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Review Article

Management of nephrotoxicity of chemotherapy and targeted agents: 2020

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Abstract: Nephrotoxic effects of certain chemotherapeutic agents such as cisplatin and ifosfamide has been well documented and these effects are carefully managed by oncologists during their usage. The introduction of targeted agents has added a new challenge to cancer management as their nephrotoxic effects and associated management is in the process of being adopted by oncologists. This work is a compilation of side effects on the renal system due to various chemotherapeutic, immunotherapeutic and targeted agents followed by their recommended management.

Keywords: Nephrotoxicity, side effects, tumor lysis syndrome, acute kidney injury, chronic kidney disease

Introduction

Recent advances in cancer treatments such as targeted therapy, radiotherapy, immunotherapy, and aggressive and minimally invasive surgery have resulted in improvements in cancer control and prolonged survival for many types of malignancies. Despite this progress, anticancer drug nephrotoxicity has grown to be an increasingly important factor that limits the efficacy of cancer treatments. The field of onco-nephrology is rapidly expanding and evolving, requiring close work and familiarity between both fields [1, 2].

Nephrotoxicity is an important aspect that should be considered during the administration of cancer therapy [3]. It occurs when the normal filtration, detoxification, and excretion functions of the kidneys are deranged due to damage of the nephron architecture. The kidneys are a common elimination pathway utilized by many anticancer drugs and their metabolites. Drug-induced nephrotoxicity affects many components of the nephron structure such as the glomerulus, tubules, and renal microvasculature. Pathogenic mechanisms of drug-induced renal damage may vary with the drug and include altered glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy (TMA). Furthermore, renal damage results in delayed drug excretion and metabolism and systemic toxicity. As a result, many drugs may require dosage adjustment in the context of renal insufficiency [4].

Furthermore, intravascular volume depletion, simultaneous use of non-chemotherapeutic drugs, and radiographic ionic contrast media can contribute to or potentiate nephrotoxicity of anticancer drugs. Conventional cytotoxic agents such as cisplatin, alkylating agents like cyclophosphamide, antimetabolites such as methotrexate, and targeted therapeutics of epidermal growth factor receptor (EGFR) pathway inhibitors and checkpoint inhibitor immunotherapy are a few examples of cancer treatments with nephrotoxic effects. Potential for nephrotoxicity should be identified early, permitting dosage adjustments or cessation of the causal drug [5].

Nephrotoxicity consists of a wide range of complications, including those associated with anticancer treatment and with the malignancy itself (paraneoplastic renal manifestations). Some of the most common clinical neph-

rotoxic manifestations of anticancer drugs include acute kidney disease (AKI) due to tubular necrosis, proteinuria from glomerulopathy, hypertension, tubulopathies due to electrolyte disturbances, and chronic kidney disease (CKD) [6]. While some exceptions exist, drug-induced nephrotoxicity generally resolves if the complication is detected early and the causal drug is discontinued [7]. Common patient-related risk factors for drug-induced nephrotoxicity are age over 60 years, underlying renal insufficiency (GFR < 60 mL per minute per 1.73 m^2), diabetes, volume depletion, congestive heart failure, and hypertension [4].

Tables 1 and **2** provide an overview to two groups of anticancer drugs: standard chemotherapy and targeted agents. Chemotherapeutic agents that induce nephrotoxicity include alkylating agents, antimetabolites, antitumor and antimicrotubule agents, and the widely used anticancer platinum agent cisplatin. EGFR, BRAF, vascular endothelial growth factor (VEGF), and immune checkpoint inhibitors are common targeted cancer therapies that may also cause nephrotoxicity. Common forms of immunotherapy such as CAR-T and cytokine therapy are also associated with induced nephrotoxicity and are discussed further.

Epidemiology of chemotherapy-induced nephrotoxicity

Drug-induced acute kidney injury (AKI) has an estimated frequency of 14-26% in the adult population based on prospective cohort studies [8-10]. 16% of hospitalized pediatric nephrotoxicity cases are primarily attributable to a drug [11]. Cancer may affect renal function either directly or indirectly, and nephrotoxic effects of chemotherapeutic agents can pose a heightened risk for kidney injury. A study on the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) data from 2011 to 2015 found a high number of renal adverse events are also associated with novel targeted therapies [12].

The importance of monitoring for nephrotoxicity

Several anti-cancer agents are associated with renal toxicity. The kidney is one of many organ systems that are vulnerable to the toxicities of cancer treatment drugs. This can be attributed to the renal systems rich blood supply, high tubular reabsorptive capacity, and function as a common elimination pathway for toxic antineoplastic drugs and their metabolites. In general, such drugs may cause renal damage by a variety of mechanisms, including inducing varied intrarenal vasoconstriction, and causing direct tubular toxicity or intratubular obstruction [4]. Monitoring for renal insufficiency is important before starting chemotherapy. It has been reported that renal insufficiency in cancer patients, in addition to comorbid conditions like heart failure, can potentiate the nephrotoxic effects of anticancer drugs. Previous studies have found increased prevalence of renal dysfunction in patients with newly diagnosed cancer [13-15]. The first IRMA studies (*Insuffisance Rénale et Médicaments Anticancéreux*-Renal Insufficiency and Anticancer Medications) on patients with solid tumors (mainly breast, colorectal, and lung) discovered that approximately half of the 5000 adult patient population had a reduced glomerular filtration rate (GFR). Only about one third of the patient cohorts with cancer had normal GFRs of ≥90 mL/min/1.73 m^2 [13]. Furthermore, Yang et al observed elevated all-cause mortality among patients with eGFR < 60 mL/min/1.73 m^2 stratified by cancer stage in the entire cohort. Subgroup analysis of gynecological and hematologic cancer patients found that eGFR < 60 mL/min/1.73 m^2 independently predicted death [15]. A GFR under 60 ml/min per 1.73 m^2, indicating moderate CKD, and a creatinine clearance below 30 mL/min, seen in severe CKD, are critical measurements that necessitate precaution with use of cancer treating agents [16]. Thus, it is crucial to monitor renal functioning before starting cancer treatment. In doing so, clinicians can adjust the dosage of anticancer drugs in cases of renal insufficiency, thereby avoiding drug accumulation and reducing overdosage-related side effects. In addition, monitoring during and after cancer treatment is essential to detect progression of reversible AKI into irreversible states of CKI. Although most chemotherapeutic nephrotoxicity is reversible following drug discontinuation, longer durations of nephrotoxicity has been discovered with treatments such as doxorubicin, ifosfamide, cisplatin, methotrexate, and pemetrexed [6, 17-20].

Table 1. List of chemotherapy agents which cause nephrotoxicity

	Nephrotoxic mechanism	Associated conditions	Management	References
Alkylating agents Cyclophosphamide Ifosfamide	Damage to proximal and distal tubules by metabolites and increased cellular oxidative stress	SIADH induced severe hyponatremia, Fanconi's syndrome in children	Hyponatremia management with continuous infusion or bolus hypertonic saline; adequate hydration; AVP (V_2) receptor antagonist (tolvaptan); Mesna or N-acetylcysteine electrolyte monitoring; discontinuation	[3, 32, 33, 99-101]
Cytotoxic agents Cisplatin Carboplatin	Drug accumulation in proximal tubules resulting in proximal tubular dysfunction	AKI, TMA, Fanconi's syndrome, salt-wasting hyponatremia, Hypomagnesemia	Aggressive Short-duration, low-volume hydration; dose adjustment for preexisting renal impairments; magnesium supplementation; mannitol supplementation for preexisting renal impairment and high-dose cisplatin; Forced diuresis; Amifostine radical scavenger; discontinuation; eculizumab for TMA resolution	[3, 21, 25]
Antimetabolites Methotrexate Pemetrexed Gemcitabine	Vasoconstriction of afferent arteries, reducing GFR; crystal precipitation in renal tubules	Tubular acidosis, AKI, SIADH induced hyponatremia, hemolytic uremic syndrome and TMA	Urinary alkylation, hydration, high-flux hemodialysis, carboxypeptidase-G(2) (CPDG2), leucovorin rescue; oral corticosteroids; hyponatremia management with hypertonic saline infusion, fluid restriction, AVP (V_2) receptor antagonist (tolvaptan); discontinuation	[3, 28, 29]
Vinca Alkaloids Vincristine Vinblastine	Neurotoxic effect on hypothalamus-pituitary axis resulting in altered osmotic control of ADH	SIADH induced hyponatremia	Hyponatremia management with continuous infusion or bolus hypertonic saline, fluid restriction, AVP (V_2) receptor antagonist (tolvaptan); discontinuation	[3, 101-103]
Antitumor antibiotics Doxorubicin Mitomycin C	Induced glomerular endothelial cell and podocyte apoptosis, mesangiolysis	Focal segmental glomerular sclerosis, nephrotic syndrome, hemolytic uremic syndrome, TMA, AKI	Eculizumab for TMA resolution; nephrotic syndrome management through fluid and sodium restriction, oral or IV diuretics, and ACE inhibitors or ARBs	[3, 104-107]
Proteasome inhibitors Bortezomib Carfilzomib	Decreased vascular endothelial growth factor (VEGF) synthesis resulting in TMA; increased ADH secretion and effect on kidneys	Acute interstitial nephritis, TMA, AKI, Tumor lysis syndrome, SIADH induced hyponatremia	Glucocorticoid therapy for management of interstitial nephritis (inconclusive); N-acetyl-l-cysteine upon chemotherapy re-challenge (inconclusive); Hyponatremia management with continuous infusion or bolus hypertonic saline, fluid restriction, AVP (V_2) receptor antagonist (tolvaptan); discontinuation	[3, 39, 40, 51, 108]

Table 2. List of targeted agents which cause nephrotoxicity

Agent	Nephrotoxic effect	Associated conditions	Management	References
EGFR inhibitors Cetuximab Panitumumab	Inhibition of EGFR signaling at the distal convoluted tubule, which functions in transepithelial magnesium transport; failure to maintain tubular integrity through EGFR	Electrolyte disturbance (hypomagnesemia, hypophosphatemia, hypokalemia), diffuse proliferative glomerulonephritis, nephrotic syndrome, hypoalbuminemia	Nephrotic syndrome management through fluid and sodium restriction, oral or IV diuretics, and ACE inhibitors; magnesium wasting management by IV magnesium infusion and oral magnesium supplementation; discontinuation	[3, 61, 109, 110]
mTOR inhibitors Temsirolimus	Inconclusive and multifactorial mechanism with possible increased glomerular permeability and injury and suppression of tubular renal cell compensatory proliferation/survival/repair processes	Glomerulopathy, AKI, proteinuria	Close monitoring of proteinuria and renal damage; early use of ACE inhibitors and ARBs with sirolimus; discontinuation	[67-71]
B-Raf inhibitors Vemurafenib	Damage to proximal tubules, inhibiting tubular secretion; reduction in GFR and creatinine clearance	Acute interstitial nephritis, acute tubular necrosis, AKI, Fanconi's syndrome, hypertension	Routine monitoring of serum creatinine and electrolytes; discontinuation	[3, 75, 76, 111]
Anti-angiogenesis (VEGF and VEGFR inhibitors) Bevacizumab Sorafenib Sunitinib	Anti-VEGF antibodies inhibition of endothelial cell proliferation and blood vessel formation, resulting in loss of filtration barrier; nitric oxide pathway inhibition and oxidative stress inducing endothelial dysfunction and capillary rarefaction	Nephrotic syndrome with high-grade proteinuria, AKI, TMA, hypertension	Hypertension management through ACE inhibitor, ARBs; discontinuation	[3, 57, 112, 113]
Immune Checkpoint Inhibitors Ipilimumab Pembrolizumab Nivolumab	Enhanced T cell response with migration of activated T cells into the kidney; immune responses leading to inflammatory cell infiltrates; podocyte effacement	Acute tubulointerstitial nephritis, immune complex glomerulonephritis, TMA, AKI with possible granulomas	Corticosteroids; discontinuation	[3, 58, 80]
CAR-T therapy	CAR-T cell expansion and stimulation of immune cell-secreting cytokines; fever, hypotension, renal failure	CRS; AKI	Tocilizumab	[86, 88, 89, 91, 92]
Cytokine therapy IL-2	Activation of TNF-alpha and other cytokines to induce capillary leak syndrome and renal hypoperfusion	Pre-renal azotemia; AKI	Fluid bolus; intermediate-dose dopamine; discontinuation	[93-98]

Nephrotoxic broad-spectrum chemotherapeutic drugs & management

Cisplatin

Cisplatin is a platinum compound and one of the most nephrotoxic and widely utilized chemotherapeutic agent used in the treatment of sarcomas, carcinomas, and lymphomas. In addition to severe ototoxicity, nephrotoxicity is cisplatin's major adverse effect, causing apoptosis and necrosis of renal cells. Cisplatin's toxic effects to the kidneys spread throughout several compartments including blood vessels, glomeruli, and primarily the tubules. Inside tubular cells, cisplatin activates caspases, cyclin dependent kinases, and p-53. The drug also induces inflammation and oxidative stress, resulting in vascular injury and reduced GFR. The most common findings of renal damage are acute renal injury (AKI), hypomagnesemia, proximal tubular dysfunction (Fanconi's syndrome), and thrombotic microangiopathy (TMA) [21]. TMA, characterized by thrombocytopenia, hemolytic anemia, hypertension, hematuria, proteinuria, and organ damage, is a consequence of both antineoplastic drugs like mitomycin C, doxorubicin, gemcitabine, and VEGF inhibitors and of cancer itself [22]. TMA has been reported mainly in cases of mucin-producing adenocarcinomas. It has been postulated that mucin causes endothelial dysfunction in organ vasculature. Aggressive tumor growth may also injure vascular endothelial cells [23]. Case reports have shown success of eculizumab, a terminal complement inhibitor, in treating TMA [24, 25]. AKI induced by cisplatin therapy has been found to be generally transient and reversible, but may progress into irreversible CKD due to chronic tubulointerstitial fibrosis and chronic tubulopathies [20, 26].

Prevention of kidney injury is a point of focus for patients undergoing cisplatin therapy. Forced diuresis with intravenous normal saline or hypertonic saline, with or without addition of mannitol, is used to counteract the drug's toxic effects. Magnesium supplementation is used to counteract hypomagnesemia. Nephrotoxicity is also prevented with amifostine, a glutathione analog and free radical scavenger that is taken up by healthy cells and blunts the effects of cisplatin.

Methotrexate & pemetrexed

Like cisplatin, methotrexate is one of the most widely used antineoplastic drugs. Methotrexate is a dihydrofolate reductase inhibitor used to treat high-grade lymphomas in high doses. While nephrotoxicity is a known complication of high-dose methotrexate, long-term conventional dosing rarely results in renal injury [20, 27]. High doses of methotrexate can lead to AKI due to crystal precipitation in the distal tubular lumen. In addition to the nephrotoxic effects of impaired clearance and prolonged exposure to toxic concentrations, high doses of methotrexate (HDMTX) also induce severe myelosuppression. Hepatotoxicity, mucositis, and pulmonary fibrosis are other adverse effects commonly seen with methotrexate therapy. Leucovorin "rescue" at 24-36 hours of methotrexate therapy is an effective treatment against the crystalizing damage of HDMTX, preventing myelosuppression, gastrointestinal toxicity, and neurotoxicity [28, 29]. Carboxypeptidase G2 (glucarpidase) rescue has also been shown to help treat nephrotoxic effects of HDMTX by hydrolyzing the drug to inactive metabolites [30]. It is reserved for use when methotrexate levels indicate a significant risk of systemic toxicity [31]. However, crystalline nephropathy associated with methotrexate may result in irreversible kidney damage with interstitial fibrosis and tubular atrophy due to either prolonged drug exposure, late recognition, or inability to correct for volume depletion [18, 19].

Pemetrexed is a methotrexate derivative that inhibits enzymes involved in folate metabolism and purine and pyrimidine synthesis, thereby impairing RNA/DNA synthesis in cells of malignant mesothelioma and non-small cell lung cancer. While its major adverse effects include myelosuppression and neutropenia, pemetrexed is also associated with reversible AKI. However, similar to drugs like doxorubicin, irreversible AKI and interstitial fibrosis have been reported despite discontinuation of pemetrexed and treatment with oral prednisone [6].

Ifosfamide & cyclophosphamide

Ifosfamide is an alkylating agent that is widely associated with Fanconi's syndrome. Fanconi's is caused by proximal tubule damage, and characterized by hypophosphatemia, hyponatre-

mia, hypokaliemia, glucosuria and proteinuria. Isofosfamide nephrotoxicity is also found to result in severe, irreversible proximal tubulopathy and even chronic kidney failure [32, 33]. Although ifosfamide and cyclophosphamide are both nitrogen mustards and alkylating agents, they differ in their adverse effects. While cyclophosphamide's metabolite acrolein primarily results in hemorrhagic cystitis and bladder cancer, ifosfamide's metabolite chloroacetaldehyde causes nephrotoxicity [34, 35]. Ifosfamide is often associated with severe and irreversible kidney damage, with chronic kidney failure diagnosed months after chemotherapy completion. However, it is important to note that the irreversible nephrotoxic effects from ifosfamide in children have been linked to concomitant administration of ifosfamide and cisplatin. Vitamin D supplementation is essential in the affected pediatric population [32, 33].

Treatment of nephrotoxicity induced by ifosfamide is generally supportive. Dialysis, supplementation of electrolyte disturbances, and monitoring for CKD progression are indicated. Although mesna is used to prevent hemorrhagic cystitis and bladder cancer caused by cyclophosphamide, it is of limited use for ifosfamide-related renal injury. Because ifosfamide enters proximal tubular cells through OCT2, cimetidine is being investigated as a preventive treatment by serving as a competitive inhibitor to OCT2 [35]. It has been shown that cyclophosphamide, even at doses as low as < 10 mg, is linked to severe adverse effects of hyponatremia from drug induced SIADH. SIADH develops as a result of aberrant ADH release or enhanced ADH action on the kidneys. Cyclophosphamide metabolites have been shown to have both direct toxic effect on renal collecting tubules and ADH-like activity [36, 37]. Hyponatremia in cancer patients is often caused by SIADH, inducible by volume depletion and antineoplastic agents such as cyclophosphamide, vinca alkaloids, and methotrexate [38]. Mesna is primarily used as a preventative treatment of cyclophosphamide-induced nephrotoxicity due its ability to bind toxic metabolites with sulfhydryl groups.

Nephrotoxic targeted agents & management

Proteasome inhibitors

Bortezomib is a reversible proteasome inhibitor, inducing arrest at the G2-M phase and apoptosis in treatment of multiple myeloma and mantle cell lymphoma. It is one of multiple chemotherapy agents that have been associated with interstitial nephritis, inflammation of renal interstitiam and a cause of AKI. This is characterized by infiltration of lymphocytes, monocytes, and granulomas and results in reduced creatinine clearance and proteinuria. Although interstitial nephritis is commonly associated with use of PD-1 inhibitor ipilimumab, it is increasingly common amongst cases of bortezomib treatment for multiple myeloma [39]. Cases of TMA have also been frequently reported with use of bortezomib. This can be attributed to the mechanistic action of proteasome inhibitors in inhibition of IκB ubiquitination, thereby preventing NF-κB from entering the nucleus and ultimately leading to decreased vascular endothelial growth factor (VEGF) [40-43]. Carfilzomib is a tetrapeptide epoxyketone irreversible proteasome inhibitor with similar nephrotoxic effects as bortezomib. It is used in the treatment of relapsed refractory multiple myeloma. Many cases of AKI have been presented with use of carfilzomib due to TMA, prerenal insults, and tumor lysis-like phenomenon [44-46]. In addition to carfilzomib, bortezomib and thalidomide are immunomodulatory drugs associated with tumor lysis syndrome (TLS) [47, 48]. Characteristic findings of TLS include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, resulting in renal insufficiency, and potential multi organ failure or death [49]. These effects are most notable in multiple myeloma patients with significant disease burden treated with bortezomib [50]. The benefit of glucocorticoid therapy like prednisone for treatment of interstitial nephritis caused by bortezomib remains inconclusive, although several reports suggest improvements in kidney function [51-53]. The severity of carfilzomib-induced renal injury may be ameliorated with N-acetyl-l-cysteine upon chemotherapy re-challenge [54].

VEGF/VEGFR inhibitors

Bevacizumab is an anti-VEGF inhibiting antibody that functions by injuring renal vasculature and causing TMA and nephrotic syndrome. Recognizing that tumors growth is highly dependent on vascularization induced by VEGF was a hallmark for the development of VEGF inhibitor chemotherapeutics. Produced by renal epithelial cells, VEGF signaling is essential for normal functioning of glomerular endotheli-

al cells, mesangial cells, and peritubular capillaries. Anti-VEGF therapy involves the inhibition of the nitric oxide (NO) pathway and oxidative stress, inducing endothelial cell dysfunction and vasoconstriction. As a result of endothelial loss, glomerular injury and improper maintenance of a filtration barrier may develop with disrupted epithelial cell slit diaphragms and downregulation of nephrin evident on histopathology [55]. The most common nephrotoxic effects of bevacizumab are new or worsening hypertension, AKI and proteinuria, characteristic of nephrotic syndrome. This condition is associated with edema, proteinuria, hypoalbuminemia, and hyperlipidemia, and is primarily attributable to focal segmental glomerulosclerosis and membranous nephropathy [56]. In addition to VEGF inhibitors, immune checkpoint inhibitors have been shown to cause nephrotic syndrome [57, 58].

VEGF normally stimulates endothelial cells to upregulate the synthesis and release of NO, thereby increasing endothelial permeability and relaxation of smooth muscle cells. The resulting dilatation of blood vessels in response to VEGF decreases blood pressure. Thus, inhibition of VEGF signaling results in an increase in blood pressure. However, severe hypertension is positive indicator of therapy response and should thus not prompt discontinuation of bevacizumab. Rather, physicians should continue therapy with the addition of antihypertensive agents [59]. Sorafenib and Sunitinib are both multikinase inhibitors that target various VEGF and platelet-derived growth factor (PDGF) receptors. Both targeted agents have similar adverse hypertensive effects as bevacizumab, so treatment should be accompanied by conventional antihypertensives such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), and β-adrenoceptor antagonists (β-blockers).

EGFR inhibitors

Cetuximab is a chimeric monoclonal antibody targeted against epidermal growth factor receptor (EGFR) and is used in the treatment of various malignancies, including colorectal, head and neck cancer, and lung cancers. Cetuximab is an effective targeted agent against tumor growth due to its higher affinity for EGFR compared to the receptor's natural ligands, TNF-α and EGF. The major nephrotoxicity associated with cetuximab is hypomagnesemia. This is due to magnesium's dependence on EGF singalling at the basolateral membrane for absorption in the distal convoluted tubule. Cetuximab competitively inhibits EGF at the level of its receptor, resulting in renal magnesium wasting [60, 61]. Electrolyte disorders from hypomagnesemia are also associated with panitumumab, an anti-EGFR antibody, but to a lesser severity than cetuximab [62]. Additionally, anti-EGFR antibody therapy has been connected to cases of hypoalbuminemia, a well-known marker of poor renal prognosis and poor outcome in certain patients [63, 64].

Nephrotoxic hypomagnesemia is reversible, as magnesium wasting improves within 4-6 weeks of EGFR inhibitor discontinuation nut in some instance can become a chronic wasting condition. Intravenous magnesium repletion, along with calcium and potassium repletion, is generally required in the treatment of hypomagnesemia [65, 66].

mTOR inhibitors

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase involved in growth factor and cytokine signaling pathways, and its inhibition by sirolimus leads to cell-cycle arrest. Although sirolimus has been designated as a "non-nephrotoxic" drug as it does not share renal adverse effects exhibited by calcineurin inhibitors like cyclosporine, cases of sirolimus-induced nephrotoxicity have been documented [67]. Administration of sirolimus has been associated with proteinuria and AKI [67, 68]. The way by which sirolimus induces nephrotoxicity appears to be multifactorial, with inconclusive evidence of mechanisms such as a direct increase in glomerular permeability and injury. In vitro studies suggest that sirolimus damage to the glomerular podocyte-endothelial axis may be related to inhibition of VEGF [69, 70]. Renal damage may also be due to suppression of tubular renal cell proliferation and survival/repair processes, inducing apoptosis [67, 69, 70]. Pre-existing chronic renal damage is a common risk factor for sirolimus nephrotoxicity [67].

Since high baseline proteinuria and poor renal function are associated with sirolimus-induced nephrotoxicity, sirolimus should only be used in appropriate patient populations without any

early indicators of glomerular damage. Along with close monitoring, early treatment with ACE inhibitors and ARBs has been shown to reduce proteinuria and improve outcomes [71].

BRAF inhibitors

B-raf is a protein involved in the RAS/MAPK pathway and responsible for several cell functions such as cell-cycle regulation, cell division, and differentiation. When mutated, proto-oncogene B-raf promotes cell proliferation and carcinogenesis [72]. The B-raf V600E mutation is known for its involvement in metastatic melanoma, with targeted molecular therapies such as vemurafenib inhibiting B-raf for treatment [73, 74]. Vemurafenib is mostly associated with tubule interstitial damage, impairing tubular creatinine secretion and increasing serum creatinine levels [75, 76]. Electrolyte disorders such as hypokalemia, hyponatremia, and hypophosphatemia have also been reported. Thus, monitoring of serum creatinine and electrolytes prior to and during treatment with B-raf inhibitors is essential [75, 77]. Of note, vemurafenib has been shown to cause renal injury disproportionately in males [76, 77].

Renal damage induced by vemurafenib is generally reversible with discontinuation [76]. In addition to treatment of electrolyte disturbances, monitoring for such changes in renal function during vmurafenib treatment is of importance [77].

Nephrotoxic immunotherapy & management

Immune checkpoint inhibitors

Checkpoint inhibitors (CPIs) are monoclonal antibodies directed against inhibitory receptors present in T cells and tumor cells. CPIs inhibit T cell inactivation, causing tumor cells susceptibility to immune reactions. They predominantly target programmed cell death 1 receptor (PD-1), programmed cell death 1 ligand (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and are used to treat cancers such as melanoma and non-small-cell lung cancer (NSCLC) [78, 79]. While nivolumab and pembrolizumab inhibit PD-1, ipilimumab targets CTLA-4. On biopsy, the most common pathological finding from CPIs is acute tubulointerstitial nephritis (ATIN) [58, 80]. The precise mechanism for CPI-induced ATIN is not well understood. However, pathogenesis hypotheses are derived from mouse-models that exhibit autoimmunity against specific organs due to a lack of co-inhibitory signals PD-1 and CTLA-4 and an emergence of self-antigen-reactive T cells [81, 82]. One hypothesis for nephrotixicity is that a blockade of PD-1 or CTLA-4 may disrupt self-tolerance and trigger an autoimmune response against a specific antigen in the kidney [58, 83]. Another hypothesis is that nephrotoxicity occurs through loss of tolerance to effector T cells due to prior exposure to drugs such as proton pump inhibitors (PPIs) [84, 85].

In patients with ATIN, CPI discontinuation and corticosteroid therapy are recommended steps [80].

CAR-T

Chimeric antigen receptor T cell (CAR-T) therapy is now becoming the standard of care for some forms of aggressive, relapsed, or refractory non-Hodgkin lymphoma and leukemias such as acute lymphoblastic leukemia (ALL) [86]. The purpose of CAR-T is to use a patient's own T cells to treat his/her cancer. The therapy starts by drawing blood and separating out the T cells. These cells are then genetically engineered to produce chimeric antigen receptors on their surfaces which allow T cells to recognize and attach to tumor antigens. The engineered T cells are multiplied and then infused back into the patient so that they can selectively target and kill cells expressing antigens such as CD19 [87]. Although CD-19 specific CAR-T cells have shown efficacy against B cell malignancies, cytokine-associated toxicity, commonly known as cytokine release syndrome (CRS) is a major adverse reaction to CAR-T therapy [86, 88]. The current understanding of CRS is that massive T cell stimulation and expansion causes macrophage and other immune cell degranulation and cytokine secretion resulting in fever, hypotension, and renal failure [89]. The incidence and severity of CRS-associated AKI are low, with most patients recovering renal function after early detection and management of CAR-T complications [90].

CRS induced by CAR-T therapy is reversible with administration of tocilizumab, an IL-6 receptor antagonist. IL-6 is thought to play a role in CRS due to its elevated levels in patients with the condition [91, 92]. In most cases, a single dose

of tocilizumab can induce a rapid decrease in CRS-related symptoms following CAR-T cell infusions [88].

Cytokine therapy

Interleukin 2 (IL-2) is a cytokine used in the treatment of metastatic renal cell carcinoma and metastatic melanoma. IL-2 therapy causes tumor necrosis factor alpha (TNF-alpha) and other cytokine-driven capillary leak syndrome, resulting in intravascular volume depletion, GFR reduction, oliguria, and edema. Renal toxicity associated with IL-2 is attributed to prerenal azotemia as a result of hypoperfusion and hypotension [93, 94]. IL-2 discontinuation revealed normal levels of urine protein and normal serum creatinine [95]. Nephrotoxicity from IL-2 is generally reversible and managed by administering fluid boluses at the onset of oliguria [95, 96]. Additionally, vasopressors such as low and intermediate-dose dopamine are used in treatment of oliguria and hypotension by cross-talk with adrenergic receptors [97, 98].

Conclusion

In conclusion, there are many common nephrotoxic clinical manifestations associated with cancer treatment across the antineoplastic drug classes. It is important to be aware of the effects that cancer therapeutic agents have on the body, particularly the kidneys. As more advanced and specific cancer treatments become available, monitoring for nephrotoxicity becomes increasingly important to prevent damage and manage changes in oncologic intervention, hence the need for onconephrology. This overview provides various nephrotoxic manifestations of many commonly used chemotherapeutic and targeted therapy drugs. It is essential to recognize these different renal manifestations of cancer agents for appropriate decision making, rapid diagnosis, and therapeutic interventions.

Disclosure of conflict of interest

None.

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