REVIEW ARTICLE

# Cancer Chemotherapy and Acute Kidney Injury: Nephrotoxic Mechanisms, the Limits of Prevention, and Mechanism-Informed Renoprotection — A Narrative Review

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## Abstract

Acute kidney injury (AKI) is among the most frequent and consequential organ toxicities of cancer chemotherapy, contributing to dose reduction, treatment discontinuation, chronic kidney disease, and mortality. Chemotherapy-induced AKI is, in most cases, not idiosyncratic: it reflects a mechanistically defined pharmacological injury determined by the interaction between a nephrotoxic agent and specific renal transport, metabolic, and vascular pathways. Cisplatin enters proximal tubular cells through organic cation transporter 2 (OCT2) and copper transporter 1 (CTR1), triggering mitochondrial dysfunction and apoptosis; ifosfamide generates the tubular toxin chloroacetaldehyde, producing Fanconi syndrome; high-dose methotrexate precipitates within the acidic tubular lumen; antiangiogenic agents disrupt podocyte-endothelial vascular endothelial growth factor (VEGF) signaling, producing proteinuria, hypertension, and thrombotic microangiopathy; and immune checkpoint inhibitors provoke acute interstitial nephritis. However, mechanistic intelligibility should not be conflated with clinical preventability. For several agents — most notably ifosfamide tubulopathy and checkpoint inhibitor nephritis — no effective prophylaxis exists, and even for cisplatin, AKI occurs in approximately a quarter to a third of patients despite optimal hydration. This review therefore advances a deliberately calibrated thesis: mechanistic understanding reliably guides monitoring and mitigation, and identifies rational renoprotective targets, but does not yet render chemotherapy-induced AKI reliably preventable across agents. We critically evaluate the evidence for established renoprotective strategies, the real-world limitations of emerging biomarkers and rescue therapies including glucarpidase, the diagnostic pitfalls of creatinine-based AKI definition in sarcopenic cancer patients, and the underappreciated transition from AKI to chronic kidney disease in cancer survivors. A four-domain framework for nephrotoxicity risk stratification is proposed, with explicit attention to where current evidence is strong and where it remains aspirational.

## 1. Introduction

The kidney occupies a position of unique vulnerability in cancer pharmacology. It receives approximately a quarter of cardiac output, concentrates filtered solutes and drugs within the tubular lumen, and expresses a dense complement of transporters that actively accumulate xenobiotics within renal epithelial cells. The physiological features that make the kidney an efficient organ of drug elimination also make it a preferential target of drug-induced injury (1). AKI complicating cancer chemotherapy is correspondingly common, with reported incidences ranging from 10% to over 30% depending on the agent, the diagnostic criteria, and the population studied (2).

The consequences of chemotherapy-induced AKI extend well beyond the acute episode. AKI necessitates dose reduction or discontinuation of potentially curative therapy, alters the pharmacokinetics of renally cleared co-administered drugs, independently predicts mortality in hospitalized oncology patients, and — through incomplete tubular repair and maladaptive fibrosis — accelerates progression to chronic kidney disease (CKD) (3). The growing population of cancer survivors has made these long-term renal sequelae an increasingly important determinant of survivorship quality, a theme developed in Section 9. In most cases, chemotherapy-induced AKI is mechanistically traceable: a transporter- mediated cellular uptake, a metabolic activation to a nephrotoxic species, a physicochemical precipitation within the tubular lumen, or a disruption of glomerular or microvascular integrity.

It is tempting to infer from this mechanistic intelligibility that nephrotoxicity is therefore predictable and preventable. That inference, however, overreaches. Mechanistic understanding reliably illuminates how injury occurs and identifies where to look for it; it does not, for most agents, yet translate into reliable prevention. Cisplatin nephrotoxicity occurs in a substantial minority of patients even with optimal prophylaxis; ifosfamide tubulopathy has no effective preventive agent; checkpoint inhibitor nephritis has no validated early-prediction biomarker.

This review accordingly maintains a deliberate distinction between mechanistic understanding, which is well advanced, and clinical preventability, which remains partial and agent-dependent. We examine the molecular pharmacology of the principal nephrotoxic classes, then turn to risk stratification, renoprotection, and the practical and chronic dimensions that determine real-world outcomes.

## 2. Methods

This is a narrative review. It was not conducted according to a pre-registered systematic review protocol, and no formal risk-of-bias or quality-grading instrument was applied to the included sources. The aim was to synthesize the pharmacological mechanisms, monitoring approaches, and renoprotective strategies relevant to chemotherapy-induced acute kidney injury, with explicit attention throughout to the strength of evidence underlying each claim and to the distinction between mechanistic plausibility and demonstrated clinical benefit. Literature was identified through structured searches of PubMed/MEDLINE, Embase, and Scopus for English-language

publications, with a primary focus on articles published between January 2010 and June 2026 and supplemented by earlier foundational mechanistic studies where these remain the primary evidence base for a given pathway.

Search terms combined the Medical Subject Headings (MeSH) "Acute Kidney Injury," "Drug-Related Side Effects and Adverse Reactions," "Antineoplastic Agents," "Cisplatin," "Ifosfamide," "Methotrexate," "Tumor Lysis Syndrome," "Immune Checkpoint Inhibitors," and "Renal Insufficiency," combined using Boolean operators with free-text keywords including “chemotherapy nephrotoxicity,” “cisplatin nephrotoxicity,” “ifosfamide tubulopathy,” “organic cation transporter 2,” “thrombotic microangiopathy,” “acute interstitial nephritis,” “glucarpidase,” “rasburicase,” “onco-nephrology,” and “chronic kidney disease AND cancer survivors.” Reference lists of identified reviews and major clinical practice guidelines — including the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, National Comprehensive Cancer Network (NCCN) guidance, and the Japanese clinical practice guidelines for the management of kidney injury during anticancer drug therapy — were hand-searched to identify additional relevant primary studies not captured by the database searches. Priority was given to systematic reviews, mechanistic reviews published in high-impact nephrology and oncology journals, consensus and expert-panel guidelines, and large cohort studies; case reports and small case series were used selectively, principally to illustrate the clinical presentation of less common entities for which larger studies are unavailable. Non-English-language publications, conference abstracts without an accompanying peer- reviewed full text, and unreviewed preprints were excluded. Because this is a narrative rather than a systematic review, the selection and synthesis of sources reflect the authors’ judgment regarding mechanistic coherence and clinical relevance rather than a reproducible, pre-specified algorithm; this is stated explicitly as a limitation of the review, and readers seeking a quantitative or exhaustive synthesis of the primary literature are referred to the systematic reviews cited throughout.

## 3. Defining and Classifying Chemotherapy-Induced Acute Kidney Injury

AKI is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine of at least 0.3 mg/dL within 48 hours, an increase to at least 1.5 times baseline within 7 days, or a urine output below 0.5 mL/kg/h for 6 hours (4). These functional criteria detect injury only after a substantial fall in glomerular filtration has occurred, a limitation that has driven interest in earlier tubular biomarkers. They carry an additional, underrecognized limitation specific to the oncology population, addressed in Section 3.1. Chemotherapy-induced AKI is most usefully classified by anatomical site and mechanism rather than by drug class alone, since a single agent may injure the kidney through several pathways.

The principal categories are tubular toxicity (cisplatin, ifosfamide), crystal or precipitation nephropathy (methotrexate, tumor lysis syndrome), glomerular and microvascular injury (antiangiogenic agents, gemcitabine-associated thrombotic microangiopathy), and interstitial nephritis (immune checkpoint inhibitors). This mechanistic classification informs both monitoring and renoprotective strategy.

### 3.1 Limitations of Creatinine-Based AKI Detection in the Cancer Patient

Serum creatinine, the substrate of the KDIGO definition, is generated from skeletal muscle, and its concentration therefore depends on muscle mass as well as on glomerular filtration. Sarcopenia and cachexia — prevalent in advanced malignancy and a defining feature of many cancer populations — substantially lower baseline creatinine generation, with the consequence that a creatinine within the laboratory reference range may conceal a markedly reduced glomerular filtration rate (5). A patient whose true filtration has fallen by half may show a creatinine that still appears reassuring, leading to underdosing-related undertreatment in some contexts and, more dangerously, to inadvertent overdosing of renally cleared nephrotoxins whose clearance is overestimated. Conversely, because the relationship between creatinine and filtration is curvilinear, a small absolute creatinine rise from a low cachectic baseline may represent a proportionally severe injury that the fixed 0.3 mg/dL threshold underweights.

Cystatin C, a low-molecular-weight protein produced by all nucleated cells at a relatively constant rate and largely independent of muscle mass, offers a complementary filtration marker less confounded by body composition, and combined creatinine-cystatin C estimating equations improve filtration estimates in patients with abnormal muscle mass (6). Despite this advantage, cystatin C is not yet universally available, is influenced by corticosteroid use and thyroid dysfunction, and has not been incorporated into the consensus AKI definition. The practical implication is that creatinine-based AKI detection should be interpreted with explicit awareness of the patient's muscle status, and that measured or cystatin C-based filtration estimates merit consideration before nephrotoxic therapy in cachectic patients.

## 4. Tubular Toxicity: Transporter-Mediated and Metabolic Mechanisms

### 4.1 Cisplatin: Transporter-Mediated Nephrotoxicity and the Limits of Prophylaxis

Cisplatin, central to the treatment of testicular, ovarian, bladder, lung, and head and neck malignancies, is the prototypal nephrotoxic chemotherapeutic. Its selectivity for the S3 segment of the proximal tubule is determined by transporter-mediated accumulation rather than passive diffusion. Cisplatin enters proximal tubular cells primarily through OCT2 (encoded by SLC22A2) on the basolateral membrane and CTR1 (encoded by SLC31A1) apically (7). OCT2-knockout mice are protected from cisplatin nephrotoxicity, and SLC22A2 polymorphisms modulate risk in patients — yet these polymorphisms account for only a fraction of the interpatient variability, an important caveat against overinterpreting pharmacogenomic prediction.

Once intracellular, cisplatin undergoes aquation in the low- chloride cytosol to a reactive species that forms adducts with nuclear and mitochondrial DNA, RNA, and protein (8). Mitochondrial DNA damage impairs oxidative phosphorylation in the energy-demanding tubule, depletes ATP, and generates reactive oxygen species, while p53 activation, caspase-dependent apoptosis, regulated necrosis, and NLRP3 inflammasome activation propagate injury (9). The pharmacological basis of cisplatin renoprotection follows from this mechanism, but so do its limits. Isotonic saline hydration increases tubular flow and, through chloride loading, suppresses intracellular aquation to the reactive species (10).

Amifostine, a thiophosphate prodrug dephosphorylated to a free thiol that scavenges reactive platinum and oxygen species, is the only

agent specifically approved for cisplatin nephroprotection, but its use is limited by hypotension and emesis and it is, in practice, rarely employed. Magnesium supplementation counters cisplatin-induced magnesium wasting and may attenuate OCT2- mediated uptake. Carboplatin, far less OCT2-dependent, reduces nephrotoxicity at the cost of greater myelosuppression. The central clinical reality, however, is that even with optimal hydration and magnesium repletion, clinically significant AKI still occurs in approximately a quarter to a third of patients receiving conventional cisplatin dosing (11).

Cisplatin nephrotoxicity is mechanistically well understood and partially mitigable, but it is not, with current tools, reliably preventable — a paradigmatic illustration of the gap between mechanistic insight and clinical prevention.

### 4.2 Ifosfamide: Metabolic Activation and the Absence of Effective Prevention

Ifosfamide, an oxazaphosphorine alkylating agent, produces a distinctive proximal tubular toxicity that may manifest as Fanconi syndrome — generalized proximal tubular dysfunction with normoglycemic glycosuria, aminoaciduria, phosphaturia, bicarbonate wasting, and renal tubular acidosis. The nephrotoxicity is mediated not by the parent compound but by chloroacetaldehyde, a metabolite generated through CYP-mediated side-chain oxidation (12). Chloroacetaldehyde depletes glutathione, inhibits mitochondrial complex I, and disrupts the energy-dependent reabsorptive machinery of the proximal tubule. Risk factors include high cumulative dose (particularly above 60-90 g/m²), young age, prior or concurrent cisplatin exposure, and reduced nephron mass.

Ifosfamide tubulopathy is the clearest counterexample to the notion that mechanistic understanding confers preventability. Although the uroprotective agent mesna (2- mercaptoethane sulfonate) effectively prevents the hemorrhagic cystitis caused by the shared metabolite acrolein, mesna does not prevent the tubular toxicity of chloroacetaldehyde: it does not achieve adequate intracellular concentrations within tubular cells, and its protective action is confined to the urothelial surface (13). This distinction is clinically important and frequently misunderstood. No pharmacological agent currently provides reliable protection against ifosfamide tubulopathy; risk is reduced only by limiting cumulative dose and avoiding the combination of ifosfamide with other tubular toxins — a risk-mitigation strategy, not a renoprotective intervention.

Table 1. Nephrotoxic chemotherapeutic agents, mechanisms of renal injury, and pharmacological determinants of risk Agent / Class Site & Mechanism Clinical Manifestation Key Risk Determinants Cisplatin Proximal tubule (S3); OCT2/ Non-oliguric AKI; Mg wasting; Cumulative dose; volume CTR1 uptake; mitochondrial/ CKD depletion; SLC22A2 variants; DNA injury concurrent nephrotoxins Ifosfamide Proximal tubule; Fanconi syndrome Cumulative dose >60 g/m²; chloroacetaldehyde metabolite; (normoglycemic glycosuria); young age; prior cisplatin; complex I inhibition RTA; AKI reduced nephron mass Methotrexate (high- Tubular lumen; crystal Crystal nephropathy; oliguric Volume depletion; acidic urine; dose) precipitation at acidic pH AKI; delayed clearance third-space fluid; drug interactions Antiangiogenics Glomerulus; VEGF inhibition inP roteinuria; hypertension; TMAPre-existing hypertension; (bevacizumab, TKIs) podocytes/endothelium baseline proteinuria; cumulative exposure Gemcitabine Glomerular endothelium; TMA; hemolysis; AKI; Cumulative dose; prior thrombotic microangiopathy hypertension mitomycin C exposure Immune checkpoint Interstitium; autoreactive T-cell Acute interstitial nephritis; Combination ICI; concurrent inhibitors infiltration sterile pyuria PPI/NSAID/antibiotics; prior irAEs Abbreviations: OCT2, organic cation transporter 2; CTR1, copper transporter 1; AKI, acute kidney injury; CKD, chronic kidney disease; RTA, renal tubular acidosis; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; TMA, thrombotic microangiopathy; ICI, immune checkpoint inhibitor; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; irAE, immune-related adverse event.

## 5. Crystal and Precipitation Nephropathy

### 5.1 High-Dose Methotrexate Crystal Nephropathy and the Practical Limits of

Glucarpidase High-dose methotrexate, used in osteosarcoma, acute lymphoblastic leukemia, and primary central nervous system lymphoma, causes AKI through intratubular precipitation of methotrexate and its metabolite 7-hydroxymethotrexate, whose solubility falls sharply at the acidic pH of unmodified urine (14). Because methotrexate is cleared predominantly by renal excretion, the resulting AKI impairs its own clearance, generating a dangerous feedback loop of rising systemic concentrations and amplified marrow, mucosal, and hepatic toxicity. Prevention follows from the pH-dependent solubility: urinary alkalinization with sodium bicarbonate to maintain urine pH above 7.0 increases methotrexate solubility several-fold, accompanied by vigorous isotonic hydration and leucovorin rescue, the last bypassing dihydrofolate reductase blockade in normal tissues without itself preventing renal injury. In established methotrexate-induced AKI with delayed clearance, glucarpidase (recombinant carboxypeptidase G2) rapidly hydrolyzes circulating methotrexate to inactive metabolites independent of renal function (15).

Glucarpidase is, however, subject to substantial real- world constraints that temper its utility. It is extremely expensive — on the order of tens of thousands of US dollars per dose — and is not universally available, particularly in resource- limited settings. Its benefit is greatest when administered early, within approximately 48-60 hours of methotrexate infusion, yet AKI may not be recognized within that window. Critically, glucarpidase acts only on extracellular methotrexate and does not clear the intracellular drug responsible for ongoing cytotoxicity, so delayed administration yields diminishing returns.

These limitations mean that glucarpidase, though mechanistically elegant, is neither a universal nor a complete solution, and prevention through alkalinization and hydration remains paramount.

### 5.2 Tumor Lysis Syndrome, Rasburicase, and G6PD Considerations

Tumor lysis syndrome (TLS), a consequence of chemotherapy-induced tumor cell death rather than direct drug nephrotoxicity, is among the most important causes of AKI in bulky, rapidly proliferating malignancies. Cytolysis releases intracellular contents producing hyperuricemia, hyperkalemia, hyperphosphatemia, and secondary hypocalcemia (16). Renal injury results from intratubular precipitation of uric acid in the acidic distal tubule and of calcium phosphate when the calcium-phosphate product is elevated, compounded by urate- mediated vasoconstriction and inflammation. Allopurinol, a xanthine oxidase inhibitor, blocks new urate formation but does not remove existing urate and may cause xanthine accumulation.

Rasburicase, a recombinant urate oxidase, enzymatically converts existing uric acid to the far more soluble allantoin, rapidly reversing established hyperuricemia (17). Several safety considerations qualify its use. Rasburicase is contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficiency, because the hydrogen peroxide generated by urate oxidation precipitates hemolysis in G6PD-deficient erythrocytes; it can also induce methemoglobinemia through the same oxidative mechanism, an adverse effect less frequently emphasized but clinically important. Because G6PD deficiency is X-linked and many affected individuals are asymptomatic until oxidative challenge, and because it is prevalent in populations of African, Mediterranean, Middle Eastern, and Southeast Asian ancestry, screening is essential — yet in acute high-risk TLS, waiting for a quantitative G6PD result may unacceptably delay treatment.

A practical approach is to obtain a rapid G6PD assay where available and, when deficiency is known or strongly suspected and rapid testing is not feasible, to rely on aggressive isotonic hydration and allopurinol rather than empiric rasburicase. Routine urinary alkalinization is no longer recommended in TLS, as it promotes calcium phosphate precipitation.

## 6. Glomerular and Microvascular Injury

### 6.1 Antiangiogenic Agents and VEGF Pathway Inhibition

VEGF inhibitors — the monoclonal antibody bevacizumab and small-molecule receptor tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib) — produce a characteristic glomerular toxicity that reveals the physiological role of VEGF in maintaining the filtration barrier. Within the glomerulus, VEGF-A secreted by podocytes acts on VEGFR-2 on the adjacent endothelium to maintain fenestrae, glycocalyx, and barrier integrity (18). Pharmacological interruption of this paracrine axis causes endothelial dysfunction, loss of fenestration, downregulation of nephrin, and proteinuria. The resulting hypertension and proteinuria are mechanistically linked on-target effects of the drug class rather than idiosyncratic toxicities; in severe form, VEGF inhibition produces a renal thrombotic microangiopathy with endothelial swelling, fibrin thrombi, microangiopathic hemolysis, and AKI (19).

Management centers on renin-angiotensin system blockade, which addresses both hypertension and proteinuria, with dose modification or discontinuation for nephrotic-range proteinuria or TMA.

### 6.2 Gemcitabine-Associated Thrombotic Microangiopathy

Gemcitabine causes a dose-dependent thrombotic microangiopathy through direct glomerular endothelial toxicity. Its cumulative pattern and endothelial histology distinguish it from immune-mediated TMA such as thrombotic thrombocytopenic purpura, and plasma exchange is generally ineffective (20). Recognition requires vigilance: new or worsening hypertension, proteinuria, falling hemoglobin and platelets, and rising lactate dehydrogenase in a gemcitabine-treated patient should prompt evaluation and consideration of discontinuation. Complement involvement has been implicated in some cases, generating interest in complement inhibition, though evidence remains limited.

## 7. Immune Checkpoint Inhibitor-Associated Acute Interstitial Nephritis

Immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 most commonly injure the kidney as acute tubulointerstitial nephritis, occurring in an estimated 2-5% of treated patients and increasingly recognized as use expands (21). The mechanism involves loss of peripheral tolerance and infiltration of the interstitium by autoreactive CD4 and CD8 T- lymphocytes. A distinctive pharmacological feature is the frequent association with concurrently administered drugs independently capable of causing interstitial nephritis — proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs), and certain antibiotics — with checkpoint blockade hypothesized to reverse tolerance to these haptenating agents (22). Presentation is typically a subacute creatinine rise weeks to months after initiation, sometimes with sterile pyuria and modest proteinuria.

Checkpoint inhibitor nephritis exemplifies a toxicity for which no validated predictive biomarker exists: the diagnosis remains clinical and frequently requires biopsy to distinguish it from other causes of AKI, and the decision to rechallenge after recovery is empirical rather than evidence-based. Management requires checkpoint inhibitor discontinuation and corticosteroids (prednisone 0.5-1 mg/kg/day), with concurrent discontinuation of PPIs, NSAIDs, and non-essential antibiotics where clinically feasible. Most patients recover renal function, but the absence of predictive tools means that prevention, in the strict sense, is not currently achievable for this entity. Table 2.

Mechanism, risk factors, and monitoring strategy for chemotherapy-associated acute kidney injury Mechanism / Agent High-Risk Features Onset Monitoring Strategy (evidence status) Cisplatin tubular Volume depletion; cumulative Days 3-7 post-dose Serum creatinine and Mg; urine toxicity dose; concurrent output. NGAL/KIM-1 remain aminoglycosides/contrast; investigational, not routine SLC22A2 variants Ifosfamide Cumulative dose >60 g/m²; During/after therapy; may be Electrolytes, phosphate, tubulopathy young age; prior cisplatin delayed bicarbonate; urine for normoglycemic glycosuria and low-molecular-weight proteinuria Methotrexate crystal Acidic urine; volume depletion; Within 24-48 h of infusion Serial MTX levels; urine pH; nephropathy third-space fluid; NSAID/PPI serum creatinine q24h co-use Tumor lysis syndromeHigh tumor burden; high-grade 12-72 h after cytotoxic therapy Urate, K , phosphate, Ca² , lymphoma/leukemia; pre- creatinine q6-12h; G6PD status existing renal impairment; before rasburicase elevated LDH Antiangiogenic Pre-existing hypertension; Weeks to months Blood pressure; urine glomerular injury baseline proteinuria; cumulative protein:creatinine ratio each exposure cycle ICI interstitial Combination ICI; concurrent Weeks to months Serum creatinine each cycle; nephritis PPI/NSAID/antibiotics; prior urinalysis for sterile pyuria (no irAEs validated predictive biomarker) Abbreviations: Mg, magnesium; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; MTX, methotrexate; LDH, lactate dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; ICI, immune checkpoint inhibitor; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; irAE, immune-related adverse event.

## 8. A Framework for Risk Stratification and Mechanism-Informed Renoprotection

In each mechanism examined above, a pharmacologically defined cascade precedes the clinical rise in serum creatinine. This supports a structured approach to risk stratification, provided it is paired with explicit honesty about where intervention is effective and where it is not. We propose a four-domain framework, annotating each domain

with its current evidentiary strength. The first domain, baseline renal reserve assessment, quantifies the functional starting point.

Estimated glomerular filtration rate — ideally measured, or cystatin C-based, in patients with reduced muscle mass — establishes excretory capacity; baseline proteinuria identifies glomerular vulnerability before antiangiogenic therapy; and baseline electrolytes including magnesium and phosphate characterize tubular function. This domain rests on strong evidence and is broadly actionable. The second domain, drug interaction and pharmacogenomic mapping, minimizes concurrent nephrotoxins (aminoglycosides, iodinated contrast, NSAIDs, calcineurin inhibitors) and ascertains pharmacogenomic modifiers. Among the latter, G6PD status before rasburicase is well established and clinically essential; SLC22A2 genotyping for cisplatin, by contrast, remains investigational and explains only a portion of variability, and should not be presented to patients as a reliable predictor.

The third domain, mechanism-aligned monitoring, matches surveillance to injury pathway. Serial drug-level monitoring for methotrexate, and blood pressure with proteinuria quantification for antiangiogenic agents, are evidence-based and routine. Tubular injury biomarkers — neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and the TIMP-2/IGFBP7 product — detect proximal tubular injury before creatinine rises and are mechanistically attractive for cisplatin and ifosfamide, but they are not standardized, not widely available, and not endorsed by KDIGO for routine clinical decision-making in this setting; they should be regarded as investigational rather than ready for practice (23). The fourth domain, renoprotective intervention, is where the distinction between mechanistic rationale and proven benefit matters most.

Interventions of established benefit include isotonic saline hydration and magnesium repletion for cisplatin, urinary alkalinization and hydration for high-dose methotrexate, rasburicase (with G6PD screening) for high-risk TLS, and renin-angiotensin system blockade for antiangiogenic hypertension and proteinuria. Interventions of limited or absent benefit must be stated as such: mesna does not prevent ifosfamide tubulopathy; no agent reliably prevents checkpoint inhibitor nephritis; and amifostine, though approved for cisplatin, is constrained by toxicity and infrequently used. Dose capping for ifosfamide is a risk-mitigation measure, not a renoprotective pharmacological intervention, and is classified accordingly in Table 3. Table 3.

Renoprotective and risk-mitigation strategies, classified by strength of evidence Agent / Syndrome Strategy Pharmacological Rationale Evidence / Classification Cisplatin Isotonic saline hydration; Mg Chloride loading suppresses Established benefit; residual supplementation aquation; flow reduces tubular ~25-30% AKI persists despite residence optimal use Cisplatin Amifostine Thiol scavenges reactive platinum/Approved but limited by ROS hypotension/emesis; rarely used Ifosfamide Mesna; dose capping Mesna detoxifies acrolein in Mesna does NOT prevent bladder only; capping limits tubulopathy (common cumulative exposure misconception); capping is risk mitigation, not renoprotection High-dose Urinary alkalinization; MTX solubility is pH-dependent; Alkalinization/hydration methotrexate hydration; leucovorin; glucarpidase cleaves circulating established; glucarpidase limited glucarpidase (rescue) MTX by cost (tens of thousands USD), 48-60 h window, and no intracellular clearance Tumor lysis Hydration; rasburicase (high- Rasburicase converts urate to Established; rasburicase syndrome risk); allopurinol (lower-risk) soluble allantoin contraindicated in G6PD deficiency (hemolysis, methemoglobinemia); avoid routine alkalinization Antiangiogenic RAAS blockade; BP control; ACEi/ARB address VEGF- Established for BP/proteinuria; agents dose modification inhibition hypertension and hold drug for nephrotic-range proteinuria proteinuria or TMA ICI nephritis Discontinue ICI; Steroids suppress autoreactive T- Treatment, not prevention; no corticosteroids; stop cell infiltrate validated predictive biomarker; concurrent PPI/NSAID/ rechallenge empiric antibiotics Abbreviations: ROS, reactive oxygen species; MTX, methotrexate; G6PD, glucose-6-phosphate dehydrogenase; RAAS, renin-angiotensin-aldosterone system; BP, blood pressure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; VEGF, vascular endothelial growth factor; TMA, thrombotic microangiopathy; ICI, immune checkpoint inhibitor; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug. Table 4. Representative hydration and supportive protocols for nephrotoxic regimens Regimen Representative Hydration Approach Practical Considerations Cisplatin Isotonic saline (0.9% NaCl): commonly 1-2 L Monitor for fluid overload in elderly and cardiac over 2-4 h pre-infusion and 1-2 L post-infusion;p atients; reduce volume/rate and consider maintain urine output >100 mL/h. Chloride- monitored diuresis if signs of congestion.

Avoid containing (saline) fluid preferred over balancedc oncurrent nephrotoxins and contrast in the peri- solutions to favor aquation suppression. treatment window. Magnesium 1-2 g added per cycle. High-dose methotrexateIsotonic fluid with sodium bicarbonate to Verify urine pH frequently; bicarbonate vs. saline alkalinize urine to pH >7.0 before, during, and balance to avoid volume overload; ensure after infusion; high flow (e.g. 2.5-3 L/m²/day) glucarpidase access plan for delayed clearance; maintained until MTX level is safe. Begin check interacting drugs (NSAIDs, PPIs, leucovorin per protocol. penicillins) that impair MTX clearance.

Tumor lysis syndrome Aggressive isotonic hydration to maintain high Monitor for fluid overload, especially with urine output (target often 2 mL/kg/h); no routineo liguria; check G6PD before rasburicase; alkalinization. Rasburicase or allopurinol per risfkre quent electrolyte monitoring; nephrology and tier. critical-care involvement for established AKI. Abbreviations: NaCl, sodium chloride; MTX, methotrexate; PPI, proton pump inhibitor; NSAID, non-steroidal anti- inflammatory drug; G6PD, glucose-6-phosphate dehydrogenase; AKI, acute kidney injury. Protocols are representative and illustrative; institutional and guideline-specific protocols should govern actual practice, and volumes require individualization for cardiac and renal status.

## 9. From Acute Injury to Chronic Kidney Disease: The Long-Term Burden in Survivors

A focus on the acute episode risks obscuring what is, for the growing population of cancer survivors, often the more consequential outcome: the transition from AKI to chronic kidney disease. Normalization of serum creatinine after an episode of chemotherapy-induced AKI does not signify full structural recovery. Cisplatin and ifosfamide produce tubular atrophy and interstitial fibrosis that may persist after functional markers improve, and repeated subclinical injury across treatment cycles can drive a stepwise decline in nephron mass that manifests only years later as CKD (24). Childhood cancer survivors treated with ifosfamide or cisplatin carry a measurable long-term burden of tubular dysfunction and reduced glomerular filtration into adulthood.

Antiangiogenic therapy may leave sustained hypertension and proteinuria after discontinuation, themselves drivers of progressive renal and cardiovascular disease. The mechanistic link between acute tubular injury and chronic fibrosis — incomplete epithelial repair, cell-cycle arrest in a profibrotic secretory phenotype, pericyte-to-myofibroblast transition, and sustained inflammatory signaling — is increasingly well characterized and represents a target for future antifibrotic intervention, though none is yet established in this context. These observations argue for structured long-term renal surveillance in survivors of nephrotoxic chemotherapy, an element absent from much of oncological follow-up. Reasonable components include periodic estimated glomerular filtration rate, urine protein quantification, and blood pressure monitoring, with the interval and intensity matched to the cumulative nephrotoxic exposure and the severity of any acute episodes.

Integrating nephrology into survivorship care — the emerging discipline of onco-nephrology — is a practical expression of the principle that the renal consequences of cancer treatment extend well beyond the treatment period itself.

## 10. Special Populations and Compounding Vulnerabilities

Elderly patients exhibit age-related declines in nephron number, glomerular filtration, and regenerative capacity, reducing both the reserve available to absorb a nephrotoxic insult and the capacity for recovery. Creatinine-based filtration estimates overstate true function in elderly patients with low muscle mass, risking overdosing of renally cleared agents (25). Patients with pre-existing CKD begin with diminished reserve and impaired clearance, a self-amplifying hazard for agents such as methotrexate whose own elimination depends on renal function; patients with a solitary functioning kidney face analogous vulnerability. Contrast-associated AKI deserves specific attention because cancer patients undergo frequent contrast-enhanced computed tomography for staging and response assessment, making it a common confounder in attributing AKI to chemotherapy and a preventable injury in its own right.

Risk is concentrated in patients with estimated glomerular filtration below roughly 30-45 mL/min/1.73 m², prior AKI, diabetes, volume depletion, and certain plasma-cell disorders such as multiple myeloma. Mitigation includes using the minimum necessary contrast volume, ensuring isotonic volume expansion before and after contrast in higher-risk patients, deferring elective nephrotoxic chemotherapy around the time of contrast exposure where feasible, and coordinating imaging and treatment schedules to avoid superimposing two nephrotoxic insults. Recognizing contrast as a distinct and modifiable contributor improves both the accuracy of nephrotoxicity attribution and patient outcomes. Pharmacogenomic and population-level variation is a meaningful, not incidental, determinant of risk.

G6PD deficiency — prevalent in populations of African, Mediterranean, Middle Eastern, and Southeast Asian ancestry — must be ascertained before rasburicase, and its X-linked inheritance with frequent asymptomatic carriage demands active screening rather than reliance on history. Polymorphisms in drug transporters and metabolizing enzymes modulate nephrotoxin handling across populations. Incorporating these considerations, alongside the practical realities of feasibility and cost in resource-limited settings, advances both the equity and the precision of supportive oncological care (26).

## 11. Conclusions and Future Directions

Cancer chemotherapy-induced AKI is, for most agents, mechanistically intelligible: cisplatin through transporter-mediated tubular accumulation and mitochondrial injury, ifosfamide through chloroacetaldehyde-mediated tubulopathy, methotrexate through pH-dependent crystal precipitation, antiangiogenic agents through disruption of podocyte-endothelial VEGF signaling, and checkpoint inhibitors through autoreactive interstitial nephritis. This understanding specifies where to monitor and identifies rational renoprotective targets. It does not, however, equate to reliable prevention. For cisplatin, a substantial residual incidence persists despite optimal prophylaxis; for ifosfamide and checkpoint inhibitor nephritis, no effective prevention currently exists; and several promising tools — tubular biomarkers, pharmacogenomic prediction, enzymatic rescue — remain constrained by validation, availability, cost, or timing.

An honest account, the one most useful to patients and clinicians, holds that mechanistic understanding guides monitoring and mitigation while prevention remains partial and agent-dependent. Several priorities follow. First, clinical validation and equitable implementation of early tubular biomarkers could shift monitoring from a lagging to a leading indicator, but only if accompanied by evidence that biomarker-guided intervention improves outcomes. Second, pharmacogenomically informed dosing requires larger and more diverse cohorts — including the populations most affected by relevant variants — before it can responsibly guide care.

Third, targeted renoprotective agents, such as selective OCT2 inhibitors that spare antitumor efficacy or agents interrupting specific cell-death and profibrotic pathways, represent a rational frontier for both acute protection and prevention of the AKI-to-CKD transition. Fourth, embedding nephrology within survivorship care addresses the chronic renal burden that outlasts treatment. The prevention and mitigation of chemotherapy-induced AKI is a pharmacological problem whose solutions must be grounded in mechanism but disciplined by evidence and by the realities of cost, access, and feasibility. Stated without overreach, the goal is achievable and worth pursuing: to ensure, as far as current tools allow, that the pursuit of cure inflicts the least possible lasting renal harm, and to be candid about the substantial distance that remains between mechanistic insight and reliable prevention.

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