Management of Renal Complications Encountered in Cancer Care

J. W. Lee
National Cancer Center Korea
May 24th, 2019
Contents

• Acute kidney injury associated with targeted therapies
  • Anti-angiogenesis agents
  • Immune checkpoint inhibitors
  • Chimeric antigen receptor T cells
  • Tumor lysis syndrome with venetoclax
Hanahan D and Weinberg RA. Cell 2011
Targeted Therapy can cause Hypertension, Proteinuria, and Electrolyte disorders. These can lead to AKI, which in turn can manifest in the form of TMA, AIN, and ATN.

Jhaveri KD  [https://www.youtube.com/watch?v=prmaujWxWYM](https://www.youtube.com/watch?v=prmaujWxWYM)
Contents

• Acute kidney injury associated with targeted therapies
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  • Immune checkpoint inhibitors
  • Chimeric antigen receptor T cells
  • Tumor lysis syndrome with venetoclax
VEGF in the glomerulus
VEGF in the glomerulus

- Podocyte-specific heterozygous knockdown of VEGF leads to nephrotic syndrome and end-stage renal failure by 9 weeks of age.

- VEGF-null glomeruli do not form filtration barriers or fenestrations.
Bevacizumab and the risks of proteinuria and hypertension

• Zhu et al. (2007)
  • A meta-analysis of 1,850 patients from 7 clinical trials
  • Increased risk of proteinuria (RR 1.4 with low dose; RR 2.2 with high dose)
  • Increased risk of hypertension (RR 3.0 with low dose; RR 7.5 with high dose)

• Ranpura et al. (2010)
  • 12,656 patients from 20 studies
  • RR for high-grade hypertension: 5.28 (6.1-10.2)
  • RR for hypertensive crisis: 3.16 (0.91-10.90)
  • RR for hypertension: 2.49 with mesothelioma; 14.80 with breast cancer
Bevacizumab and TMA

- Eremina V et al. (2008)

- 6 cases of bevacizumab-associated thrombotic microangiopathy

- Podocyte-specific VEGF deletion in mice recapitulated the renal effect of bevacizumab in humans.

- 59/M with hepatocellular ca.
  - Bevacizumab for 24 doses
  - Proteinuria: 0.5 g/d → 3.4 g/d
  - Hypertension
  - Platelets: 103,000/mL
  - No schistocytes
Modified from Estrada CC et al. JASN 2019

**Podocyte**

- **VEGFR2**
  - Bevacizumab, ranibizumab
  - Aflibercept
  - VEGF
  - Ramucirumab

**Glomerular endothelial cells**

- **VEGFR2**
  - PI3/AKT
  - MAPK
  - BRAF
  - mTORC1
  - eNOS

**TKIs (sunitinib … )**

**BRAF/MEK inhibitors** (vemurafenib, dabrafenib)

**mTOR inhibitors**
**Anti-VEGF agents**

- **Monoclonal Abs**
  - Bevacizumab
  - Ramucirumab

- **VEGF trap**
  - Aflibercept

- **Tyrosine kinase inhibitors**
  - Sunitinib
  - Sorafenib
  - Pazopanib
  - Regorafenib
  - Axitinib

**TKIs**
- Receptor
  - VEGFR
  - PDGFR
  - EGFR
- Cellular
  - BCR-ABL
  - Bruton’s kinase

**Jhaveri KD et al. KI Reports 2016**
Nephrotoxicities of anti-angiogenesis agents

- Hypertension (common)
- Proteinuria / nephrotic syndrome (common)
- Thrombotic microangiopathy
- Acute interstitial nephritis (rare)
Renal complications associated with anti-VEGF

• Izzedine et al. (2014)
  • A series of 94 patients referred for anti-VEGF-associated kidney ds.
  • Median onset: 6.8 months
  • Proteinuria (100%)
  • Hypertension (74%)
  • Renal failure (40%; eGFR < 60)
  • TMA (n=73)
    • Bevacizumab in 61; aflibercept in 5
    • Hypertension in 83%
    • 71% female
  • MCN/FSGS-like (n=21)
    • Sunitinib in 13; sorafenib in 5
    • Hypertension in 48%
  • Renal function improved only following antihypertensive therapy and cessation of anti-VEGF therapy.

VEGF regulates local complement activity

- VEGF increases CFH production.
- Anti-VEGF therapy reduces CFH production, making the cells vulnerable to complement activation.

VEGF signaling and associated nephrotoxicities

Estrada CC et al. JASN 2019
Intravitreal bevacizumab and/or aflibercept

- Worsening hypertension, proteinuria, and kidney injury
- Detectable in bloodstream up to 30 days post-intravitreal injection

EXCEPTIONAL CASE

Three patients with injection of intravitreal vascular endothelial growth factor inhibitors and subsequent exacerbation of chronic proteinuria and hypertension

- Intravitreal bevacizumab and/or aflibercept
- Worsening hypertension, proteinuria, and kidney injury
- Detectable in bloodstream up to 30 days post-intravitreal injection
BRAF inhibitors

- BRAF-V600-mutant metastatic melanomas

- Vemurafenib
  - 44/74 (59.5%) patients had a rise in serum Cr > 1.5 x baseline
  - Pathology: acute focal tubular damage, interstitial fibrosis
  - 80% reversible within 3 months of discontinuation


- Inhibition of tubular secretion of Cr

BRAF/MEK inhibitors and the podocyte

- Nephrotic syndrome with dabrafenib and trametinib
  - Loss of podocytes
  - Glomerular endothelial injury
  - Reduction in PLCε1 and nephrin expression
  - Inhibition of VEGF system

BRAF/MEK inhibitors and the podocyte

• Nephrotic syndrome with dabrafenib and trametinib
  • Loss of podocytes
  • Glomerular endothelial injury
  • Reduction in PLCε1 and nephrin expression
  • Inhibition of VEGF system
## Clinical manifestations of VEGF inhibition

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Class</th>
<th>Renal Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>mAb against VEGFA</td>
<td>Proteinuria 21-62%; HTN 23.7%; TMA, MCD, ABMR-intraocular</td>
</tr>
<tr>
<td>Ranibizumab (intraocular)</td>
<td>mAb against VEGFA</td>
<td>TMA, proteinuria, ABMR-intraocular</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>Recombinant VEGF trap</td>
<td>HTN 42.4%; proteinuria, TMA, ABMR-intraocular</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>mAb against VEGFR2</td>
<td>HTN 21%; proteinuria 9%</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Multitargeted TKIs</td>
<td>HTN 14.9%; MCD/cFSGS</td>
</tr>
<tr>
<td>Pazofanib</td>
<td>Multitargeted TKIs</td>
<td>HTN 47%; proteinuria 13.5%</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multitargeted TKIs</td>
<td>HTN 18.1%; MCD/cFSGS; TMA; proteinuria 11.6%</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF inhibitor</td>
<td>AKI, ATN</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>BRAF inhibitor</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Trametinib</td>
<td>MEK inhibitor</td>
<td>Nephrotic syndrome</td>
</tr>
</tbody>
</table>
Clinical considerations

• Optimize cardiovascular risk prior to anti-VEGF therapy

• BP < 140/90 mmHg

• Inhibition of renin-angiotensin system

• Stop anti-VEGF agents if frank AKI(+) or nephrotic-range proteinuria
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Immune Checkpoint Inhibitors

Immune checkpoints

• Protect tissues from an activated immune system

• Primary mechanism is a downregulation of T cell activation or effector functions.

Molecular targets

• CTLA-4 (cytotoxic T lymphocyte-associated protein 4)

• PD-1/PD-1L (programmed cell death protein-1 / programmed cell death protein-1 ligand)
“Immune checkpoint”
Immune Checkpoint inhibitors

• Anti-CTLA4
  • Ipilimumab
  • Tremelimumab

• Anti-PD-1/PD-L1
  • nivolumab, pembrolizumab
  • atezolizumab, durvalumab, avelumab

Indications

• First-line treatment of:
  • Melanoma
  • Non-small cell lung cancer

• Pembrolizumab
  • Any solid tumor harboring microsatellite instability-high (MSH-H) or a deficient DNA mismatch repair system (dMMR)
Immune-related adverse events (irAEs)

- Of autoimmune nature

- Ipilimumab: 75%; high-grade (grade 3 or 4) irAEs in 43%

- Anti-PD-1/PD-L1: 30%; high-grade in 20%

- Combined treatment: irAEs in 95%; 55% in grade 3 or 4
## Immune-related adverse events (irAEs)

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Skin</td>
<td>• Renal: AKI - AIN, ATN</td>
</tr>
<tr>
<td>• GI tract: colitis, hepatitis</td>
<td>• 1-2% with monotherapy</td>
</tr>
<tr>
<td>• Endocrine: hypophysitis, thyroiditis</td>
<td>• 4.9% with combined therapy</td>
</tr>
<tr>
<td></td>
<td>• Pulmonary: pneumonitis</td>
</tr>
<tr>
<td></td>
<td>• Cardiovascular: myocarditis</td>
</tr>
<tr>
<td></td>
<td>• Neurological</td>
</tr>
</tbody>
</table>
Renal irAEs

- Acute tubulointerstitial nephritis

- Acute tubular injury


Izzedine H et al, Clin Kidney J 2019
<table>
<thead>
<tr>
<th>Pt</th>
<th>Urine sediment&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Proteinuria&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Day of AKI&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Days since last dose of CPI</th>
<th>Eos</th>
<th>HTN&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Oliguria&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Kidney size (cm)</th>
<th>Peak SCR (mg/dl)</th>
<th>Requirement for RRT</th>
<th>IRAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5–10 WBCs&lt;sup&gt;e&lt;/sup&gt; 2 RBCs</td>
<td>1+/0.6</td>
<td>54</td>
<td>54</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 12.8 L 13.8</td>
<td>6.2</td>
<td>No</td>
<td>Hypophysitis</td>
</tr>
<tr>
<td>2</td>
<td>2–3 WBCs 3–5 RBCs</td>
<td>Trace/NA</td>
<td>91</td>
<td>49</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 12.2 L 13.2</td>
<td>4.1</td>
<td>No</td>
<td>Thyroiditis; ileitis</td>
</tr>
<tr>
<td>3</td>
<td>5–10 WBCs 0 RBCs</td>
<td>Trace/NA</td>
<td>69</td>
<td>14</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 11.6 L 12.6</td>
<td>9.7</td>
<td>3 HD treatments starting on day 130</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>4</td>
<td>0–2 WBC casts 16–34 WBCs</td>
<td>NA/NA</td>
<td>70</td>
<td>28</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>R 13.0 L 13.0</td>
<td>3.6</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>5 WBCs&lt;sup&gt;e&lt;/sup&gt; 1 RBC</td>
<td>Neg/0.26</td>
<td>245</td>
<td>63</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 13.2 L 13.0</td>
<td>2.9</td>
<td>No</td>
<td>Hypophysitis; thyroiditis</td>
</tr>
<tr>
<td>6</td>
<td>0 WBC 0 RBC</td>
<td>Neg/0.74</td>
<td>183</td>
<td>36</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>R 10.9 L 13.5</td>
<td>11.7</td>
<td>HD-dependent starting on day 183</td>
<td>Hypophysitis; colitis</td>
</tr>
<tr>
<td>7</td>
<td>0 WBC&lt;sup&gt;e&lt;/sup&gt; 0 RBC</td>
<td>Neg/NA</td>
<td>224</td>
<td>14</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 11.8 L 12.2</td>
<td>3.8</td>
<td>No</td>
<td>Sicca syndrome with sialadenitis on lip biopsy; colitis</td>
</tr>
<tr>
<td>8</td>
<td>6–9 WBCs 0–3 RBCs</td>
<td>1+/0.98</td>
<td>154</td>
<td>7</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>R 12.8 L 12.2</td>
<td>5.6</td>
<td>HD-dependent starting on day 210</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>9 WBCs&lt;sup&gt;e&lt;/sup&gt; 8 RBCs WBC casts</td>
<td>2+/0.12</td>
<td>42</td>
<td>21</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>R 12.4 L 13.0</td>
<td>7.3</td>
<td>No</td>
<td>Rash; colitis</td>
</tr>
<tr>
<td>10</td>
<td>3 WBCs&lt;sup&gt;e&lt;/sup&gt; 3 RBCs WBC casts</td>
<td>1+/0.73</td>
<td>120</td>
<td>57</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 8.0 L 10.0</td>
<td>2.9</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>50–100 WBCs 0–2 RBCs WBC casts</td>
<td>1+/0.18</td>
<td>60</td>
<td>18</td>
<td>14.7%</td>
<td>No</td>
<td>No</td>
<td>R 10.2 L 10.0</td>
<td>4.5</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>20–50 WBCs 0–2 RBCs</td>
<td>1+/NA</td>
<td>21</td>
<td>21</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>13.3</td>
<td>3 HD treatments starting on day 21</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>11–20 WBCs 0 RBCs</td>
<td>Neg/0.36</td>
<td>231</td>
<td>21</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>R 10.7 L 11.9</td>
<td>2.5</td>
<td>No</td>
<td>Iritis; colitis</td>
</tr>
</tbody>
</table>

Median: 0.48, IQR: 0.24–0.73

Cortazar F et al, Kidney Int 2016
A case of AKI associated with ICI treatment

- 64/M, Advanced gastric cancer

- Progressive azotemia over 2 weeks after cycle #3 of anti-CTLA4 (tremelimumab) and anti-PD-L1 (durvalumab)

- BUN/Cr 30/2.64 mg/dL

- U/A with microscopy: protein 1+, glucose -, RBC 5-9/HPF, WBC >100/HPF
Serum Creatinine

#1

#2

#3

Bx

PD 1 mg/kg

32
Tubular injury with pembrolizumab

- 12/676 (1.77%) cases in France
- 4 patients with AIN
- 5 patients with ATI
- 1 patient with MCD + ATI
- 1 patient with MCD
- Steroid + withdrawal of pembrolizumab

### 6.1 Nephritis

**Additional considerations**
- Monitor creatinine weekly
- Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted

| Cr rise > 0.3 mg/dL; Cr 1.5-2.0 x over baseline | Consider temporarily holding ICPi |
| Cr 2-3 x above baseline | Hold ICPi temporarily; 1-2 mg/kg PD |
| Cr > 3 x baseline or > 4 mg/dL | Permanently discontinue ICPi |
Use of ICIs in a transplant recipient

- 70/M
- Bilateral RCC → Nx → KT
- GC + tacrolimus + MMF
- Duodenal ca. m/liver
- Nivolumab therapy

Table 1. Immunosuppressive Regimen in a Patient Who Had Undergone Kidney Transplantation.

<table>
<thead>
<tr>
<th>Timing</th>
<th>Drug and Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Wk before</td>
<td>Prednisone — 40 mg daily</td>
</tr>
<tr>
<td>Concurrent</td>
<td>Prednisone — 20 mg daily; sirolimus — target goal, 4–6 ng per milliliter</td>
</tr>
<tr>
<td>1 Wk after</td>
<td>Prednisone — 20 mg</td>
</tr>
<tr>
<td>&gt;2 Wk and ≤6 mo after</td>
<td>Prednisone — 10 mg/day; sirolimus — target goal, 10–12 ng per milliliter</td>
</tr>
<tr>
<td>&gt;6 Mo after</td>
<td>Glucocorticoid — gradually decreased to 5 mg/day; sirolimus — continued to maintain goal of 10–12 ng per milliliter</td>
</tr>
</tbody>
</table>

* Timing represents the initiation of the immunosuppressive regimen in relation to the administration of nivolumab.

# Summary of renal effects of ICIs

<table>
<thead>
<tr>
<th></th>
<th>CTLA-4 antagonists</th>
<th>PD-1 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common toxicity</td>
<td>AIN in 10 patients</td>
<td>AIN in 16; 6 patients receiving combination CTLA-4 therapy</td>
</tr>
<tr>
<td>Timing of onset</td>
<td>6 to 12 wk after initiation</td>
<td>3 to 12 mo after initiation</td>
</tr>
<tr>
<td></td>
<td>Late onset related to severe AKI</td>
<td></td>
</tr>
<tr>
<td>Glomerular findings</td>
<td>Membranous nephropathy in 1</td>
<td>MCD in 1</td>
</tr>
<tr>
<td></td>
<td>TMA in 1</td>
<td>IgA nephropathy in 1</td>
</tr>
<tr>
<td></td>
<td>MCD in 2</td>
<td></td>
</tr>
<tr>
<td>Outcomes after kidney</td>
<td>No transplant rejection reported in 2 patients</td>
<td>Transplant rejection reported in 7 of 10 patients including 3 who had received</td>
</tr>
<tr>
<td>transplantation</td>
<td></td>
<td>combination therapy with CTLA-4 antagonants</td>
</tr>
</tbody>
</table>
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CAR T-cell Therapy

Remove blood from patient to get T cells

Make CAR T cells in the lab
- Insert gene for CAR
- Chimeric antigen receptor (CAR)

CAR T cells bind to cancer cells and kill them

Grow millions of CAR T cells

Infuse CAR T cells into patient

Disease
- Leukemia
  - B-cell acute lymphoblastic leukemia (in adults): 83–93
  - B-cell acute lymphoblastic leukemia (in children): 68–90
- Chronic lymphocytic leukemia: 57–71
- Lymphoma
  - Diffuse large B-cell lymphoma: 64–86
  - Follicular lymphoma: 71
  - Transformed follicular lymphoma: 70–83
  - Refractory multiple myeloma: 25–100
- Solid tumors
  - Glioblastoma: ND
  - Pancreatic ductal adenocarcinoma: 17

June CH et al. N Engl J Med 2018

Chimeric Antigen Receptor T cell therapy and the kidney

- Cytokine release syndrome
- Tumor lysis syndrome
- Electrolyte disorders
  - Hypokalemia (47%)
  - Hypophosphatemia (37%)
  - Hyponatremia (5%)
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Tumor lysis syndrome

Tumor Lysis Syndrome

Uric acid release
Hyperuricemia
Uric acid crystals
Acute kidney injury

Phosphorus release
Hyperphosphatemia
Calcium phosphate crystals

Potassium release
Hyperkalemia

Arrhythmias
Venetoclax

- Anti-bcl-2 agent
- Second-line treatment for CLL (17p deletion)
- Can cause rapid-onset tumor lysis syndrome
- 6 TLS, 2 deaths during dose escalation; many TLS cases
- Other agents: dinaciclib, favopiridol, ibrutinib, idelalisib
- High risk of tumor lysis
  - Any LN > 10 cm
  - Lymphocytes > 25,000/microliter + LN > 5 cm
- First doses should be inpatient dosing
- TLS prophylaxis
- Labs at 0, 4, 8, 12, and 24 h

Wanchoo R et al. CKJ 2018
Acknowledgment

• Glomerular Disease Study & Trial Consortium (GlomCon)
  • https://www.youtube.com/channel/UC7FG1vWfVQSwOcJHO35lOA
  • https://www.youtube.com/watch?v=jqYq6kLR8B
  • https://www.youtube.com/watch?v=prmaujWxWYM (Dr. Kenah Jhaveri)
  • Twitter: @GlomCon