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REVIEW

Cancer therapy in patients with reduced kidney function

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ABSTRACT

Chronic kidney disease (CKD) and cancer constitute two major public health burdens, and both are on the rise. Moreover, the number of patients affected simultaneously by both conditions is growing. The potential nephrotoxic effect of cancer therapies is particularly important for patients with CKD, as they are also affected by several comorbidities. Therefore, administering the right therapy at the right dose for patients with decreased kidney function can represent a daunting challenge. We review in detail the renal toxicities of anticancer therapies, i.e. conventional chemotherapy, targeted therapy, immune checkpoint inhibitors and radioligand therapies, issue recommendations for patient monitoring along with guidance on when to withdraw treatment and suggest dosage guidelines for select agents in advanced stage CKD. Various electrolytes disturbances can occur as the result of the administration of anticancer agents in the patient with decreased kidney function. These patients are prone to developing hyponatremia, hyperkalemia and other metabolic abnormalities because of a decreased glomerular filtration rate. Therefore, all electrolytes, minerals and acid base status should be checked at baseline and before each administration of chemotherapeutic agents. Moreover, studies on patients on kidney replacement therapy are very limited and only single cases or small case series have been published. Therefore, clinical therapeutical decisions in cancer patients with decreased function should be made by multidisciplinary teams constituted of medical oncologists, nephrologists and other specialists. Onconephrology is an evolving and expanding subspecialty. It is crucial to consider anticancer drug treatment in these patients and offer them a chance to be treated effectively.

Keywords: anticancer therapy, cancer, decreased kidney function, electrolytes disturbances, onconephrology

INTRODUCTION

Chronic kidney disease (CKD) and cancer constitute two major public health burdens and are on the rise [1, 2]. Moreover, the number of patients affected simultaneously by both conditions is growing [2]. Access to high-quality screening protocols and targeted anticancer therapies has transformed the oncology landscape but has also led to an increasing number of patients who are vulnerable to the potential nephrotoxic effect of cancer therapies. This is particularly important for those patients with CKD. In addition, as cancer survivorship increases, so do the number of patients with CKD which can negatively affect long-term outcomes [3]. The rise in CKD in this population is due to factors such as older age, comorbid conditions, and the effects of prior therapies including nephrotoxicity and partial or complete nephrectomy. Unfortunately, administering the right therapy at the right dose for patients with severely decreased kidney function can represent a daunting challenge to the treating team as historically, these patients have been excluded from clinical trials of anticancer drugs because of a suspected increased risk for major dose-limiting toxicity. In addition, patients with cancer and decreased kidney function are often affected by multiple comorbidities such as diabetes and hypertension, and management of advanced CKD complications such as electrolyte abnormalities, acid–base disturbances and fluid overload can be impacted by numerous anticancer therapies. For optimal management of these patients, we review in detail the renal toxicities of anticancer therapies, issue recommendations for patient monitoring along with guidance on when to withdraw treatment and suggest dosage guidelines for select agents in advanced stages of CKD.

OVERVIEW OF SELECTED DRUG RENAL TOXICITIES IN ONCOLOGY

A major risk factor for drug toxicities and worsening glomerular filtration rate (GFR) in patients with cancer is the presence of pre-existing CKD which increases the susceptibility to injury and may also alter the pharmacokinetics and pharmacodynamics of anticancer drugs thereby increasing their toxicity (Table 1).

Conventional chemotherapeutic agents

Cisplatin administration is complicated by dose-limiting nephrotoxicity [4]. Direct tubular toxicity occurs due to activation of intracellular injury pathways leading to renal tubular apoptosis and necrosis, which typically develops ~3–5 days after drug exposure. While acute kidney injury (AKI) is generally reversible, repeated cisplatin doses (>100 mg/m^2) may cause permanent kidney injury and CKD. Saline administration and avoidance of other

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Table 1: Anticancer drug-related nephrotoxicity.

Medication	Clinical renal syndrome	Renal histopathology
Conventional chemotherapy		
Platinum compounds (cisplatin, carboplatin, oxaliplatin)	• AKI • Hypomagnesemia • Nephrogenic diabetes insipidus • Proximal tubulopathy • Salt wasting	• Acute tubular injury • TMA
Ifosfamide	• AKI • Nephrogenic diabetes insipidus • Proximal tubulopathy	• Acute tubular injury
Methotrexate	• AKI	• Crystalline nephropathy • Acute tubular injury
Gemcitabine	• AKI • Hematuria/proteinuria • Hypertension	• TMA
Mitomycin C	• AKI • Hematuria/proteinuria • Hypertension	• TMA
Pemetrexed	• AKI • Proximal tubulopathy • Nephrogenic diabetes insipidus	• Acute tubular injury • Chronic interstitial fibrosis
Nitrosureas	• CKD	• Chronic tubulointerstitial nephritis
Targeted cancer agents		
Anti-VEGF agents (aflibercept, bevacizumab)	• AKI • Hypertension • Proteinuria	• TMA • Acute tubular injury
Tyrosine kinase inhibitors (axitinib, pazopanib, sorafenib, regorafenib, sunitinib)	• AKI • Hypertension • Proteinuria	• FSGS • TMA • Acute tubulointerstitial nephritis • Acute tubular injury
BRAF inhibitors (dabrafenib, vemurafenib)	• AKI • Electrolyte disorders	• Acute tubulointerstitial nephritis • Acute tubular injury
ALK inhibitors (crizotinib)	• AKI • Electrolyte disorders • Acquired kidney micro-cysts	• Acute tubulointerstitial nephritis • Acute tubular injury
EGFR inhibitors (cetuximab, erlotinib, gefitinib, panitumumab)	• Hypomagnesemia • Hypokalemia and hypocalcemia due to hypomagnesemia	• None
Bcr-abl tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib)	• AKI • CKD	• Acute tubular injury
Rituximab	• AKI • Tumor lysis syndrome	• Acute tubular injury • Uric acid nephropathy
Cancer immunotherapies		
Interferons (alpha, beta, gamma)	• AKI • Nephrotic-range proteinuria	• FSGS • TMA
IL-2	• AKI • Capillary leak syndrome	• Hemodynamic • Acute tubular injury
Chimeric antigen receptor T-cells (CAR-T)	• Capillary leak syndrome • AKI • Tumor lysis syndrome • Electrolyte disorders	• Hemodynamic • Acute tubular injury • Uric acid nephropathy (?)
CTLA-4 inhibitors (ipilimumab, tremelimumab)	• AKI • Proteinuria	• Acute tubulointerstitial nephritis • Acute tubular injury • Lupus-like glomerulonephritis • MCD • Necrotizing glomerulonephritis and vasculitis • TMA

Table 1: Continued

Medication	Clinical renal syndrome	Renal histopathology
PD-1 inhibitors (nivolumab, pembrolizumab, cemiplimab)	• AKI • Proteinuria	• Acute tubulointerstitial nephritis • Acute tubular injury • MCD • Immunoglobulin A nephropathy • FSGS • Necrotizing glomerulonephritis and vasculitis • AA amyloidosis • Electrolyte abnormalities
PD-L1 inhibitors (atezolizumab, avelumab, durvalumab)	• AKI	• Acute tubulointerstitial nephritis
Other drugs		
Bisphosphonates (pamidronate, zoledronate)	• AKI • Nephrotic syndrome	• Acute tubular injury • FSGS • MCD
Sirolimus	• AKI • Proteinuria	• FSGS

EGFR, epidermal growth factor receptor.

nephrotoxins can prevent or ameliorate cisplatin-induced nephrotoxicity. Amifostine, by improving DNA repair and elimination of free radicals, may reduce cisplatin injury; however, its use has been limited by adverse side effects [4]. Carboplatin and oxaliplatin are less nephrotoxic than cisplatin, but can still cause AKI in high-risk patients [5].

The alkylating agent ifosfamide is also associated with renal tubular injury, especially when combined with other tubular toxins. Ifosfamide and its metabolite chloracetaldehyde cause direct tubular epithelial cell damage by multiple mechanisms leading to both AKI and proximal tubular dysfunction, including Fanconi syndrome [6]. Risk factors for ifosfamide-related AKI include previous cisplatin exposure, underlying CKD and high cumulative doses (>84 g/m^2) [7].

Methotrexate when administered in high doses (>1 g/m^2) can lead to precipitation of the insoluble parent drug and metabolites (7-OH methotrexate) within tubular lumens and AKI from crystalline nephropathy [8]. Volume depletion and a low urine pH urine are risk factors for AKI. The overall incidence rate of AKI is approximately 1.8% (range 0%–12%), but is as high as 50% in at-risk patients [8]. In general, kidney injury is reversible. Preventive measures include volume repletion to achieve high urine flow rates as well as urine alkalinization (pH >7.5). Once AKI develops, methotrexate excretion is reduced and systemic toxicity may occur leading to severe pancytopenia. High-dose leucovorin therapy can reduce the systemic toxicity. Prolonged hemodialysis (6 h) can reduce plasma methotrexate levels by ∼70%, but due to rebound, must be performed daily for several days [9]. Glucarpidase, an enzyme that inactivates methotrexate, is an option during AKI when concerns for toxicity are high [10].

Pemetrexed, a new-generation multitargeted structural analogue of methotrexate antifolate agent, is currently primarily used to treat nonsquamous non-small-cell lung cancer (NSCLC) and mesothelioma [11]. It has mostly renal elimination via the organic anion tubular pathway, therefore its use is contraindicated for a creatinine clearance (CrCl) <45 mL/min [11]. Several cases of AKI associated with treatment with pemetrexed have been reported, and acute tubular nectosis, tubular atrophy, tubulointestitial nephritis and interstitial fibrosis have been described in kidney biopsies [12]. In a few cases AKI was associated with diabetes insipidus or distal tubular acidosis [12]. The incidence of AKI in the retrospective studies ranged from 6% to 20% [11], whereas in the one prospective study by Visser *et al.* [13] among patients with IIIB/IV stage NSCLC treated with pemetrexed developed acute kidney disease, leading in 55% to CKD and therapy discontinuation. Cumulative systematic dose of pemetrexed is the risk factor for AKI [14] and its nephrotoxicity is often irreversible, leading to CKD [15]. Pemetrexed could be used alone or in combination, mainly with cisplatin or with immunotherapy, therefore diagnosis of AKI is particularly challenging with regard to distinguishing between potential causes and stopping the corresponding treatment [16–18].

Cancer immunotherapies

Drugs that modulate the immune system are employed in cancer therapy and can be associated with AKI (Table 1).

Interferon therapy may be complicated by AKI as well as proteinuria from focal segmental glomerulosclerosis (FSGS) or minimal change disease (MCD), which develops after many weeks to months of drug exposure [19].

High-dose interleukin-2 (IL-2) is associated with a cytokine release syndrome (CRS) and capillary leak, which causes a prerenal form of AKI that develops within 24–48 h and is generally reversible with supportive care [20].

Immune-checkpoint inhibitors (ICPIs) leverage the immune response against cancer [21]. Tumors capitalize on normal immune checkpoints by overexpressing ligands that bind inhibitory cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) receptors—an effect that decreases T-cell infiltration into the tumor and inhibits antitumor T-cell responses [22]. To bypass this effect, monoclonal antibody drugs that block ligand binding to PD-1 and CTLA-4 receptors were designed to restore anti-tumor immunity. Ipilimumab and tremelimumab are humanized monoclonal antibodies against CTLA-4, while nivolumab, pembrolizumab and cemiplimab are humanized monoclonal antibodies against PD-1 receptors [22]. In addition, humanized monoclonal antibodies (atezolizumab, avelumab, durvalumab) target programmed cell death ligand 1 (PD-L1) [14]. A byproduct of these agents is that ICPI therapy may lead to autoimmunity and end-organ injury

such as AKI [21, 22]. The reported incidence of AKI is approximately 2%–3% when biopsy proven or clinically adjudicated [23, 24]. Development of AKI following ICPI exposure occurs from several weeks to many months after drug initiation. Acute tubular interstitial nephritis (ATIN) is the most frequently observed form of AKI with ICPIs [23, 24]. Some experts recommend kidney biopsy for stage 2/3 AKI, however a trial of corticosteroids may be considered without biopsy in some patients [23, 24]. Approximately one-third completely recover kidney function, while slightly less than half have partial kidney function recovery [23, 24].

Chimeric antigen receptor T-cells (CAR-T) are host cells that are harvested and engineered to express receptors that recognize and bind tumor antigens [25]. CRS is a common complication that can lead to AKI due to severe capillary leak with hemodynamic effects [25]. AKI was noted in 17%–24% of patients [25]. Prevention and treatment of AKI includes chemotherapy and corticosteroids prior to CAR-T exposure to reduce the tumor burden and IL-6 receptor blocker may reduce adverse systemic effects [26].

Targeted cancer therapies

Drugs that target mutated or overexpressed oncoproteins in cancers may also lead to nephrotoxicity (Table 1). Anti-angiogenesis drugs effectively treat several cancers through inhibition of the vascular endothelial growth factor (VEGF) pathway. These drugs lead to glomerular and peritubular capillary endothelial cell dysfunction, resulting in thrombotic microangiopathy (TMA) and AKI [27].

Selective B-RAF inhibition by vemurafenib and dabrafenib is effective against malignant melanoma, which frequently has a B-RAF V600 mutation. AKI develops in some patients treated with these agents [28]. Of 74 patients treated with vemurafenib, ∼60% developed AKI, primarily KDIGO stage 1, within 3 months of drug exposure [28]. Biopsy in two patients revealed tubulointerstitial injury; kidney function recovered within 3 months of B-RAF discontinuation [28]. Although the mechanism of kidney injury is unknown, these drugs may increase susceptibility to ischemic tubular injury by interfering with the downstream mitogen activated protein kinase (MAPK) pathway.

Small molecules inhibitors of anaplastic lymphoma kinase (ALK) are used in the treatment of NSCLC harboring a rearrangement of the *ALK* gene, fusion with echinoderm microtubule-associated protein-like 4 or the *ROS1* oncogenes [29]. The rise in serum creatinine during treatment with ALK inhibitors (first generation: crizotinib; second generation: alectinib, ceritinib, brigatinib; third generation: ensartinib, entrectinib) may be due inhibition of a creatinine transporter, thus interfering with the secretion of creatinine in the proximal tubule—it is therefore called pseudo-AKI [30]. True AKI due to both tubular and glomerular diseases was also described [31]. Crizotinib use could be also complicated by renal cyst development and progression [29]. Crizotinib treatment induces fibrosis and dysfunction of the kidneys by activating the tumor necrosis factor-α/nuclear factor-κB signaling pathway [32].

Radioligand therapies

Radioligand therapies have opened new treatment possibilities for oncology patients. They offer precise tumor targeting with a favorable efficacy-to-toxicity profile. Specifically, the kidneys, once regarded as the critical organ at risk for radiation toxicity from radiopharmaceuticals undergoing kidney excretion, also show excellent tolerance to radiation doses as high as 50–60 Gy [33]. Nephrotoxicity is one of the dose-limiting toxicities of these therapies due to renal retention of the radiopharmaceutical, such as in somatostatin receptor targeting PRRT (peptide receptor radionuclide therapy) and PSMA (prostate specific membrane antigen) targeting radioligand therapy. In patients with decreased kidney function, including those on dialysis, a modified protocol (Ulm University) should be used for PRRT including dose reduction (1.5–2 GBq of ^{177}Lu-DOTATATE instead of a higher dose) and timing of therapy (immediately after dialysis) (Fig. 1). Also, reduction of the empirical I^{131} dose should be considered in CKD patients, with just 50% of the dose in hemodialysis patients and dialysis to be performed 48 h before and after the administration of the radioisotope. Similarly, dose reduction is required in peritoneal dialysis [33].

CRITICAL PARAMETERS TO BE MONITORED IN CANCER PATIENTS WITH DECREASED KIDNEY FUNCTION RECEIVING ANTICANCER DRUGS

Electrolytes

Various electrolytes disturbances can occur as the result of the administration of anticancer agents in the patient with decreased kidney function. These patients are prone to developing hyponatremia, hyperkalemia and other metabolic abnormalities because of a decreased GFR. Therefore, all electrolytes, minerals and acid–base status should be checked at baseline and before each administration of chemotherapeutic agents. Hyponatremia is the most common abnormality and has been reported with multiple agents (Table 2). Hyponatremia can occur as the result of various mechanisms such as stimulation of anti-diuretic hormone (ADH) secretion (vincristine, cyclophosphamide) [34], tubular losses of salt (cisplatin) [35], and endocrinopathies such as adrenal insufficiency and hypothyroidism caused by ICPIs [36]. While fluid restriction is generally advisable for patients with advanced CKD and recommended for ADH-mediated mechanisms, it can exacerbate hyponatremia secondary to tubular losses [37]. Calcineurin inhibitors, platinum drugs and VEGF pathway inhibitors are the classes of drugs most often incriminated in the genesis of hypomagnesemia. Supportive drugs such as proton-pump inhibitors and diuretics commonly used in patients with cancer and/or decreased kidney function can also cause or exacerbate hypomagnesemia [38]. Hypomagnesemia can lead to secondary electrolyte imbalances such as hypokalemia, hypocalcemia and hypophosphatemia, and has also been linked to the development of AKI [39]. Among the supplements available for repletion, magnesium hydroxide should be avoided in patients with decreased kidney function [38]. Hypocalcemia most commonly occurs as the result of hypomagnesemia or secondary to anti-osteoclast agents such as bisphosphonates (e.g. zoledronic acid) and receptor activator of nuclear factor κ-B (RANK) ligand (RANKL) inhibitors (e.g. denosumab) use (especially in the setting of vitamin D deficiency). More rarely, it can be caused by autoimmune hypoparathyroidism with ICPI use or in response to calcium-sensing receptor–activating antibodies [40]. Denosumab is more likely than bisphosphonates to be administered to the patient with decreased kidney function due to its renal safety, however it is associated with an increased risk of hypocalcemia in this patient population and particularly in individuals with end-stage kidney disease (ESKD) [41]. Therefore, optimization of CKD-associated mineral bone disease and appropriate supplementation of calcium and vitamin D are essential prior to its administration. Hypoparathyroidism due to ICPIs use can also cause hyperphosphatemia, although hyperphosphatemia is most

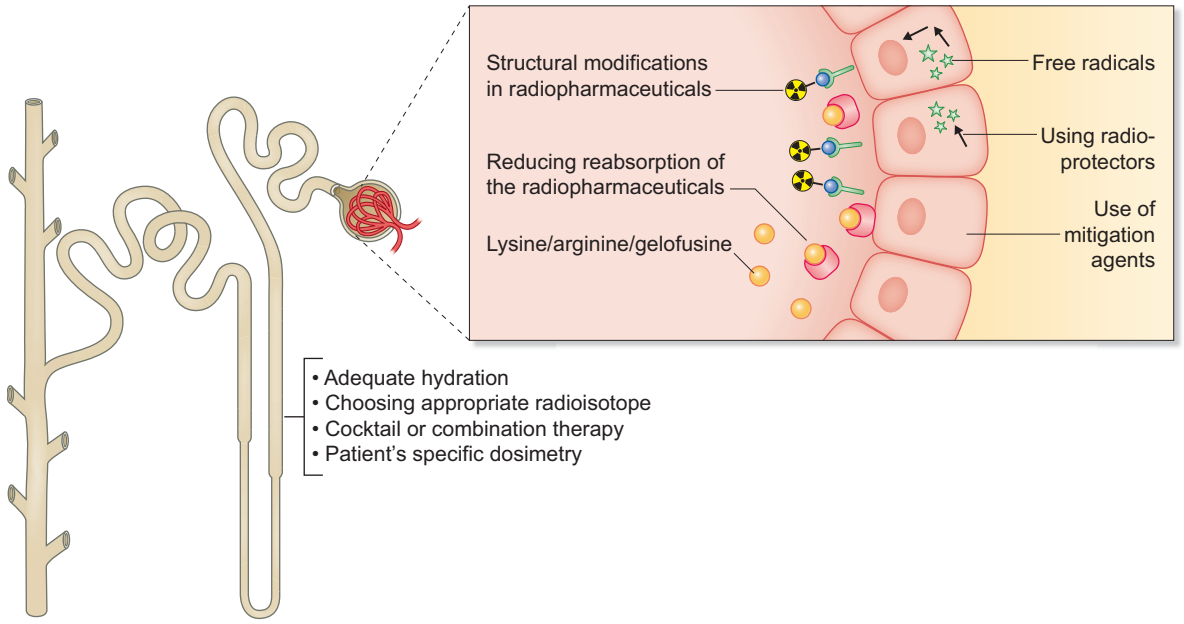

Figure 1: Mechanisms protecting against radioligand therapy (modified from [33]).

Table 2: Anticancer drug-related hyponatremia [34, 35, 40].

Class	Drug sub-class/name	Mechanisms
Vinca alkaloids	Vincristine Vinblastine	Increase vasopressin production/release
Alkylating agents	Cyclophosphamide, ifosfamide	Increase vasopressin production/release Increase water permeability of distal nephron
Platinum compounds	Cisplatin Carboplatin Methotrexate	Increase vasopressin production/release Increase vasopressin production/release
Immunomodulators	Interferon-α Interferon-γ IL-2	Increase vasopressin production/release Hypovolemia, capillary leak syndrome
Tyrosine kinase inhibitors	Imatinib Brivanib Cetuximab Pazopanib	Increase vasopressin production/release SiAD SiAD SiAD
BRAF/MEK inhibitors	 Selinexor	SiAD SiAD
ICPIs	PD-1 PD-L1/CTLA-4	Cortisol deficiency (hypophysitis panhypopituitarism, isolated ACTH deficiency, adrenalitis, primary adrenal insufficiency)
T-cell transfer therapy	Tumor-infiltrating lymphocyte therapy CAR-T cell therapy	SiAD Hypovolemia, capillary leak syndrome

SiAD, syndrome of inappropriate diuresis

often due to tumor lysis syndrome. Pemigatinib, a tyrosine kinase inhibitor of fibroblast growth factor receptor, has also been reported to cause hyperphosphatemia [42]. Finally, ICPI-related hypercalcemia has been noted with these drugs and can occur through different postulated mechanisms such as immune-mediated endocrinopathies, for instance secondary adrenal insufficiency due to hypophysitis, sarcoid-like granuloma, the release of parathyroid-related hormone and hyper-progressive disease following their initiation [43].

Blood pressure

Hypertension coexists in approximately 80%–85% of patients with CKD with a prevalence that increases as kidney function declines [44] and preexisting hypertension is an independent risk factor for increased blood pressure (BP) during anticancer therapy [45]. In addition, several classes of cancer therapeutics have been associated with the development of hypertension (Table 3). VEGF signaling pathway inhibitors (VSPIs), are the most common class of drugs associated with new or worsening hypertension, which

Table 3: Anticancer drug-related hypertension [45, 48].

Class of anticancer agents	Examples of agents	Estimated incidence if known
VSPIs	Acalabrutinib, axitinib, bevacizumab, bosutinib, cabozantinib, dasatinib, ibrutinib, imatinib, lenvatinib, nilotinib, pazopanib, tivozanib, vandetanib, sorafenib, sunitinib	20%–90%
Proteasome inhibitors	Bortezomib Carfilzomib Ixazomib	10% 32% NA
Alkylating agents Platinum agents	Cyclophosphamide, ifosfamide Cisplatin, carboplatin, oxaliplatin	36% 53%
	Vinca alkaloids Vincristine Vinblastine	
Taxanes	Abraxane, docetaxel, cabazitaxel, paclitaxel	
Antimetabolites	Gemcitabine	
mTOR inhibitors	Everolimus, sirolimus, temsirolimus	13%
Steroids	Dexamethasone, hydrocortisone, methylprednisolone, prednisolone	

NA, not available

occurs in up to 80% of the patients receiving these drugs [46]. BP monitoring and management constitute an important component of the management of the patient with decreased kidney function and cancer. It is advisable to obtain a baseline BP prior to initiating cancer therapy and to optimize management prior to therapy initiation. Patients should be counselled about the potential of worsening BP and should play an active role in monitoring their BP. Insufficient evidence exists to recommend one class of anti-hypertension medication over the other in this patient population, and therefore the general guidelines that apply to patients with CKD should be applied. First-line drugs usually include an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, with the additive benefit of reducing the proteinuria that can be seen with certain cancer drugs such as VSPIs. Dihydropyridine calcium channel blockers (e.g. amlodipine and nifedipine) are also often used due to their potent vasodilatory properties. Anticancer agents associated with hypertension should be held if BP rises above 180/110 mmHg and should not be restarted until BP is controlled to <160/100 mmHg. The goal for therapy control is usually <130/80 mmHg unless life-expectancy is limited. Cancer therapy–induced hypertension, especially that caused by VSPIs and proteasome inhibitors, is often reversible after discontinuation of these agents [47].

Proteinuria

Proteinuria is an early marker of drug toxicity and should be monitored in patients exposed to selected cancer therapeutics. An example would be renal-limited TMA associated with VSPIs. Other examples of cancer therapeutics leading to proteinuria include: (i) tyrosine kinase inhibition of the VEGF receptors has been associated with glomerulopathies such as MCD and FSGS [48]; and (ii) inhibitors of mammalian target of rapamycin (mTOR) can lead to albuminuria and podocyte injury [49]. Proteinuria should be quantified prior to initiation of therapy and thereafter at regular intervals by checking a spot urine protein and creatinine ratio. In the cases of proteinuria >2 g/day, hematuria and worsening kidney function, a kidney biopsy should be done to differentiate between drug toxicities and paraneoplastic disorders, which would require different therapeutic approaches [50]. Proteinuria after inhibition of VEGF signaling will frequently disappear upon stopping the responsible agent but others etiologies may lead to persistent proteinuria and renal injury.

Fluid retention

Fluid retention can be a major concern in the patient with cancer and decreased kidney function and caused through a variety of mechanisms. Both traditional chemotherapy such as anthracyclines and targeted therapies such as HER2-targeted therapies can cause cardiac toxicity, most commonly left-ventricular dysfunction leading to fluid retention and volume overload [51]. Imatinib, a tyrosine kinase inhibitor (TKI) commonly used in the treatment of chronic myelocytic leukemia and gastrointestinal stromal tumors, can cause significant edema through the blockage of platelet-derived growth factor receptors signaling which is responsible for the homeostasis of interstitial fluid [52]. However, edema in the cancer patient is not necessarily synonymous with excessive fluid retention and it is important in this population to distinguish lymphedema that can result from lymph node resection, surgical disruption of lymphatic vessels, or radiation therapy to lymph nodes and lymphatic vessels, from general edema. Compression and pneumatic therapies for lymphedema have been shown to improve quality of life [53]. Diuretic therapy should be avoided in this case unless there is evidence of concomitant fluid overload.

DOSAGE GUIDELINES FOR ADVANCED STAGE CKD

A lack of data is the most important hurdle to appropriate dosing of anticancer agents in patients with decreased kidney function. In patients with kidney dysfunction both the pharmacokinetic and pharmacodynamic properties of a drug can be altered. First, gastrointestinal absorption can be significantly altered: it can be decreased due to reduced gastrointestinal absorption due to edema of the gut wall but can also be increased due to impaired barrier function and/or altered expression of drug transporters. Second, it has been reported that uremic toxins can influence CYP450 activity and hepatic drug transporters [54]. Third,

even patients with moderately decreased kidney function have changes in volume of distribution (V_d) that occur with changes in body composition, hypoalbuminemia, decreased serum albumin binding or increased tissue binding or decreased V_d due to sarcopenia. Finally, in patients with kidney dysfunction, tubular elimination tends to increase relative to glomerular clearance and non-renal clearance can be altered in patients due to changes in drug-metabolizing enzymes and transporters [55]. In patients with ESKD, the impact of hemodialysis on pharmacokinetics/pharmacodynamics is dependent on several factors, such as dialysis filter characteristics, filter surface area, blood/dialysate/ultrafiltration rate and dialysis modality, in addition to drug characteristics such as molecular weight, protein binding and V_d. Peritoneal dialysis only results in a limited urea clearance and—as most drugs are larger than urea—the total drug clearance is only minimally affected by peritoneal dialysis [56].

Correct dosing of anticancer agents is essential to achieve optimal clinical outcomes. Estimation of kidney function is therefore a vital component of the dosing process. Underestimation of kidney function will result in unnecessary dose reductions and reduced effectiveness, failure of therapy, use of less effective or more toxic second- or third-line agents, and ultimately, decreased survival. Overestimation of kidney function on the other hand will result in increased toxicity and interruptions of treatment, stopping and switching to less effective or more toxic second- or third-line agents, and ultimately, decreased survival. In the cancer and non-cancer populations, to estimate the GFR (eGFR) the Chronic Kidney Disease Epidemiology Collaboration formula has proven to have superior performance over other creatinine-based GFR estimating formulae, and should be used for determination of kidney function for drug dosing [57]. There is emerging data in both adult and pediatric cancer patients that cystatin-based GFR estimating formulae might be superior to creatinine-based GFR estimating formulas in the detection of kidney dysfunction and correct dosing of anticancer drugs [57]. As the use of cystatin is not widespread at this moment, it is too early to recommend cystatin-based GFR estimating formulas for anticancer drug dosing.

GUIDANCE ON STOPPING DRUGS

The Common Terminology Criteria for Adverse Events (CTCAE) are a set of criteria for the standardized classification of oncologic drugs adverse events, prepared by of the US National Cancer Institute. The current version 5.0 was released on 27 November 2017 [58]. It uses a range of grades from 1 to 5. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is: 1, mild; 2, moderate; 3, severe; 4, life-threatening with urgent intervention indicated; and 5, death related to adverse events. Specific adverse events related to the kidney are rated as the following: CTCAE. CKD: grade 1, eGFR or CrCl < lower limit of normal (60 mL/min/1.73 m^2) or proteinuria 2+ present; urine protein/creatinine >0.5; grade 2, eGFR or CrCl 59–30 mL/min/1.73 m^2; grade 3, eGFR or CrCl 29–15 mL/min/1.73 m^2; grade 4, eGFR or CrCl <15 mL/min/1.73 m^2; dialysis or renal transplant indicated. Furthermore, AKI: grade 3, hospitalization indicated; grade 4, life-threatening consequences; dialysis indicated.

Even though a major renal adverse effect of all VEGF-targeted agents is proteinuria, there are no guidelines available for proteinuria management while on antiangiogenic therapy. It is suggested that bevacizumab be temporarily withdrawn if the 24 h proteinuria levels exceed 2 g/24 h, and permanently discontinued in nephrotic syndrome. Pazopanib should be discontinued at protein levels of 3 g/24 h or higher. There are no guidelines for other TKIs. Usually, the withdrawal of the offending drug leads to a significant reduction in proteinuria; however, persistence is common. In this case, in the absence of specific therapy directed against the underlying disease, administration of renin–angiotensin system blockade to lower intraglomerular pressure, may reduce protein excretion [59, 60]. CTLA-4 and PD-1 are -2 essential immune checkpoint receptors. The observed AKI when secondary to ATIN can be reversed upon drug discontinuation and introduction of systemic steroid therapy [61]. Another major adverse event leading to drug discontinuation or temporary withdrawal is drug-induced TMA (DITMA). It occurs from a cumulative dose, and the clinical course is characterized by gradual development of kidney injury, sometimes occurring even after the chemotherapy has been stopped. When it occurs because of an unusually high dose, the onset is sudden, like immune DITMA. Incriminated drugs include gemcitabine, mitomycin, pentostatin, vincristine, proteasome inhibitors and VSPIs. Management of DITMA involves drug discontinuation and supportive care, including platelet transfusion for clinically significant bleeding, dialysis if indicated and dose reduction of nephrotoxic chemotherapeutic agents. It is critical to withdraw the offending agent as DITMA can be fatal.

CONCLUSION

Nephrotoxicity of anticancer therapies represents an increasingly recognized problem for clinicians involved in treating oncology patients. The emergence of effective new therapies including targeted therapies for cancer patients significantly improved patients' prognoses, at the cost of a whole new spectrum of renal adverse events other than observed during conventional chemotherapy. As these adverse events can lead to dose reductions or interruption/withdrawal of treatment, which might negatively affect the overall and/or progression-free survival, proper recognition and management of specific toxic effects are of utmost importance. Associations between anticancer drugs, in particular targeted agents, and kidneys remain largely unexplored since randomized, controlled, phase III trials exclude patients with impaired kidney function; kidney adverse events are not frequently reported; and the methodology and terminology differ across trials in oncology (i.e. definitions of rise in serum, CKD or AKI). Moreover, studies on patients on KRT are very limited and only single cases or small case series have been published. Therefore, clinical therapeutical decisions in cancer patients with decreased function should be made by multidisciplinary teams constituted of medical oncologists, nephrologists and other specialists. Onconephrology is an evolving and expanding subspecialty. It is crucial to consider anticancer drug treatment in these patients and to offer them a chance to be treated effectively.

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CONFLICT OF INTEREST STATEMENT

None declared.

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