Acute Kidney Injury Associated with Cancer: Focus on Chemotherapeutic Nephrotoxicity

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Vicenza 2019
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
Chemotherapy drug-induced injury: Multiple sites along the Nephron

Mitomycin C, Gemcitabine
Anti-angiogenesis Drugs

Platinums
Ifosfamide
Pemetrexed
Crizotinib
Zoledronate

Checkpoint Inhibitors
TKIs, BRAF inhibitors

Pamidronate, Interferon,
Anti-angiogenesis Drugs

TMA

FSGS

Crystalline nephropathy

Methotrexate

ATI

TIN
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

• 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
    • Cl⁻ at 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

• 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 alkalinization
- Leukovorin rescue

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

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

Adv Chronic Kid Dis 21;56-63 (2014)
VEGF Therapies and Renal Toxicities

Lamiere N. Clin Kidney J 2013;0:1-12
VEGF Targeted Cancer Therapies

• VEGF growth of vasculature in tissues; inhibition reduces vasculature growth- treatment of cancers.
• VEGF is also integral in normal functioning of fenestrated endothelial cells; induces and maintains fenestration.
• VEGFR1 and VEGFR2 mediate the permeability of endothelial cells.
• Renal adverse events occur secondary to off-(tumor) target VEGF and VEGFRs.
Renal-Related Adverse Effects to Anti-VEGF Treatments

- Hypertension: decreased endothelial NO production and vasoconstriction; secondary to kidney injury.
  - Occurs within 3-4 weeks of initiation
  - Dose-related
  - Biomarker of anti-tumor efficacy (PFS and OS)
  - Controlled with anti-hypertensives
  - Watch BP upon stopping treatment – acute declines in BP

- Proteinuria: knock-down of VEGF in podocytes
  - Discontinue for Grade 4
  - ACEI/ARBs

- AIN
- Thrombotic Microangiopathy
- Elevations in serum creatinine
VEGF Targeted Therapies

• VEGF targeted therapeutic antibodies
• Bevacizumab (VEGF-A)
  – Proteinuria 21-64%
  – Elevations in SCr – rare
  – Thrombotic microangiopathy
Tyrosine Kinase Inhibitors: Target the VEGFRs (VEGFR1 and VEGFR2)

<table>
<thead>
<tr>
<th></th>
<th>Hypertension</th>
<th>Proteinuria</th>
<th>SCr Elevations</th>
<th>TMA</th>
<th>AIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>17%</td>
<td>1-10%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>27% to 34%</td>
<td>&lt;1%</td>
<td>&gt;10% (RCC: 70%; GIST: 12%)</td>
<td>rare</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Panzopanib</td>
<td>40%</td>
<td>&lt;10%</td>
<td>NR</td>
<td>rare</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Axitinib</td>
<td>40%</td>
<td>5%</td>
<td>55%</td>
<td>1-15%</td>
<td>NR</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>33% to 61%</td>
<td>2% to 12%</td>
<td>58%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>30% to 59%</td>
<td>33% to 84%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>53% to 74%</td>
<td>NR</td>
<td>21%</td>
<td>&lt;1%</td>
<td>NR</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>&gt;10% to &lt;33%</td>
<td>10%</td>
<td>16%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>45% to 73%</td>
<td>26% to 34%</td>
<td>2% to 3%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
EGFR Targeted Cancer Therapies

• EGFR involved in cancer growth
• Family of 4 TKs
  – erbB-1 (EGFR)
  – erbB-2 (Her2)
  – erbB-3
  – erbB-4
• Six binding ligands
  – EGF, TGF, ampiregulin, betacellulin, epiregulin, heparin-binding EGF
• TKIs: erlotinib, gefitinib, lapatinib
• Monoclonal abs: cetuximab, panitinumab, trastuzumab, pertuzumab, ertuxmaxomab
• EGFR expressed in proximal and distal tubules, collecting duct, glomerular capillary walls, mesangial cells, parietal epithelial cells, peritubular capillaries and arterioles.
• Renal adverse events occur secondary to off-(tumor) target EGF and EGFRs.
Renal-Related Adverse Effects to Anti-EGFR Treatments

- Nephrotic syndrome
- Proteinuria
- Interstitial infiltration of lymphocytes
- Interstitial damage from the inhibition of normal turnover of tubular epithelial cells
- Magnesium wasting – may also be a biomarker for treatment response
  - most relevant for cetuximab and panitumumab – up to 34% incidence
# EGFR Targeted TKI Cancer Therapies

<table>
<thead>
<tr>
<th></th>
<th>Proteinuria</th>
<th>SCr Elevations</th>
<th>AIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>NR</td>
<td>&lt;1%</td>
<td>NR</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>8% to 35%</td>
<td>2%</td>
<td>NR</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Neratinib</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>10%</td>
<td>16%</td>
<td>NR</td>
</tr>
<tr>
<td>Dacomitinib</td>
<td>NR</td>
<td>24%</td>
<td>NR</td>
</tr>
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</table>
PDGF Targeted Cancer Therapies

• PDGF-α and PDGF-β
• PDGF-β expression in proximal tubules, mesangium, interstitial cells

• Renal related adverse effects to PDGFR targeted treatments:
  – acute tubular necrosis
  – thrombotic microangiopathy
  – Fanconi syndrome
  – Tubular vacuolization of both proximal and distal tubules
### PDGF Targeted Cancer Therapies

<table>
<thead>
<tr>
<th></th>
<th>ATN</th>
<th>Fanconi Syndrome</th>
<th>SCr Elevations</th>
<th>TMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>NR</td>
<td>NR</td>
<td>≤44%</td>
<td>NR</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>NR</td>
<td>NR</td>
<td>&lt;1%</td>
<td>Post-marketing case reports</td>
</tr>
</tbody>
</table>

Other PDGF acting agents were mentioned in previous classes: Sunitinib, Sorafenib, Pazopanib, Nilotinib, Ponatinib, Axitinib
BRAF Inhibitors

Renal Related Toxicities to BRAF Inhibitors

• ATN – within 1-2 weeks of treatment
• AIN
• Fanconi Syndrome
• Electrolyte Wasting
  – Phosphate
  – Sodium
  – Potassium
• Proteinuria
Proteasome Inhibitors

- Target the ubiquitin proteasome pathway
- Bortezomib, Carfilzomib
- Renal Adverse Events
  - Increased SCr – 24%
  - AKI – 5%
  - TMA

- Vasoconstriction of renal arteries proposed as mechanism for AKI.

- Decreased NF-κB levels in nucleus leads to decreased VEGF production as a mechanism for TMA.
Immune Checkpoint Inhibitors and AKI

- Associated with development of acute interstitial nephritis or granulomatous interstitial nephritis
- RRT needed in some patients
- Time course variable but can occur several weeks to months after starting therapy
- Steroids and drug withdrawal associated with recovery for majority

Immune Checkpoint Inhibitors

- Anti-CTLA-4 (cytotoxic T-lymphocyte antigen-4) targeted
  - Ipilimumab
- Anti-PD-1 (programmed cell death-protein 1) targeted
  - Nivolumab
  - Pembrolizumab
- Adverse events are due to augmented immune responses leading to autoimmune related inflammation
- Renal-related AEs
  - Elevated SCr
  - Autoimmune nephritis
  - Interstitial nephritis
## Management of Renal Toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Serum Creatinine</th>
<th>Work-up</th>
<th>Immunotherapy</th>
<th>Initial Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>1–1.5× baseline;</td>
<td>Monitor creatinine at least weekly</td>
<td>Continue</td>
<td>If creatinine worsens, treat as grade 2/3 or 4</td>
</tr>
<tr>
<td></td>
<td>&gt;1–1.5× ULN, 1+ proteinuria or urinary protein &lt; 1.0 g/24h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>1.5–3.0× baseline;</td>
<td>Monitor creatinine at least weekly</td>
<td>Withold therapy and resume if symptoms are mild severity, resolve or return to baseline</td>
<td>(I) Administer methylprednisolone 0.5–1.0 mg/kg/day IV or equivalent and continue until improvement to mild severity. Taper over 1 month. (II) If creatinine increased &gt;7 days or symptom worsen, treat as grade 4</td>
</tr>
<tr>
<td></td>
<td>&gt;1.5–3.0× ULN, 2+ proteinuria or 1.0–3.4 g/24h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt;3.0× baseline;</td>
<td>Monitor creatinine daily; (II) Consider nephrologist consultation with consideration of renal biopsy</td>
<td>Permanently discontinue</td>
<td>Administer methylprednisolone 1–2 mg/kg/day IV or equivalent and continue until improvement to mild severity. Taper over at least 1 month</td>
</tr>
<tr>
<td></td>
<td>&gt;3.0–6.0× ULN; proteinuria &gt;3.5 g/24h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>6.0× ULN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAR-T Cell Therapy and AKI

Jhaveri K and Rosner MH, CJASN 2018 in press
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.