Chapter 11. Chemotherapy and Kidney Injury

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INTRODUCTION

By January 1, 2011, 4,594,732 people in the United States carried the diagnosis of invasive malignancy. On the other hand, with significant advances in anticancer therapies, the 5-year survival for cancer patients has increased from 48.9% in 1975–1979 to 68.5% in 2006 (1). These statistics show that a significant percentage of the population is likely to be exposed to chemotherapy and suffer various short-term and, in case of survivors, long-term adverse effects of treatment.

Kidneys are vulnerable to the development of drug toxicity due to their role in the metabolism and excretion of toxic agents. The kidneys receive close to 25% of cardiac output, and the renal tubules and proximal segment in particular have significant capacity for uptake of drugs via endocytosis or transporter proteins. The high rate of delivery and uptake results in high intracellular concentration of various substances that then undergo extensive metabolism, leading to formation of potentially toxic metabolites and reactive oxygen species (ROS) (2). Numerous chemotherapy agents have been associated with various renal toxicities including tubulointerstitial damage, glomerular disease, electrolyte abnormalities, hypertension, and proteinuria (Table 1).

AGENTS WITH PREDOMONANLTY TUBULAR TOXICITY

Platinum compounds

Cisplatin (*cis*-dichlorodiammineplatinum)–platinum coordination complex is an effective chemotherapy against a wide spectrum of tumors such as testicular, head and neck, ovarian, lung, cervical, and bladder cancers. Nephrotoxicity is the dose-limiting toxicity of cisplatin. Cisplatin induces the production of ROS and inhibits several antioxidant enzymes, leading to oxidative stress injury. It increases renal expression of tumor necrosis factor α, leading to increased tubular cell apoptosis and production of ROS (3). Cisplatin is excreted and concentrated in the kidneys entering renal tubular cells via organic cation transporter 2, which is kidney specific (3).

Initial renal toxicity manifests as a decrease in renal blood flow and subsequent decline in GFR within 3 hours of cisplatin administration. These changes are probably due to increased vascular resistance secondary to tubulo-glomerular feedback and increased sodium chloride delivery to macula densa. The decline in GFR appears to be dose dependent. In a group of patients who received four cycles of 100 mg/m^2, the ^{51}Cr-EDTA–measured GFR declined by 11.7%, whereas in patients who received three cycles of 200 mg/m^2, the mean decline was 35.7%. This effect was noted to be lasting, as GFR was still 30% below baseline at 2 years (4). Acute tubular toxicity of cisplatin causes mitochondrial dysfunction, decreased ATPase activity, impaired solute transport, and altered cation balance. As a result, sodium and water reabsorption is decreased, and salt and water excretion is increased, leading to polyuria (3). Cisplatin also causes dose-dependent renal magnesium wasting.

Tubulointerstitial injury is a predominant finding on pathologic examination of human kidneys affected by cisplatin toxicity. Both proximal and distal tubules are affected, and in patients with AKI, there is usually acute tubular necrosis. Long-term cisplatin exposure may also cause cyst formation and interstitial fibrosis (Figure 1) (3).

Patients with cisplatin toxicity typically present with progressive azotemia in the setting of bland urinalysis and minimal proteinuria. Although renal function improves in most patients, a subgroup of patients developed permanent renal impairment. Hypomagnesemia is common and may be present in

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Table 1. Nephrotoxicity of common chemotherapy drugs

Agent	Common pathologic finding	Clinical syndromes
Drugs with tubular toxicity		
Cisplatin	ATN	AKI, hypomagnesemia, renal sodium wasting, CKD
	Chronic interstitial fibrosis and cyst formation	
Ifosfamide	ATN	Fanconi syndrome (partial or complete)
		AKI
		ESRD
Methotrexate	Crystal nephropathy	Nonoliguric AKI
Pemetrexed	ATN	AKI
	AIN	CKD
	Tubular atrophy and interstitial fibrosis	Nephrogenic diabetes insipidus
Ipilimumab	AIN	AKI
Drugs with glomerular toxicity		
Gemcitabine	Thrombotic microangiopathy	AKI
		MAHA
		Hypertension
Mitomycin	Thrombotic microangiopathy	Dose dependent: AKI, MAHA
		Hypertension
Bevacizumab	Thrombotic microangiopathy	Proteinuria
		Hypertension
		Less common: Nephrotic syndrome
		AKI, MAHA
VEGFR mTKI	Thrombotic microangiopathy	Proteinuria
Sunitinib	MCD/cFSGS	Hypertension
Sorafenib		Less common: Nephrotic syndrome
Axitinib		AKI, MAHA
Pazopanib		
Drugs causing electrolyte abnormalities		
EGFR antibody	Inhibition of TRMP6 in distal convoluted tubule	Hypomagnesemia
Cetuximab		
Panitumumab		
Imatinib	Unknown	Hypophosphatemia

ATN, acute tubular necrosis; AIN, acute interstitial nephritis; MAHA, microangiopathic hemolytic anemia; VEGFR mTKI, vascular endothelial growth factor multitarget tyrosine kinase inhibitors; MCD/cFSGS, minimal change disease and/or collapsing-like focal segmental glomerulosclerosis; EGFR, epithelial growth factor receptor; TRMP, transient receptor potential cation channel, subfamily M, member 6.

42%–100% of patients depending on total cisplatin dose and length of exposure. Hypomagnesemia and renal magnesium wasting may persist for up to 6 years after initial dose (5). Renal salt wasting syndrome has been reported in up to 10% of patients, manifesting as hyponatremia and severe orthostatic hypotension in the setting of high urinary sodium concentration. This syndrome may present 2–4 months after initiation of cisplatin therapy (6). Rare cases of thrombotic microangiopathy have been reported in patients who were also receiving bleomycin with cisplatin (4). Syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been documented in patients receiving vigorous hydration (7) but is less common now as cisplatin-associated nausea is treated with new-generation antiemetics, diminishing the stimulus for antidiuretic hormone secretion.

Vigorous hydration has been shown to reduce the incidence of AKI in patients receiving cisplatin. Both mannitol and loop diuretics have also been used to ameliorate toxicity; however, randomized studies have not shown a clear benefit (8). Numerous compounds have been studied to prevent cisplatin nephrotoxicity but only amifostine is US Food and Drug Administration (FDA) approved for protection against cumulative nephrotoxicity from cisplatin therapy. Amifostine is protective by increasing the binding of ROS to thiol groups. Side effects, cost, and concerns that it also diminishes antitumor effect have limited its use in clinical practice (3). A recent study in a murine model showed that magnesium supplementation during cisplatin therapy may attenuate renal damage; however, further studies in humans are needed to validate these findings (9).

Carboplatin is also a platinum-based agent with a lower potential for nephrotoxicity compared with cisplatin but can be nephrotoxic at myeloablative doses of >800 mg/m^2 (10). Oxaliplatin, another platinum compound, has no nephrotoxic potential.

Ifosfamide

Ifosfamide is an alkylating agent used in the treatment of a variety of childhood and adult malignancies. Its use, however, is

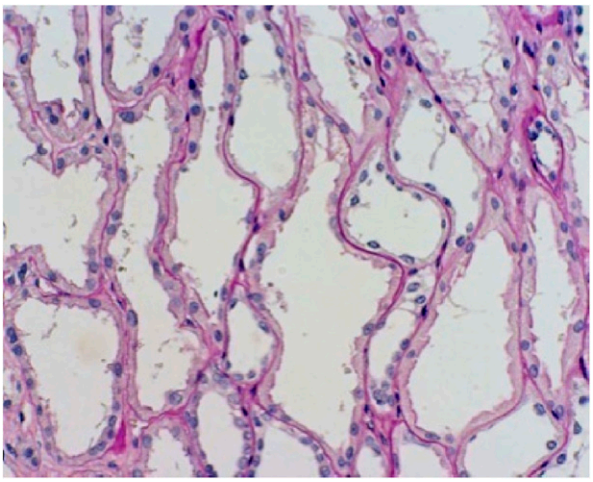

Figure 1. Cisplatin-induced acute tubular injury and necrosis (ATI/ATN). Light microscopy of the kidney biopsy specimen reveals dilated tubules with flattened epithelium. There is also apical blebbing of tubular cells and drop out of tubular cells from the basement membrane.

associated with a significant risk for nephrotoxicity. Because it is commonly used in children, most of the data pertaining to nephrotoxicity of ifosfamide have been obtained in pediatric patients. It has been reported that GFR goes to $<$90 mL/min per 1.73 m^2 in 50% of and $<$60 mL/min per 1.73 m^2 in 11% of patients treated with ifosfamide, with an average reduction of GFR of 35.1 mL/min per 1.73 m^2 at a median of 6 months after treatment (range, 1–47 months) (11). In adults, ifosfamide has been shown to reduce mean GFR from 81.5 to 68.5 mL/min per 1.73 m^2 1 year after treatment in patients with prior exposure to cisplatin (12).

Fanconi syndrome characterized by proximal tubular dysfunction with variable degrees of glucosuria in the setting of normoglycemia, renal phosphate and potassium wasting, proximal tubular acidosis, hypouricemia, and aminoaciduria has been reported in 5% of patients treated with ifosfamide (13). Patients who receive cumulative dose $<$60 g/m^2 are at lower risk of renal toxicity, whereas patients receiving $>$100 g/m^2 are at highest. Platinum combination therapy, renal irradiation, nephrectomy, and hydronephrosis are additional risk factors (14). Renal disease may progress even after ifosfamide is discontinued and may lead to ESRD (15). Although the precise incidence of severe kidney dysfunction after ifosfamide exposure is unknown, recent review indicates that it appears to be a sporadic complication without clear relationship to cumulative dose (16).

Methotrexate

Methotrexate (MTX) is an antifolate agent that inhibits dihydrofolate reductase (DHFR), an important step in DNA synthesis. Fifty percent to 70% of the drug is bound to plasma proteins, and 95% is found in the urine 30 hours after administration in subjects with normal renal function (17). MTX is both filtered and secreted by the kidneys. It is a weak organic acid and is poorly soluble in acidic urine (18).

Although it is administered over a large therapeutic range, only high-dose methotrexate (HDMTX) therapy of $>$1 g/m^2 has the potential for nephrotoxicity. MTX renal toxicity is presumed to be due to direct precipitation of the drug, as well to direct toxic effects on renal tubules. In a large clinical trial of 3,887 patients treated with HDMTX, renal dysfunction occurred in 1.8% of the subjects and was associated with a 4.4% mortality in this group (19). Affected patients usually develop nonoliguric and in more severe cases oliguric AKI shortly after the administration of HDMTX. Urinalysis is generally bland and without proteinuria. Because MTX is excreted in the urine, renal impairment affects the clearance of the drug. Prolonged exposure to toxic levels of MTX ($>$10 μmol/L at 24 hours; $>$1 μmol/L at 48 hours, and $>$0.1 μmol/L at 72 hours) may lead to life-threatening nonrenal toxicities such as prolonged cytopenias, mucositis, neurotoxicity, and hepatic dysfunction.

MTX solubility is 10-fold higher in urine with a pH of 7.5 than in acidic urine, and therefore urinary alkalinization and aggressive hydration (2.5–3.5 L/m^2 per 24 hours starting 12 hours prior to chemotherapy administration) are important steps to establish brisk diuresis and prevent methotrexate precipitation in the tubules. Probenecid, penicillins, salicylates, sulfisoxazole, and nonsteroid anti-inflammatory drugs may increase the risk of nephrotoxicity as they interfere with renal tubular secretion of MTX and delay excretion. Leucovorin rescue is used in patients who develop nephrotoxicity and is aimed at prevention of nonrenal complications. Leucovorin acts as an antidote by bypassing blocked DHFR pathway. In patients who have toxic levels of MTX, the leucovorin rescue dose is given according to established nomograms (17) with doses of 100–1,000 mg/m^2 administered every 6 hours. Leucovorin rescue is an effective sole therapy in patients with MTX toxicity (20).

Hemodialysis and hemoperfusion have been used in attempt to remove MTX from circulation. Although both modalities result in lower MTX plasma levels immediately after treatment, there is significant rebound effect with levels reaching 90%–100% of preprocedure MTX concentrations (19).

Glucarpidase (carboxypeptidase-G_2), a recombinant bacterial enzyme that rapidly metabolizes MTX to inactive compounds, is able to decrease MTX plasma level $>$98% within 15 minutes after administration and is effective as a single dose (21,22). Although a number of studies showed rapid rates of MTX removal in patients with HDMTX nephrotoxicity, none had a control group, and true clinical impact of glucarpidase is difficult to assess (22). Time to renal recovery in most studies was similar to that of the leucovorin rescue case series (20,22). In one study, glucarpidase was associated with lower risk of grade 4 nonrenal toxicity if administered $<$96 hours after HDMTX, but in the same study, inadequate leucovorin rescue was predictive of nonrenal toxicities. Glucarpidase only affects extracellular levels of MTX, which may explain the delay in renal recovery after MTX removal from circulation (23). The use of glucarpidase is limited by its high cost ($>$$100,000/patient),

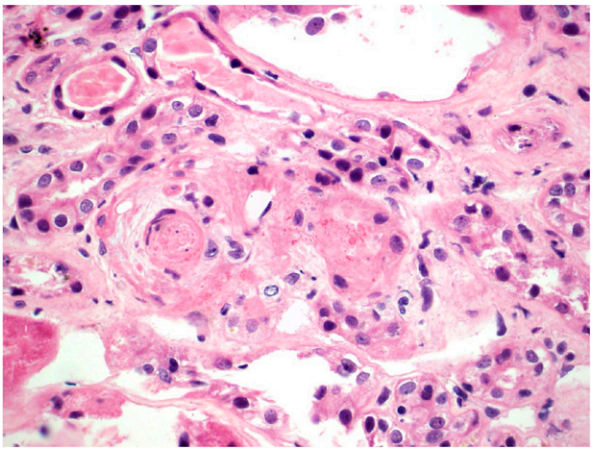

Figure 2. Gemcitabine-induced thrombotic microangiopathy. Light microscopy (H&E stain) of the kidney biopsy shows intra-arteriolar microthrombus. (Courtesy of Dr. Surya V. Seshan.)

and therefore its use should be considered only after standard supportive measures are maximized (22). For most patients, supportive care in the form of leucovorin rescue results in recovery of renal function, and additional doses of HDMTX may be given without untoward side effects (20).

Pemetrexed

Pemetrexed is an antifolate agent that inhibits several enzymes involved in DNA synthesis. This drug is not metabolized significantly, and 70%–90% of the drug is excreted unchanged in the urine within the first 24 hours after administration. The half-life of pemetrexed is 3.5 hours in patients with normal renal function but is increased in patients with renal insufficiency resulting in higher exposure to the drug (24). Pemetrexed has not been studied in patients with creatinine clearance (CrCl) $<$ 45 mL/min, but a fatality was reported in a patient with CrCl of 19 mL/min who received this drug (25). Mild and reversible renal toxicity has been reported in patients who received high-dose therapy ($\geq$600 mg/m^2). Recently, several cases of pemetrexed-induced tubular injury were reported (26–29) including interstitial nephritis and fibrosis, as well as diabetes insipidus. After discontinuation of pemetrexed, the renal function stabilized in these patients, but did not return to pretreatment baseline.

Ipilimumab

Ipilimumab is a novel immunotherapy agent that has shown significant promise in the treatment of metastatic melanoma. Ipilimumab is a fully human monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4), a key negative regulator of T-cell activation. Because of its immunomodulatory effects, ipilimumab has been associated with a number of immune-mediated side effects involving skin, liver, gastrointestinal tract, and endocrine system (30). Renal involvement appears less common, but two cases of biopsy proven granulomatous acute interstitial nephritis (AIN) and one case of lupus nephritis have been reported (30,31). Three other patients had AKI but did not undergo a kidney biopsy (30). Most patients improved with prompt discontinuation of ipilimumab and steroid therapy.

AGENTS WITH PREDOMINANTLY GLOMERULAR TOXICITY

Gemcitabine

Gemcitabine is a pyrimidine analog used in the treatment of a variety of solid tumors. Nephrotoxicity of this agent manifests as thrombotic microangiopathy (TMA). During early clinical experience, TMA was reported at a low rate of 0.015%; however, as the drug became more widely used, the incidence was noted to increase to as high as 2.2%. TMA presents as new-onset renal insufficiency, various degrees of microangiopathic hemolytic anemia (MAHA), and new or worsening hypertension (HTN). In a single institution experience of 29 cases of gemcitabine-induced TMA, *de novo* renal dysfunction or worsening of pre-existing CKD was noted in all patients (32). Kidney biopsies were performed in four cases and showed thrombi in small blood vessels, glomerular mesangiolysis, and widening of subendothelial space with detachment of endothelial cells from the glomerular basement membrane consistent with TMA (Figure 2). In this study, the development of TMA was independent of cumulative dose, which ranged from 4 to 81 g/m^2. After discontinuation of gemcitabine 28% of patients had complete recovery of renal function, and 48% had partial recovery or stable renal function. Although patients in this study did not undergo plasmapheresis, some authors advocate this treatment for patients with TMA due to gemcitabine. Literature reviews show no difference in outcomes between patients treated with plasmapheresis and conservative management with drug withdrawal (32,33).

Eculizumab, a monoclonal antibody directed against the complement protein C5 approved for treatment of atypical hemolytic uremic syndrome, has been used to treat gemcitabine-induced TMA (34–36). Of the six patients reported, two had complete renal response, two had partial improvement in renal function, and two patients showed no improvement. Given the response rates similar to supportive care alone, the use of eculizumab should be carefully weighed against its high cost.

Mitomycin

Mitomycin is an antitumor antibiotic isolated from *Streptomyces caespitosus* used for treatment of gastrointestinal and other solid tumors. It has been associated with life-threatening TMA with renal failure and MAHA. Mitomycin nephrotoxicity is dose dependent, with the risk of TMA being 1.6% with cumulative doses $\leq$49 mg/m^2 and as high as 30% at doses exceeding 70 mg/m^2 (37). Therefore, doses exceeding 40 mg/m^2 are not recommended.

Antiangiogenic agents

In the last several years, a group of agents called antiangiogenic therapies have been utilized in the treatment of a variety of solid

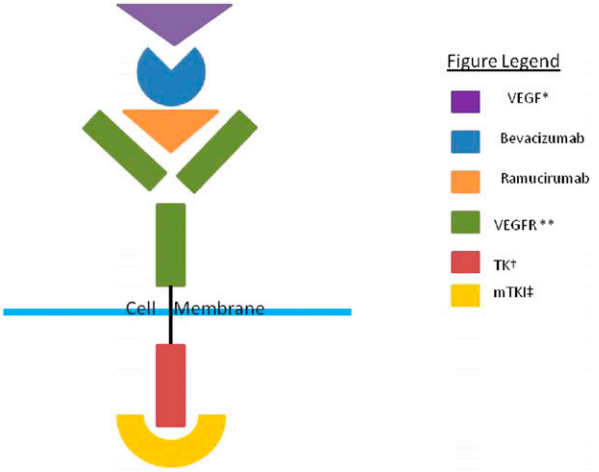

Figure 3. Vascular endothelial growth factor angiogenic pathway inhibition. VEGF binds its receptor expressed on the surface of endothelial cells and podocytes triggering intracellular and extracellular processes resulting in vascular proliferation. Several drugs classes have been employed to inhibit the activation of VEGFR and prevent angiogenesis, which is seminal for tumor growth. VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; TK, intracellular VEGFR tyrosine kinases; mTKI, multitarget tyrosine kinase inhibitors.

tumors. Angiogenesis is seminal for tumor growth and development of metastases, making it an attractive target for therapeutic intervention. Vascular endothelial growth factor (VEGF) is a proangiogenic factor that binds to a family of VEGF receptors (VEGFRs), with tyrosine kinase activity (TKR). The receptor binding triggers intracytoplasmic signaling pathways, leading to proliferation of endothelial cells and pericytes, recruitment of endothelial cell precursors, and growth of capillaries (38). In the kidneys, VEGF is expressed in podocytes, signals glomerular endothelial cells, and regulates survival of podocytes via autocrine mechanisms. VEGF maintains podocyte cytosolic calcium concentration and selective barrier to macromolecules (39). In addition, VEGF influences BP by up-regulating the synthesis of nitric oxide in the vascular endothelium and increasing the production of prostacycline resulting in vasodilatation (40).

Several classes of antiangiogenic therapies targeting VEGF pathway are now available (Figure 3). Bevacizumab is a blocking humanized monoclonal antibody directed against VEGF. Another class is represented by a group of drugs known as small molecule multitarget tyrosine kinase inhibitors (mTKIs). These agents inhibit VEGFR and a number of other TKRs and include sunitinib, sorafenib, axitinib, and other drugs. Ramucirumab is a recombinant human monoclonal antibody directed against VEGFR.

The renal effects of VEGF inhibition have been studied in murine models. When the *VEGF* gene is deleted only from podocytes in mice, they become hypertensive and proteinuric. Pathologic findings in the kidneys revealed typical features of TMA with intracapillary thrombi, endotheliosis, and obliterated capillary loops (41). In humans, a similar spectrum of disorders has been associated with VEGF inhibition. Hypertension, proteinuria, and TMA have all been reported after VEGF inhibition.

The effects of anti-VEGF antibody therapy on blood pressure were recently reviewed in a meta-analysis of seven randomized clinical trials that included 1,850 patients treated with bevacizumab. In patients who received a low dose (3–7.5 mg/kg/dose) of the drug, the relative risk (RR) of developing HTN was 3.0 (95% CI, 2.2–4.2; $P<0.001$). In a high-dose group (10–15 mg/kg/dose), the RR was 7.5 (95% CI, 4.2–13.4; $P<0.001$). Grade III HTN (requiring therapy or more intense therapy) was observed in 8.7% of patients in low-dose and 16.0% in high-dose groups. Proteinuria was also more common in treated patients. In the low-dose group, RR for proteinuria was 1.4 (95% CI, 1.1–1.7; $P=0.003$), and in the high-dose group, RR was 2.2 (95% CI, 1.6–2.9; $P<0.001$). Grade III (>3.5 g/24 h) proteinuria was noted in 1.8% of patients in the high-dose group vs. only 0.1% of controls (42).

TMA is the predominant glomerular lesion associated with anti-VEGF antibody therapy. It has been reported after intravenous (41,43–45) and ntraocular administration (46). However, concurrent mesangial IgA deposits, cryoglobulinemic glomerulonephritis (47), and immune complex–mediated focal proliferative glomerulonephritis (48) have also been reported. In patients with kidney biopsy findings of TMA, the clinical course varied from subnephrotic range proteinuria to more fulminant disease with worsening renal function, hypertension, and microangiopathic anemia (41,43–45).

Hypertension is another major side effect of mTKI therapy. In a meta-analysis of 13 clinical trials that included 4,999 patients with renal cell carcinoma (RCC) and other malignancies treated with sunitinib, the incidence of all-grade hypertension was 21.6% and high grade was 6.8%. However, the RR was only statically significant for patients with high-grade hypertension at 22.72 (95% CI, 4.48–115.3). Furthermore, when patients were analyzed by the type of malignancy, only those with RCC had a statistically significant RR of developing both all-grade and high-grade HTN. More pronounced effects of mTKI in RCC may be due to higher VEGF levels in patients with RCC, resulting in a more evident anti-VEGF effect. In addition, the majority of patients with RCC also undergo nephrectomies, resulting in reduction in renal function and decreased excretion of sunitinib, leading to prolonged exposure to the drug (49).

In phase 2 trials of axitinib proteinuria, all-grade proteinuria was reported in 18%–36% of subjects and grade ≥3 was 0%–5% (50). Proteinuria and nephrotic syndrome due to sunitinib or sorafenib have been described in a number of case reports and one case series (51–55). In these publications, proteinuria of up to 20 g/24 h has been reported, usually in association with new or worsening hypertension. These side effects generally resolved after discontinuation of mTKI. Two patients had a kidney biopsy that showed features of TMA in one patient and TMA and podocyte effacement in another. MAHA was not present in either case (53,55).

Several more fulminant cases of TMA with worsening renal function, severe hypertension and MAHA with low haptoglobin, high lactate dehydrogenase levels, and schistocytosis have also been reported (43,56–58). However, in a cohort study of 29 patients treated with mTKIs who developed proteinuria and HTN and underwent a biopsy, minimal change disease and/or collapsing-like focal segmental glomerulosclerosis (MCD/cFSGS) was found in 20 cases (45). However, >55.5% of these patients had a history of nephrectomy, and hyperfiltration injury as a cause of MCD/cFSGS could not be completely ruled out.

Because the putative mechanism of hypertension in patients treated with anti-VEGF therapies is intricately related to the antitumor action of these drugs, it has been proposed that the development of HTN could be used as biomarker of response (59). Two small retrospective studies showed that the development of hypertension was associated with improved oncologic outcomes in patients with RCC treated with axitinib and sunitinib (60,61). In a retrospective analysis of >500 patients treated with sunitinib for RCC, the overall survival (OS) and progression-free survival (PFS) was more than four-fold higher in the group of patients who developed sunitinib-induced hypertension defined as a maximum systolic blood pressure of ≥140 mmHg. However, hypertensive patients had more renal adverse events (5% versus 3%, $P = 0.013$) (62). OS and PFS were also improved in patients with advanced non–small-cell lung cancer treated with bevacizumab who developed treatment-related hypertension. In this study, hypertension was defined as BP >150/100 mmHg or a ≥20-mmHg rise in diastolic blood pressure (DBP) (63).

Nephrologists should be aware of these data as recommendations to discontinue anti-VEGF therapy due to the development of hypertension and proteinuria should be weighed against the possible enhanced antitumor effects in this setting. An expert panel from the National Institute of Cancer has issued guidelines in management of anti-VEGF therapy–induced hypertension. It recommends careful assessment of the patients prior to the initiation of therapy to identify those with cardiovascular risk factors, addressing preexisting hypertension prior to initiation of anti-VEGF therapy, and frequent monitoring of BP particularly during the first cycle. The patients should be treated if they develop BP >140/90 mmHg or DBP ≥20 mmHg higher than baseline. The panel did not make any specific recommendations about antihypertensive regimen due to lack of data and stated that treatment should be individualized to fit the patient's comorbid conditions and to minimize drug interaction (64). Other considerations include concurrent development of proteinuria as a complication of anti-VEGF therapy. In this setting, it may be appropriate to use angiotensin converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) for their antiproteinuric effect. Additionally, use of ACE-Is or ARBs in combination with anti-VEGF therapy may have a synergistic effect on OS in patients with RCC (65). Although long-term effects of anti-VEGF therapy–induced HTN and proteinuria are unknown, it is probably prudent to continue the anticancer therapy if HTN and proteinuria are controlled with medical therapy. However, if complications such as nephrotic syndrome, HTN with end-organ damage, renal insufficiency, or evidence of MAHA develop, discontinuation of antiangiogenic therapy should be considered promptly.

In addition to HTN, proteinuria, and TMA, both mTKI and anti-VEGF antibody agents have been reported to cause acute AIN (54,66–69). Although some cases have been confirmed by renal biopsy, in others the diagnosis was made on clinical grounds because biopsy was precluded by thrombocytopenia or the presence of a solitary kidney. These patients had eosinophilia, eosinophiluria, and kidney dysfunction, and renal function either improved or stabilized after discontinuation of antiangiogenic therapy. In two cases, mTKI was administered intermittently (4 weeks on and 2 weeks off), and the patients exhibited "saw tooth" fluctuations in eosinophilia and SCr levels, with both parameters improving just before the initiation of the next cycle (54).

AGENTS ASSOCIATED WITH ELECTROLYTE ABNORMALITIES

Hypomagnesemia as a common complication of cisplatin therapy and Fanconi syndrome due to ifosfamide treatment have been addressed by this review already. However, a number of targeted biological agents have been associated with electrolyte imbalance.

Cetuximab

Cetuximab is a chimeric monoclonal antibody directed against epithelial growth factor receptor (EGFR). The EGFR is overexpressed in several tumors of epithelial origin, and cetuximab is often used in combination with chemotherapy for their treatment. Although in initial clinical trials hypomagnesemia was not reported (70), numerous published reports have established a link between low serum Mg^{2+} and use of cetuximab.

Active Mg^{2+} transport in the kidney occurs predominantly in the distal convoluted tubule (DCT) and where EGFR is also expressed. TRPM 6 (transient receptor potential cation channel, subfamily M, member 6) has been demonstrated to play a role in this process. The epithelial growth factor (EGF) markedly increases the activity of TRMP 6, leading to the hypothesis that EGFR activation is necessary for reabsorption of Mg^{2+} and that blockade of EGFR leads to renal Mg^{2+} wasting (71) by blocking the activity of TRMP6. In one of the earlier reports, 34 patients on cetuximab had their Mg^{2+} level measured at least once. Of these patients, 23% had grade 3 (<0.9–0.7 mg/dL) and 6% had grade 4 (<0.7 mg/dL) hypomagnesemia (72). In another report, the incidence of grade 3/4 hypomagnesemia was 27% (73). The severity of hypomagnesemia appears to correlate with duration of exposure and is difficult to manage. Daily infusions of up to 6–10 g of $MgSO_4$ were required to correct the deficit in one cohort (73). Hypomagnesemia resolved in all cases after 4 weeks of discontinuation of cetuximab.

Patients who develop clinically significant hypomagnesemia are also hypocalcemic due to parathyroid hormone resistance,

which is often seen in the presence of hypomagnesemia and resolves after Mg^{2+} levels are normalized (72,73).

In more recent randomized trials, the incidence of grade 3/4 hypomagnesemia ranged between 1.8%–5.8% in the cetuximab arm and 0%–0.4% in chemotherapy or best supportive care (BSC) arms. However, in these studies, the Mg^{2+} levels were not routinely measured, which likely explain the lower incidence of hypomagnesemia (74).

Panitumumab

Panitumumab is a fully human antibody directed at EGFR and is used in treatment of metastatic colorectal cancer. In randomized trials, it has also been shown to cause low serum Mg^{2+} levels, with an incidence of grade 3/4 hypomagnesemia ranging between 3%–5% in the panitumumab arm and 0%–$<$1% in chemotherapy or BSC arms (75,76).

Imatinib

Imatinib is a small molecule mTKI with specificity for BCR-Abl, C-kit, and platelet-derived growth factor receptor (PDGFR) and activity against tumors characterized by dysregulation of function of these enzymes. Use of imatinib has been shown to cause hypophosphatemia. In the initial report, hypophosphatemia developed in 25 (51%) of 49 patients who had at least one measurement of serum phosphorus. Patients with both low and normal serum phosphate levels were found to have high urine fractional excretion of phosphate compared with controls, but only hypophosphatemic patients had elevated parathyroid hormone (PTH) levels (77). In another study, 14 (39%) of 36 patients treated with imatinib developed hypophosphatemia and low PTH levels (78). Additionally, serum phosphate levels were measured routinely in two clinical trials of 403 patients with chronic myeloid leukemia receiving imatinib. Hypophosphatemia was observed in 50% of the patients, but hypophosphatemia as an adverse event was only reported in 3% of the patients (79). The exact mechanism by which imatinib causes hypophosphatemia is unknown, but it has been proposed that it may inhibit bone resorption via inhibition of PDGFR and lead to decreased calcium and phosphate efflux from the bone. Lower calcium egress from bone has been postulated to cause mild secondary hyperparathyroidism, which in turn leads to increased renal phosphate losses (77).

CONCLUSIONS

Despite advances in diagnosis, treatment, and prevention of chemotherapy-induced kidney injury, significant challenges still remain. In many cases, the only therapeutic intervention available is the discontinuation of the offending agent. Future research should be directed toward development of antidote agents that protect normal cells and allow continuation of chemotherapy without compromising antitumor effects. In addition to traditional cytotoxic agents, new targeted biological therapies have been associated with kidney disease due to interference with signaling pathways in nonmalignant cells.

TAKE HOME POINTS

- A high percentage of the US population undergoes chemotherapy treatments and is at risk for renal complications because kidneys are a major route of elimination of these drugs.
- Cisplatin and ifosfamide are major tubular toxins leading to both AKI and CKD.
- Glomerular toxicity of chemotherapy most commonly manifests as TMA, with gemcitabine and mitomycin as major offenders.
- VEGF antagonists such as anti-VEGF antibody and VEGFR TKI are associated with development of hypertension and proteinuria and in severe cases TMA. Most patients are managed with antihypertensive drugs, with discontinuation of therapy only in patients who develop nephrotic syndrome, malignant hypertension, or TMA.

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REVIEW QUESTIONS

1. The best treatment options for gemcitabine induced thrombotic microangiopathy are:
   a. Plasmapheresis
   b. Administration of eculizumab
   c. Discontinuation of gemcitabine and best supportive care
   d. All of the above

Answer: c is correct. Whereas both plasmapheresis and eculizumab have been used in the treatment of gemcitabine-induced thrombotic microangiopathy, there is little evidence that outcomes of these treatments are superior to supportive care alone.

2. Which presentation is most consistent with cisplatin nephrotoxicity?
   a. Elevated serum creatinine, minimal proteinuria, hypomagnesemia
   b. Hypertension, elevated serum creatinine, low platelet count
   c. Nephrotic range proteinuria, hypertension, and edema
   d. Elevated serum creatinine, hypophosphatemia, glucosuria

Answer: a is correct. Cisplatin toxicity involves damage to the tubulo-interstitial compartment and manifests as AKI with relatively normal urinalysis. Hypomagnesemia is a common manifestation of cisplatin tubular toxicity. Cisplatin does not cause nephrotic syndrome, and thrombotic microangiopathy and Fanconi syndrome are rare.

3. A 55-year-old man with a history of metastatic renal cell carcinoma was begun on treatment with sunitinib (VEGFR TKI). Two months after starting the treatment, he was noted to have a BP of 154/90 mmHg, and his random urinary protein to creatinine ratio was 2.3. The patient was asymptomatic. His renal function remained normal, and there was no evidence of hemolysis on his blood work. The next step is:
   a. Discontinue sunitinib and offer best supportive care
   b. Begin antihypertensive therapy aimed at reducing his blood pressure to $<$140/90 mmHg and continue to monitor urinary protein to creatinine ratio closely
   c. Reduce sunitinib dose
   d. Switch the patient from sunitinib to sorafenib

Answer: b is correct. There are no evidence-based recommendations on management of proteinuria and hypertension induced by VEGF inhibitors. In practice, these agents are generally continued unless patients develop nephrotic syndrome, malignant hypertension, or thrombotic microangiopathy. Reduction of the sunitinib dose may be attempted as a next step if hypertension is difficult to control (answer c). Sorafenib is likely to have a similar side effect profile (answer d).