Nephrotoxicity From Chemotherapeutic Agents: Clinical Manifestations, Pathobiology, and Prevention/Therapy

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Summary: Nephrotoxicity remains a vexing complication of chemotherapeutic agents. A number of kidney lesions can result from these drugs, including primarily tubular-limited dysfunction, glomerular injury with proteinuria, full-blown acute kidney injury, and long-term chronic kidney injury. In most cases, these kidney lesions develop from innate toxicity of these medications, but underlying host risk factors and the renal handling of these drugs clearly increase the likelihood of nephrotoxicity. This article reviews some of the classic nephrotoxic chemotherapeutic agents and focuses on examples of the clinical and histopathologic kidney lesions they cause as well as measures that may prevent or treat drug-induced nephrotoxicity.

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Rapid advances in cancer therapy have changed the landscape of oncology for patients and practitioners. Patients are deriving significant benefit with increased survival, decreased tumor progression, and in some cases with less severe overall adverse drug effects. Unfortunately, nephrotoxic effects of these agents remain a significant untoward complication, and sometimes limit effective therapy.[1-6] Clinicians ordering these drugs and nephrologists consulting when an adverse renal event develops should be familiar with the patient factors that increase nephrotoxic risk, clinical and histopathologic manifestations of renal toxicity, and prevention and treatment of chemotherapy-induced nephrotoxicity. This article reviews these areas, focusing on drugs that represent examples of the various types of kidney toxicity that develop from these agents.

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RISK FACTORS FOR ENHANCED NEPHROTOXICITY

The nephrotoxicity of chemotherapeutic agents is enhanced by underlying host risk factors, general renal handling of these drugs, and innate toxicity of the individual agent (Table 1). More than one of these factors commonly conspires to increase risk for nephrotoxicity. Importantly, various forms of malignancy are associated with risk for many of these factors. For example, both true and effective decreases in circulating blood volume, hepatic dysfunction and obstructive jaundice, metabolic disturbances, and numerous forms of acute or chronic kidney injury result from either direct cancer effects or other indirect effects of the malignant process. As many as 60% of patients manifest some form of kidney disease.[1] Examples include myeloma-associated kidney disease, renal infiltration by tumor, secondary glomerulonephritides (ie, membranous glomerulonephritis), urinary obstruction from various cancers, tumor lysis syndrome, hypercalcemia, and other forms of neoplastic injury. Host factors, kidney drug handling pathways, and drug toxicity factors are briefly reviewed later.

Table 1. Risk Factors for Chemotherapy-Induced Renal Toxicity

Host factors
Older age and female sex
Nephrotic syndrome, cirrhosis, obstructive jaundice
Acute or chronic kidney disease
True or effective circulating blood volume depletion
Diminished GFR
Increased proximal tubular toxin reabsorption
Sluggish distal tubular urine flow rates
Metabolic disturbances
Hypokalemia, hypomagnesemia, hypocalcemia
Hypercalcemia
Alkaline or acid urine pH
Immune response genes
Increased allergic reactions to drugs
Pharmacogenetics favoring drug/toxin toxicity
Gene mutations in hepatic and renal cytochrome P450 enzyme systems
Gene mutations in transport proteins and renal transporters
Renal drug handling
High blood (and drug) delivery rate to the kidneys
Relatively hypoxic renal environment
Increased drug/toxin concentration in renal medulla and interstitium
Biotransformation of substances to reactive oxygen species, causing oxidative stress
High metabolic rate of tubular cells in the loop of Henle
Proximal tubular uptake of toxins
Apical tubular uptake via endocytosis or other pathway
Basolateral tubular transport via organic anion transporter and organic cation transporter pathways
Innate drug toxicity
High-dose drug/toxin exposure and prolonged course of therapy
Insoluble drug or metabolites form crystals within the intratubular lumens
Potent direct nephrotoxic effects of the drug or toxin
Drug combinations enhance nephrotoxicity
Nonsteroidal anti-inflammatory drugs, aminoglycosides, radiocontrast

Host Factors

Nonmodifiable risk factors such as older age and female sex are associated with reductions in total body water and unrecognized lower glomerular filtration rate (GFR) despite normal serum creatinine levels, leading to drug overdosage. The elderly, often afflicted by cancer, have increased propensity to vasoconstriction from excessive angiotensin-II and endothelin and higher levels of oxidatively modified biomarkers.[7]

Vomiting, diarrhea, and diuretic use lead to true volume depletion, while congestive heart failure, ascites, and sepsis promote effective volume depletion in cancer patients receiving chemotherapy and increase renal vulnerability to various agents. In addition, malignancy-induced nephrotic syndrome and hepatic dysfunction increase risk through multiple mechanisms that include altered renal perfusion from reduced effective circulating blood volume, hypoalbuminemia with increased free circulating drug, and unrecognized renal impairment.[8-10] Cancer-associated obstructive jaundice also enhances toxicity to certain drugs through decreased renal blood flow and direct effects of bile salts on tubular epithelia.[11] Renal hypoperfusion and prerenal azotemia increase nephrotoxicity of drugs excreted primarily by the kidney, in those reabsorbed in the proximal tubule, and in those that are insoluble in the urine, where crystal precipitation occurs within distal tubular lumens with sluggish flow.[8-10,12]

Metabolic disturbances resulting from certain tumors also increase renal vulnerability to certain drugs and potential toxins. Severe hypercalcemia, which often complicates myeloma and lung cancer, induces afferent arteriolar vasoconstriction and renal sodium/water wasting, leading to prerenal physiology, which enhances nephrotoxic drug injury. Systemic metabolic acidosis may decrease urine pH and increase intratubular crystal deposition with drugs such as methotrexate and its metabolites, which are insoluble in a low pH environment.[12] Hyperuricemia and acute tumor lysis exacerbate renal injury further.

Underlying acute kidney injury (AKI) and chronic kidney disease (CKD) are important risk factors for increasing vulnerability to neph-