Nephrotoxicity from new and emerging anti-cancer therapies

Michael Powell
Pharmacist Advanced – Cancer & Blood Disorders
Gold Coast University Hospital
Chair, COSA Cancer Pharmacists Group

Introduction
• AKI and electrolyte disturbances are the most common forms of renal disease that may occur in the cancer inpatient
• With new agents, continued need for vigilance amongst all clinicians treating cancer patients including cancer pharmacists
• Remember, vulnerability of the kidneys is based on some of the key attributes of the organ:
  • Rich blood supply (25% of cardiac output): ensuring high levels of drug/metabolite delivery
  • High tubular reabsorptive capacity: leading to high intracellular tubular cell concentrations
  • Ability to concentrate toxins to high levels within the medullary interstitium via renal countercurrent mechanisms
  • Major elimination pathway for many anticancer compounds and their metabolites
• Important factors potentiating AKI in these patients may be innate patient factors or specific drug-related issues
Risk Factors: Drug Induced Renal Dysfunction

**Innate patient risk factors**
- Age > 60, smoking, overweight, female
- Hypoalbuminaemia
- Underlying kidney failure (AKI and CKD)
- Family history of CKD
- Acute hepatic failure or advanced cirrhosis
- Metabolic disturbances (e.g. ↓K⁺/Mg²⁺/Ca²⁺)
- Intravascular volume depletion (e.g. dehydration)
- Tumour presence (e.g. RCC)
- Co-morbidities (HT, diabetes, etc.)

**Drug-related risk factors**
- Route (IV vs oral), dose and duration of potentially nephrotoxic drugs
- High renal drug handling
- Concomitant nephrotoxic drugs/polypharmacy

**Main categories of DI-AKI**

- Acute vascular disease
  - Thrombotic microangiopathy: direct endothelial injury, VEGF deficiency, antibody mediated – often associated with severe AKI
  - Vasculitis: immune-mediated injury
- Acute glomerular disease
  - Minimal change disease: direct cellular injury
  - Glomerulonephritis, lupus nephritis: immune mediated injury
- Acute tubular disease
  - Acute tubular necrosis
- Acute interstitial disease
  - Acute interstitial nephritis
Anti-angiogenic agents

- VEGF ligand inhibitors (bevacizumab, aflibercept) bind to the VEGF molecule
  - Prevents it from binding to VEGFR
  - Inhibits endothelial cell proliferation and vessel formation
- These compounds can cause:
  - Asymptomatic proteinuria (associated with hypertension)
  - Nephrotic syndrome
  - Thrombotic microangiopathy (TMA)
Mechanisms of renal injury and hypertension caused by anti-angiogenic agents

TMA

- A spectrum of disorders characterised by:
  - Occlusive microvascular thrombosis
  - Microangiopathic haemolytic anaemia
  - Thrombocytopenia
  - Variable and potentially fatal end-organ damage, commonly renal

- Two main idiopathic or primary forms of this syndrome which cause TMA are:
  - TTP
  - aHUS
TMA

- Secondary causes which can precipitate TMA include:
  - Infection
  - Connective tissue and autoimmune diseases
  - BM/solid organ transplantation
  - Pregnancy and the puerperium
  - Exposure to toxins, radiation, vaccination
  - Disseminated malignancy
  - Medications including chemotherapy
- Incidence of cancer drug-induced TMA over last 2-3 decades is >15%, primarily due to the introduction of anti-VEGF agents

Possible mechanisms of drug-induced TMA

• Which older cytotoxic drugs are associated with the development of TMA?

<table>
<thead>
<tr>
<th>Characteristics of Cancer Drug-Induced TMA</th>
<th>Type I Cancer Drug-Induced TMA</th>
<th>Type II Cancer Drug-Induced TMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy regimen</strong></td>
<td>Mitomycin C and/or gemcitabine</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Delayed; usually 6-12 mo after starting therapy</td>
<td>Occurs any time after the initiation of treatment and may be involved after prolonged treatment (1 dose to 29 mo)</td>
</tr>
<tr>
<td><strong>Dose effect</strong></td>
<td>Cumulative, dose related</td>
<td>Not dose related</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Appears to be permanent and irreversible; hematologic manifestations usually present; hypertension, acute renal failure, pulmonary edema, and ARDS are common</td>
<td>High likelihood of recovery after interruption (reversible); hematologic manifestations only in half of pts; hypertension, and varying degrees of proteinuria usually without kidney failure</td>
</tr>
<tr>
<td><strong>Effect of rechallenge</strong></td>
<td>High probability of recurrent dysfunction that is progressive; may result in intractable kidney failure</td>
<td>Some evidence for the relative safety of rechallenge (additional data needed)</td>
</tr>
<tr>
<td><strong>Pathologic</strong></td>
<td>Arteriolar and glomerular capillary thrombosis</td>
<td>Exclusive glomerular capillary thrombosis</td>
</tr>
<tr>
<td><strong>Therapy and prognosis</strong></td>
<td>High incidence of acute mortality (4-month mortality up to 75%) and chronic kidney disease requiring dialysis despite drug discontinuation, steroids, or plasma exchange before rituximab and eculizumab use</td>
<td>Patient and kidney survival rates are excellent after stopping drug in association with antihypertensive drugs</td>
</tr>
</tbody>
</table>

Management of drug-induced TMA

• Effective management requires accurate and rapid diagnosis
  • If on meds associated with TMA, monitor for HPT, proteinuria and reduced RF
  • If positive for these, may signal isolated kidney TMA and responds to temporary cessation of therapy and renal biopsy
• Historically, chemo induced TMA prognosis was catastrophic with mortality rate >50% (with use of steroids, PEX etc)
• No clear guidelines exist but Izzedine et al\textsuperscript{1} suggest:
  • Step 1: supportive care – may be all that is needed in some especially pts on anti-VEGF therapy; includes immediate cessation of offending drug, BP control with ACE-I, careful reintroduction of drug with strict monitoring
  • Step 2: specific treatments – rituximab, eculizumab

\textsuperscript{1}Izzedine et al Am J Kidney Dis 2015; 66(5): 857-68

EGFR Inhibitors

• Cetuximab/panitumumab well known to cause urinary magnesium wasting leading to hypomagnesaemia
• Risk factors:
  • Duration of treatment
  • Age
  • Baseline Mg values
• Prevalence: grade 3-4 in up to one-third of treated patients
• Consequences – may lead to hypokalaemia, hypocalcaemia and cardiac arrhythmias
• Some evidence of improved RR/TTP/OS, especially in mod-severe low Mg
• Management: review for other offending meds; G1-2 oral Mg supps; more severe or unresponsive to oral, use IV (some case reports - amiloride)
• Renal failure: incidence 2% (cause unknown but EGFR is expressed in distal/collecting tubules and is involved in maintaining tubular integrity)
EGFR Inhibitors

- EGFR TKIs can also cause renal adverse effects
  - Erlotinib: hypomagnesaemia, hypophosphataemia, AKI
  - Gefitinib: hypokalaemia, fluid retention, MCD, proteinuria, AKI
- Lower incidence of hypomagnesaemia than MAbs – possibly due to tablet excipient (magnesium stearate)
- AKI mechanism unclear

BRAF inhibitors

- No renal toxicity of note reported in initial clinical trials
- Post-marketing reviews have shown evidence\(^1\) of AKI:
  - Asymptomatic serum creatinine elevations
  - AIN/ATN – especially in setting of dehydration
  - Vemurafenib > dabrafenib
  - Male > female (2x)
  - Incidence unknown (one study – 60%)
- Often occurs in patients with co-morbidities e.g. diabetes, hypertension
- Mode of injury likely to be tubular interstitial damage – mechanism: interference with MAP-kinase pathway increasing susceptibility to ischaemic tubular injury
- Hypo-natraemia/kalaemia also reported
- Monitoring RF/electrolytes essential, AKI usually resolves on ceasing

\(^1\)Jhaveri et al JAMA Onc 2015; 1(8): 1133-34

ALK inhibitors

- All currently marketed ALK inhibitors (crizotinib, ceritinib and alectinib) can cause:
  - Electrolyte disturbances (including low PO4, Na)
    - Some cases may be related to TKI-induced diarrhoea/vomiting
    - Caution: ceritinib induced QTc prolongation
  - GFR reduction and increased serum creatinine observed
    - PI: 8% crizotinib, 17.7% ceritinib, 31% alectinib
    - May be at least partly due to ALK inhibitor interference of tubular creatinine secretion (remember upto 20% serum creatinine is actively secreted via tubules with 80% filtered) so may represent a “pseudo-AKI”
    - Rapidly improves on cessation of drug
  - Little evidence of acute kidney damage (some case reports of ATN)
  - Development and progression of renal cysts also observed (upto 4% of patients on crizotinib and rapidly reversible on cessation) – more common in patients treated with multiple lines of therapy, longer duration and Asian ethnicity
cKIT inhibitors

- Imatinib associated with renal failure in <1% of patients in pivotal CML study
  - Likely dose dependent (more commonly observed in 600-800mg dosing)
  - Mechanism may be related to high PDGF-β and cKIT expression in kidney tubules and interstitial cells
  - Several cases of ATN reported on renal biopsy, and one case of TMA
  - More likely to occur in patients with pre-existing renal impairment
  - May be related to TLS, especially in Ph+ ALL patients

- Hypophosphataemia is a common electrolyte abnormality (upto 10%)
  - Often associated with low Ca/vit D levels
  - Mechanism is likely inhibition of renal tubular reabsorption of phosphorus

mTOR inhibitors

- Renal toxicities associated with mTOR inhibitors include:
  - Hypertension
  - Proteinuria
  - Hypophosphataemia
  - Hyponatraemia
  - Serum creatinine increase

- Low incidence of renal failure reported, however recent case report of four cases of biopsy-proven ATN after commencing everolimus\(^1\)
  - Two cases fully reversible on cessation, two were not (including one case of continued dialysis dependence)

- More common in RCC (compared with breast cancer)
  - Baseline GFR often lower (considered main risk factor) – due to prior nephrectomy, tumour presence, prior exposure to VEGFR-TKIs

\(^1\)Izzedine et al Ann Oncol 2013; 24: 2421-25
Immunotherapy: checkpoint inhibitors

- Ipilimumab was first CPI associated with kidney disease, with Izzedine et al\(^1\) (2014) reporting 5 cases of AIN associated with ipilimumab
- Kidney injury can be divided into:
  - Increased serum creatinine: remains rare (upto 4% across multiple studies, onset of effect highly variable, can indicate impending renal failure)
  - Renal parenchymal damage:
    - AIN
    - Immune complex glomerulonephritis
  - In setting of renal failure and/or nephrotic range proteinuria, renal biopsy is critical for early detection and commencing management

\(^1\)Izzedine et al Invest New Drugs 2014; 32: 769-73

AKI incidence: checkpoint inhibitors

![AKI incidence graph](chart)

Cortizar et al Kidney Intl 2016; 90: 638-47
Renal toxicities comparison: anti-CTLA4 vs anti-PD1/PDL1

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CTLA-4 antagonists (ipilimumab)</th>
<th>PD-1 inhibitors (nivolumab and pembrolizumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of AIN</td>
<td>AIN appears 6–12 weeks after initiation of therapy</td>
<td>AIN appears 3–12 mo after initiation of therapy</td>
</tr>
<tr>
<td>Glomerular findings</td>
<td>Podocytopathy reported</td>
<td>No cases of podocytopathy reported</td>
</tr>
<tr>
<td>Electrolyte disorders</td>
<td>Hyponatremia cases related to hypophysitis</td>
<td>Hyponatremia is rare</td>
</tr>
</tbody>
</table>


Pathophysiology

- Two likely underlying mechanisms:
  A. CPIs disrupt CTLA-4/PD-1 signalling (which usually maintains peripheral self-tolerance to exogenous drug antigens), so loss of tolerance occurs with reactivation of exhausted memory T-cells previously primed by nephrotoxic drugs
  B. Auto-immunity due to immunostimulatory effects: demonstrated with importance of PD-1 signalling in minimising T-cell mediated renal inflammation

Suggested management

• Similar to other irAEs
• Grade 1 renal toxicity: continue treatment with weekly SeCr, promote hydration, cease concurrent nephrotoxic drugs
• Grade 2-3 renal toxicity: withhold CPI until SeCr reduced back to at least Grade 1, monitor SeCr every 2-3 days, commence oral Prednisolone 0.5-1mg/kg/d (upto 2mg/kg), conduct renal biopsy
• Grade 4 renal toxicity: permanently stop CPI, monitor SeCr daily, commence IV methylpred 1-2mg/kg/d, conduct renal biopsy and consider referral to nephrologist
• Use of steroids is almost always successful and results in resolution (for grade 3-4 toxicity, within 3-6 weeks)

Tumour lysis syndrome

1Izzedine et al Nephrol Dial Transplant 2017; 32: 936-42
TLS – Risk factors

- Pre-existing renal impairment
- Tumours with high growth fraction
- High chemosensitivity
- Large tumour burden
- Leukaemia (ALL), Lymphoma (Burkitts), SCLC, Germ cell tumours
- Raised LDH
- Elevated WCC

Consequences of TLS

| Uric Acid          | Nausea, vomiting, oliguria, haematuria
|                   | Azotemia, flank pain, renal failure
| Potassium          | Weakness, parasthesia
|                   | Cardiac symptoms
| Phosphate          | Oliguria, anuria
|                   | Azotemia, renal failure
| Calcium            | Tetany, laryngospasm
|                   | Arrhythmias, convulsions
TLS in the era of novel targeted agents......

- Recent literature review conducted to examine propensity of these newer agents to cause TLS\(^1\) (often under-reported in trials)
- Identified published phase I – III trials of:
  - MAbs – BV, obinutuzumab, ofatumumab
  - TKIs – ibrutinib, dasatinib, nilotinib, idelalisib, venetoclax
  - PIs – carfilzomib
  - CAR-T cells
  - Lenalidomide
- As expected, incidence varies by treatment regimen, haem malignancy, number of prior relapses and supportive care employed
  - Highest TLS prevalence: venetoclax and lenalidomide in CLL

\(^1\)Howard et al Ann Hematol 2016; 95: 563-73

Venetoclax

- Orally available, highly selective B cell lymphoma/leukaemia 2 (BCL-2) inhibitor
- TGA approved for patients with RR-CLL and 17p deletion, or patients with RR-CLL for whom no further treatment options (PBAC recommended July 2017)
Venetoclax

Incidence of TLS in early studies before and after implementation of TLS mitigation measures

- Before implementation (N=77):
  - Laboratory TLS: 12% (n=9)
  - Clinical TLS: 5.2% (n=4)
  - Overall TLS: 6.5% (n=5)

- After implementation (N=66):
  - Laboratory TLS: 6% (n=4)
  - Clinical TLS: 5.2% (n=4)

No clinical TLS events were reported after implementation of ramp-up dosing, prophylaxis, and monitoring.


Venetoclax

Apply recommended TLS prophylaxis and monitoring (consider all patient comorbidities before final determination)

<table>
<thead>
<tr>
<th>Tumor burden assessment</th>
<th>Prophylaxis</th>
<th>Blood chemistry monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Hydration*</td>
<td>Outpatient</td>
</tr>
<tr>
<td>ALLN &lt;5 cm</td>
<td>Oral (1.5-2 L)</td>
<td>Pre-dose at initial and all ramp-up doses</td>
</tr>
<tr>
<td>and &lt;25 x 10^9/μL</td>
<td></td>
<td>Post-dose: 6-8, 24 hours after initial dose of 20 mg and 50 mg</td>
</tr>
</tbody>
</table>

| Medium                  |             |                           |
| Any LN 5 cm to <10 cm   | Oral (1.5-2 L) | Pre-dose at initial and all ramp-up doses |
| OR: ≥25 x 10^9/μL       | Consider additional IV |

| High                    |             |                           |
| Any LN ≥10 cm           | Oral (1.5-2 L) | Pre-dose and at initial dose of 20 mg and 50 mg |
| OR: ≥25 x 10^9/μL       |             | Post-dose: 4, 8, 12, 24 hours after initial dose of 20 mg and 50 mg |

Consider inpatient if CrCl <80 mL/min at initial dose of 20 mg and 50 mg. Please see below for monitoring in hospital.

Venetoclax