Onco-Nephrology: Renal Toxicities of Chemotherapeutic Agents

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Summary
Despite dramatic improvements in patient survival and drug tolerability, nephrotoxicity remains an important complication of chemotherapy. Adverse renal effects occur because of innate drug toxicity and a number of patient- and drug-related factors. To provide cutting edge care for these patients, nephrologists and oncologists must be familiar with the nephrotoxicity of these drugs, particularly their associated clinical and laboratory manifestations. Rapid diagnosis, targeted treatment, and supportive care are critical to improving care for these patients. Unfortunately, some patients who develop nephrotoxicity will be left with long-term complications such as chronic tubulopathies and CKD. Onco-Nephrology is a new area that is rapidly expanding and requires a close working relationship between oncologists and nephrologists.

Introduction
Treatment of cancer has undergone many significant advances in recent times. As such, the oncology landscape has changed and improved dramatically for many patients. Those patients previously considered therapy failures are now deriving significant benefit with decreased tumor progression and increased survival, often with less severe adverse systemic drug effects. Despite this positive advancement in chemotherapeutics for various malignancies, drug nephrotoxicity remains a complication and sometimes limits life-saving therapy (1–3).

As a number of effective but potentially nephrotoxic chemotherapeutic regimens are released into clinical practice, oncologists and consulting nephrologists should be familiar with their adverse renal effects. These effects include the clinical and histopathologic manifestations of renal toxicity (1–6). Clinicians should also be well versed in preventive measures available for the various chemotherapy regimens, as well as effective treatment options for nephrotoxic consequences (1–6). The relationship of nephrologists and oncologists in the care of these patients has given rise to the nascent but growing area of Onco-Nephrology.

Renal Susceptibility to Chemotherapeutic Agents
Not all patients exposed to nephrotoxic chemotherapeutic agents develop kidney injury, suggesting the presence of several factors that enhance patient risk for nephrotoxicity. In addition to innate drug toxicity, certain host characteristics and renal handling of the drug increase renal injury. In general, one or more of these factors combine to increase risk for kidney injury (Table 1).

Many cancers involve the kidneys either directly or indirectly—heightening the risk for kidney injury with exposure to a potential nephrotoxin. In fact, nearly 60% of patients with cancer have some form of renal disease (1,2). Direct malignant effects include myeloma-related kidney injury, infiltration of the renal parenchyma as seen with leukemias and lymphomas, urinary tract obstruction from various cancers, and secondary glomerulopathies (2). Indirect effects include true or effective volume depletion from nausea/vomiting, diarrhea, overdiuresis, malignant ascites or pleural effusions, sepsis, and cardiac involvement, which sensitizes the kidney to nephrotoxins by inducing a prerenal state (2). Also, susceptibility to drug toxicity occurs with metabolic disturbances such as hyperuricemia and hypercalcemia.

Undoubtedly, the toxicity of the chemotherapeutic agent used importantly determines both the development and type of kidney injury sustained. High doses and prolonged therapy increase the chance of renal injury developing, regardless of the absence of other risk factors (2–6). Furthermore, combined exposure of chemotherapeutic agents with other nephrotoxins will raise the risk for kidney injury (7–9).

There are a number of patient-specific risk factors that must be considered with chemotherapy-associated nephrotoxicity. Many patients are elderly—possessing reduced total body water and an unrecognized depressed GFR, higher rates of renal oxidative stress, and excessive levels of angiotensin-II/endothelin, all of which increase drug nephrotoxicity (10,11). Another nonmodifiable risk factor is the host’s underlying genetic makeup, which is likely a powerful explanation for the heterogeneous response to chemotherapeutic agents (12–14). Gene polymorphisms in the renal cytochrome P450 enzyme system, which favor reduced metabolism and renal excretion, enhance nephrotoxic risk. Other examples are loss of function mutations in apical secretory transporters and mutations in kinases...
that regulate drug carrier proteins, which can impair drug excretion and induce nephrotoxicity by increasing intracellular drug concentrations (13,15).

Last, the renal handling of drugs is another risk factor for the development of nephrotoxicity. The kidney is exposed to considerable drug concentrations based on the high renal blood flow rate—approximately 25% of cardiac output. Significant drug uptake occurs in the proximal tubular cells through both apical uptake and basolateral transport (16,17). Trafficking of these agents through tubular cells explains, in part, their nephrotoxicity. The high metabolic rate and hypoxic environment of loop of Henle and medullary collecting duct cells impart nephrotoxic drug risk (18,19). Metabolism of drugs by several enzyme systems present in the kidney favors toxic metabolite and reactive oxygen species formation. Renal injury may occur, because drug byproducts cause harm through lipid peroxidation, protein damage, nucleic acid alkylation or oxidation, and DNA strand breaks (18–20).

### Classification of Chemotherapy-Associated Renal Lesions

There are a number of ways that one can approach classifying the kidney lesions caused by the various chemotherapeutic agents. For example, one could categorize the chemotherapy-related kidney lesions based on the nephron sites primarily affected by the drug. Agents that injure the renal vasculature, glomerulus, proximal and distal tubular segments, and collecting ducts are described (Table 2), recognizing that all nephrotoxic drugs cannot possibly be covered.

#### Renal Vasculature: Thrombotic Microangiopathy

Chemotherapeutic agents, such as bevacizumab and gemcitabine, can injure the renal vasculature and cause thrombotic microangiopathy (TMA). TMA presents clinically as microangiopathic hemolytic anemia, thrombocytopenia, hypertension, and AKI with hematuria and proteinuria, although renal-limited TMA does occur.

#### Bevacizumab

Recognition that tumor growth was highly dependent on pathologic angiogenesis induced by local production of vascular endothelial growth factor (VEGF) paved the way for the development of drugs targeting this pathway (21). This pathway was a logical point of attack to supplement other tumor-directed therapies—and turned out to be a beneficial addition to the therapeutic armamentarium. Although there are numerous drugs that target VEGF effects, the anti-VEGF antibody bevacizumab will be the focus of discussion, recognizing that there are differences among the agents.

VEGF importantly regulates vasculogenesis and angiogenesis during development and in disease through regulation of vascular permeability, endothelial cell migration, proliferation, and survival (21). This regulation raises the possibility that these drugs may be associated with adverse effects. In fact, this finding is the case, because a number of adverse systemic end-organ effects have been described, including kidney injury. This finding is not surprising, because VEGF is produced by renal visceral epithelial cells and binds to VEGF receptors located on glomerular endothelium and mesangium, as well as peritubular capillaries (21). Local VEGF production maintains normal functioning of all of these cells, including injury repair and cell turnover. Importantly, there is crosstalk between the glomerular endothelium and epithelium, maintaining the integrity of the filtration barrier.

The most important renal effects described with antiangiogenesis therapy are new or worsened hypertension and kidney-specific injury, including proteinuria and AKI. Importantly, the development of hypertension in patients predicts a better tumor response to therapy (22), and it should prompt clinicians to continue therapy and control BP with antihypertensive agents rather than discontinuing antiangiogenic therapy. Animal experiments documented a
two- to threefold increase in proteinuria in mice injected with a single dose of anti-VEGF antibody (23). Renal histopathology revealed glomerular endothelial cell swelling, vacuolization, and detachment, as well as disruption of epithelial cell slit diaphragms. Immunohistochemistry also showed downregulation of nephrin, which was partially restored with administration of recombinant VEGF. The renal effects of bevacizumab therapy in six patients with various malignancies were described in detail (24). Renal findings developed within 3–17 months of drug exposure: proteinuria occurred in all patients, with five patients having at least 1 g/d and two patients having nephrotic-level proteinuria. Hypertension and AKI developed in 50% of patients, and all had TMA on kidney histology (Figure 1). Importantly, proteinuria, hypertension, and AKI generally improved on withdrawal of bevacizumab.

Although a number of renal lesions have been described with the antiangiogenesis drugs, the predominant histopathology is TMA. Other lesions described on kidney biopsy include focal segmental glomerulosclerosis (FSGS), mehanoproliferative GN, glomerular endotheliosis, cryoglobulinemic GN, nonspecific immune complex GN, and acute interstitial nephritis (21,24,25).

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**Table 2. Kidney injury associated with chemotherapeutic agents**

**Figure 1.** A glomerulus exhibits mesangiolysis, endothelial denudation, red blood cell congestion, and glomerular basement membrane duplication in this example of thrombotic microangiopathy. (Jones methenamine silver stain; original magnification, ×600.) Courtesy of Glen S. Markowitz.

**Gemcitabine**

Gemcitabine is a cell cycle–specific pyrimidine antagonist that is an effective therapy for certain malignancies, primarily carcinomas of the lung, pancreas, bladder, and breast. Unfortunately, as with other chemotherapeutic agents, it is complicated by kidney injury. Numerous case reports and case series have documented AKI from gemcitabine, primarily from TMA. In addition, hypertension, microangiopathic hemolytic anemia, and ischemic skin lesion may be present. A recent case series of 29 patients treated with gemcitabine described the various clinical renal manifestations (26). All patients developed AKI; TMA was seen in four patients who underwent kidney biopsy. New or worsening hypertension occurred in 26 of 29 patients, whereas edema (21/29) and congestive heart failure (7/29) also complicated gemcitabine therapy. Classic systemic TMA occurred in all patients and was manifested by anemia, thrombocytopenia, and increased lactate dehydrogenase levels. Suppressed haptoglobin levels (23/26) and schistocytes on peripheral smear (21/24) were also noted. Urinalysis revealed hematuria/proteinuria (27/29) and red blood cell casts (n=8).

Gemcitabine-associated TMA is relatively rare, with the major risk factors being previous therapy with mitomycin-C and total drug dose. Often, it is impossible to predict who will develop this complication, although new or worsened hypertension may precede other clinical manifestations of TMA. Unfortunately, therapy is generally limited and mainly supportive, consisting of drug discontinuation, antihypertensive medications, and dialysis when indicated. Plasmapheresis has been used with minimal or no success. Renal outcomes are highly variable. In the largest cases series (26), 19 patients had full or partial renal recovery, whereas 3 patients developed CKD and 7 patients had dialysis-requiring ESRD.

**Glomerulus: Podocytopathy**

IFN

IFN is a glycoprotein synthesized and released by leukocytes, fibroblasts, T cells, and natural killer cells in
response to pathogens, such as viruses, parasites, and bacteria, as well as tumor cells. It is a protective defense that allows communication between cells to eradicate infection or malignant cells. In general, IFN-α and -β reduce viral replication and protein synthesis in neighboring cells, whereas IFN-γ activates macrophage and MHC expression (27,28). Based on these characteristics, exogenous IFN has a number of therapeutic uses. The most commonly used agent is IFN-α, which is used to treat hepatitis C and B viruses and various malignancies. IFN-β is used to treat multiple sclerosis, whereas IFN-γ was studied as a treatment for chronic granulomatous disease but has been abandoned.

Chronic IFN therapy is associated with clinical renal disease, which seems to be associated primarily with podocyte injury (27,28). Based on published cases, minimal change disease has been described with both IFN-α (n=6) and -β (n=2). The lesion developed anywhere from 5 days to 22 months after therapy (27). Nephrotic syndrome with urinary protein levels of 2.3–28 g/d occurred in all patients, whereas AKI complicated the course of two patients. In follow-up ranging from 53 days to 12 months, complete remission was noted in all patients, with discontinuation of IFN and steroid therapy in three patients (27,28).

FSGS constitutes another form of podocytopathy that can complicate IFN therapy. The lesion FSGS—not otherwise specified has been described in 10 patients treated with IFN therapy (IFN-α in 9 patients and -γ in 1 patient) (27,28). In these cases, IFN therapy ranged from 19 days to 20 months and was associated with nephrotic syndrome in all 10 patients, with proteinuria of 6.3–42 g/d and AKI in 8 patients. With follow-up ranging from 1 to 16 months in 9 of 10 patients, complete or partial remission was noted in 4 of 9 patients with discontinuation of IFN. Six patients received steroids, of which only two patients benefited with remission.

Collapsing FSGS (Figure 2) also complicates IFN therapy. In 14 patients with this lesion, IFN-α was the causative agent in 9 patients, whereas IFN-β and -γ therapy was used in 3 and 2 patients, respectively (27,28). IFN exposure ranged from 1 to 48 months; nephrotic syndrome was present in 12 of 13 patients, with proteinuria ranging from 1.9 to 27 g/d. AKI occurred in 11 patients. Urine sediment was bland in nearly one-half of the patients, whereas red and white blood cells were seen in five and one patients, respectively. Remission was inconsistent and incomplete in most patients after IFN discontinuation. With follow-up in 10 patients, which ranged from 2 to 54 months, complete remission was noted in 1 patient and partial remission was noted in 3 patients, whereas some improvement in proteinuria and kidney function was described in 5 patients. Of these 10 patients, 8 patients received steroids, and 1 patient received cyclophosphamide. Thus, although IFN discontinuation sometimes helps, it is not always associated with remission. Steroids seem unhelpful, especially in FSGS.

The mechanism of podocyte injury with IFN is incompletely understood. A number of putative mechanisms have been put forward (27). A direct IFN effect on the podocyte is possible through receptor binding and activation that promotes two potential injurious effects: (1) altered cellular proliferation and metabolism of the podocyte and (2) increased podocyte oxidative capacity and increased MHC class II antigen expression. Indirect IFN effects on the podocyte may also contribute to the development of FSGS. IFNs activate adaptive immune mechanisms that increase macrophage activation—an example is hemophagocytic syndrome, which is associated with collapsing FSGS. Viral diseases such as HIV and parvovirus B19, which increase IFN production, are also associated with collapsing FSGS. Finally, IFN may enhance synthesis of pathogenic cytokines such as IL-6 and -13, which are permeability factors in FSGS and minimal change disease.

**Tubules: Acute Tubular Injury**

**Cisplatin**

Cisplatin is a platinum compound that is an effective therapy for many carcinomas and sarcomas, as well as lymphomas. Its major adverse effect is nephrotoxicity, although ototoxicity also occurs. Both are dose-related toxicities, causing apoptosis and necrosis of cells (29–32). Cisplatin injures multiple renal compartments, including blood vessels, glomeruli, and most commonly, the tubules (29). Nephrotoxicity is generally reversible, but it can be permanent. Tubular injury as manifested by AKI and tubular dysfunction syndromes will be described.

Cisplatin’s mechanism of nephrotoxicity is related to its drug characteristics, its renal handling, and the kidney response to the cisplatin molecule (29–32). Chloride at the cis-position of the molecule is one such factor that promotes kidney injury, whereas the pathway of excretion through the cell (in through organic anion transporter 1 and out through efflux transporters) potentially increases intracellular concentrations (Figure 3). After it is inside the tubular cell, a number of intracellular injury pathways occur. These pathways include caspase activation, cyclin-dependent kinases, mitogen-activated protein kinase activation, and p53 signaling. In addition, cellular injury also develops from inflammation and oxidative stress, whereas vascular injury and decreased GFR with ischemic injury also occur (29–32). These pathways of injury result

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Figure 2. | A glomerulus exhibits global wrinkling and retraction of the glomerular basement membrane and diffuse swelling and hyperplasia of overlying visceral epithelial cells in this example of collapsing focal segmental glomerulosclerosis. (Jones methenamine silver stain; original magnification, ×600.) Courtesy of Glen S. Markowitz.
in renal tubular cell apoptosis and necrosis—resulting in clinical AKI and/or a tubulopathy.

Tubular injury without AKI also complicates cisplatin therapy and manifests as a number of tubulopathies, which include isolated proximal tubulopathy (proteinuria and phosphate wasting) or full-blown Fanconi syndrome (2,29). Sodium wasting is another consequence of cisplatin therapy, which can be associated with hypovolemia, orthostasis, and prerenal AKI. In the distal nephron, cisplatin can impair reabsorption of magnesium, causing refractory hypomagnesemia. Finally, water absorption in the collecting duct can be disturbed, resulting in a form of nephrogenic diabetes insipidus.

AKI is a dose-related complication of cisplatin—it can be a functional decline in GFR or caused by TMA, but most commonly, it is a result of acute tubular injury/necrosis.

Although AKI can recover, renal outcomes such as progressive CKD from chronic tubulointerstitial fibrosis and irreversible chronic tubulopathies may result (2,29).

A focus of care for patients receiving cisplatin is prevention of kidney injury (2,29). Forced diuresis with intravenous normal saline or hypertonic saline is used to counteract the toxic effect of chloride on the cis-position of the molecule. The addition of mannitol to induce a forced diuresis is sometimes used, but evidence of benefit is lacking; in some cases, this approach may cause worsened kidney function (33). Amifostine is a glutathione analog taken up by normal cells that blunts cisplatin-induced cellular injury. It is, however, complicated by nausea and vomiting. A number of other agents have been used to reduce nephrotoxicity, such as sodium thiosulfate, nucleophilic sulfur thiols, neurotrophins, phosphonic acid, melanocortins, and free oxygen radical scavengers, but their utility is unclear. In high-risk patients, other platinums such as carboplatin and oxalaplatin are used based on their less nephrotoxic profile compared with cisplatin. Two potential explanations for reduced nephrotoxicity exist. Neither of these molecules is transported by organic cation transporter 2 (OCT-2), thereby reducing proximal tubular intracellular concentrations (29–32). In addition, the chloride at cis-position in cisplatin is replaced by carboxylate and cyclobutane in carboplatin and oxalaplatin, respectively, which may further reduce toxicity (29–32).

Treatment of toxic renal manifestations is primarily supportive (2,28). There are no effective therapies to reverse AKI or tubular dysfunction. Dialysis is reserved for advanced AKI as manifested by uremia, metabolic disturbances, and hypervolemia. There is no role for dialytic removal of cisplatin. Maneuvers to correct hypovolemia from salt wasting (intravenous normal saline or oral sodium chloride) and address symptomatic hypomagnesemia with intravenous and/or oral magnesium are required. Fanconi syndrome is notoriously difficult to treat.

Ifosfamide

Ifosfamide is an alkylating agent used for certain cancers, including sarcomas, testicular cancer, and some forms of lymphoma. Ifosfamide’s major adverse effect is kidney injury. Nephrotoxic manifestations include tubulopathies such as proximal tubular injury or Fanconi syndrome and nephrogenic diabetes insipidus; additionally, AKI is often reversible but can be permanent (2,34,35). Histopathology
reveals features of tubular cell injury/necrosis with swollen, dysmorphic mitochondria.

The difference in adverse effects for ifosfamide (nephrotoxicity) and cyclophosphamide (hemorrhagic cystitis), which are related compounds, is caused by the major toxic metabolite that they produce. Acrolein produced by cyclophosphamide is non-nephrotoxic, whereas chloracetaldehyde produced by ifosfamide injures kidney tissue. At equivalent doses, ifosfamide produces 40 times more chloracetaldehyde than cyclophosphamide (2,34,35). Furthermore, ifosfamide enters proximal tubular cells through OCT2, whereas cyclophosphamide does not (2,35). Risk factors for adverse renal effects include previous cisplatin exposure, cumulative dose >90 g/m², and underlying CKD.

Preventive measures are limited for ifosfamide. Mesna, which is effective for hemorrhagic cystitis, is of limited value for ifosfamide-induced kidney injury. Dose reduction helps but also limits the efficacy of tumor killing. Because this agent is transported into cells through OCT2, competitive inhibition of this pathway with cimetidine is being evaluated (35). Treatment, as with many of these agents, is supportive. Attention to supplementing electrolyte deficiencies, monitoring for progressive CKD, and dialysis as indicated are important. In addition to CKD and ESRD, long-term complications include a permanent proximal tubulopathy (1%) and isolated renal phosphaturia in up to 20%. This latter complication may cause osteomalacia or growth problems in children and exacerbate osteoporosis in the elderly (2,34,35).

**Pemetrexed**

Pemetrexed is an antifolate agent that inhibits enzymes involved in purine/pyrimidine metabolism, thereby impairing RNA/DNA synthesis in tumors such as malignant mesothelioma and non-small cell lung cancer. This agent is excreted unchanged by the kidneys (70%-90% in 24 hours), with a half-life of 3.5 hours (36). Its renal handling may explain some of the drug’s nephrotoxicity. It is postulated that pemetrexed enters proximal tubular cells through two separate pathways. One cell entry site is the basolateral membrane, where pemetrexed is transported through reduced folate carrier, whereas the other is apical drug uptake through the folate receptor-α transport pathway (Figure 4).

After inside the cell, pemetrexed is polyglutamylated with two resulting effects. First, with polyglutamation, the drug can no longer be transported out of the cell, increasing intracellular concentrations. Second, the higher drug concentrations more fully inhibit folate metabolism enzymes and impair cellular RNA/DNA synthesis.

Although its major adverse effects are myelosuppression and neutropenia, reversible AKI has been noted with high-dose therapy (600 mg/m²). Pemetrexed nephrotoxicity has been described in several case reports: acute tubular necrosis (n=5), acute interstitial nephritis (n=2), nephrogenic diabet¬es insipidus/renal tubular acidosis (n=1), and nephrogenic diabetes insipidus (n=1) (36). A decline in CrCl from 88 to 77 ml/min was reported after four cycles of pemetrexed in a mesothelioma trial (36). Most patients present with AKI and minimal proteinuria, which stabilizes with drug discontinuation but can lead to permanent CKD. Renal histology reveals primarily chronic tubulointerstitial fibrosis and tubular atrophy, consistent with a toxic tubular injury (36).

**Tubules: Magnesium Wasting**

**Cetuximab**

Cetuximab is a chimeric monoclonal antibody against EGF receptor (EGFR) used to treat various epithelial malignancies,
including colorectal, head/neck, breast, and lung cancers. EGF overexpression present in these malignancies reduces apoptosis and enhances tumor cell growth. Cetuximab has a 10-fold greater affinity for EGFR than natural ligand, making it an effective targeted therapy in these cancers. However, one of the drug’s adverse effects is hypomagnesemia (37–41).

Cetuximab-induced hypomagnesemia results from a renal leak of magnesium. Magnesium reabsorption in the distal convoluted tubule is, in part, dependent on EGF binding its receptor on the basolateral membrane (37,38,41). Activation of the EGFR sets in motion intracellular signals that stimulate the movement of the cation channel transient receptor potential M6 into the apical membrane, which facilitates the reabsorption of magnesium from the urinary space into the cell (37,38,41). Cetuximab competitively inhibits EGF binding to its receptor (Figure 5), thereby blunting the placement of transient receptor potential M6 into the apical membrane and causing renal magnesium wasting (37,38,41).

The incidence of hypomagnesemia with cetuximab in initial colorectal cancer trials was only 1.8%–5.8% (37,38). However, a higher incidence was noted when magnesium levels were measured more rigorously. More than one-half of patients develop hypomagnesemia with cetuximab, and nearly 100% of patients have some decline in serum magnesium concentrations (37,38,41). In fact, a meta-analysis of randomized controlled trials of cetuximab versus other therapies showed an odds ratio of 4.7 for all-grade hypomagnesemia and 5.3 for grade 3/4 hypomagnesemia (42). In addition, hypokalemia and hypocalcemia occur with severe hypomagnesemia. Risk factors for hypomagnesemia include duration of cetuximab therapy, older age, and baseline magnesium concentration. Panitumumab is also complicated by hypomagnesemia (36%) but of less severe grade, because only 3% developed grade 3/4 hypomagnesemia (1,2).

Treatment of hypomagnesemia requires intravenous repletion, because oral magnesium is ineffective and often complicated by diarrhea. Along with magnesium supplementation, calcium and potassium repletion are also commonly required. In general, renal magnesium wasting improves and eventually resolves approximately 4–6 weeks after discontinuation of cetuximab.

**Tubules: Crystal Nephropathy Methotrexate**

The dihydrofolate reductase inhibitor methotrexate is widely used, especially in high dose, to treat malignancies such as high-grade lymphomas. Nephrotoxicity is a known complication of high-dose therapy (1–12 g/m²) but rarely occurs with long-term conventional dosing (1,2). The incidence is highly variable depending on the patient’s risk factors and the appropriate employment of preventive measures, such as intravenous fluids (1,2,43).

Methotrexate and its major metabolite, 7-OH methotrexate, are filtered by the glomerulus and secreted into the urinary space by proximal tubules. AKI is primarily the result of acute tubular injury from precipitation of methotrexate/7-OH methotrexate in distal tubular lumens (2,43). However, tubular apoptosis/necrosis may also develop from oxygen radicals associated with decreased adenosine deaminase activity (44). AKI incidence, when defined as grade >2 nephrotoxicity, ranges from 1.8% to 12% (2,43).

Risk factors for nephrotoxicity include intravascular volume depletion with sluggish urinary flow, acid urine pH, and underlying kidney disease (GFR<60 ml/min) (2,42). Based on these factors, prevention is focused on volume repletion before/during drug infusion, appropriate drug dosing, and alkalinization of the urine (pH>7.1).

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**Figure 5.** Cetuximab (C) is an EGF receptor (EGFR) antibody that causes renal magnesium wasting by competing with EGF for its receptor. Normally, EGF binds its receptor (EGFR) and stimulates magnesium reabsorption in the distal convoluted cell. EGFR activation is associated with magnesium absorption through transient receptor potential M6 (TRPM6) in the apical membrane. NCC, sodium chloride cotransporter.
Treatment is comprised of leucovorin rescue at 24–36 hours of methotrexate therapy to reduce nonmalignant cell injury (2,43,45). Glucaribidase cleaves methotrexate to noncytotoxic metabolites. It is reserved for use when methotrexate levels are toxic, and there is significant risk for systemic toxicity (45). High-flux hemodialysis clears the plasma of methotrexate fairly well (76%) but is associated with immediate postradiation plasma rebound (1,2). It may have a role when severe AKI is present, but it may become unnecessary with the availability of glucaridase.

**Conclusion**

Chemotherapeutic agents have improved cancer patient survival; however, nephrotoxicity remains an important complication. A number of patient- and drug-related factors increase risk for adverse renal events; some events are modifiable, and others are not. Clinicians must be familiar with the nephrotoxicity of these drugs, particularly the associated clinical and laboratory manifestations. Preventive measures should be used when possible, as well as supportive care and available therapies. Some patients will be left with long-term complications such as chronic tubulopathies and CKD. Onco-Nephrology is a rapidly expanding area that requires a close working relationship between oncologists and nephrologists.

**Disclosures**

None.

**References**


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