend on dosage adjustment, discontinuation of treatment and/or symptom management (Chiruvella, Annamaraju, & Guddati, 2020), a comprehensive understanding of nephrotoxic mechanisms of anticancer drugs is necessary to more effectively mitigate nephrotoxicity in cancer patients. This chapter presents an overview of fundamental risk factors associated with nephrotoxicity in cancer patients, findings during the last decade related to some novel molecular pathways putatively involved in the nephrotoxicity as well as efforts to minimize cancer therapeutics-induced nephrotoxicity.

2. Risk factors for renal toxicities in cancer therapy

2.1 General risk factors for nephrotoxicity of anticancer drugs and treatment

A variety of risk factors can exacerbate the course of renal dysfunction and are likely to enhance the nephrotoxicity of cancer therapeutic agents. Renal toxicities can be initiated by the antitumor drugs themselves, elevated doses or prolonged treatment, formation of toxic crystals within intratubular lumens or concomitant use of other nephrotoxic drugs (including aminoglycosides, nonsteroidal anti-inflammatory drugs, radiographic ionic contrast media or other anticancer drugs). In addition, gene variants in hepatic and renal cytochrome P450 (CYP) enzymes or renal transporters that result in decreased metabolism or reduced drug excretion can increase intracellular anticancer drug concentrations, thereby elevating nephrotoxic risk (Miteva-Marcheva, Ivanov, Dimitrov, & Stoyanova, 2020). Fluid deficits are also one of the most common factors that potentiate nephrotoxic effects due to vomiting or diarrhea caused by antineoplastic drugs (Hassan Izzedine & Mark A. Perazella, 2017; Mark A. Perazella, 2009; Perazella, 2012; Perazella & Moeckel, 2010). A spectrum of risk factors for renal toxicity in cancer therapeutics are listed in Table 1.

2.2 Patient-specific factors

Several patient-specific risk factors contribute to increased risk of anticancer agent-induced nephrotoxicity, including underlying disease, advanced age and (female) gender. Those factors can be associated with decreased estimated glomerular filtration rates (eGFR), reduced body water or lower serum albumin levels, resulting in increases in drug concentration. However, there is still no consensus as to sex difference in acute kidney injury (AKI) (Schiffl, 2020). Additionally, preexisting AKI and chronic kidney disease (CKD) may raise the risk for nephrotoxicity. For instance, AKI resulting from intravascular volume depletion results in increased drug exposure to renal cells. Nephrotic syndrome with hypoalbuminemia can lead to decreased drug binding and increased active unbound drug concentrations (Perazella, 2018). Patients with advanced hepatic failure are especially at high risk for drug-induced nephrotoxicity, given that advanced hepatic failure exhibits hypoalbuminemia, intravascular volume depletion, and underlying AKI or CKD (Yeung, Yong, & Wong, 2004). In addition to these factors, comorbidities in cancer patients such as multiple myeloma, lymphoma, leukemia, renal cancer, diabetes, sepsis and acid-base disturbances can also enhance the risk for nephrotoxicity (H. Izzedine & M. A. Perazella, 2017).

2.3 Kidney-specific factors

The kidney and its segments are vulnerable to drugs-induced nephrotoxicity owing to the high renal blood flow rate (25% of cardiac output). The nephrotoxic potential of drugs is highly related to the renal microenvironment. High concentration of drugs or drug metabolites can present in the glomerular ultrafiltrate. Furthermore, the renal cortex is likely to be exposed to high concentrations of toxic metabolites as this portion of the kidney receives approximately 80% of total renal blood flow; consequently, many anticancer drugs can accumulate in proximal tubular cells through both apical uptake and basolateral transport (Drozdzik, Drozdzik, & Oswald, 2021; Enomoto & Endou, 2005; Hucke & Ciarimboli, 2016). In addition to the proximal tubules, epithelial membranes of distal and collecting tubules express several carriers and transporters that facilitate bidirectional movement of substrate molecules. In contrast to the cortex region, the loop of Henle and medullary collecting duct cells in the renal medulla require high metabolic rates for energy-consuming active transport of many solutes; these excess cellular workloads generate hypoxic environments, thereby increasing susceptibility to the nephrotoxicity of anticancer drug therapies (Hassan Izzedine & Mark A. Perazella, 2017; Perazella, 2010).

Renal biotransformation of drugs also plays a critical role in drug-related nephrotoxicity. Renal biotransformation involves several enzyme systems, where the generation of oxidative stress and the formation of injurious reactive oxygen species are likely to damage the kidney. For instance, Glutathione S-transferases (GSTs) are well-known to catalyze the conjugation of glutathione (GSH) to xenobiotics electrophilic compounds, a central step in drug detoxication and biotransformation (Townsend & Tew, 2003). On the other hand, this mechanism could also produce strong mutagens or carcinogens due to GST polymorphisms.

GST-α is primarily expressed in the convoluted proximal tubule with some existing in the thin loops of Henle (Bauchet, Masson, Guffroy, & Slaoui, 2011). GST-π is

mainly localized in podocytes, parietal cells of the Bowman's capsule, distal convoluted tubules and collecting ducts, with significantly lower levels in proximal tubules (Harrison, Kharbanda, Cunningham, McLellan, & Hayes, 1989). Glutathione (GSH) has been found to protect against cisplatin-induced renal and systemic toxicity without affecting its antitumor activity (Y.-Y. Xu, Jiang, Liu, Qu, & Wang, 2012; Zunino et al., 1989); however, biotransformation of trichloroethylene (TCE) conjugated GSH can result in nephrotoxic metabolites such as S-(1,2-dichlorovinyl)-L-cysteine (DCVC) through γ-glutamyltransferase and subsequent β-elimination reaction as well as the metabolite trichloroethylene-cysteine S-conjugate sulfoxide (DCVCS , a highly reactive Michael acceptor) via flavin-containing monooxygenase 3. N-acetylcysteine (NAC, or acetylcysteine) is a widely available nutritional supplement and a medication that can rescue the GSH depletion. NAC has been extensively studied for its antioxidant effects against both cancers and kidney injuries (Kwon, 2021; Mlejnek, Dolezel, Kriegova, & Pastvova, 2021; D. Y. Zhang et al., 2021). NAC has been shown to prevent radiocontrast, cisplatin- and radiation-induced nephrotoxicity in preclinical studies (Güntürk et al., 2019; S. Huang et al., 2019; Mercantepe et al., 2019; Richter & Crannage, 2015). Moreover, a relatively recent study demonstrated the development of tumor-selective GSH-dependent Michael acceptor prodrugs of 6-Mercaptopurine (6-MP) and 6-thioguanine (6-TG) which can have antitumor effects with reduced toxicity in mice (X. Y. Zhang & Elfarra, 2018).

P450 isoenzymes and UDP-glucuronosyltransferase (UGT) also play significant roles in drug biotransformation and detoxification in the kidneys. Of note, some of these enzymes are particularly expressed in the kidneys and specific renal segments (Bauchet et al., 2011; Knights, Rowland, & Miners, 2013). Consequently, alternations in transporter activity such as loss of function mutations and/or competition for carrier proteins/enzymes can hinder parent drug/metabolite excretion and induce nephrotoxicity. Alternation in the activity of these enzymes can be attributed to various factors, such as age, ethnicity, disease states and genetic polymorphisms.

2.3.1 Genetic polymorphisms, sex and other kidney-related factors in renal enzymes—The activity of metabolizing enzymes in the renal tubules can differ between individuals and sexes (Bozina, Bradamante, & Lovrić, 2009). Genetic polymorphisms may affect enzyme expression. Multiple single nucleotide polymorphisms (SNPs) for the organic cation transporter (OCT) genes (SLC22A1, SLC22A2 and SLC22A3) are found to alter their transport functions, where a gain-in-function mutation results in drug accumulation in renal proximal tubule cells (K. M. Huang et al., 2020; Yee et al., 2018; Zazuli et al., 2020). However, Fujita et al showed that a polymorphism in renal ATP-binding cassette transporters (ABC transporters) or renal solute carrier (SLC) transporter did not directly affect cisplatin-induced nephrotoxicity in patients with esophageal cancer (Fujita K, 2016). A study of AKI outcome based on serum creatinine (SCr) showed associations between genetic variants of ERCC1, ERCC2, SLC22A2 and cisplatin-induced nephrotoxicity in adult testicular cancer, suggesting that genetic variations are involved in the inter-individual susceptibility to cisplatin-induced nephrotoxicity (Trendowski et al., 2019).

Interestingly, the expression levels of transporters in renal proximal tubules also differ across species and sexes. A recent study showed that the sex differences in protein abundance

of 12 transporters were only significant in rodents and dogs but not in humans (Basit, Radi, Vaidya, Karasu, & Prasad, 2019), indicating that cross-species and sex-dependent protein abundance data should be taken into consideration when evaluating interspecies scaling in drug clearance and assessing kidney toxicity for new therapeutic candidates under development.

2.4 Drug-specific factors

Nephrotoxicity can be augmented and prolonged with repeated drug dosing. Hartmann et al showed that patients who received 2 cycles of a single 50-mg/m^2 dose of cisplatin had a 24% decrease in GFR after the second cycle (Hartmann, Kollmannsberger, Kanz, & Bokemeyer, 1999). Patients with higher doses and prolonged durations of treatment with aminoglycosides or amphotericin showed increase nephrotoxicity (M. A. Perazella, 2009). In addition, the cumulative dose, rate of administration, and increased frequency of anticancer drug administration are associated with an increased risk for nephrotoxicity (Caglar et al., 2002; Kobayashi et al., 2016).

Combinations of nephrotoxic drugs with anticancer drugs also contribute to enhanced nephrotoxicity. Many drugs, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), immunosuppressants such as cyclosporins, tacrolimus and nonsteroidal anti-inflammatory drugs (NSAIDs), can influence intraglomerular hemodynamics and decrease glomerular filtration rates (Ghane Shahrbaf & Assadi, 2015; Patel JB, 2021; Perazella, 2005). Furthermore, drugs such as aminoglycosides, amphotericin B, adefovir, foscarnet and cisplatin can potentiate tubular cell toxicity via the formation of free radicals, mitochondrial dysfunction, and transport systems damage (Perazella, 2018). Importantly, the use of drugs that cause drug-related acute interstitial nephritis (AIN) should not be ignored; these include the antituberculosis drug, rifampin, antibiotics, proton pump inhibitors (PPI), NSAIDs and many types of anticancer drugs (Martínez-Valenzuela et al., 2021; Mérida & Praga, 2019; Moledina & Perazella, 2016; Nagata, Ohji, & Iwata, 2019; Perazella & Markowitz, 2010). In addition, chronic interstitial nephritis can arise from medications, including analgesics, lithium, anticancer drugs, and calcineurin inhibitors (Patel JB, 2021). Of note, despite the high frequency of NSAIDs-induced AIN, the occurrence of nephrotic syndrome does not appear to be similarly increased (González et al., 2008). This suggests that patients exposed to NSAIDs-related AIN rarely reach the nephrotic range; instead, they are prone to present increased proteinuria rather than other types of drug-induced AIN (Markowitz & Perazella, 2005). Therefore, monitoring of renal injury and function is crucial for patients receiving combinations of anticancer drugs and other nephrotoxic drugs.

Drugs or metabolites that are insoluble in the urine may cause acute crystalline nephropathy upon precipitation in distal tubular lumens and collecting ducts. This process can occur with or without an interstitial reaction and can result from the reduction of urinary flow rates, change of urine pH/drug pKa, excessive doses and rapid drug infusion rates (Markowitz & Perazella, 2005; Perazella, 2018). Agents such as the antiviral, acyclovir, and the antibiotic, ampicillin, have demonstrated common etiologies of insoluble crystal formation within renal tissue (Chávez-Iñiguez et al., 2018; Garnier et al., 2020; Yarlagadda & Perazella, 2008).

Certain drugs that interfere with renal transporters may also enhance the nephrotoxicity of anticancer agents. For instance, cimetidine, trimethoprim, pyrimethamine and salicylates block tubular secretion of creatinine with or without affecting their glomerular filtration (Andreev, Koopman, & Arisz, 1999). In addition, a variety of drugs can act as substrates competing for a renal transporter and further increase drug deposition in kidneys (Drozdzik et al., 2021; S. Zhou, Zeng, & Shu, 2021). Moreover, Hong et al. demonstrated that repeated contrast-enhanced computed tomography (CECT) within 72 h can predispose cancer patients to contrast-induced nephropathy (CIN) (Hong et al., 2016). Therefore, concomitant use of radiocontrast and NSAIDs should be avoided with nephrotoxic anticancer drugs (Ozkok & Ozkok, 2017; Mark A. Perazella, 2009). The involvement of novel anticancer drugs in AIN and other kidney injuries has been discussed in previous review articles (Hassan Izzedine & Mark A. Perazella, 2017; Martínez-Valenzuela et al., 2021). Renal manifestations associated with commonly used anticancer drugs and recent novel cancer therapies are listed in table 2.

3. Nephrotoxicity of chemotherapeutic agents and management

As basic information describing anticancer drug-induced nephrotoxicity has been extensively reviewed and summarized elsewhere in the literature, this review will focus on the most recent findings related to the kidney damage and promising management for the nephrotoxicity of anticancer drugs. A summary of current and potential strategies for the management of cancer therapeutics-induced nephrotoxicity is provided in Table 3.

3.1 Platinum agents

Cisplatin has been used as an effective platinum-containing chemotherapeutic drug for several decades in a wide range of cancers (Brown, Kumar, & Tchounwou, 2019). Cisplatin elicits its antitumor effects through binding to DNA, generation of DNA cross links and damage, a blockade to cell division and, in many cases, the promotion of apoptosis (Tchounwou, Dasari, Noubissi, Ray, & Kumar, 2021). Nephrotoxicity has been recognized as the most critical side effect that limits the clinical use of cisplatin (Sandhya Manohar & Leung, 2018). Current measures to reduce cisplatin-induced nephrotoxicity are limited to hydration and magnesium preloading (McKibbin et al., 2016; Workeneh, Uppal, Jhaveri, & Rondon-Berrios, 2021; Yoshida et al., 2014). Unfortunately, the effectiveness of these approaches is modest, at best. The pathways that contribute to cisplatin-induced kidney damage are complex and include apoptosis, necrosis, necroptosis, oxidative stress, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, autophagy, inflammatory responses, and cell cycle dysregulation (Duan, Cai, Li, & Chen, 2020; Sharp & Siskind, 2017; Y. Xu et al., 2015; J. Zhang, Ye, Tew, & Townsend, 2021). In the course of the last decade, numerous studies have explored potential therapeutic strategies involving inhibition of drug uptake transporters such as organic cation transporter 2 (OCT2) and copper transporter 1 (CTR1), and reducing the inflammation response (McSweeney et al., 2021).

Nonetheless, clinical applications by targeting the above mechanistic pathways in cisplatin-induced kidney toxicity are challenging as many of these molecular pathways are at the

same time crucially involved in the cytotoxic activity of cisplatin against tumor cells; consequently, alterations in their functions could possibly interfere with cisplatin-induced anti-tumor effects (Volarevic et al., 2019). Notable efforts have also been made in the potential application of over-the counter (OTC) drugs and prescription drugs against cisplatin-induced nephrotoxicity. The most recent findings on the potential applications of clinically used drugs in cisplatin-induced nephrotoxicity are discussed below.

3.1.1 Prospective use of diabetes drugs—A retrospective study revealed that the dipeptidyl peptidase-4 (DPP-4) inhibitors reduced cisplatin-induced AKI in cancer patients with diabetes mellitus by suppressing inflammation and promoting tubular regeneration. (Takamasa Iwakura et al., 2020; T. Iwakura et al., 2019). Another DPP-4 inhibitor, gemigliptin, was shown to protect against cisplatin-induced nephrotoxicity through the inhibition of apoptosis and inflammatory responses by increasing heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1) expression (Choi, Leem, & Lee, 2017). The outcome of a clinical trial evaluating the effect of gemigliptin on cisplatin-induced nephrotoxicity is not yet known (ClinicalTrials.gov Identifier: NCT02250872). Cisplatin-induced nephrotoxicity was also found to be prevented by the thiazolidinedione-type diabetes drugs, pioglitazone, via inhibition of the p53-mediated mitochondrial apoptotic pathway via SIRT1 activation (J. Zhang et al., 2020). These findings suggest the potential benefits of these drugs in cancer patient with diabetes, and possibly, non-diabetic cancer patients. However, more clinical data are needed for their use as a renoprotective strategy against cisplatin-induced nephrotoxicity.

3.1.2 Prospective use of antihypertensive agents—Several types of antihypertensive agents appear to represent potential strategies for mitigation of cisplatin nephrotoxicity. One study demonstrated protective effects of enalaprilat, an angiotensin-converting enzyme inhibitor (ACEi), for cisplatin-induced renal toxicity in mice not only by reducing the formation of angiotensin II, but also by reversing cisplatin-induced upregulation of the kinin B1 receptor and decreased aminopeptidase P activity, thereby preventing tubular cell apoptosis and inflammation. (Estrela et al., 2020). In contrast, a recent single-center observational study revealed that patients exposed to target or above target dosage of ACEi or angiotensin II receptor blockers (ARBs) had a higher risk of AKI in emergency medical admissions (Feidakis et al., 2021). Hence, dosage adjustment of ACEi for cisplatin-treated patients should not be overlooked for future potential application in cisplatin-induced nephrotoxicity.

Amlodipine, a calcium channel blocker (CCB), was shown to inhibit the gamma-glutamyl transpeptidase (GGT) enzyme, which metabolizes platinum-glutathione (Pt-GSH)-conjugates to a reactive toxic thiol that causes tubular cell death. Amlodipine can also interfere with the GGT-associated inflammatory pathway (Azouz, Abdel-Nassir Abdel-Razek, & Abo-Youssef, 2020). Although the β-adrenoceptor blockers carvedilol and high-dose propranolol exhibited renoprotection against cisplatin renal dysfunction, they failed to improve cisplatin-induced electrolyte imbalance (Esmaeeli, Keshavarz, Dehdar, Assadi, & Seyedabadi, 2020). As a result, we should carefully interpret the effects of β-adrenoceptor

blockers on electrolyte levels in cisplatin-treated patients. Overall, these findings indicate potential uses of these antihypertensive agents in cisplatin-induced nephrotoxicity.

3.1.3 Prospective use of other clinically available drugs—Some other types of clinically available drugs are also found to mitigate cisplatin nephrotoxicity. A thrombin inhibitor, dabigatran (Pradaxa), may offer beneficial effects against cisplatin-mediated nephrotoxicity through inhibiting the thrombin-associated apoptotic and oxidative effects (Ewees et al., 2021). In addition, proton pump inhibitors (PPIs), omeprazole and pantoprazole, were demonstrated to provide protection against cisplatin-induced kidney injury in both *in vivo* animal studies and randomized controlled clinical trial (ClinicalTrials.gov Identifier: NCT04217512) (Gao et al., 2020; Ghonaim, El-Haggar, & Gohar, 2021; Ismail, El-Awady, & Hassan, 2020). The underlying mechanism for the renoprotection of PPIs could be by suppressing the release and production of inflammatory cytokines stimulated by cisplatin. On the other hand, data from the US FDA adverse event reporting system showed a high correlation between PPIs use and the AKI and CKD events. Hence, monitoring of renal function and dosage modification of PPIs would be necessary in patients receiving cisplatin treatment. Finally, aprepitant is an antiemetic drug provided for cisplatin-treated patients. Interestingly, a novel role for aprepitant was revealed as an effective option for cisplatin-induced nephrotoxicity through anti-oxidative and anti-inflammatory effects (Un et al., 2020).

3.1.4 Prospective targets and other compounds—Several novel mechanisms underlying protective effects against cisplatin-induced renal injury were discovered recently. Pregnane X receptor (PXR), a master transcription factor of xenobiotic detoxification, was shown to play a protective role in cisplatin-AKI mediated by activating the PI3K/AKT pathway (Luan et al., 2021). The hydrogen sulfide metabolite, sodium thiosulfate (STS), was identified as a promising candidate molecule that could protect against renal toxicity following hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin; this protection was possibly mediated by the binding of STS to free platinum (Laplace et al., 2020; M. Y. Zhang, Dugbartey, Juriasingani, & Sener, 2021). In addition, supplementation with the probiotics *Lactobacillus reuteri* and *Clostridium butyricum* was demonstrated to alleviate cisplatin nephrotoxicity by restoring gut microbiome dysbiosis, thus further reducing uremic toxin production in rats (Hsiao et al., 2021). Other compounds, such as the epoxyeicosatrienoic acid analog (EET-F01) by kidney-targeted delivery, and Pevonedistat, a NEDD8-activating enzyme inhibitor, were recently found to downregulate the expression of inflammatory mediators to relieve cisplatin-induced nephrotoxicity (El-Far & El-Mesery, 2021; Imig et al., 2021).Tempol is a nitroxide that has an antioxidant property and is shown to reverse cisplatin AKI in mice through decreasing kidney injury markers and restoration of aquaporins (AQP2) (Afjal et al., 2020). Currently, Tempol is undergoing clinical trial in head and neck cancer patients with cisplatin and radiation treatment (ClinicalTrials.gov Identifier: NCT03480971).

Overall, the exploration of new targets and mechanism of mitigation by clinically available medications should provide a pathway for the discovery of novel and readily translatable treatments for kidney protection in cancer therapy. Also, targeting the prospective

signaling pathways, such as those discussed above, the transcription factor of xenobiotic detoxification, microbiome, supplementation of sodium thiosulfate and kidney-targeted drug delivery, are promising strategies to attenuate kidney injury caused by cisplatin.

3.2 Alkylating agents

Ifosfamide and cyclophosphamide are two of the most widely used alkylating chemotherapeutic drugs that are also currently undergoing clinical trials in combination treatment with different novel cancer therapies (Fox et al., 2021; S. Zhou et al., 2021; Zsiros et al., 2021). This class of drugs is quite frequently associated with kidney dysfunction (Bhat, Kalthur, Padmashali, & Monappa, 2018; Ensergueix et al., 2020). Either the prodrug forms, their metabolites or intermediates may mediate nephrotoxic effects to renal tubular cells (Dobrek, Nalik-Iwaniak, Fic, & Arent, 2020). A retrospective study revealed that in patients who received ifosfamide treatment, kidney biopsies showed tubular necrosis, vacuolation and nuclear atypias in renal epithelial cells, as well as interstitial inflammation and renal fibrosis (Ensergueix et al., 2020). Management of ifosfamide-induced nephrotoxicity has generally been limited to supportive care. However, a growing body of reports have identified several new targets mediating alkylating agents-induced kidney injury through e.g. increased oxidative stress, mitochondrial dysfunction, apoptosis or activation of the arginine vasopressin V2 receptor that leads to anticancer drug-induced nephrogenic syndrome of inappropriate antidiuresis (NSIAD) (S. Kim, Jo, & Kim, 2021).

A recent study found that the antioxidant, Carnosine, alleviated ifosfamide-induced oxidative stress as well as mitochondrial impairment, and consequently attenuated renal injury and electrolyte imbalance (Ommati et al., 2020). Similarly, *Annona* species ethanolic extracts reduced the renal toxicity of ifosfamide by suppressing oxidative stress, inflammation and apoptosis in a rat kidney model (Abd-Elrazek, Shapana, Shukry, & Galilah, 2021). Mesna is the clinically approved drug to prevent ifosfamide- and cyclophosphamide-induced hemorrhagic cystitis; however, its preventive action towards tubular toxicity of ifosfamide and cyclophosphamide remains undetermined (Reddy V, 2021). In the rat model of cyclophosphamide- and ifosfamide-induced cystitis, the antioxidant, acetylcysteine, which acts as a donor of -SH groups similar to the action of mesna, was reported to produce both uro- and nephron-protective effect against cyclophosphamide and ifosfamide treatment (Dobrek et al., 2020). Alogliptin, a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), is an FDA-approved drug for type 2 diabetes. Interestingly, Alogliptin was recently shown to produce beneficial effects in cyclophosphamide-induced nephrotoxicity as indicated by inhibiting the MAP3K/JNK/SMAD3 signaling cascade, which can initiate oxidative stress and production of inflammatory and fibrotic mediators (Salama, Nasr, Abdelhakeem, Roshdy, & ElGamal, 2020). The dual beneficial effects of Alogliptin could be a novel therapeutic approach for cancer patients with diabetes.

A pentadecapeptide derived from Cyclina sinensis was shown to mitigate cyclophosphamide-induced kidney injury by activating the antioxidative enzymes superoxide dismutase, glutathione peroxidase and catalase (Jiang et al., 2020). A more recent study reported that cyclophosphamide-induced inflammation and oxidative stress

could be ameliorated by pretreatment with gallic acid, a nature phenolic compound, in mice (Baharmi et al., 2021). Cyclophosphamide is known to be one of the major causes of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in cancer patients (M. I. Khan, Waguespack, & Ahmed, 2019; Abhijat Kitchlu & Rosner, 2019). Tolvaptan, a selective vasopressin V2 receptor antagonist, is used for the treatment of hyponatremia in patients with heart failure or SIADH in cancer patients. The protective effect of tolvaptan against cyclophosphamide-induced nephrotoxicity was recently demonstrated through the attenuation of apoptosis markers in rat models (El-Shabrawy et al., 2020). While this growing body of evidence does identify new potential strategies for mitigation of alkylating agents-induce nephrotoxicity, it should be noted that those findings need to be confirmed in clinical trials.

3.3 Antitumor antibiotics

Patients receiving antitumor antibiotics such as mitomycin C, actinomycin and doxorubicin can develop nephrotoxicity (Groff, Kozak, Boehmer, Demko, & Diamond, 1997; Y. B. Sun et al., 2013). While mitomycin C was described to be involved in end-stage renal disease, a retrospective report showed that the combination of cisplatin and mitomycin C in laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) did not, in fact, increase the incidence of AKI in gastric cancer (Kapoor et al., 2019).

Doxorubicin (adriamycin) has been reported to cause AKI and nephrotic syndrome (Carron, Padilla, & Maurizi Balzan, 2014; Yemm, Alwan, Malik, & Salazar, 2019). More recent studies identified several new compounds/agents to protect against doxorubicin-induced nephropathy, such as omega-3 fatty acids, flavonoids, Acacia hydaspica tannin-rich ethyl acetate fraction and naringenin, through mechanisms of reducing oxidative stress, inflammation, apoptosis as well as renal podocyte detachment (Afsar, Razak, Almajwal, & Al-Disi, 2020; T. H. Khan et al., 2020; Navarro-Hortal et al., 2020; Saleh et al., 2020). A novel compound, YH0618, was reported to reduce renal toxicity of adriamycin through a FOXO4-mediated Bcl-2 Bax/Bcl-2 mechanism (You et al., 2019). Curcumin demonstrated improvement of doxorubicin-induced toxicity in renal podocytes through the activation of Nrf2, inhibition of NF-κB activity, and the upregulation of podocin (Fan et al., 2020). Loss of podocytes is one of the mechanisms involved in adriamycin-induced glomerulosclerosis; however, the mechanistic pathway is unclear. Deficiency of angiopoietin-like-3 (ANGPTL3) was found to protect against adriamycin-induced glomerulosclerosis and podocyte loss in mice (Dai et al., 2019). Though inhibition of ANGPTL3 seems a promising approach against adriamycin nephrotoxicity, it might block the beneficial effect of ANGPTL3 in renal cell carcinoma metastasis (Y.-j. Zhang, Zhang, Feng, & Cao, 2021; Zhao et al., 2019). Therefore, the prospective treatment using the ANGPTL3 inhibitor, evinacumab, which is currently tested in patients with homozygous familial hypercholesterolemia (Raal et al., 2020), in adriamycin-induced nephropathy should be carefully evaluated in patients with renal cell carcinoma metastases (Wilson et al., 2021).

3.4 Antimetabolites cancer drugs

Antimetabolites including methotrexate, 5-fluorouracil, clofarabine, and gemcitabine have been shown to cause renal insufficiency and tubular injury. Methotrexate (MTX) is a

classical antifolate, which interferes with folate metabolism. MTX is used to treat a broad range of cancers such as acute lymphoblastic leukemia, head and neck cancer, and breast cancer, among others (Koźmiński, Halik, Chesori, & Gniazdowska, 2020). In addition to plasma MTX concentration monitoring, hydration, and alkalinization to prevent/ameliorate the MTX-induced nephrotoxicity (Howard, McCormick, Pui, Buddington, & Harvey, 2016), recent consensus guidelines and case reports have suggested that glucarpidase (Carboxypeptidase G2) can provide nonrenal elimination of MTX and should be used with folic acid rescue to attenuate MTX-induced nephrotoxicity (Misra, Santagostino, Dine, & Bonhomme Faivre, 2019; Ramsey et al., 2018; Young et al., 2019).

A number of studies have identified natural compounds and other potential approaches to mitigate nephrotoxicity of MTX. Natural compounds such as Rosmarinic Acid and Apigenin that exhibit antioxidant and anti-inflammatory properties have been reported to attenuate MTX nephrotoxicity in rodent models (Jafaripour et al., 2021; Sahindokuyucu-Kocasari, Akyol, Ozmen, Erdemli-Kose, & Garli, 2021). Another natural product, Dioscin, can relieve MTX-induced kidney damage via inhibiting miRNA-145–5p-mediated oxidative stress (Y. Li et al., 2021). A MTX metabolite, 7-OH MTX, has been considered as a primary toxic metabolite responsible for nephrotoxicity due to its lower water solubility than MTX (Holmboe, Andersen, Mørkrid, Slørdal, & Hall, 2012). A study found that Nobiletin, a flavonoid isolated from *Citrus aurantium* L, could reduce 7-OH MTX nephrotoxicity via endoplasmic reticulum stress-dependent PERK/CHOP signaling and protect tubular cell survival (Song et al., 2021). A compound modified from Paeoniflorin, paeoniflorin-6′-O-benzene sulfonate (CP-25), showed protection against MTX-renal toxicity by preventing tubular cells apoptosis and facilitating MTX excretion through recovering OAT3 expression (Wei et al., 2021).

Rebamipide is a gastroprotective drug for the treatment of gastric ulcers and gastritis. It was found that Rebamipide could potentially mitigate nephrotoxicity of MTX through activation of NRF-2/SIRT-1/FOXO-3 and mTOR/PI3K/AKT signaling while inhibiting NF-κB-p65/TLR-4 (Elmansy, Seleem, Mahmoud, Hassanein, & Ali, 2021). Moreover, using HA-230 adsorber in hemadsorption procedure was found to be a new therapeutic approach to reduce MTX toxicity in pediatric patients with acute lymphocytic leukemia who had delayed MTX clearance after high-dose MTX treatment (Sazonov et al., 2021).

5-fluorouracil (5-FU), another antimetabolite cancer drug, has multiple mechanisms of action through inhibition of DNA synthesis and misincorporation into DNA. Although patients with renal impairment do not require dose adjustment of 5-FU (Lexicomp, 2022), there is increasing *in vivo* and *in vitro* evidence that 5-FU can cause renal dysfunction as indicated by the promotion of apoptosis, induction of oxidative stress, and tubular injury. Recent studies have demonstrated potential approaches to mitigate 5-FU nephrotoxicity. Inhibition of miR-181a has been found to attenuate 5-FU-induced mesangial cell apoptosis, inflammation and kidney injury (X.-Y. Liu et al., 2018). Camel milk is shown to have renoprotection against 5-FU, which could be mediated by suppressing MAPKs, NF-kappaB and PI3K/Akt/eNOS (Arab, Salama, & Maghrabi, 2018). In addition, hesperidin and curcumin play beneficial roles in 5-FU-induced nephrotoxicity by inhibiting oxidative stress, lipid peroxidation, apoptosis, and renal dysfunction (Gelen et al., 2021). Herein, we have

summarized some recently discovered targets and pathways, such as nonrenal metabolizing enzyme, transporter, the utilization of HA-230 adsorber and natural compounds, which could be used as potential therapeutic strategies in MTX and 5-FU nephrotoxicity in the future.

3.5 Epidermal growth factor receptor pathway inhibitors (EGFR inhibitors)

EGFR inhibitors have been used in the treatment of various malignancies including colon, head, neck, and non-small cell lung cancers. Monoclonal antibodies such as cetuximab and panitumumab are EGFR inhibitors associated with tubular toxicity, glomerulopathies and electrolyte disorders. (H. Izzedine, Boostandoost, & Mathian, 2017; Jhaveri, Wanchoo, Sakhiya, Ross, & Fishbane, 2017). Panitumumab-induced immune complex glomerulonephritis could be mitigated by drug discontinuation and glucocorticoids treatment (H. Izzedine et al., 2017). Hypomagnesaemia of EGFR inhibitors is the most common side effect that could lead to renal toxicity (Jhaveri et al., 2017). Therefore, electrolyte disturbances should be carefully monitored and managed with subsequent fluid and sodium restriction, diuretics treatment, and magnesium supplementation or discontinuation of EGFR inhibitors.

3.6 Vascular endothelial growth factor pathway inhibitors (VEGF inhibitors)

The vascular endothelial growth factor (VEGF) plays an essential role in angiogenesis, which provides oxygen and nutrients to support tumor growth and metastasis. The VEGF inhibitors bevacizumab, sorafenib and sunitinib are clinically used for metastatic colon cancer, rectal cancer, non-small cell lung cancer, and breast cancer, among others (Qin et al., 2019). Common renal toxicities of VEGF inhibitors include proteinuria, glomerular disease and thrombotic microangiopathy (TMA) (Hanna et al., 2019; Shye et al., 2020). Currently, there are no molecule-specific targeted therapies for VEGF inhibitor-induced renal adverse effects, except for supportive care, dose reduction, medication discontinuation or treatment with ACEi or ARBs for proteinuria. It should be noted that ACEi and ARBs also contribute to an increased risk of AKI under certain conditions. Hence, it would be appropriate to monitor renal function and individualize treatment in patients with VEGF inhibitor if using ACEi or ARBs for renal side effects (Porta et al., 2020).

Results from a rat experimental model demonstrated that the phosphodiesterase type 5 (PDE5) inhibitor, sildenafil, reduced sunitinib-induced proteinuria (S. Lankhorst et al., 2014). Unfortunately, the clinical application of sildenafil in sunitinib-induced nephrotoxicity has not yet been verified. A better understanding of the underlying mechanism(s) of VEGF inhibitor-induced nephrotoxicity could lead to the development of a selective compound or adjuvant drug to minimize the off-target effects of VEGF inhibitors. The side effects of VEGF inhibitors are partially attributed to the off-target effect from VEGF inhibitors-induced circulating endothelin-1 levels (Stephanie Lankhorst et al., 2015). A recent study showed that sunitinib-induced albuminuria can be improved by a selective endothelin (ET_A) receptor antagonist (sitaxentan) but not $ET_{A/B}$ receptor antagonist (macitentan) in rats. Sitaxentan and ambrisentan are FDA-approved selective ET_A receptor antagonists for pulmonary hypertension treatment. Despite the withdrawal of Sitaxentan, ambrisentan seems a promising therapeutic approach against VEGF inhibitor-

induced nephrotoxicity. Moreover, it is possible that targeting downstream of the ET-1 signaling pathway could also provide the renoprotection against VEGF inhibitors (Mirabito Colafella et al., 2020). Therefore, it is clear that additional research is needed to develop new strategies for mitigation of VEGF inhibitor-induced nephrotoxicity.

3.7 Immune checkpoint inhibitors

Immune checkpoint inhibitors (CPIs) directly target inhibitory receptors on immune and tumor cells, allowing for the activation of T cells and antitumor action. These receptors include programmed cell death 1 ligand (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). CPIs can reactivate the immune cells to attack the cancer cells (Robert, 2020; Weber, 2010). Immune checkpoint inhibitors such as CTLA-4 antagonists (ipilimumab) and PD-L1 antagonists (nivolumab and pembrolizumab) are approved by the FDA for treatment of renal cell cancer, non-small lung cancer, and melanoma (Wanchoo, Karam, et al., 2017). Extensive evidence has shown that CPIs are often associated with the incidence of AKI and acute interstitial nephritis (AIN) (Belliere et al., 2016; Cortazar et al., 2020; Gupta et al., 2021; Oleas et al., 2020; Patel et al., 2020). Current management for CPIs-induced AIN involves treatment with glucocorticoids (GCs) or discontinuation of the medications (S. Manohar et al., 2019; Oleas et al., 2020; Qu et al., 2021). A recent multicenter study recommends that patient can return to CPIs treatment after renal injury has been relieved (Cortazar et al., 2020; Koks et al., 2021); nonetheless, fewer than 50% of patients receiving GCs can fully recover from kidney injury. A retrospective study reported that infliximab, an TNF-α (tumor necrosis factor) blocker, would be another treatment option for relapsed CPI-AIN in patients who do not respond to or tolerate the side effects of GCs (J. S. Lin et al., 2021). However, a larger sample size and standardization in the timing of the infliximab treatment in CPI-AIN are required for future clinical studies.

A study suggested that the checkpoint inhibition was not a major mechanism for efficacy of anti-CTLA-4 antibodies. The investigators identified a weak checkpoint blockade by the anti-CTLA-4 antibody, GIGA-564, which had reduced kidney damage compared with the CTLA-4 antagonist, ipilimumab, in murine models without affecting antitumor effects. This finding suggests a novel strategy for optimizing anti-CTLA-4 drugs based on regulatory T cells instead of checkpoint inhibition (Stone et al., 2021). Considering the very limited strategies available for mitigation of CPIs-induced kidney adverse effects, further research should emphasize the structure or affinity-guided design of antagonist/inhibitors for immune cells or tumor cells.

3.8 Proteasome inhibitors

Carfilzomib is a proteasome inhibitor used to treat patients with relapsed and refractory myeloma. Carfilzomib-induced renal manifestations include thrombotic microangiopathy (TMA), proteinuria and AKI (Fotiou, Roussou, Gakiopoulou, Psimenou, & Gavriatopoulou, 2020). The pathophysiology behind carfilzomib-induced nephrotoxicity is associated with tumor lysis syndrome, endothelial injury, and podocyte injury (Fotiou et al., 2020). Current management for acute renal function impairment is achieved by hydration and drug discontinuation (Bringhen et al., 2019). A case report showed that acetylcysteine could prevent carfilzomib-induced vasoconstriction-related renal injury (Wanchoo, Khan, Kolitz,

& Jhaveri, 2015). Rutin, a bioflavonoid, ameliorates carfilzomib-induced oxidative stress and inflammation in nephrotoxicity through the inhibition of the iNOS-mediated NF-κB signaling pathway (Al-Harbi et al., 2019).

Another proteasome inhibitor, Bortezomib, is effective in multiple myeloma and mantle cell lymphoma. Common renal side effects of bortezomib include TMA and acute interstitial nephritis (AIN) (Chiruvella et al., 2020). A case reported showed that the bortezomib renal impairment was improved after glucocorticoid therapy and discontinuation, but AKI reoccurred following reinitiating bortezomib (Cheungpasitporn et al., 2015). Therefore, the utilization of glucocorticoid therapy for bortezomib-induced AIN remains undetermined.

3.9 mTOR protein kinase inhibitors

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase, which regulates many biological processes, including cell survival, proliferation, autophagy, and metabolism (Hua et al., 2019). Inhibitors of mTOR, sirolimus and everolimus, are used for the treatment of breast cancer, renal cell carcinoma and pancreatic neuroendocrine tumors (Roskoski, 2019). It has been shown that both everolimus and sirolimus induce proteinuria and AKI. Although the chances of mTOR inhibitors leading to life-threatening AKI is minimal, they may cause development of CKD and other long-term complications (Chandra, Rao, Malhotra, Rastogi, & Khurana, 2017; Paluri et al., 2019; Wanchoo, Abudayyeh, et al., 2017). Novel therapeutics and strategies are not currently available. Current strategies to mitigate mTOR inhibitors-induced nephrotoxicity depend primarily on monitoring of renal injury and proteinuria, early use of ACEi and ARBs and drug discontinuation.

3.10 Biologic agents

Biologic agents such as interleukin-2 (IL-2) and interferon alpha (IFN-α) have utility in cancer therapy. High-dose interleukin-2 (IL-2) is effective in metastatic renal cancer, and metastatic melanoma (Marabondo & Kaufman, 2017; Perazella & Shirali, 2018). However, high-dose IL-2 causes severe hypotension and cytokine-mediated inflammation, leading to AKI (Guleria et al., 1994; Marabondo & Kaufman, 2017). Current managements for IL-2 nephrotoxicity are primarily reliant on urine output monitoring and fluid management, which can improve mild oliguria or increased serum creatinine caused by IL-2 (Marabondo & Kaufman, 2017). Low and intermediate-dose of vasopressors such as dopamine can also be used in the treatment of hypotension and oliguria (Perazella & Shirali, 2018). However, advanced therapeutic approaches are limited.

A novel mechanism underlying IL-2-induced vascular leak syndrome is associated with increased circulating angiopoietin-2 levels. Endothelial damage is one of the major causes of AKI. A study revealed that diabetes mellitus can increase angiopoietin-2. Angiopoietin-2 is the competitive antagonist for angiopoietin-1 and a partial agonist/antagonist of the receptor tyrosine kinase TIE2 in endothelial cells (Yuan, Khankin, Karumanchi, & Parikh, 2009). Increased circulating angiopoietin-2 leads to vascular wall destabilization and promotes neovascularization (Fiedler & Augustin, 2006). Vascular endothelial protein tyrosine phosphatase (VE-PTP) is involved in balancing TIE2 signaling to stabilize the vasculature. Inhibition of VE-PTP by AKB-9778 can reset TIE2 signaling and therefore

decrease serum angiopoietin-2 level and rescue vascular stability (G. Li, Sachdev, Peters, Liang, & Lotze, 2019). In addition, targeting VE-PTP phosphatase was demonstrated to protect against diabetic kidney injury (Carota et al., 2019).

Therefore, VE-PTP inhibitor AKB-9778 could be a promising candidate to attenuate IL-2-induced vascular leak and endothelial dysfunction which could lead to AKI.

3.11 BRAF inhibitors

BRAF is a member of rapidly accelerated fibrosarcoma kinase family proteins, and also a proto-oncogene. BRAF inhibitors (dabrafenib and vemurafenib) are approved for the treatment of BRAF V600E mutation-positive melanoma (Holderfield, Deuker, McCormick, & McMahon, 2014). BRAF inhibitors can cause tubular interstitial nephritis, acute tubular necrosis, increases of serum creatinine, proteinuria, and electrolyte disorders, including hypophosphatemia, hyponatremia and hypokalemia (Wanchoo, Jhaveri, Deray, & Launay-Vacher, 2016). Overall, compared with vemurafenib, dabrafenib is associated with a lower incidence of kidney disease (Wanchoo et al., 2016). A vemurafenib-induced increase in serum creatinine is usually immediate and reversible (Hurabielle et al., 2016). Routine monitoring of electrolytes and serum creatinine are recommended during treatment with BRAF inhibitors (Hurabielle et al., 2016). A recent study showed that combined therapy of MEK inhibitor, cobimetinib, and BRAF inhibitor, vemurafenib, in the treatment of BRAF V600-mutated metastatic melanoma exhibited a 60% reduction of AKI compared with BRAF inhibitor monotherapy (Teuma et al., 2017). Therefore, it is important to note that patients with different combined therapies of BRAF and MEK inhibitors could result in different responses in renal disorders (Meirson, Asher, Bomze, & Markel, 2020). In this regard, future investigations should also highlight the optimal timing of drug switching and the best combination therapy to reduce renal toxicities.

3.12 Anaplastic lymphoma kinase inhibitor

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase, which regulate diverse cellular process, including cellular proliferation, survival, and proliferation. Mutation of ALK is associated with the development of neuroblastoma, diffuse large B-cell lymphoma, anaplastic large-cell lymphoma, myofibroblastic tumor, esophageal and squamous cell carcinoma, as well as other malignancies (Webb et al., 2009). Crizotinib is an ALK inhibitor for the treatment of non-small cell lung cancer with the ALK mutation. To this point in time, only a few cases of crizotinib-associated nephrotoxicity have been described. Electrolyte disorder and renal cyst are common adverse events in crizotinib treatment, which can be reversed after crizotinib discontinuation (H. Izzedine, El-Fekih, & Perazella, 2016; Y. T. Lin et al., 2014). Crizotinib was reported to increase serum creatinine and reduce the eGFR, which could be recovered after cessation of therapy (Brosnan et al., 2014; Camidge, Brosnan, DeSilva, Koo, & Chonchol, 2014; Martín Martorell, Huerta Alvaro, Solís Salguero, & Insa Molla, 2014). Recently, kidney biopsy data on cirzotinib-induced renal injury showed that cirzotinib induced acute tubular necrosis and glomerular mesangiolysis after drug rechallenge (Gastaud et al., 2013). Another case study described arteriolar myocyte vacuolization following crizotinib treatment (Hassan Izzedine, Brocheriou, Amoura, & Mathian, 2021). However, the mechanism of crizotinib-induced kidney damage remains

unknown. In a rodent study, it was demonstrated that long-term crizotinib treatment could induce fibrosis and renal dysfunction via activating the TNF-α/NF-κB signaling pathway (Yasuma et al., 2018). It is also speculated that the crizotinib-induced kidney damage can be mediated by the inhibition of the mesenchymal epithelial transition growth factor (c-Met) pathway (Hassan Izzedine et al., 2021). Due to limited data and unclear pathophysiological explanations for the kidney damage induced by crizotinib, careful monitoring of renal function and examination of kidney biopsies during crizotinib therapy are recommended.

4. Renoprotective effects of some novel anticancer therapeutics

Because emerging preclinical and clinical studies are devoted to developing and testing promising novel anticancer drugs, efforts should be made to prevent/reduce the potential nephrotoxicity. Developing and discovering an anticancer drug that exhibits dual action of anti-tumor and renoprotection would be very beneficial for cancer patients. Therefore, identifying the common targets and mechanisms shared by both carcinogenesis and nephrotoxicity could serve to develop a novel and effective drug that simultaneously provides anticancer as well as renoprotective activities. Herein, we discuss some strategies associated with novel anticancer therapies in mitigating renal toxicities in the context of the immune system, sphingolipid signaling, DNA repair, histone modifications, and non-coding RNAs.

4.1 The immune system

The innate immune system contributes to the destruction of tumor cells that present tumor antigens through various pattern recognition receptors (PRRs), including toll-like receptors (TLRs) and macrophage-inducible C-type lectin (Mincle). TLRs can regulate immune responses both positively and negatively (Bai et al., 2020). A specific TLR2 agonist designed by Feng et al can generate macrophages that have strong anti-tumor properties in mice (Feng et al., 2019). Furthermore, the combination of TLR9 agonists and immune checkpoint inhibitors can maximize TLR9-incduced T-cell activity and provoke the antitumor immune response (Buss & Bhatia, 2020; Chuang et al., 2020). TLRs have been recognized to play multifaceted roles in AKI (Habib, 2021). TLR-2 and TLR-9 were shown to protect against cisplatin-caused nephrotoxicity in mice (Alikhan et al., 2016; Andrade-Silva et al., 2018). However, recent studies showed that depletion of TLR9 reduced renal ischemia-reperfusion injury and that nanoparticle-mediated selective targeting of renal tubular TLR9 decreased renal tubular inflammation, apoptosis and necrosis after ischemia reperfusion (Han et al., 2020; Zheng et al., 2021). These apparent discrepancies could be due to disease/cells-dependent effects of TLR9. In addition to the anticancer effects, TLR agonists may at the same time exert renal protective effects. However, care should be taken in the interpretation of these preclinical data because either overaction of TLRs by agonist or deletion/blockade of TLRs can dysregulate tissue repair during different phases of AKI in human.

Mincle (Macrophage-inducible C-type lectin), a pattern recognition receptor, was recently demonstrated as a novel target for cancer treatment (C. Li et al., 2020). Furthermore, it was found to be associated with M1 macrophage activation during cisplatin-induced

AKI. Interestingly, adoptive transfer of Mincle-knockdown macrophages reduced the nephrotoxicity caused by cisplatin (Inoue, 2017). Additionally, the natural anti-inflammatory compound curcumin elicits inhibitory effect on the Mincle-maintained M1 macrophage phenotype, providing a promising therapeutic strategy for cisplatin-induced nephrotoxicity (Tan et al., 2019).

Cytokines released from innate immune cells are responsible for regulating the host innate immune response toward tumor cells and promoting their apoptosis. Cytokine therapy has drawn attention to treat cancers in recent years (Xue, Hsu, Fu, & Peng, 2021). Interestingly, an IL-2 and IL-33 hybrid cytokine, IL233, was shown to protect mice from cisplatin- and doxorubicin-induced nephrotoxic injury in mice (Sabapathy, Cheru, Corey, Mohammad, & Sharma, 2019; Stremska et al., 2017). Thus, modulation of the immune system could be a promising strategy for mitigation of nephrotoxicity in cancer treatment.

4.2 Sphingolipid signaling

Sphingolipids, including ceramide, sphingosine and sphingosine-1-phosphate (S1P) have been proposed to participate in important cellular functions, such as cell growth, cell senescence, differentiation, cellular inflammation and cell cycle regulation (Hannun & Obeid, 2018). It has been increasingly recognized that inflammatory mediators, growth factors, and cellular stress could disrupt the balance between ceramide-induced cell death and S1P-induced cell growth, which are responsible for the cell fate. Sphingosine kinases (SPHKs) represent two isoforms, SPHK1 and SPHK2, that catalyze the conversion of sphingosine to sphingosine-1-phosphate (S1P). SPHKs are shown to be involved in tumorigenesis in many types of cancers (Pitman, Oehler, & Pitson, 2021; Pyne & Pyne, 2020). Recently, SPHK1 and SPHK2 inhibitors have been under development to treat breast cancer, ovarian cancer and cholangiocarcinoma (Alshaker, Thrower, & Pchejetski, 2020; Ding et al., 2016; F. I. Khan, Lai, Anwer, Azim, & Khan, 2020). ABC294640, a specific SPHK2 inhibitor, enhanced the antitumor effects of TNF-related apoptosis-inducing ligand (TRAIL) by inducing apoptosis in non-small-cell lung cancer (Yang et al., 2015). Moreover, ABC294640 (Yeliva ®) is currently being tested in a phase IIa clinical trial with hydroxychloroquine sulfate in treatment of patients with advanced cholangiocarcinoma (ClinicalTrials.gov Identifier: NCT03377179). It has also been reported that the antitumor action of ABC294640 can be enhanced by sorafenib, a multiple tyrosine kinase inhibitor in human cholangiocarcinoma cells (Ding et al., 2016; Evangelisti et al., 2016).

Despite the role of sphingolipids in cancers, they are increasingly being viewed as bioactive factors in the regulation of renal physiology. It has been shown that the activation of the sphingosine kinase/S1P/S1P receptor (SphK/S1P/S1PR) pathway contributes to different kidney diseases (Lyu, Wang, Ji, Ritter, & Li, 2020; Yokota, Bhunu, Toba, & Intapad, 2021; Xiwen Zhang, Ritter, & Li, 2018; X. Zhang, Wang, Ji, Ritter, & Li, 2019). A more recent study demonstrated that oral administration of ABC294640 could attenuate cisplatin-induced nephrotoxicity in mice (Xie et al., 2020). Therefore, sphingolipid signaling is a novel potential target for anticancer agent-induced nephrotoxicity in combination with the antitumor effect.

4.3 DNA repair pathway

Many antitumor therapies, including antimetabolites (5-fluorouracil, Methotrexate), DNA cross linking and alkylating agents (cisplatin, temozolomide, ifosfamide), topoisomerase II inhibitors (etoposide, doxorubicin), and radiotherapy, target proliferating cells. Several inhibitors of DNA damage repair have been tested in clinical trials; these include poly (ADP-ribose) polymerase (PARP) inhibitors, ataxia-telangiectasia mutated (ATM) inhibitors, checkpoint kinases (CHK1/2) inhibitor and DNA methyltransferases (DNMT1) inhibitor (Chan, Tan, & Cornelissen, 2021; Isono, Okubo, Asano, & Sato, 2021; Smith, Southgate, Tweddle, & Curtin, 2020; Wong, 2020; Yap et al., 2021). Generally, these agents could impair DNA repair ability or cause excessive DNA damage resulting in cell death following DNA replication (R. Huang & Zhou, 2021). Herein, we discuss the current inhibitors targeting DNA damage repair and their role in kidney injury.

Poly (ADP-ribose) polymerase (PARP), PARP-1: Poly (ADP-ribose) polymerase (PARP) is responsible for single-stranded DNA break (SSB) or double-strand DNA break (DSB) repair. The occurrence of SSB or DSB will increase the activity of PARP-1, enhancing poly (ADP-ribose) (PAR) activity, which in turn helps synthesize long branched PAR chains in order to recruit base excision repair (BER) enzymes to the damage site (Cerrato, Morra, & Celetti, 2016; Y. Huang et al., 2018). Several PARP inhibitors have been approved for the treatment of breast and ovarian cancers. However, three PARP inhibitors (olaparib, rucaparib, and velaparib) also increase serum creatinine by inhibiting proximal tubular transporter channels such as multidrug and toxin extruder 1 and 2 (MATE1 and MATE 2) and the organic cationic transporters 1and 2 (OCT 1 and OCT 2) (LaFargue, Dal Molin, Sood, & Coleman, 2019). A more recent study showed that creatinine-derived eGFR may not actually reflect the renal function affected by olaparib. An alternative renal marker, cystatin C should be considered to more accurately measure eGFR in patients taking olaparib (Bruin et al., 2021), which would be more helpful in the evaluation of kidney damage by this class of drugs. A clinical trial is active to test whether cystatin C could be an early renal function marker for children with nephrotoxic chemotherapy (ClinicalTrials.gov Identifier: NCT02822404).

Recently, niraparib (ZEJULA), a PARP inhibitor, was approved in 2020 for patients with advanced ovarian cancer following front-line platinum treatment (González-Martín et al., 2019). Based on previous studies, it is not necessary for the renal adjustment of niraparib dosage in patients with mild or moderate declines in kidney function (Deshpande, Perazella, & Jhaveri, 2021; Zibetti Dal Molin et al., 2020). However, it remains undetermined to what extent dosing modification for PARP inhibitors might be indicated in cancer patients with advanced CKD and end stage kidney disease (ESKD). It is still unclear about the long-term effects of PARP inhibitors on kidney function and proteinuria (Deshpande et al., 2021). Therefore, it should be noted that patients could develop nephrotoxicity due to preexistent changes in intrarenal homeostasis (Lazareth et al., 2020). While PARP-1 inhibition was demonstrated to attenuate ischemic AKI (Jang et al., 2020), one study revealed that PARP-1 deficiency promoted an alkylating agent methyl methanesulfonate (MMS)-induced nephrotoxicity in alkyladenine DNA glycosylase-transgenic mice, which was sex dependent, i.e. MMS-induced nephrotoxicity was observed in male, but not female

mice (Calvo et al., 2016). This discrepancy of PARP inhibition impact in kidney damage could be due to different phases of AKI caused by different insults. Therefore, more studies are required to determine the role of PARP on anticancer agents-induced nephrotoxicity.

4.4 Histone modifications

4.4.1 Histone acetyltransferases (HATs)—Histone acetyltransferases (HATs) are the enzymes responsible for transferring an acetyl group to the lysine residue of cellular proteins, including transcription factors and histones, to promote gene expression. p300, a member of HATs, plays a definitive role in cell proliferation, differentiation, and apoptosis. p300 has been implicated in tumorigenesis and epithelial-mesenchymal transition in non-small cell lung cancer cells (Hou et al., 2018; Iyer, Özdag, & Caldas, 2004). Cisplatin was reported to induce kidney injury through activating one member of HATs, p300 activity, thereby increasing acetylation of histone H3 and further enhancing oxidative stress, inflammation, and apoptosis. It was shown that a potent p300 inhibitor, Garcinol, reversed cisplatin-induced kidney injury (J.-Y. Kim, Jo, Leem, & Park, 2020). It is speculated that targeting HAT could be a potential strategy to treat anticancer drug-induced kidney damage. Interestingly, p300 inhibition has demonstrated anticancer effects (Liu et al., 2020; Y. M. Wang et al., 2017). Targeting p300 may provide dual action of protection against renal chemotoxicity and an enhanced antitumor effect.

4.4.2 Histone deacetylases (HDACs)—Histone deacetylases (HDACs) are enzymes involved in the removal of acetyl group from lysine residue of histones or non-histones proteins. HDACs are grouped into four classes, which have distinct functions. HDACs participate in tumorigenesis in several cancers (Pant, Peixoto, Richard, & Gradilone, 2020; P. Wang, Wang, & Liu, 2020). HDAC inhibitors have shown synergistic antitumor effects in combination with other cancer drugs in preclinical and clinical tests (Hontecillas-Prieto et al., 2020; Jenke, Reßing, Hansen, Aigner, & Büch, 2021). Emerging studies suggest that HDAC inhibitors are a potential strategy to decrease the AKI induced by cisplatin. For example, HDAC inhibitors such as trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA) are effective in reducing cisplatin-induced AKI through increasing autophagy in renal tubular cells (J. Liu et al., 2018; Tang et al., 2018). More recently, a highly selective HDAC6 inhibitor, 2-Methylquinazoline derivative 23BB, was demonstrated to improve cisplatin-induced AKI (Hao et al., 2020). Another selective HDAC6 inhibitor, Ricolinostat (ACY-1215), elicited suppressive effects on TGF-β and EGFR signaling pathways to mitigate kidney damage in obstructive nephropathy (Chen et al., 2020). Given their antitumor potential, HDAC inhibitors could represent an additional candidate to protect against renal chemotoxicity and simultaneously enhance the antitumor action of cisplatin.

4.4.3 Sirtuins (SIRT)—Sirtuins (SIRT) are NAD+-dependent histone deacetylases belonging to class III HDACs. Unlike other HDACs, the SIRT are not affected by the inhibitors of HDACs. Different SIRTs have distinct roles in cancers as some SIRTs act as oncoproteins or as tumor suppressors. Accumulating evidence have indicated diverse roles of SIRT in kidney injuries (Peasley, Chiba, Goetzman, & Sims-Lucas, 2021). Activation of SIRT1, SIRT3 or SIRT6 has demonstrated attenuation of cisplatin-induced kidney damage through various mechanisms such as repressing apoptosis, inflammation and oxidative stress

(J. Y. Kim et al., 2019; Z. Li et al., 2018; Yoon & Kim, 2016). Additionally, SIRT5 mediates the balance between mitochondrial and peroxisomal fatty acid oxidation in proximal tubular epithelial cells, which protect against injury in AKI (Chiba et al., 2019). Downregulation of SIRT3 by cisplatin can be restored through PARP-1 inhibition, which mediates protection against cisplatin-induced oxidative stress in tubular cells (Yoon & Kim, 2016). Consistent with this finding, deletion of SIRT3 exacerbates cisplatin nephrotoxicity via increasing apoptosis and inflammatory response (D. Kim et al., 2018). Moreover, upregulation of SIRT6 inhibits ERK1/2 expression and thereby mitigates renal dysfunction, inflammation and apoptosis caused by cisplatin (Z. Li et al., 2018). Recently, SIRT2 overexpression was show to reverse cisplatin-downregulated mitogen-activated protein kinase phosphatase-1 (MKP-1) and further ameliorate renal injury (Jung, Park, Kang, & Kim, 2020). Hence, manipulation of SIRT could be a potential approach to simultaneously mitigate cancer and anticancer drugs-induced nephrotoxicity by targeting various pathways. However, it should be noted that either overactivation or deactivation of HDAC or SIRT could lead to opposing effect in cancers and kidneys. Further testing in animal studies and human are needed due to distinct functions of HDACs and SIRTs.

4.5 Non-Coding RNAs

Non-Coding RNAs, such as miRNA, lncRNAs, and circRNAs, are believed to account for a variety of physiological and pathological functions at both transcriptional and posttranscriptional regulations. In addition to numerous studies in cancers, they have gained increasing attentions from researchers in the kidney area in the recent decade. Their roles in cisplatin-induced renal injuries have also been extensively studied (Du et al., 2017; Guo et al., 2018; Loren et al., 2021; Pavkovic et al., 2016). A natural steroid saponin, Dioscin, exerts antioxidant effect against cisplatin-induced nephrotoxicity through a mechanism of increased SIRT1 expression regulated by microRNA-34a (Y. Zhang et al., 2017). Urolithin A (UA) is a gut metabolite of dietary polymeric polyphenols ellagitannins. Oral gavage of biocompatible nanoparticle urolithin A attenuates the reduction of miRNA (miR-192–5p and miR-140–5p) by cisplatin and reduces renal oxidative stress. Liposomes carrying microRNA-500a-3P elicit inhibitory effect on necroptosis-related protein expression and inflammatory responses by cisplatin (S. Zhang, Sun, Kong, & Zhang, 2020). Several potential agents such as scutellarin, puerarin, curcumin and pentoxifylline also show renoprotective effect involving miRNAs regulation (El Magdoub, Schaalan, Rahmo, Farag, & Khedr, 2020; S. J. Huang et al., 2020; C. Y. Sun et al., 2019; Wu, Li, Li, Li, & Lu, 2020).

Ginkgo Biloba extract mediates renoprotection against methotrexate-induced renal injury by interrupting the PI3K/Akt/mTOR signaling and the expression of long non-coding RNA (lncRNA), metastasis-associated lung adenocarcinoma transcript-1 (MALAT1) (Sherif, Al-Shaalan, & Sabry, 2019). Overexpression of lncRNA XLOC_032768 is revealed to repress the gene expression of TNF-α thus attenuating cisplatin-induced apoptosis and inflammatory effects of renal tubular cells (X. Zhou et al., 2020). Interestingly, cisplatin-induced IL-1β upregulates lncRNA9884 expression via the NF-κB pathway; lncRNA9884 subsequently activates transcription of macrophage migration inhibitory factor (MIF) gene via binding to MIF promoter region, which in turn promotes IL-1β/NF-κB signaling and triggers a cytokine storm (Y. Zhang et al., 2020). Furthermore, lncRNA PRNCR1

overexpression is shown to reduce cisplatin-induced renal epithelial cell apoptosis through interference with the miR-182–5p/EZH1 axis (J. Li, Fan, Wang, Gong, & Guo, 2021).

Besides microRNAs and lncRNAs, circular RNAs (circRNAs) have recently attracted increasing attention as promising targets in both cancers and kidney diseases (van Zonneveld, Kölling, Bijkerk, & Lorenzen, 2021). One study uncovered that 368 circRNAs were expressed differentially in cisplatin treatment mice (C.-M. Li et al., 2019). Another study demonstrated that the elevated circRNA, circ-0114427, was found in the early stage of a cisplatin-AKI model, which was implicated in the binding of miR-494 and the increase of ATF3 expression; as a result, circ-0114427 led to a decrease in the production of inflammatory cytokines. Therefore, circ-0114427 could be a novel target for early treatment strategies for cisplatin-induced AKI (Cao et al., 2020). Overall, studies have demonstrated that the non-coding RNAs, including miRNA, lncRNAs, and circRNAs, are involved in both cancer therapy and kidney chemotoxicity, indicating that non-coding RNAs could be promising targets for developing novel drugs in the management of anticancer agent-induced nephrotoxicity, and intriguingly, bear potential dual action of renoprotection and anticancer.

5. Conclusions

There are currently no effective drugs targeting specific biochemical or molecular pathways associated with anticancer therapy-induced nephrotoxicity in clinical use or clinical trials, although several clinically used drugs, such as gemigliptin (DPP-4 inhibitor), pantoprazole (proton pump inhibitor) and Tempol, are under clinical trials for renal chemotoxicity. This chapter reviews and summarizes the kidney- and drug-associated risk factors of anticancer drug-induced nephrotoxicity that will allow clinicians and researchers to carefully assess the risk and benefits of treatments. This review also proposes prospective strategies to diagnose/mitigate nephrotoxicity arising from cancer therapeutics. In addition to the assessment of route of drug administration, timing of drug treatments, and pharmacodynamics, pharmacokinetics and pharmacogenetics among patients with cancer, future studies should also focus on identifying novel mechanisms and targets that may lead to the development of new approaches in the management of chemotherapy-induced nephrotoxicity.

Abbreviations

ABC transporters	ATP-binding cassette transporters
ACEi	angiotensin-converting enzyme inhibitors
AIN	acute interstitial nephritis
AKI	acute kidney injury
ARBs	angiotensin receptor blockers
CCB	calcium channel blocker
CECT	contrast-enhanced computed tomography
CIN	contrast-induced nephropathy

CKD	chronic kidney disease
CPIs	immune checkpoint inhibitors
CYP450	cytochrome P450
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
FSGF	focal segmental glomerulosclerosis
5-FU	5-fluorouracil
GCs	glucocorticoids
GGT	gamma-glutamyl transpeptidase
GSTs	glutathione S-transferases
HDACs	histone deacetylases
IL-2	interleukin-2
MCD	minimal change disease
mTOR	mammalian target of rapamycin
MTX	methotrexate
NAC	N-acetylcysteine or acetylcysteine
NSAIDs	nonsteroidal anti-inflammatory drugs
OAT	organic anion transporters
OCT	organic cation transporters
PDE5	phosphodiesterase type 5
PPI	proton pump inhibitors
SLC	renal solute carrier transporter
TLR	toll-like receptor
TMA	thrombotic microangiopathy
TNF-α	tumor necrosis factor-α

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Table 1.

Risk factors for renal toxicities in cancer therapy

Patient-specific factors
Older age
Female sex
Preexisting AKI or CKD
Hepatic failure
Other comorbidities (multiple myeloma, lymphoma, leukemia, renal cancer, diabetes, sepsis, and acid-base disturbances)
Kidney-specific factors
High rate of blood delivery (20–25% of cardiac output)
Proximal tubular uptake of toxins apical tubular uptake by endocytosis/pinocytosis basolateral tubular transport through OAT and OCT pathways
Relatively hypoxic renal environment high metabolic rate of tubular cells in the loop of Henle Increased drug/toxin concentration in renal medulla and interstitium
Biotransformation of substances to reactive oxygen species causing oxidative stress
Sex difference/ species difference
Tumor cell-induced alternation in expressions of renal transporters
Drug-specific factors
Prolonged dosing periods, rapid infusion rates of drugs
Potent direct nephrotoxic effects of the drug or compound
Concomitant use of nephrotoxic drugs
Competition between endogenous and exogenous toxins for transporters, increasing toxin accumulation within the tubular cell
Insoluble parent compound and metabolite with intratubular crystal precipitation (urine pH/drug pKa)

AKI: acute kidney injury; CKD: chronic kidney disease; OAT: organic anion transporters; OCT: organic cation transporters. Modified from (Mark A. Perazella, 2009).

Table 2.

Renal manifestation associated with commonly used anticancer drugs and recent novel cancer therapies

Renal manifestation						
Tubular injury	**Glomerular injury**	**TMA**	**Fanconi syndrome**	**Proteinuria**	**AKI**	**Tubulointerstitial disease**
Anticancer agents						
Ifofamide	MitomycinC	Ipilimumab	Ifosfamide	Bevacizumab	Doxorubicin	Ipilimumab
Cisplatin	Doxorubicin	Bevacizumab	Lenalidomide	Carfilzomib	Nivobumab	Nivobumab
Doxorubicin	Actinomycin	Carfilzomib		Everolimus	Pembrolizumab	Pembrolizumab
Cetuximab	Bevacizumab	Bortezomib		Sirolimus	Cisplatin	Sorafenib
Panitumumab	Carfilzomib			Clofarabine	Carfilzomib	Sunitinib
Methotrexate	IFN-α			Vemurafenib	Sirolimus	Vemurafenib
Vemurafenib	Lenalidomide				Clofarabine	
Cirzotinib					Dabrafenib	
Everolimus					Vemurafenib	

TMA: thrombotic microangiopathy; AKI: acute kidney injury; IFN-α: interferon alpha

Table 3.

Summary of current and potential strategies for the management of cancer therapeutics- induced nephrotoxicity

Agent	Nephrotoxicity	Management	Potential Strategies
Platinum agents (Cisplatin)	AKI; CKD; Fanconi-like syndrome (hypomagnesemia, fanconi-like syndrome, hypocalcemia, proteinuria, hyperuricemia)	Hydration; Mannitol; Furosemide; Magnesium supplement	N-acetylcysteine; Inhibition of renal uptake transporters; Reducing inflammation response and cellular death; Use of DPP-4 inhibitors and pioglitazone; Appropriate dose of ACEi, ARB, CCB, aprepitant, thrombin inhibitor or PPI; Targeting GGT enzyme and GGT-associated inflammatory pathway; Activation of Pregnane X receptor; Use of sodium thiosulfate or probiotics; Tempol (an antidoxant)
Alkylating agents (Ifosfamide, cyclophosphamide)	Tubular damage (glucosuria, aminoaciduria; Polyuria, and proteinuria); Interstitial inflammation and renal fibrosis	Control total dose usage; Monitor and supplementation of electrolyte	N-acetylcysteine; Targeting oxidative stress, mitochondrial dysfunction, apoptosis, DPP-4 or vasopressin V2 receptor and use of acetylcysteine
Antitumor antibiotics (Mitomycin C, Doxorubicin, Actinomycin)	AKI; Nephrotic syndrome; Endothelial cell and podocyte injury	Control total dose usage	Combination of cisplatin with mitomycin C, targeting oxidative stress, inflammatory, apoptosis. Inhibition of renal podocyte detachment (angiopoietin-like-3).
Antimetabolites cancer drugs (Methotrexate, Clofarabine)	Decreased GFR; Tubular injury; AKI; Proteinuria	Hydration; Alkalinization; Hemodialysis	Use of Glucarpidase; Targeting oxidative stress and inflammation, apoptosis; Inhibiting miRNA-145–5p-mediated oxidative stress; Targeting ER stress signaling; Restoring OAT3 expression; Use of Rebamipide or HA-230 adsorber; Targeting miR-181a; Use of camel milk, hesperidin and curcumin
EGFR inhibitors (Etuximab, Panitumumab	Tubular injury; Glomerupathy; Nephritic syndrome; Electrolyte disorder	Glucocorticoid; Discontinuation; Monitor and supplementation of electrolyte	Sodium restriction and diuretics treatment
VEGF inhibitors (Bevacizumab, Sorafenib, Sunitinib)	Proteinuria; TMA; Hypertension; Glomerulopathy; Electrolyte disorder; Interstitial nephritis	ACEi or ARBs	Use of PDE5 inhibitor or selective ETA receptor antagonists; Targeting downstream of ET-1 signaling
Immune checkpoint inhibitors (Ipilimumab, Nivolumab, Pembrolizumab)	AKI; Acute tubulointerstitial nephritis; Electrolyte disturbance and TMA	Glucocorticoids; Discontinuation	Use of weak checkpoint blockade; TNF-α blocker
Proteasome inhibitors (Carfilzomib, Bortezomib)	TMA; Proteinuria; AKI; Podocyte injury	Anti-hypertension; Intravenous hydration; Reduction of dose; ACEI or ARBs	Use of acetylcysteine or glucocorticoid; Targeting oxidative stress and inflammation
mTOR protein kinase inhibitors (Sirolimus, Everolimus)	AKI; Proteinuria	ACEI or ARBs; Discontinuation	NA
Biologic agents (IL-2, IFN-α)	Hypotension; Edema; Oliguria; MCD; FSGF; TMA	Fluid management; Discontinuation Urine output monitoring	Low and intermediate-dose of vasopressors (dopamine); Targeting vascular endothelial protein tyrosine phosphatase (VE-PTP)
BRAF inhibitors (Dabrafenib, Vemurafenib)	Hyperkalemia; Fanconi syndrome; MCD; AKI; Crystal nephropathy	Routine monitoring of electrolytes and serum creatinine	Combined therapy of MEK inhibitor, cobimetinib and vemurafenib
ALK inhibitor (Crizotinib)	Electrolyte disorder; Renal cyst; Acute tubular necrosis; Glomerular mesangiolysis;	Discontinuation	Monitoring of renal function and examination of kidney biopsy

AKI: acute kidney injury; TMA: thrombotic microangiopathy; CKD: chronic kidney disease; ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; DPP-4: dipeptidyl peptidase-4; CCB: calcium channel blocker; GGT: gamma-glutamyl transpeptidase; PPI: proton pump inhibitors; PDE5: phosphodiesterase type 5; MCD: minimal change disease; FSGF: focal segmental glomerulosclerosis; GGT: gamma-glutamyl transpeptidase; ET: endothelin, NA: not available; OAT: organic anion transporters