Acute Kidney Injury Associated with Malignancies

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AKI in Patients with Malignancies

• Common occurrence
• Negative impacts across the care continuum
  – Impacts chemotherapeutic regimens
  – Longer length of stay
  – Lower cancer remission rates
  – Higher mortality
• Differences in etiologies, prevention and therapies between solid and hematological malignancies
AKI Epidemiology: Population

- Denmark: among 1.2 M people, there were 37,267 incident cancer patients between 1999-2006.
- One-year risk of AKI: 17.5% (>50% rise in SCr)
- Five-year risk of AKI: 27%
- Highest risk among kidney cancer (44%), liver cancer (33%) and myeloma (31.8%)

AKI is common among cancer patients

Christiansen, Johansen et al., Eur J Intern Med 2011
AKI in Hospitalized Cancer Pts

- Among all admissions in a cancer ICU (288)

<table>
<thead>
<tr>
<th>Change in SCr</th>
<th>(%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>45.9</td>
<td>13.6</td>
</tr>
<tr>
<td>&gt;50% rise</td>
<td>33.3</td>
<td>49</td>
</tr>
<tr>
<td>&gt;100% rise</td>
<td>10.4</td>
<td>62.3</td>
</tr>
<tr>
<td>&gt;200% or HD</td>
<td>10.4</td>
<td>86.8</td>
</tr>
</tbody>
</table>

Liborio, Abreu et al., Oncology, 2011
Etiologies of AKI in Solid Organ Cancers

• Similar to the general population with over-representation of:
  – Obstructive causes (prostate, ovarian, cervical)
  – Nephrotoxic associated with chemotherapies
  – Sepsis associated (neutropenic)
  – Hypercalcemia-associated

• AKI associated with adverse prognosis and lower remission rates

• In critically ill patients with cancer, AKI usually occurs in the context of multiple organ dysfunctions and is associated with mortality rates ranging from 72% to 85% when renal replacement therapy is needed
AKI in Hematological Malignancies

Incidence with various malignancies
-Multiple myeloma (31.8%)
-Leukemia (27.5%)
Lymphoma (18.8%).

Prognosis
Adversely affects the survival of patients with hematological malignancies through multiple factors: it reduces remission rates, increases relapse rates, and increases the likelihood of refractory disease.

Among patients with hematological malignancies who develop AKI, dependence on dialysis is associated with a particularly poor prognosis, with 85% mortality reported 6 months after discharge from the intensive care unit.

PLoS ONE 8, e55870 (2013)
Etiologies of AKI: Prerenal

• The most frequent cause of AKI in patients with hematological and other malignancies is thought to be prerenal azotemia which often results from volume depletion as a consequence of chemotherapy-related nausea, vomiting and diarrhea, and/or use of medications unrelated to cancer therapy, such as diuretics.
# Prerenal Azotemia

## Hematological Cancer
- Poor oral intake owing to chemotherapy-induced anorexia, emesis and diarrhoea
- Sepsis with renal hypoperfusion
- Coexistant cirrhosis or heart failure
- Hypercalcemia
- Medication (ACE inhibitors, angiotensin-receptor blockers, NSAIDs, diuretics)

## Solid Malignancy
- Poor oral intake owing to chemotherapy-induced anorexia, emesis and diarrhoea
- Sepsis with renal hypoperfusion
- Coexistant cirrhosis or heart failure
- Hypercalcemia
- Medication (ACE inhibitors, angiotensin-receptor blockers, NSAIDs, diuretics)

## Stem Cell Transplant
- Poor oral intake owing to chemotherapy-induced anorexia, emesis and diarrhoea
- Sepsis with renal hypoperfusion
- Coexistant cirrhosis (veno-occlusive disease) or heart failure
- Medication (ACE inhibitors, angiotensin-receptor blockers, NSAIDs, diuretics)
- Cytokine release syndrome
Selected Etiologies

- Tumor lysis syndrome
- Lysozymuria
- Tumor infiltration
- Obstruction
- Hypercoagulable states
- Post-nephrectomy
- Nephrotoxins/chemotherapy
- Associated with hematological stem cell transplant
Tumor Lysis Syndrome
Cairo-Bishop Definition

- Hyperuricemia
  - > 8 mg/dl or 25% increase
- Hyperkalemia
  - > 6 mmol/L or 25% increase
- Hyperphosphatemia
  - > 4.5 mg/dl (6.5 mg/dl in children) or 25% increase
- Hypocalcemia
  - < 7 mg/dl (corrected) or 25% decrease
- AKI: serum creatinine > 1.5 X upper limit of normal
Risk Factors

• Acute lymphocytic/lymphoblastic leukemia  
  – WBC $\geq$ 100,000
• Acute myeloid leukemia  
  – WBC $\geq$ 50,000
• Burkitt, lymphoblastic, diffuse large B-cell lymphoma

• Large tumor burden
• LDH $> 1500$ IU
• Chemotherapy responsive tumor
• Extensive BM involvement

• Can occur spontaneously
• Has been seen with XRT, interferon, rituximab, tyrosine kinase inhibitors
Pathophysiology

- Volume depletion
- Uric acid
- Phosphate-calcium precipitation
  - Intratubular crystals
  - Nephrocalcinosis
Pathophysiology

Adenosine Monophosphate → Inosine Monophosphate → Hypoxanthine

Hypoxanthine/Xanthine: Less soluble at alkaline pH

Guanosine → Guanine

Uric acid/Urate: Poorly soluble

Allantoin: More soluble than uric acid/urate

Hypoxanthine/Xanthine: Xanthine Oxidase

Guanine: Xanthine Oxidase

Xanthine: Allantoin

Oxypurinol: Allopurinol

Urate Oxidase (Absent in Humans)

Rasburicase

Urinary excretion
Role of Uric Acid in TLS AKI

• Micro- and macrocrystal formation in distal tubules and collecting ducts
  – Acid urine pH favors urate (soluble) \(\rightarrow\) uric acid (less soluble)
  – Tubulo-glomerular feedback reduces RPF and GFR

• Crystals induce active inflammatory response, induce cytokine release: MCP-1, interleukins, TNF-\(\alpha\)
Urine Alkalization

- Favors uric acid $\rightarrow$ urate
  - Solubility of urate = 200 mg/dl at pH 7
  - Solubility of uric acid = 15 mg/dl at pH 5
- Increases calcium-phosphate precipitation risk
- Reduces ionized calcium
- Xanthine and hypoxanthine have low solubility even at pH 7
  - Risk of xanthine crystal uropathy with allopurinol

- NOT RECOMMENDED
Allopurinol

- Isomer of hypoxanthine—inhbits xanthine oxidase
  - Rapidly absorbed, ~67% bioavailability
  - T ½ ~ 1-2 hrs
  - Oxypurinol T ½  18–30 hrs (normal kidney function)
    - Up to a week with severe kidney failure
    - With CrCL <10 ml/min = virtually no renal clearance

- Reduces uric acid synthesis but does not directly reduce uric acid levels

- Side effects: fever, rash, eosinophilia, systemic hypersensitivity reactions, Stevens-Johnson syndrome, hepatitis, AIN, bone marrow suppression

- Dose reductions recommended with reduced kidney function but to evidence based and not clear that dose reduction reduces toxicity; balance efficacy vs. toxicity risk
Rasburicase

• Recombinant urate oxidase
  – Produced by a genetically modified Saccharomyces cerevisiae

• Indicated for a single course of treatment for the management of plasma uric acid levels in pediatric and adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and elevation of plasma uric acid.

• 10-20% of patients develop anti-rasburicase antibodies

• Cost--~$390 for 1.5 mg vial; ~ $4000 per day for adult at recommended dose of 0.2 mg/kg
Rasburicase--Cautions

- Anaphylaxis risk
- Contra-indicated with G6PD deficiency
- Methemoglobinemia risk

- Interferes with uric acid measurement
  - Collect blood specimen in chilled heparinized tube, immerse in ice, assay within 4 hours
Summary: Prophylaxis and Treatment of TLS

- IV fluids (> 100 ml/hr)
- Urinary alkalinization **NOT** recommended
- Allopurinol
  - Prophylaxis in patients with low-moderate risk for TLS
- Rasburicase
  - For patients with TLS or at high risk for TLS
- Treat hyperkalemia and hyperphosphatemia

- Dialysis when indicated
  - CRRT may avoid “rebound” metabolic disturbances
Lysozymuria and AKI

- Rare disorder that has been observed in patients with acute promyelocytic, monocytic leukemia or chronic myelomonocytic leukemia
- Clonal proliferation of mononuclear cells produces large quantities of lysozyme, which is reabsorbed by proximal tubular cells, a process that leads to toxic proximal tubular injury.
- Often associated with hypokalemia
- Diagnosis: urine protein electrophoresis can identify lysozyme in the urine

Obstructive Uropathy

- Due to massive tumor burden leading to bilateral obstruction
- Rarely due to retroperitoneal fibrosis
- Most often due to prostate or cervical cancer
- Diagnosis with ultrasound
- Treatment with decompression (stent, nephrostomy tube) followed by chemo- or radiotherapy
Tumor Infiltration

• Kidney is the most common extrareticular and extrahematopoietic organ infiltrated by leukemia and lymphoma and rates of infiltration are as high as 60%
• However, it is usually subclinical in most cases
• Patients present with flank pain, hematuria, abdominal distension and/or hypertension, as well as bilateral renal enlargement that is detectable with ultrasonography.
• AKI is uncommon and may result from tumor cell infiltration of the interstitium and tubular compression with disruption of the renal microvasculature.
• Rapid improvement in kidney function (within 2–3 days) and regression of renal masses has been achieved with chemotherapy.

Lymphomatous Infiltration of the Kidney

Insidious presentation
Kidney enlargement on ultrasound
Subnephrotic proteinuria
High index of suspicion needed, as LIK is an indication to initiate therapy in lymphoma

<table>
<thead>
<tr>
<th>Renal Lesion</th>
<th>Prevalence</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomatous infiltration</td>
<td>34% of lymphomas (13% of patients with Hodgkin lymphoma) in autopsy series</td>
<td>Often asymptomatic; can present with kidney failure, proteinuria, flank pain</td>
</tr>
<tr>
<td>Minimal change nephrosis</td>
<td>0.4% in Hodgkin lymphoma; few cases in NHL</td>
<td>Nephrotic syndrome, sometimes with associated AKI</td>
</tr>
<tr>
<td>Monoclonal immunoglobulin deposition</td>
<td>Rare</td>
<td>Proteinuria, kidney failure</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Rare</td>
<td>Nephrotic syndrome ± kidney failure</td>
</tr>
<tr>
<td>Immunotactoid glomerulopathy</td>
<td>Rare</td>
<td>Heavy proteinuria (60%-70% nephrotic range³), kidney failure</td>
</tr>
<tr>
<td>Membranous glomerulopathy</td>
<td>Rare</td>
<td>Proteinuria, kidney failure</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; NHL, non-Hodgkin lymphoma.

Cohen and Humphreys, AJKD 2010
Hypercoagulable States and Thrombotic Microangiopathy

• AKI can be a complication from either renal or arterial thrombosis or from cancer-associated TMA.
• TMA may be associated with the primary cancer or more likely with therapeutic regimens such as gemcitabine or bevacizumab.
• TMA may also occur in the setting of HSCT and can coexist with GVHD and radiation nephropathy and is more often associated with cyclosporine use.
• In the absence of well-controlled clinical trials, no specific therapy can currently be recommended, but case series have reported success with use of plasmapheresis, changing therapy from cyclosporine to tacrolimus, and the use of rituximab.

Nephrectomy

- Usually for renal cell carcinoma
- 519 adults undergoing radical nephrectomy with GFR > 60 ml/min:
  - 33.7% developed AKI
  - AKI was associated with a 4.24% increase in risk of CKD one year post-op.
- Partial nephrectomy: 19% developed AKI

Nephrol Dial Transplant 2011; 26: 3496-3501
Urology 2012; 79: 356-360
Chemotherapy drug-induced injury: Multiple sites along the Nephron

Other major nephrotoxin is contrast media

Interferon Pamidronate

Afferent Arteriole

Anti-angiogenesis Gemcitabine

Renal (arcuate & interlobular) Arteries

Efferent Arteriole

Proximal convoluted tubule

Cisplatin Ifosfamide

Nitrosureas

Loop of Henle

Thick ascending limb

Distal convoluted tubule

Mg^{2+}

Mg^{2+}

Mg^{2+}

Cetuximab

Methotrexate

Collecting duct

Interstitium

Chemotherapy drug-induced injury: Multiple sites along the Nephron
Acute tubular injury/ATN

- Cisplatin
- Ifosfamide
- Zoledronate
- Pentostatin
- Imatinib
- Pemetrexed
- Others

Courtesy of Gilbert Moeckel
Cisplatin

- Cisplatin is a platinum compound that is an effective therapy for many cancers
- Major adverse effect is nephrotoxicity (ototoxicity)
- Both are dose-related toxicities
  - Apoptosis and necrosis
- Nephrotoxic manifestations include:
  - Tubulopathies: Fanconi syndrome, salt wasting, magnesium wasting, and nephrogenic DI
  - AKI: increased vascular resistance and tubular injury with ATN; TMA (HUS) seen rarely
- Nephrotoxicity is often reversible, but can be permanent with CKD and chronic tubulopathies
Cisplatin uptake by RTE cell

TNF-α

Inflammation

ROS
MAPK + p53
-p21

RTE Cell Death

Kidney Tissue Damage

Decreased GFR

Acute Kidney Injury

Modified from Pabla N, Dong Z. KI, 2008
Cisplatin

• Prevention of AKI/Tubulopathies
  • Forced diuresis with IV NS/ Hypertonic (3%) saline
  • Amifostine
    • Glutathione analog taken up by normal cells
    • Complicated by N/V
  • Sodium thiosulfate
  • Other agents:
    • nucleophilic sulfur thiols, neurotrophins, phosphonic acid, melanocortins, free oxygen radical scavengers
• Other Platinums (carboplatin, oxalaplatin)
  • Less nephrotoxic than cisplatin
    • Not transported by OCT-2
    • $\text{Cl}^-$ at \textit{cis} position in cisplatin replaced by carboxylate and cyclobutane in carboplatin/oxalaplatin
Ifosfamide

- Ifosfamide is an alkylating agent utilized for certain cancers
- Major adverse effect is nephrotoxicity (vs hemorrhagic cystitis with cyclophosphamide)
- Cytoxan’s major toxic metabolite is acrolein; ifosfamide’s major toxic metabolite is chloracetaldehyde
- Nephrotoxic manifestations include:
  - Tubulopathies: Proximal tubular injury/Fanconi syndrome, and nephrogenic diabetes insipidus
  - AKI: acute tubular injury/necrosis with single or multiple high doses
- AKI is often reversible, but can be permanent
Ifosfamide

Nephrotoxicity

- Mechanisms:
  - At equivalent doses, ifosfamide produces $40\times$ more toxic metabolite chloroacetaldehyde than cyclophosphamide.
  - Ifosfamide enters RTEC via OCT2, cyclophosphamide does not.

- Risk factors:
  - Previous cisplatin exposure, cumulative dose > 90g/m$^2$, and underlying CKD are associated with nephrotoxicity.
Ifosfamide

• Prevention:
  – Mesna given with ifosfamide of limited value
  – Dose reduction
  – Cimetidine to block OCT2 transport into the cell (?)

• Treatment:
  – Supportive care, supplement electrolyte deficiencies, monitor for CKD and permanent kidney injury

• Long term:
  – Permanent tubulopathy (1%)
  – Isolated renal phosphaturia (20%)
    • May cause osteomalacia or growth problems in children
    • May cause/exacerbate osteoporosis in elderly
Crystal Nephropathy: Methotrexate

• Acute and chronic nephrotoxicity resulting from precipitation and deposition of crystals (most often uric acid or methotrexate) within the renal tubular lumen.

• Risk increased when tubular urine flow rates are low (volume depletion)

• Risk also increased with GFR < 60 ml/min or with excessive drug dosing

Adv Chronic Kid Dis 21;56-63 (2014)
Methotrexate

- 90% cleared by kidney
- Precipitation in tubules enhanced by acidic pH
  - Urinary alkalinization results in 5- to 8-fold increase in MTX solubility
- AKI manifests as non-oliguric and is often associated with high serum drug and metabolite levels.
- Risk of MTX levels subsequently rising and leading to severe bone marrow suppression and neurotoxicity
Methotrexate

High Risk Patient
- High dose
- Volume depletion
- Acid urine

Preventative Measures
- IV fluids
- Urine alkalization
- Leukovorin rescue

If AKI:
Leukovorin rescue
Glucarpidase
High flux HD (rebound)

Glucarpidase
- Metabolizes MTX to soluble, nontoxic derivatives
- Rapid action
- Measurement of MTX levels once given is problematic
- No rebound

Adv Chronic Kid Dis 21;56-63 (2014)
Hematopoietic Stem Cell Transplant (HCST)

• **Types of HSCT**
  – Autologous (bone marrow, peripheral blood) vs. Allogenic (bone marrow, cord blood or peripheral blood)
  – Myeloablative vs. Non-Myeloablative

• **3 Basic steps of HSCT**
  – Intensive Conditioning
  – Donor cell infusion to rescue patient from myeloablation
  – Post-graft immunosuppression to prevent GVHD
Overall, incidence of AKI is 30-70% and AKI requiring RRT occurs in 1-19% of patients.
Risk is greatest within first 100 days.
Mortality of those requiring RRT is nearly 100%.
# Etiologies of HSCT-AKI

<table>
<thead>
<tr>
<th>Prerenal</th>
<th>Reduced oral intake owing to chemotherapy-related mucositis and/or graft versus host disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neutropenic sepsis with hypotension</td>
</tr>
<tr>
<td></td>
<td>Cytokine release syndrome (capillary leak)</td>
</tr>
<tr>
<td></td>
<td>Hepatic veno-occlusive syndrome</td>
</tr>
</tbody>
</table>

Nat Rev Nephol 2015; 11: 478-490
| Intrinsic | - Acute tubular necrosis from sepsis, nephrotoxic agents (cytarabine, carmustine, busulphan, fludarabine), antibiotic treatment for neutropenic sepsis (aminoglycosides, amphotericin-B), treatment for prophylaxis of graft versus host disease (calcineurin inhibitors, methotrexate), and/or marrow transfusion toxicity  
| - Thrombotic microangiopathy  
| - Acute tubulointerstitial nephritis that results from infection with BK virus or adenovirus |

Nat Rev Nephrol 2015; 11: 478-490
### HSCT-AKI

<table>
<thead>
<tr>
<th>Post-renal</th>
<th>Intratubular obstruction by acyclovir crystals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retroperitoneal fibrosis after radiation treatment</td>
</tr>
<tr>
<td></td>
<td>Retroperitoneal lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Bladder clots from haemorrhagic cystitis owing to infection with BK virus or adenovirus, or to chemotherapy (cyclophosphamide, busulphan)</td>
</tr>
</tbody>
</table>

Nat Rev Nephrol 2015; 11: 478-490
Veno Occlusive Disease (VOD) or Sinusoidal Obstruction Syndrome (SOS)

- Busulfan, cyclophosphamide, and TBI are risk factors

**Pathophysiology**
- Sinusodial obstruction, portal HTN, microvascular intrahepatic portosystemic shunting

- Less common with less intensity myeloablative

**Clinical Presentation**
- Leads to hepatorenal syndrome

**AKI Differential Diagnosis**
- Hepatorenal, pigment nephropathy or thrombotic microangiopathy
Prevention/Treatment of VOD/SOS

Preventing and treating VOD/SOS might reduce the occurrence of kidney damage

• Ursodeoxycholic acid
• Parenteral glutamine supplementation
• Low dose heparin
• T-cell depleted donor marrow
  – Lower incidence of VOD/SOS
• Antioxidants
• Defibrotide
• Nephrologist Role
  – Supportive care
    • HCT >35%, avoid albumin, Na restriction, Gentle diuresis, Paracentesis, lactulose, CRRT (?)
Prognosis of AKI

• Mortality rates of critically ill cancer patient with AKI are similar to general population and are very high.
• Recent study of AKI patients with cancer admitted to ICU:
  – ICU mortality: 55%
  – Hospital mortality: 64%
  – 6 month mortality: 73%
• In general, dialysis decisions should be guided by global severity and reversibility of the acute illness more than the specific cancer diagnosis unless the cancer is very advanced or pre-illness QoL was very poor.
Summary

• AKI is common in patients with cancer and has some unique features that require specific diagnostic and therapeutic approaches.
• Medications are a common etiology of AKI.
• Decision making in patients with AKI and cancer can be very complex and is best done within a multi-disciplinary model with patient and family input.