Student Handout: Chemotherapy Nephrotoxicity

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> **Learning objective:** Understand the epidemiology, mechanisms, prevention, and management of traditional chemotherapy and targeted therapy-induced kidney injury

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Overview

Chemotherapy-induced nephrotoxicity is one of the most important medication-related complications in oncology. This handout focuses on:

1. **Platinum agents** (cisplatin) — most common & most toxic
2. **VEGF/TKI agents** (tyrosine kinase inhibitors) — increasingly used, different injury pattern

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PLATINUM NEPHROTOXICITY (Cisplatin-Focused)

Epidemiology

- **Cisplatin:** Highly effective chemotherapy for solid tumors (lung, testicular, ovarian, bladder)
- **Frequency of AKI:** 10–30% at standard doses; up to 60% with high-dose regimens
- **Chronic kidney disease:** 10–20% of patients develop long-term renal insufficiency
- **Risk factors:**
  - Age >60 years
  - Pre-existing CKD or low GFR
  - Dehydration
  - Concomitant nephrotoxic drugs (NSAIDs, aminoglycosides, amphotericin B)
  - Smoking
  - Hypomagnesemia

Mechanism of Cisplatin Nephrotoxicity

Step-by-step (simplified):

1. **Glomerular filtration** → Cisplatin freely filtered into tubular lumen
2. **Uptake** → Proximal tubular cells take up cisplatin via organic cation transporters

3. **Intracellular activation** → Cisplatin undergoes aquation, loses chloride, forms reactive platinum species
4. **DNA binding** → Binds DNA in tubular cell nuclei → Formation of DNA adducts
5. **Cell death** → Apoptosis and necrosis of proximal tubular cells
6. **Clinical result:** Acute tubular necrosis (ATN), primarily proximal tubule damage

Clinical Presentation

Acute Kidney Injury (usually 3–7 days post-infusion):

Finding	Details
Timing	Typically 3–7 days after cisplatin dose
Labs	↑ Creatinine (20–30% of baseline is "normal"; >50% is concerning)
BUN	Often ↑ proportionally (BUN/Cr ratio ~20)
Urinalysis	Muddy casts, epithelial cells, hyaline casts
K+	Often ↓ (hypokalemia from renal wasting)
Mg2+	Often ↓ (renal wasting)
Ca2+	May be ↓ (secondary to Mg2+ loss)

Chronic Kidney Disease (develops over weeks–months): - Progressive ↓ GFR even after cisplatin discontinuation - Irreversible tubular atrophy and fibrosis in severe cases

Prevention Strategy (CRITICAL)

Aggressive hydration is the #1 prevention tool:

1. **Before cisplatin:**
   - 1–2 L IV normal saline over 30–60 min pre-infusion
   - Goal: Urine output >150 mL/h during chemotherapy
2. **During cisplatin infusion:**
   - Continuous 0.9% or 0.45% NaCl at rates to maintain urine output >100 mL/h
3. **After cisplatin:**
   - 1–2 L IV hydration post-infusion (24–48 hours)
   - Encourage PO hydration if tolerated

Additional preventive measures:

Strategy	Details	Evidence
Amifostine	Mesna analog; free radical scavenger	↓ AKI risk by 30–40%; use if CrCl >60
Magnesium repletion	Keep Mg >2 mg/dL; supplement if low	Prevents renal Mg wasting
Loop diuretics	Furosemide during hydration	Maintains high urine flow
Avoid NSAIDs	Hold for ≥48 h pre and post	Reduces GFR; increases cisplatin uptake

Strategy	Details	Evidence
ACEi/ARB consideration	May offer some protection	Not first-line prevention
Antiemetics	Ondansetron, aprepitant	Prevent dehydration from vomiting

Management of Acute Cisplatin Nephrotoxicity

Grade 1–2 (Cr ↑ <50% or <2× baseline): - Continue hydration (1–2 L daily) - Monitor daily Cr, BUN, K+, Mg - Supplement Mg if low - Consider dose reduction or interval prolongation for next cycle - Most recover within 2–3 weeks

Grade 3–4 (Cr ↑ >50% or >2× baseline, or need RRT): - Aggressive hydration (3–4 L daily) - Renal replacement therapy if oliguria, severe hyperkalemia, or fluid overload - Discontinue or substantially delay cisplatin - Nephrology consult recommended - Expect some permanent renal function loss; recovery incomplete

Long-Term Outcomes

- **Recovery timeline:** Most recovery occurs within 4–6 weeks; full recovery can take months
- **Chronic sequelae:** 10–20% of patients develop CKD even after initial recovery
- **Monitoring:** Annual renal function checks for 5+ years post-treatment

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VEGF/TKI NEPHROTOXICITY

Common Agents

Drug Class	Examples	Cancer Types
VEGF inhibitors	Bevacizumab (antibody), aflibercept	Colorectal, lung, RCC
VEGFR TKIs	Sunitinib, sorafenib, pazopanib	RCC, hepatocellular carcinoma
Other TKIs	Axitinib, cabozantinib	RCC, various solid tumors

Mechanism of VEGF/TKI-Induced Nephrotoxicity

Unlike cisplatin:

1. **VEGF inhibition** → Blocks VEGF signaling in endothelial cells
2. **Glomerular consequence:** Loss of VEGF → Endothelial cell dysfunction, capillary rarefaction, podocyte injury
3. **Result: Proteinuria** (hallmark) + **hypertension** + mild-moderate AKI
4. **Histology:** If biopsied: FSGS, thrombotic microangiopathy (TMA), or minimal change disease

Epidemiology

- **Proteinuria:** 5–15% of VEGF/TKI patients develop proteinuria (>0.5 g/day)
- **Hypertension:** 20–35% develop or worsen hypertension
- **Severe AKI:** Less common than cisplatin (~2–5%)
- **Risk factors:**
  - Pre-existing HTN or albuminuria
  - Diabetes
  - Pre-existing CKD
  - Concomitant ACEi/ARB use (may protect against proteinuria)

Clinical Presentation

Feature	Typical Pattern
Proteinuria	0.5–3 g/day; usually non-nephrotic
Hematuria	Microscopic; not prominent
AKI	Mild-moderate; Cr ↑ 20–50%
Hypertension	New onset or worsening in ~30% of patients
Reversibility	Often **reversible** on drug discontinuation (unlike cisplatin)

Management of VEGF/TKI-Induced Nephrotoxicity

Monitoring: - Baseline: BMP, urinalysis, urine Pt-Cr, BP measurement - During therapy: BMP every 2–4 weeks; urinalysis every 1–2 months

Mild (proteinuria <1 g/day, Cr stable/↑ <20%): - Continue VEGF/TKI therapy - ACEi/ARB at standard doses to reduce proteinuria - Monitor Pt-Cr monthly; repeat q 3 months - BP control (goal <130/80)

Moderate (proteinuria 1–3 g/day, Cr ↑ 20–50%): - Continue therapy OR consider dose reduction - Intensify ACEi/ARB (use maximal tolerated doses) - Add amlodipine or hydralazine for BP control - Monitor Pt-Cr q 2 weeks - Nephrology referral if progressive

Severe (proteinuria >3 g/day, Cr ↑ >50%, or nephrotic syndrome): - Consider temporary pause or permanent discontinuation - ACEi/ARB at high doses - Diuretics if edema present - Frequent monitoring (BMP q 1–2 weeks) - Nephrology evaluation mandatory - Some patients recover fully upon discontinuation

Key Difference from Cisplatin

Feature	Cisplatin	VEGF/TKI
Injury type	ATN (tubular)	Glomerular (podocyte)
Presentation	↑ Cr, ↓ urine output	Proteinuria, HTN
Reversibility	Often permanent loss	Often reversible
Prevention	Hydration, amifostine	BP control, ACEi/ARB

Other Chemotherapy Agents (Brief Reference)

Agent	Injury	Key Features
Gemcitabine	Hemolytic uremic syndrome (HUS)	Rare; severe; monitor CBC
Ifosfamide	Tubular dysfunction, AKI	Mesna use standard; hydration critical
Methotrexate	Crystalline nephropathy	High-dose MTX → aggressive hydration, alkalinization
5-Fluorouracil	Volume depletion, AKI	Supportive care
Nitrosoureas	Chronic GFD	Cumulative dose-related

Integration with Management

Before each cycle: - ☐ Check BMP (especially K, Mg, Cr) - ☐ Baseline BP - ☐ Urine dipstick if on VEGF/TKI - ☐ Ensure adequate hydration status

After cycle: - ☐ Monitor Cr at 3–5 days (cisplatin peak AKI window) - ☐ Replace Mg if <2 mg/dL - ☐ Hydration support

Long-term: - ☐ Annual renal function check post-treatment - ☐ Ongoing HTN management (especially VEGF/TKI patients)

Clinical Pearls

☐ **Cisplatin = Hydration is prevention** (>1 L pre/post-infusion) ☐ **Cisplatin AKI = ATN** (muddy casts, high BUN/Cr ratio) ☐ **VEGF/TKI = Proteinuria + HTN** (glomerular injury pattern) ☐ **VEGF/TKI often reversible** on drug withdrawal (unlike cisplatin) ☐ **Escalate magnesium support** for cisplatin patients ☐ **Amifostine if CrCl >60 mL/min** for high-dose cisplatin

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Related Content

Onconephrology Hub: - Platinum Nephrotoxicity Review — Detailed mechanisms, advanced prevention strategies - VEGF/TKI Nephrotoxicity Review — Comprehensive pathology and management algorithms

Student Resources: - Acute Kidney Injury Hub — General AKI framework and differential diagnosis - Student Handout: ATN — Acute tubular necrosis mechanisms and management

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References

- **Kidney Cancer Association.** Chemotherapy-Induced Acute Kidney Injury. 2021.

- **Perazella MA.** Chemotherapy Agents and the Kidney. UpToDate. 2024.
- **Ronco C, et al.** Acute Kidney Injury in High-Risk Populations. Nature Reviews Nephrology. 2020;16:618–625.
- **Eremina V, et al.** VEGF Inhibition and Renal Thrombotic Microangiopathy. Nature Reviews Nephrology. 2016;12(11):643–653.

Study Tips: - **CISPLATIN:** Memorize prevention protocol (hydration + amifostine ± loop diuretic) - **VEGF/TKI:** Remember it causes glomerular proteinuria, not tubular AKI - **Use the management tables** for quick decision-making in clinical practice - **Key insight:** Different mechanisms → different prevention and management strategies

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