CHAPTER 217

Anticancer Drugs and the Kidney

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OBJECTIVES

This chapter will:

1. Characterize major nephrotoxic chemotherapy agents and their effect on kidney function and electrolyte homeostasis.
2. Describe strategies aimed at preventing and alleviating chemotherapy-induced acute kidney injury.
3. Provide guidelines for administration of chemotherapeutic agents to patients undergoing renal replacement therapy.

The kidneys represent the major elimination pathway for many chemotherapeutic agents and are vulnerable to toxic effects of chemotherapy. Antineoplastic agents are known to cause acute kidney injury (AKI) and chronic kidney failure (CKD) as well as electrolyte abnormalities. Dose, patient characteristics, and coadministration of other nephrotoxins determine the degree of kidney impairment.

CONVENTIONAL CHEMOTHERAPY

Cisplatin

Cisplatin, a platinum-based compound, is used widely as first-line chemotherapy for a variety of solid tumors. After intravenous administration, more than 90% of cisplatin is protein bound, and only 30% is eliminated by the kidneys in the first 24 hours via glomerular filtration and tubular secretion.[1] Nephrotoxicity is its dose-limiting side effect. The S3 segment of the proximal tubule in the corticomedullary region is the most common site of cisplatin nephrotoxicity in rats. More distal sites also may be affected in humans, whereas glomeruli remain unaffected.[2,3]

Cisplatin causes decreases in renal function in a dose-dependent fashion. Single doses less than 50 mg/m^2 rarely cause clinically significant AKI. Acute nonoliguric renal failure occurs with higher doses usually 3 to 5 days after exposure and is associated with minimal proteinuria (<0.5 g/day). Function usually returns to baseline within 2 to 4 weeks, although recovery may be delayed for several months.[4] CKD also may develop after prolonged exposure, but few patients progress to end-stage renal disease.[5,6]

Cisplatin-induced renal salt wasting may result in significant morbidity, including severe hyponatremia, orthostatic hypotension, mental status changes, and prerenal azotemia. This syndrome develops 2 to 4 months after starting cisplatin and is treated with normal saline hydration and oral sodium supplementation where feasible.[7,8]

Magnesium-wasting is present in virtually all patients treated with multiple courses of cisplatin. Cisplatin impairs magnesium reabsorption in the ascending limb of loop of Henle and distal tubules resulting in hypermagnesiuria despite low serum magnesium concentrations. Hypomagnesemia also may be exacerbated by coadministration of aminoglycosides, amphotericin, loop diuretics, foscarnet, and others. Cisplatin-induced hypomagnesemia may persist for up to a number of years and can be associated with hypokalemia and hypocalcemia.[9]

Vigorous saline diuresis and fractionated or continuous infusion of the total cisplatin dose have been effective in reducing cisplatin nephrotoxicity. Recent studies showed that osmotic and loop diuretics given do not significantly attenuate kidney toxicity of cisplatin and cannot be recommended at this time.[10]

Although numerous compounds have been tested to prevent cisplatin nephrotoxicity, only amifostine, an inorganic thiophosphate, has been approved for prevention of cisplatin-induced kidney damage. It likely acts via free radical scavenging mechanism and intracellular binding of the drug, but concerns that amifostine also diminishes antitumor effect have limited its use in clinical practice.[10]

Carboplatin

Carboplatin is another platinum-containing antineoplastic agent. Its dose-limiting toxicity is myelosuppression with the maximum tolerated dose of 1200 mg/m^2. Higher doses (up to 2.1 g/m^2) require stem cell transplant rescue and may lead to nephrotoxicity. High-dose carboplatin-induced renal toxicity is a transient but frequent complication occasionally requiring renal replacement therapy, although irreversible renal failure is infrequent.[11]

Methotrexate

Methotrexate (MTX) is a folic acid antagonist antimetabolite that is effective against many malignancies. When given at doses that exceed 1 g/m^2 MTX has a tendency to precipitate in the renal tubules, especially in an acidic pH. This may lead to crystal-induced nonoliguric, nonproteinuric renal failure 1 to 2 days after initial exposure. Because MTX is excreted by the kidney, renal failure leads to toxic MTX blood levels. The accumulation of MTX places patients at risk for prolonged myelosuppression, severe mucositis, and hepatitis. Vigorous intravenous saline and, when necessary, loop diuretics are administered to maintain high urine flow during infusion and afterward until nontoxic levels of MTX (<0.1 μmol/L) are achieved. Sodium bicarbonate is infused concomitantly to alkalinize the urine and inhibit crystal formation.[12] When appropriate preventative measures are employed, MTX-induced AKI is relatively rare. Only 1.8% of patients treated with high-dose MTX for osteosarcoma develop grade 2 or greater nephrotoxicity. However, once AKI develops, mortality is 4.4%.[13]

Because AKI is usually self-limited and resolves in 12 +/- 7 (mean +/- SD) days,[14] the goal of therapy is to prevent extrarenal MTX toxicity. Intravenous leucovorin is given as an antidote at doses ranging from 100 to 1000 mg/m^2 every 3 to 6 hours depending on MTX level and until such level is below the toxic threshold.[12] Glucarpidase (carboxipeptidase-G_2) selectively hydrolyzes MTX to inactive metabolites and

lowers MTX levels by a median of 97% (range 73%–99%) within 15 minutes of administration.[15] 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.[16] Time to renal recovery in most studies was similar to that of the leucovorin rescue case series.[16,17] Glucarpidase affects only extracellular levels of MTX, which may explain the delay in renal recovery after MTX removal from circulation.[18] The use of glucarpidase is limited by its high cost (>$100,000/patient), and therefore it should be considered only after standard supportive measures are maximized.[16]

Hemodialysis, high-flux hemodialysis, charcoal-based hemoperfusion, and hemofiltration have been used also to remove MTX in patients with AKI. High-flux hemodialysis appears to be most effective with a median MTX reduction ratio of 75.5% (42%–94%). All modalities exhibited significant postprocedure rebound.[13] Patients who develop MTX renal toxicity can be rechallenged successfully once renal failure resolves.[19]

Pemetrexed

Pemetrexed is excreted unchanged by the kidney (70%–90% in 24 hours).[20] Consequently, there is a risk of nonrenal toxicity secondary to accumulation of the drug in renal insufficiency. In clinical trials renal toxicity has been reported with high dose (600 mg/m^2). Cases of acute tubular necrosis, interstitial nephritis, and nephrogenic diabetes insipidus have been described.[21–24]

Gemcitabine

Gemcitabine is a nucleoside analogue with antineoplastic activity against a variety of solid tumors, including pancreatic, non–small cell lung, bladder, ovarian, and breast carcinomas. The primary toxicity of gemcitabine is myelosuppression and liver function abnormalities. Thrombotic microangiopathy (TMA) is a well-described complication with an incidence of up to 0.31%. The presentation is subacute with insidious onset of renal dysfunction, microangiopathic hemolytic anemia (MAHA), hypertension, and thrombocytopenia. When unrecognized, progression to fulminant acute renal failure and hypertensive crisis can occur.[25,26] In a report from a single institution, 29 patients with gemcitabine-induced TMA were described. Gemcitabine was discontinued as soon as TMA was recognized. Patients were treated with supportive therapy only. Nineteen patients achieved full or partial renal recovery, seven patients progressed to end-stage renal disease (ESRD), and three developed CKD but did not require dialysis.[27] 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. Although there may be rapid resolution of thrombocytopenia, improvements of MAHA and kidney function are less predictable.[28]

Mitomycin

Mitomycin is used as salvage therapy for many solid malignancies. It is an alkylating agent isolated from *Streptomyces caespitosus.* Mitomycin is associated with TMA at total cumulative doses above 40 to 60 mg/m^2. TMA usually occurs within 4 to 8 weeks after the last dose and carries a poor prognosis, with most patients dying within 4 months because of renal or pulmonary failure or from progression of cancer.[29]

Ifosfamide

Ifosfamide is a nitrogen mustard analogue alkylating agent. Its active metabolite, acrolein, is toxic to urinary epithelium and causes hemorrhagic cystitis. Ifosfamide also has significant renal toxicity with proximal tubular damage resulting in Fanconi syndrome with urinary phosphorus and potassium wasting, non–anion gap metabolic acidosis (proximal renal tubular acidosis), glycosuria at normal serum glucose levels, and aminoaciduria. Distal tubular defects also may be present, causing nephrogenic diabetes insipidus and distal tubular acidosis.[30,31] Acute as well as chronic kidney failure have been reported.[32] Moderate to severe nephrotoxicity occurs in 18% to 28% of patients treated with ifosfamide. Risk factors for the development of renal dysfunction include prior or concurrent cisplatin administration, unilateral nephrectomy, and cumulative dose of the drug exceeding 60 to 72 g/m^2.[31] A safe dose limit has not been established; doses as low as 6 g/m^2 given over 2 days have been reported to be toxic.[33] Age younger than 5 years also has been reported as risk factor, but recent reports indicate that adults may be equally susceptible to ifosfamide renal toxicity.[31,34] Saline infusion has been used for prevention of ifosfamide nephrotoxicity and hemorrhagic cystitis. Mesna compound (2-mercaptoethane sulfonic acid) given orally or intravenously is converted into active metabolites, which bind acrolein and prevent development of hemorrhagic cystitis. It is ineffective against renal toxicity.[35]

Bisphosphonates

Pamidronate and zoledronic acid are intravenous bisphosphonates used in oncology for treatment of hypercalcemia of malignancy and lytic metastatic bone lesions. Both drugs are excreted renally unchanged and have been associated with significant nephrotoxicity. Acute tubular necrosis has been reported with both agents.[36,37] Pamidronate also has been linked to focal segmental glomerulosclerosis with nephrotic syndrome and renal failure.[38] In clinical trials, 9% to 15% of the patients who received zoledronic acid developed renal dysfunction manifested by elevated serum creatinine levels. Of patients who developed AKI, 25% received only a single dose of the drug. Risk factors for nephrotoxicity include advanced cancer, previous exposure to bisphosphonates, and use of nonsteroidal antiinflammatory drugs as well as duration and dose of the infusion.[39,40] Careful monitoring of renal function in patients treated with intravenous bisphosphonates is mandatory. According to the manufacturers, pamidronate should not be given to patients with serum creatinine of 3 mg/dL or higher, and zoledronic acid should be avoided in patients with creatinine clearance of 30 mL/min or less. Treatment should be discontinued if renal function deteriorates. Patients may be rechallenged with the drug once renal function returns to within 10% of baseline.[41]

TARGETED AND BIOLOGIC THERAPY

Targeted and biologic therapies are being used more frequently in treatment of cancer. They offer potential for lower systemic toxicity and improved patient outcome.

Antiangiogenic Therapy

Angiogenesis is seminal for tumor growth and development of metastases. Vascular endothelial growth factor (VEGF) is a proangiogenic factor that binds to a family of VEGF receptors (VEGFR), with tyrosine kinase activity. The receptor binding triggers intracytoplasmic signaling pathways promoting angiogenesis.[42] In the kidneys, VEGF is expressed in podocytes and regulates their survival.[43] VEGF also influences blood pressure (BP) through a variety of mechanisms.[44] Several classes of antiangiogenic therapies targeting VEGF pathway are now available. Bevacizumab is a blocking humanized monoclonal antibody directed against VEGF. Another class is represented by a group of drugs known as small molecule multi-target tyrosine kinase inhibitors (TKI). These agents inhibit VEGFR as well as a number of other TKIs and include sunitinib, sorafenib, axitinib, and other drugs. Ramucirumab is a recombinant human monoclonal antibody directed against VEGFR.

Anti-VEGF antibody and TKI inhibitors have been associated with increased risk of hypertension (HTN) with relative risk (RR) of HTN increasing with higher doses of these agents.[45,46] Proteinuria was also more common in treated patients with greater RR in patients receiving higher doses.[46,47] Nephrotic syndrome associated with anti-VEGF therapy has been described in a number of case reports.[48–51]

TMA is the predominant glomerular lesion associated with anti-VEGF antibody therapy. It has been reported after intravenous[52–55] as well as intraocular administration.[56] Concurrent mesangial IgA deposits, cryoglobulinemic glomerulonephritis,[57] and immune complex–mediated focal proliferative glomerulonephritis[58] also have 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, HTN, and MAHA.[52–55]

Fulminant cases of TMA with worsening renal function, severe HTN, and MAHA also have been reported with TKI inhibitors.[53,59–61] However, in a cohort study of 29 patients treated with TKIs who developed proteinuria and HTN and underwent a biopsy, minimal change disease and/or collapsing-like focal segmental glomerulosclerosis was found in 20 cases.[55]

Immunotherapy

Immunotherapeutic agents represent an important advance in anticancer treatment. These are monoclonal antibodies that block inhibitory immune signals and allow for effective antitumor immune system activity. Currently, two inhibitory receptors are targeted by immune therapy: cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death 1 protein (PD-1) and its ligand (PD-1L).[62] Because these agents have an activating effect on the immune system overall, they have been associated with significant autoimmune morbidity affecting liver, lung, colon, thyroid, and pituitary.[62] Recently, they have been linked to autoimmune acute interstitial nephritis (AIN) as well. In a case series of patients receiving PD-1 inhibitors, AKI and biopsy-proven AIN developed between 3 and 16 months after initiation of the drug. The severity of AKI varied, but no patient required dialysis, and all responded to steroid taper.[63] In another case series with most patients receiving a combination of PD-1 and CTLA-4 inhibitors, the median time to onset of AKI was 91 days (21–245). The AKI was more severe with 4 out of 13 patients requiring dialysis. Biopsy revealed AIN in 12 patients with granulomatous features in 3. One patient had TMA. All patients treated with steroid taper showed partial or complete improvement.[64] Authors estimated that based on review of data from clinical trials of immunotherapy enrolling a total of 3695 patients the incidence of AKI was 2.2%. The incidence was higher (4.9%) for the combination therapy of CTLA-4 and PD-1 inhibitors.[64]

Others

Cetuximab and panitumumab are epithelial growth factor receptor (EGFR)–blocking antibodies used to treat certain tumors of epithelial origin characterized by overexpression of EGFR. EGFR activity is necessary for magnesium reabsorption in the distal convoluted tubule, and hypomagnesemia secondary to this therapy has been reported.[65–69] Hypomagnesemia can be severe, and concomitant hypocalcemia is described.[66,67] Hypomagnesemia resolved when EGFR pathway inhibitors are stopped.[66]

Crizotinib acting as an inhibitor of the anaplastic lymphoma kinase is used for the treatment of advanced non–small cell lung cancer. Its use is associated with hypophosphatemia.[70] Crizotinib also is associated with an increased risk of development and progression of renal cyst, especially for Asian patients.[71] Treatment modification is generally not necessary and spontaneous regression can occur, but close monitoring is recommended.[72] Imatinib is a TKI used mainly for the treatment of chronic myelogenous leukemias and gastrointestinal stromal tumors. Patients treated with imatinib are at risk of developing hypophosphatemia with low fractional tubular reabsorption. The exact mechanism by which hypophosphatemia occurs is not yet known.[73–75] Vemurafenib is a therapy targeting the rapidly accelerated fibrosarcoma kinase B (BRAF). It is used to treat patients with metastatic melanoma. Case reports of kidney failure secondary to this new treatment have been described. The mechanism of the kidney failure is not known yet.[76,77]

Bortezomib and carfilzomib are proteasome inhibitors (PI) used for treatment of multiple myeloma. In recent case reports they have been linked to the development of TMA. The mechanism of TMA is unclear, but the class effect is possible; therefore a high degree of suspicion for drug-induced TMA should be maintained in all patients treated with PI.[78]

Cancer Chemotherapy in Kidney Disease

Because of the aging population, a growing number of patients with CKD also carry a diagnosis of cancer. In Table 217.1 we provide recommendations for administration of chemotherapy to patients with kidney disease.[1,4,79]

CONCLUSION

Despite the progress made in recent decades, nephrotoxicity of antineoplastic agents continues to be a significant clinical challenge in treatment of patients with cancer. Appropriate prophylactic measures, dose adjustments, and early recognition of toxicity may reduce kidney morbidity and permit more effective treatment of the underlying neoplasm.

TABLE 217.1

Recommendations for Dosage Adjustment of Antineoplastic Drugs in Patients with Kidney Disease

DRUG	CKD	ESRD
Conventional Chemotherapy		
Taxanes: paclitaxel, docetaxel	Hepatic metabolism; no dose adjustment	Pharmacokinetics are not altered by HD in anephric patients; no dose adjustment
Cisplatin	Avoid if CrCl <60 mL/min	Reduce dose by 50%; administer after HD; protein bound within 2 hr of administration
Carboplatin	Dosage based on the AUC-directed method[a]	Dialyzable: administer on off HD day
Etoposide	40%; hepatic metabolism CrCl 10–50 mL/min; reduce by 25%; CrCl <10%–50%	Protein bound; poorly dialyzable
Fluorouracil	Metabolized by liver and other tissues; no dose adjustment	Metabolized by liver and other tissues; metabolism may be affected by uremia; reduce dose by 50%
Methotrexate	Predominant renal excretion. Avoid in CrCl <30 mL/min	Not recommended because of postdialysis rebound effect
Pemetrexed	Renally excreted; avoid use in CrCl <45 mL/min	Not recommended
Cyclophosphamide	Hepatic metabolism; no dose adjustment	Dialyzable; reduce dose by 25%; administer after HD
Ifosfamide	More than 80% renally excreted; dose adjustment is empiric; CrCl <10 mg/mL; reduce the dose by 25%	Dialyzable; use with caution; initial dose 1.5 g/m^2; adjust dose based on neuro- and myelotoxicity
Anthracyclines (doxorubicin, epirubicin, daunorubicin)	Hepatic metabolism; no dose adjustment	Nondialyzable because of large volume of distribution and long half-life
Vinca alkaloids (vincristine, vinblastine, vindesine)	Hepatic metabolism; no dose adjustment	Nondialyzable because of large volume of distribution, high metabolic rate and long half-life
Targeted Therapies		
Monoclonal antibodies	Reticuloendothelial system metabolism; no dose adjustment	Unlikely to be dialyzable because of biochemical properties
• Bevacizumab		
• Cetuximab		No adjustment necessary
• Trastuzumab		
Tyrosine Kinase Inhibitors		
Sunitinib	Eliminated via feces route; no dose adjustment	Nondialyzable; no dose adjustment needed
Sorafenib	Hepatic metabolism; CrCl 20–39 mL/min; reduce dose to 200 mg twice a day	Pharmacokinetics unchanged in patients on HD; may reduce dose to 200 mg daily
Imatinib	Hepatic metabolism (decreased clearance in uremic environment) no dose adjustments with CrCl >20 mg/mL	Pharmacokinetics unchanged in patients on HD

AUC, Area under concentration-time curve; *CKD,* chronic kidney disease; *CrCl,* creatinine clearance; *ESRD,* end-stage renal disease; *HD,* hemodialysis.
[a]Dose determined by Calvert formula: Dose(mg) = AUC (mg/mL × min) × (glomerular filtration rate [GFR] (mL/min) + 25).[80] Target AUC is 5–7 mg/mL × min. Assume GFR of 0 mL/min in HD patients.

Key Points

1. Nephrotoxicity of antineoplastic agents is a significant clinical challenge with a high burden of acute kidney injury risk.
2. Several chemotherapy agents are listed as potential causes of acute kidney injury, and clinicians should be well aware of the risks on kidney function the patients will run.
3. Dose, patient characteristics, and coadministration of other nephrotoxins determine degree of kidney impairment.
4. Patients with anamnesis of renal dysfunction should receive adjusted chemotherapy doses.

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A complete reference list can be found online at ExpertConsult.com.

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