Onco-Nephrology: Perspectives from Nephrology

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DISCLOSURES

• No conflicts of interest to disclose
Onco-Nephrology
The Important Providers

KDIGO Controversies Conference on Onco-Nephrology

1) Kidney Problems in Hematology
2) Kidney Impairment and Solid Organ Malignancies
3) Management and Treatment of Kidney Cancer
4) Malignancy and Kidney Transplantation
Cancer
A Common Global Problem

• Cancer is common and a leading cause of death worldwide
• Estimated 9.6 million deaths in 2018
• The most common causes of cancer death are the following:
  - LUNG (1.76 MILLION DEATHS)
  - COLORECTAL (862,000 DEATHS)
  - STOMACH (783,000 DEATHS)
  - LIVER (782,000 DEATHS)
  - BREAST (627,000 DEATHS)
Onco-Nephrology

AKI incidence

AKI is common among cancer patients

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

Onco-Nephrology

AKI incidence

AKI is common among cancer patients

- Ontario, Canada: 163,071 patients undergoing cancer therapy between 2007-2014
- One in 10 developed AKI-D or required hospitalization
- Annual incidence of AKI increased from 18 to 52 per 1000 person years
- Highest AKI incidence with myeloma (26%), bladder cancer (19%), leukemia (15%), and kidney cancer (14%)
• Single center in France over 4 years
• Solid tumors admitted to the ICU (n=204)
• KDIGO AKI (59%) and mortality (37%) are common
• Sepsis, hypovolemia, and obstruction most common causes of AKI followed by TLS, hypercalcemia, and >1 etiology
• Stage 3 AKI (28%) with higher mortality (42%)
Onco-Nephrology
Increased Mortality with AKI

- Survival rates in cancer patients with AKI associated by RIFLE Criteria
- Kaplan-Meier survival curves—dose related reduction in survival

Overall AKI Incidence = 12%

Salahudeen A, et al. CJASN 2013
Onco-Nephrology
Chronic kidney disease in Cancer

- CKD (eGFR < 60 ml/min/1.73m$^2$) is highly prevalent in cancer patients

Onco-Nephrology
Increased Mortality with CKD

- CKD in cancer patients is associated with reduced survival
  - France: CKD stage 3 (eGFR < 60ml/min/1.73m²) HR 1.27 for Mortality
  - Australia: CKD stage 3 (eGFR < 60ml/min/1.73m²) HR 1.27 for Mortality
  - Korea: CKD stage 3 (eGFR 30 - 60ml/min/1.73m²) HR 1.12 for Mortality
    CKD stage 4 (eGFR < 30ml/min/1.73m²) HR 1.75 for Mortality
  - Japan: CKD stage 3 (eGFR < 60ml/min/1.73m²) is an independent risk factor for death at 1 year


KDIGO
The Kidney-Cancer Connection
Onco-Nephrology

AKI

Electrolyte-Acid/Base Disorders

Anti-Cancer Drugs
Malignancy-related Kidney Injury
Radiation/Nephrectomy
Uremic Milieu (CKD, ESRD)

CKD

CANCER

KDIGO
Kidney Injury and Cancer

Renal Sites of Injury

Vascular
- Hemodynamic
- TMA
- Drugs

Glomerular
- TMA
- MIDD/Amyloid
- Cryo GN
- PGNMID
- C3GN
- FGN/IT
- Drugs

Proximal Tubular
- Light Chains
- Drugs

Distal Tubular
- Cast nephropathy
- Crystalline nephropathy
  - Uric Acid
  - Calcium Phosphate
- Drugs

Interstitium
- Light Chains
- Drugs (AIN)
- Lymphoma
- Leukemia

Collecting System
- Lymphoma
- Leukemia
- Crystals
- Drugs
Onco-Nephrology
Myeloma and Kidney Disease

Glomerular manifestations

Multiple myeloma

Overproduction

Kappa or lambda light chains or heavy immunoglobulin chains

Urine albumin >2 g/day

Urine albumin ≤2 g/day

Deposition of light chains or monoclonal immunoglobulins, leading to glomerulopathy and proteinuria (urine albumin typically >2 g/day)

Glomerulopathy
AL amyloidosis
AH amyloidosis
Monoclonal immunoglobulin deposition disease (light-chain, heavy-chain, or both)
Proliferative GN with monoclonal IgG deposits
Monoclonal cryoglobulinemia
Membranoproliferative GN
C3 glomerulopathy
Fibrillary GN
Immunotactoid glomerulopathy

Proximal tubulopathy
Endocytosis of LCs, leading to acute tubular injury and fibrosis
Endocytosis of LCs, leading to Fancconi’s syndrome with or without acute kidney injury

Cast nephropathy
LCs bind with THP, forming insoluble casts that obstruct tubular lumen and elicit local inflammation, leading to acute kidney injury with or without chronic kidney disease

KDIGO

Rosner MH and Perazella MA. NEJM 2017
# Acute Kidney Injury (AKI) in Patients With Leukemia or Lymphoma

<table>
<thead>
<tr>
<th>Cancer-Related AKI</th>
<th>Therapy-Related AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor infiltration of the kidneys (more common with lymphoma)</td>
<td>Therapy-related nephrotoxicity (including thrombotic microangiopathy, acute tubular injury, tubulointerstitial nephritis, intratubular obstruction, and glomerulonephritis)</td>
</tr>
<tr>
<td>Retroperitoneal lymphadenopathy leading to urinary tract obstruction</td>
<td>Tumor lysis syndrome with acute uric acid nephropathy and/or acute nephrocalcinosis</td>
</tr>
<tr>
<td>Hypercalcemia-related prerenal kidney injury</td>
<td>Nausea, vomiting, and diarrhea associated with prerenal azotemia</td>
</tr>
<tr>
<td>Various paraneoplastic glomerular disorders</td>
<td>Sepsis-associated kidney injury</td>
</tr>
<tr>
<td>Lysozymuria with acute tubular injury associated with AMoL or CMML (rare)</td>
<td>Nephrotoxicity (acute tubular injury and acute tubulointerstitial nephritis) from other common medications (NSAIDs, ACE inhibitors, ARBs, diuretics, antimicrobial agents)</td>
</tr>
<tr>
<td>Acute tubulointerstitial nephritis associated with hemophagocytic disease (rare)</td>
<td>Contrast-associated kidney injury</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (rare)</td>
<td></td>
</tr>
</tbody>
</table>

Perazella MA, Rosner MH. Oncology, 2018
Onco-Nephrology
Hematopoietic Stem Cell Transplant

AKI
- Chemotherapy
- SOS
- aTMA
- aGVHD
- Nephrotoxins
- Sepsis
- Drugs- AIN

CKD
- cTMA
- cGVHD
- Nephrotoxins
- Radiation
- Calcineurin Is
- Chemotherapy
- Drugs- CIN

Hingorani S. NEJM 2016
The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group

Nelson Leung†*1, Frank Bridoux2, Vecilt Batuman1, Aristidis Chaidos1, Paul Cockwell1, Vivette D’Agati1, Angela DISPENZIERI2, Fernando C. Fervenza1, Jean-Paul Fernand1, Simon Gibbs1, Julian D. Gillmore3, Guillermo A. Herrera4, Arnaud Jaccard15, Dragun Jevremovic1, Efstathios Kasprzak1, Vishal Kukrati1, Robert A. Kyle1, Helen J. Loehmann1, Christopher P. Larsen16, Heinz Ludwig17, Glen S. Markowitz18, Giampaolo Merli11, Peter Mollee11, Maria M. Picken11, Vincent S. Roijklumar1, Virginie Royall11, Paul W. Sanders101, Sanjeev Sishti11, Christopher P. Venner11, Peter M. Voorhees11, Asisutosh D. Wachalekar11, Brendan M. Weiss18 and Samih H. Nasr11

Leung N, et al. Nat Rev Nephrol. 2018

KDIGO
Onco-Nephrology
Renal Cell Carcinoma

• Epidemiology
  – RCC accounts for ~3% of all adult malignancies
  – RCC incidence is highest in Europe, N. America and Australia
  – Rates for new RCC have risen by 0.7% each year over the past 10 years (driven in part by imaging of small masses)
Onco-Nephrology
Renal Cell Carcinoma Therapy

• Old and New drugs
  • Conventional chemotherapy
  • Molecular targeted agents (anti-VEGF Abs, TKIs, mTORIs)
  • Immunotherapies (IL-2, ICP inhibitors)
  • Adjuvants to surgical and percutaneous techniques

• Surgical techniques
  • Spare nephron loss to reduce burden of AKI and CKD
  • Total vs. partial nephrectomy

• Percutaneous techniques
  • Cryotherapy
  • Radiofrequency ablation

Perazella MA, Driecer R, Rosner MH. KI, 2018
Onco-Nephrology
AKI/CKD in Renal Cell Carcinoma

- Retrospective cohort study of VA patients with RCC who underwent either PN or RN (2004-2013); N = 7073 veterans; Median 39 mo F/U

<table>
<thead>
<tr>
<th>Variables</th>
<th>PN (Partial)</th>
<th>RN (Radical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2278</td>
<td>4795</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>62 ± 9</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>3.5</td>
<td>3.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time point</th>
<th>eGFR Total</th>
<th>PN</th>
<th>RN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presurgery</td>
<td>78.5 ± 19.4</td>
<td>81.3 ± 18.9</td>
<td>77.2 ± 19.6</td>
</tr>
<tr>
<td>Immediately after surgery</td>
<td>60.4 ± 20.2</td>
<td><strong>71.0 ± 22.2</strong></td>
<td><strong>55.3 ± 17.0</strong></td>
</tr>
<tr>
<td>At least 180 days postsurgery</td>
<td>60.5 ± 20.5</td>
<td><strong>74.8 ± 20.3</strong></td>
<td><strong>53.6 ± 16.7</strong></td>
</tr>
<tr>
<td>Last eGFR obtained postsurgery</td>
<td>61.9 ± 21.8</td>
<td><strong>73.8 ± 21.9</strong></td>
<td><strong>56.2 ± 19.3</strong></td>
</tr>
</tbody>
</table>
Onco-Nephrology
AKI/CKD in Renal Cell Carcinoma

AKI
Partial Nx eGFR:
- 10 ml/min/1.73mm²

Radical Nx eGFR:
- 22 ml/min/1.73mm²

CKD
Partial Nx eGFR:
- 7 ml/min/1.73mm²

Radical Nx eGFR:
- 21 ml/min/1.73mm²

Median 39 months (21-60 months)

Streja E, et al. NDT, 2018
Onco-Nephrology

CKD in Renal Cancer

Radical Nephrectomy vs. Partial Nephrectomy

Risk Ratio and 95% CI of Incidence of Stage 3 CKD

Favors RN  Favors PN

Patel HD, et al. CJASN 2017
Onco-Nephrology
ESKD in Renal Cancer

Partial Nephrectomy associated with reduced ESKD

Kaplan-Meier Curves for ESKD

Cohort
Queensland Australia 2009-2014
All newly diagnosed with kidney cancer
N = 2,739

Variables for ESKD
Age > 65
aHR 2.0
Male Sex
aHR 2.3
Pre-operative kidney disease
aHR 15
Diabetes
aHR 1.8

Ellis RJ, et al. CJASN 2018
Anti-Cancer Drug-induced Kidney Disease

Vasculature
Glomerulus
Proximal Tubules
Distal Tubules
Renal Interstitium
Collecting Ducts

Thrombotic microangiopathy
Mitomycin C
Gemcitabine
Antiangiogenesis drugs

Focal segmental glomerulosclerosis
Pamidronate
Interferon
Antiangiogenesis drugs

Crystalline nephropathy
Dysproteinemia-related Drug-Induced Metabolic

Acute tubular injury
Platinum
Ifosfamide
Pemetrexed
Crizotinib
Zoledronic acid

Tubuleinterstitium
Tyrosine kinase inhibitors
BRAF inhibitors
Immune checkpoint inhibitors

KDIGO

Rosner MH, Perazella MA. NEJM 2017
Onco-Nephrology
Anti-Cancer Agents

• Conventional Agents
  – Cytotoxic drugs (platins), *Alkylating agents* (ifosfamide)
  – *Antitumor antibiotics* (mitomycin C)
  – *Antimetabolites* (methotrexate, pemetrexed, pentostatin, gemcitabine, clofarabine)

• Targeted agents
  – *Anti-angiogenesis drugs* (anti-VEGF Ab, VEGF soluble receptors, TKIs)
  – *EGFR inhibitors, BRAF inhibitors, ALK inhibitors*
  – *Proteosome inhibitors*

• Immunotherapies
  – *IL-2, interferon*
  – *Immune checkpoint inhibitors* (anti-CTLA-4, anti-PD-1, anti-PDL1)
  – *Chimeric antigen receptor T cells*
Conventional Chemotherapeutic Agents

Kidney Disease

- Gemcitabine, Mitomycin C, Cisplatin–
  - TMA

- Pamidronate–
  - Collapsing FSGS

- Platins, Ifosfamide, Pemetrexed, Zoledronate–
  - Toxic ATI/ATN

- Methotrexate–
  - Crystalline ATI
Targeted Anti-Cancer Agents
Kidney Disease

• Anti-VEGF inhibitors—
  TMA, MCD/FSGS

• ALK inhibitors—
  Pseudo-AKI, ATI/ATN, Renal cysts

• BRAF inhibitors—
  AIN/ATN

• EGFR antibodies—
  Hypomagnesemia
Cancer Immunotherapies
Kidney Disease

- Interleukin-2–
  Prerenal AKI, ATN, PI-GN

- Interferon–
  FSGS/TMA

- Immune Checkpoint Inhibitors–
  AIN/IC-GN/MCD
  Txp rejection

- CAR T-Cells–
  Prerenal AKI/ATI, TLS, electrolyte disorders
Onco-Nephrology
10 Important Areas in Onco-Nephrology

NDT Perspectives

Onco-nephrology: a decalogue

Laura Cosma1,2, Camillo Porta2,3, Maurizio Gallieni2,4 and Mark A. Perazella5

- Acute kidney injury and chronic kidney disease in cancer patients
- Nephrotoxic effects of anticancer therapy
- Paraneoplastic renal manifestations
- Pain management in patients with cancer and kidney disease
- Management of patients nephrectomized for a kidney cancer
- Renal replacement therapy and active oncological treatments
- Oncological treatment in kidney transplant patients
- Kidney transplantation in cancer survivors and cancer risk in ESRD patients
- Development of integrated guidelines for onco-nephrology patients
- Clinical trial design specific to onco-nephrology
Onco-Nephrology
Nephrology Perspective: What do we need to do?

- Basic Research in Onco-Nephrology
- Clinical Research in Onco-Nephrology
- Clinical Care in Onco-Nephrology
Basic Research in Onco-Nephrology

- Preclinical studies of anti-cancer agents to evaluate safety and nephrotoxicity
- Employ novel kidney injury biomarkers
- FDA and EMA approved 7 biomarkers
- Utilize kidney on a chip technology
Onco-Nephrology

Kidney on a Chip Technology

Static Culture/Animal Models
- Cell cultures—well-established, no or partial physiological relevance; high throughput and cost efficient
- Animal models—have physiological relevance, but costly with ethical concerns and species differences
- Both Poorly Predictive of Nephrotoxicity

Microfluidic Culture Models
- Have Physiological Relevance
- Laborious, Lack of Validation

Next Generation Models
- Have Physiological Relevance
- User friendly
- Cost efficient
- Highly predictive of nephrotoxicity
- Replace animal models

Ashammakhi N, et al. KI 2018
Biomimetic nephron (nephron-on-a-chip): Renal epithelial cells and endothelial cells cultured in a microtubular system resembling the nephron (renal tubule and neighboring vessel).

Ashammakhi N, et al. KI 2018
Onco-Nephrology
Nephrology Perspective: What do we need to do?

- **Clinical Research in Onco-Nephrology**
  - Develop better GFR estimates for *drug dosing in cancer/CKD patients*
  - Develop POC tests that rapidly provide ‘*measured GFR*’ in cancer patients
  - Include *CKD patients in Clinical Oncology Trials*
  - Utilize *Novel Biomarkers in Clinical Oncology Trials*?
# Onco-Nephrology

GFR estimates for drug dosing in Cancer patients

<table>
<thead>
<tr>
<th>Table 1.1</th>
<th>Creatinine- and Cystatin C-Based Equations to Estimate Glomerular Filtration Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft and Gault</td>
<td>( (\frac{140 \times \text{age} \times \text{weight}}{72 \times \text{SCR}}) )</td>
</tr>
<tr>
<td>MDRD</td>
<td>( 175 \times \text{SCR}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times [1.212 \text{ if black}] )</td>
</tr>
<tr>
<td>CKD-EPI SCR</td>
<td></td>
</tr>
<tr>
<td>women</td>
<td>( \text{SCR} \leq 0.7 \text{ mg/dL} ) ( 144 \times (\text{SCR}^{0.7 \times 0.329} \times 0.993^{0.05} \times [1.159 \text{ if black}] )</td>
</tr>
<tr>
<td></td>
<td>( \text{SCR} &gt; 0.7 \text{ mg/dL} ) ( 144 \times (\text{SCR}^{0.7 \times 1.209} \times 0.993^{0.05} \times [1.159 \text{ if black}] )</td>
</tr>
<tr>
<td>men</td>
<td>( \text{SCR} \leq 0.9 \text{ mg/dL} ) ( 141 \times (\text{SCR}^{0.9 \times 0.411} \times 0.993^{0.05} \times [1.159 \text{ if black}] )</td>
</tr>
</tbody>
</table>

**CKD-EPI equation is now commonly employed to dose chemotherapeutic agents in CKD**

**Cockcroft-Gault formula is still employed by some to dose chemotherapeutic agents in CKD**

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Onco-Nephrology
Drug dosing in Cancer patients

• GFR Estimating Equations
  - Employed to determine the dose of drug used to treat patients with cancer

• Benefits/Limitations
  - Available and easy to use (calculated by all labs)
  - Over- or under-estimate true GFR → Increased Toxicity or Lack of Efficacy

KDIGO
Onco-Nephrology
Improved GFR estimates for drug dosing in Cancer patients

- Development and internal validation population included 2,471 adults (all white, single center)
- External validation population included 111 men (single center)
- Index tests included 7 existing Cr-based eGFR equations
- The reference test was mGFR by plasma clearance of 51Cr-EDTA
- 1 new equation was derived in the development data set (with and without indexing for BSA)
- Median mGFRs in 2 populations were 81 (IQR, 63-103) & 113 (IQR, 101-131) mL/min, respectively

Janowitz T, et al JCO, 2017
Onco-Nephrology
Improved GFR estimates for drug dosing in Cancer patients

GFR Estimating Equations

• STRENGTHS:
  - Large sample size for comparison of existing equations
  - Evaluation of commonly used eGFR equations by comparison to an accepted reference method
  - Derivation of a new eGFR equation
  - Evaluation of the new eGFR equation in an external validation population

• WEAKNESSES:
  - All white participants
  - Single centers for development and external validation studies
  - Relatively high GFRs (Can’t extrapolate to patients with higher stage CKD)
  - Outcomes were not described (Efficacy and toxicity)
Onco-Nephrology
POC tests that provide ‘measured GFR’

METHODS
- 32 subjects enrolled in Phase 2b study
- mGFR was determined using FAST BioMedical VFI technology and iohexol clearance
- The marker used in VFI is retained in the vasculature and used to measure plasma volume (key metric in measuring GFR accurately and quickly)
- 4 Cohorts: 8 Healthy, 8 Healthy, 8 stage 3 CKD, 8 stage 4 CKD
- VFI: 3 ml injection of markers with blood samples at 5, 60 and 170 minutes
- Iohexal: 5 ml injection with blood samples at 120, 150, 180 and 320 minutes

Conclusion
- VFI is safe technology that allows accurate, rapid and highly reproducible GFR and PV measurement at the bedside in healthy subjects and stage 3 and 4 CKD patients

Linear correlation of VFI mGFR and iohexol mGFR show a coefficient of determination of R2=0.996

$y = 1.0013x$
$R^2 = 0.9961$
Onco-Nephrology

POC tests that provide ‘measured GFR’

Repeat measurements of VFI mGFR in cohort participants show very good reproducibility

Rizk DV, et al. JASN 2018
Onco-Nephrology
Nephrology Perspective: What do we need to do?

• Clinical Care in Onco-Nephrology
  – Establish collaborative Onco-Nephrology Clinics
  – Enhance education in Onco-Nephrology
  – Promote collaboration in Onco-Nephrology
Opening an onconephrology clinic: recommendations and basic requirements

Laura Cosmai¹,*, Camillo Porta²,*, Mark A. Perazella³, Vincent Launay-Vacher⁴, Mitchell H. Rosner⁵, Kenar D. Jhaveri⁶, Matteo Floris⁷, Antonello Pani⁷, Cécile Teuma⁸, Cèzary A. Szczylik⁹ and Maurizio Gallieni¹,¹⁰

¹Onco-Nephrology Clinic, Nephrology and Dialysis Unit, San Carlo Borromeo Hospital, ASST Santi Carlo e Paolo, Milan, Italy, ²Medical Oncology, IRCCS San Matteo University Hospital Foundation, Pavia, Italy, ³Section of Nephrology, Department of Medicine, Yale University School of Medicine, New Haven and Veterans Administration Medical Center, West Haven, CT, USA, ⁴Service ICAR, Pitié-Salpêtrière University Hospital, Paris, France, ⁵Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA, ⁶Division of Kidney Diseases and Hypertension, Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, USA, ⁷Nephrology and Dialysis Unit, G. Brotzu Hospital, Cagliari, Italy, ⁸Nephrology Department, Centre Hospitalier Lyon Sud Pierre-Bénite, France, ⁹Department of Oncology, University of Warsaw School of Medicine, Warsaw, Poland and ¹⁰Department of Clinical and Biomedical Sciences “Luigi Sacco”, University of Milan, Milan, Italy
<table>
<thead>
<tr>
<th>Type of patient(s)</th>
<th>Main issue(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer patients with kidney impairment before, during or after active cancer treatment</td>
<td>To guarantee the best cancer treatment possible, without unnecessary dose reduction and/or treatment interruptions, which could hamper the possibility of success of the oncological treatment</td>
</tr>
<tr>
<td>Cancer patients at risk of kidney impairment</td>
<td>To prevent the development of kidney impairment, possibly leading to dose reduction or treatment interruption</td>
</tr>
<tr>
<td>• due to concomitant illnesses (e.g. hypertension, diabetes, etc.)</td>
<td>Education of oncologists and patients about classic kidney failure risks</td>
</tr>
<tr>
<td>• due to the potential nephrotoxicity of the planned treatment</td>
<td></td>
</tr>
<tr>
<td>Cancer patients developing adverse renal events from antineoplastic treatment</td>
<td></td>
</tr>
<tr>
<td>Cancer patients at significant risk of CIN</td>
<td></td>
</tr>
<tr>
<td>Kidney cancer patients at risk for postsurgical (or postablative) AKI or progressive CKD</td>
<td>Prevention of AKI or worsening of CKD through implementation of prophylactic measures</td>
</tr>
<tr>
<td>Patients with urothelial cancer (all)</td>
<td>Prevention of AKI or worsening of CKD</td>
</tr>
<tr>
<td>Patients with suspected or de facto paraneoplastic glomerulopathies</td>
<td>Management of treatment-related AEs</td>
</tr>
<tr>
<td>Transplantation patients:</td>
<td>Prevention of AKI or worsening of CKD</td>
</tr>
<tr>
<td>• donors</td>
<td>Prevention/management of obstructions</td>
</tr>
<tr>
<td>• recipients</td>
<td>Prevention/management of chronic infections</td>
</tr>
<tr>
<td>• transplanted patient who develops cancer</td>
<td>Management of treatment-related AEs</td>
</tr>
<tr>
<td>Cancer patients on dialysis</td>
<td>Screening for an occult cancer (if any)</td>
</tr>
<tr>
<td>Haematological cancer patients</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Bone metastases in cancer patients with CKD</td>
<td>Management strategies (e.g. use of immunosuppressive agents in the cancer patient)</td>
</tr>
<tr>
<td></td>
<td>When to allow transplantation or donation in a patient with previous or active cancer</td>
</tr>
<tr>
<td></td>
<td>Management strategies (e.g. use of immunosuppressive agents in the cancer patient)</td>
</tr>
</tbody>
</table>

Cosmai L, et al. NDT, 2018
Physical examination
Evaluation of comorbidities and preexisting kidney impairment (clinical and subclinical)
Evaluation of ongoing (and previous) therapies, both oncological and not oncological
Renal function tests
  eGFR with a CKD-EPI formula
  When needed, directly measure eGFR (creatinine clearance, nuclear medicine GFR evaluation, etc.)
Basic haematology, including differential white blood cell count
Urinalysis and examination of urinary sediment examination; quantification of proteinuria
Electrolytes and serum enzymes (including serum calcium, phosphorus, uric acid and magnesium, LDH and uric acid).
Obtain trends of all pertinent labs including SCr, LDH, CBC and urine protein:creatinine ratio
Acid–base balance and abnormalities
Blood pressure (including ABPM whenever necessary)
Basic imaging: renal/abdominal US
Basic imaging: oncological disease status evaluation, as appropriate (CT, MRI, etc.)
<table>
<thead>
<tr>
<th>Diseases Managed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management of renal AEs from anticancer therapy and dose modification for</td>
</tr>
<tr>
<td>cytotoxic chemotherapy</td>
</tr>
<tr>
<td>targeted agents</td>
</tr>
<tr>
<td>immune checkpoint inhibitors</td>
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<tr>
<td>bone targeting agents</td>
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<tr>
<td>in patients with conserved or altered renal function (including ESRD and dialysis patients)</td>
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<tr>
<td>Management of renal complications from</td>
</tr>
<tr>
<td>surgery</td>
</tr>
<tr>
<td>radiation therapy</td>
</tr>
<tr>
<td>other diagnostic and therapeutic procedures (e.g. renal stenting, etc.)</td>
</tr>
<tr>
<td>Management of CIN</td>
</tr>
<tr>
<td>Management of transplantation patients’ issues:</td>
</tr>
<tr>
<td>management of kidney transplant patient that develops a cancer</td>
</tr>
<tr>
<td>clearance (or not) of a cancer patient to donate for kidney transplantation</td>
</tr>
<tr>
<td>clearance (or not) of a cancer patient to receive a kidney transplantation</td>
</tr>
<tr>
<td>administration of targeted therapy and or immunotherapy in a kidney transplant patient</td>
</tr>
<tr>
<td>Management of paraneoplastic nephrological syndromes, including screening or not these patients</td>
</tr>
<tr>
<td>Choice of antipain therapy and dose adaptation in cancer patients with renal impairment</td>
</tr>
<tr>
<td>Discussion of ethical issues (to treat or not to treat cancer patients in dialysis or with ESRD)</td>
</tr>
</tbody>
</table>

Cosmai L, et al. NDT, 2018
<table>
<thead>
<tr>
<th>Indicator of performance</th>
<th>Reason(s)</th>
<th>Value to be achieved (in Year 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients discussed by the core team</td>
<td>To ensure that (ideally) all patients presenting with onconephrology issues are adequately evaluated at least by the core team.</td>
<td>100%</td>
</tr>
<tr>
<td>Percentage of patients brought to the attention of the MDT</td>
<td>To ensure that all complex patients presenting are brought to the attention of and discussed within each given MDT.</td>
<td>100%</td>
</tr>
<tr>
<td>Number of episodes of AKI from anticancer treatment</td>
<td>AKI episodes lead to worsening of cancer patients’ prognosis (especially in terms of reduced overall survival); also increase CKD.</td>
<td>Reduction of at least 25% as compared to the previous year</td>
</tr>
<tr>
<td>Number of episodes of CIN</td>
<td>CIN episodes lead to both AKI and worsening of CKD.</td>
<td>Reduction of at least 25% as compared to the previous year</td>
</tr>
<tr>
<td>Number of visits to emergency ward due to kidney toxicity from oncological treatments</td>
<td>Increase of costs and hospitalization rates.</td>
<td>Reduction of at least 25% as compared to the previous year</td>
</tr>
<tr>
<td>Number of hospital admissions due to kidney toxicity</td>
<td>Increase of costs.</td>
<td>Reduction of at least 25% as compared to the previous year</td>
</tr>
<tr>
<td>Number of treatment interruptions due to kidney toxicity</td>
<td>Potentially hampers treatment efficacy.</td>
<td>Reduction of at least 25% as compared to the previous year</td>
</tr>
<tr>
<td>Number of treatment withdrawals due to kidney toxicity</td>
<td>Hampers treatment efficacy precluding the continuation of potentially life-extending treatments.</td>
<td>Reduction of at least 25% as compared to the previous year</td>
</tr>
<tr>
<td>Number of drug-related adverse reactions due to kidney disease</td>
<td>Increases morbidity and (potentially) also mortality, as well as hospitalization rates; increases treatment interruptions and withdrawals.</td>
<td>Reduction of at least 25% as compared to the previous year</td>
</tr>
<tr>
<td>Patients’ satisfaction</td>
<td>Linked to improved QoL.</td>
<td>100%</td>
</tr>
<tr>
<td>Health care workers’ satisfaction</td>
<td>Linked to improved medical service quality and patients’ satisfaction.</td>
<td>100%</td>
</tr>
<tr>
<td>Specific requirement</td>
<td>Obstacle(s)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Critical mass of patients</td>
<td>Presence of a small oncology/haematology service</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nihilistic approach to patients with both kidney diseases and cancer</td>
<td></td>
</tr>
<tr>
<td>Proximity to the haematology/oncology ward</td>
<td>Structural difficulties (especially in hospitals not built to favor multidisciplinarity)</td>
<td></td>
</tr>
<tr>
<td>Availability of medical records across clinics</td>
<td>Not an issue</td>
<td></td>
</tr>
<tr>
<td>Shared (electronic) database</td>
<td>Not an issue</td>
<td></td>
</tr>
<tr>
<td>Referral to the onconephrologist</td>
<td>Clear-cut identification of the onconephrology referral specialist within the hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clear-cut definition of the patients to refer for consultation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td></td>
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<tr>
<td></td>
<td>Bringing together and motivating different specialists towards a real multidisciplinary consultation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nihilistic approach to patients with both kidney diseases and cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Need for specific training and for maintaining proficiency in onconephrology</td>
<td></td>
</tr>
<tr>
<td>MDT and core team</td>
<td>Bringing together and motivating different health professionals and caregivers</td>
<td></td>
</tr>
<tr>
<td>Involvement of other health professionals</td>
<td>Not an issue</td>
<td></td>
</tr>
<tr>
<td>Availability of certain diagnostic tests</td>
<td>Clear-cut definition of the patients to refer for consultation</td>
<td></td>
</tr>
<tr>
<td>Appropriate nature of patients</td>
<td>Nihilistic approach to patients with both kidney diseases and cancer</td>
<td></td>
</tr>
<tr>
<td>Minimal workup</td>
<td>Sharing minimal requirements among different specialists</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sharing a common language</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clear-cut evaluation of kidney function where necessary</td>
<td></td>
</tr>
<tr>
<td>Disease management</td>
<td>Nihilistic approach to patients with both kidney diseases and cancer</td>
<td></td>
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<tr>
<td>Development of specific protocols</td>
<td>Identification of topics and objectives</td>
<td></td>
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<tr>
<td>Audits and indicators of performance</td>
<td>Time and personnel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variability of indicators over time</td>
<td></td>
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<tr>
<td></td>
<td>Costs</td>
<td></td>
</tr>
<tr>
<td>Hub and spoke model</td>
<td>Bringing together and motivating different structures and health professionals</td>
<td></td>
</tr>
<tr>
<td>Education and training</td>
<td>Identification of educational needs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standardization of trainees’ curriculum</td>
<td></td>
</tr>
</tbody>
</table>
Onco-Nephrology
ASN Educational Curriculum-2016

Onco-Nephrology: Growth of the Kidney-Cancer Connection 1
Mark Perazella, MD, and Mitchell Rosner, MD

Why Do We Need an Onco-Nephrology Curriculum? 2
Mark Perazella, MD, and Mitchell Rosner, MD

AKI Associated with Malignancies 3
Amit Lahoti, MD, and Benjamin Humphreys, MD, PhD

Tumor Lysis Syndrome 4
Amaka Edeani, MD, and Anushree Shirali, MD

Electrolyte and Acid-Base Disorders and Cancer 5
Anushree Shirali, MD

Glomerular Disease and Cancer 6
Divya Monga, and Kenar Jhaveri

Hematologic Diseases and Kidney Disease 7
Ala Abudayeh, MD, and Kevin Finkel, MD, FACP, FASN, FCCM

Clinical tests for Monoclonal Proteins 8
Nelson Leung, MD

Hematopoietic Stem Cell Transplant-Related Kidney Disease 9
Sangeeta Hingorani, MD, and Joseph Angelo, MD, MPH

Radiation Nephropathy 10
Amaka Edeani, MBBS, and Eric Cohen, MD

Chemotherapy and Kidney injury 11
Ilya Glezerman, MD, and Edgar Jaimes, MD

Pharmacokinetics of Chemotherapeutic Agents in Kidney Disease 12
Sheron Latcha, MD, FASN

CKD as a Complication of Cancer 13
Laura Cosmai, MD, Camillo Porta, MD, and Maurizio Gallieni, MD, FASN

Hereditary Renal Cancer Syndromes 14
Katherine Nathanson, MD

Work-up and Management of Small Renal Masses 15
Susie Hu, MD Anthony Chang, MD

Cancer in Solid Organ Transplantation 16
Mona Doshi, MD

Cancer Screening in ESRD 17
Jean Holley, MD

Ethics of RRT, Initiation and Withdrawal, in Cancer Patients 18
Michael Germain, MD

Palliative Care in Patients with Kidney Disease and Cancer 19
Alvin H. Moss, MD, FACP, FAAHPM

ASN On-Line Onco-Nephrology Core Curriculum

KDIGO
Onco-Nephrology
Educational Textbooks and Journals

Seminars in Nephrology
Onco-Nephrology: Kidney Disease in the Cancer Patient
Joseph V. Bonventre, MD, PhD, Editor
2010

NephSAP
Nephrology Self-Assessment Program
Cancer and the Kidney
Co-Editors: Benjamin D. Humphreys, MD and Paul W. Sanders, MD
Editor-in-Chief: Stanley Goldfarb, MD
Deputy Editor: Raymond R. Townsend, MD
2013

ACKD
Advances in Chronic Kidney Disease
Cancer and the Kidney: The Growth of Onco-Nephrology
Mark A. Pesudovs, MD, Jeffrey S. Brown, MD, Mitchell H. Stein, MD
2014

JON Journal of Onco-Nephrology
2017

Courtesy of Laura Cosmai
Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants to determine what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that might lead to guidelines in the future.

Background
In the 21st century, patients with malignancy make up a growing number of the subjects seen for nephrology consult and/or critical care nephrology services. The outstanding progress in the therapy of malignancy presents new possibilities and challenges for both nephrologists and medical oncologists. It is important for nephrology services to be acknowledged and to take an active participation in the care of oncology patients. In addition, nephrology services need to better understand the biology of malignancy and its treatment in order to become a valuable part of the teams working to yield the best possible outcome for cancer patients.

The links between kidney disease and malignancy were observed quite some time ago. However, it was only recently that their importance was recognized and a new subspecialty in nephrology, namely 'oncology nephrology' was established [1]. Chronic kidney disease (CKD) is often diagnosed in the general population [2], however, its...
Onco-Nephrology Collaboration

- National (AIOM, SIN) and International Scientific Society Conferences (EDTA, ASN) with dedicated onco-nephrology sessions and educational courses
- National Oncological and Urological conferences
- Epidemiological studies in Italy (surveys and other projects in progress)
- Papers published in International Journals; Textbooks on Onco-Nephrology
- Urological Guideline on kidney cancer (AURO 2012)
- TMD Project (Italian Multidisciplinary Group on GU cancers)
- Collaboration between Nefrological e Oncological International Society
- Interdisciplinary Working Group on Onco-Nephrology (AIOM-SIN) dedicated to specific projects (i.e., contrast medium use in cancer patients)
Thank You!

Questions?
ONCONEPHEROLOGY: ONCOLOGY PERSPECTIVE

Walter Stadler, MD FACP
Section Chief Hematology-Oncology
Deputy Director Comprehensive Cancer Center
University of Chicago
DISCLOSURES

• Consultant:
  • Astra-Zeneca, Bayer, BMS, Caremark/CVS, Clovis, Eisai, Genentech, Pfizer, Sotio

• Speakers Bureau:
  • CME providers (sponsorship unknown): Applied Clinical Education, Dava Oncology, Global Academy for Medical Education, OncLive, PeerView, Vindico

• Grant/Research Support (to institution):
  • Abbvie, Astra-Zeneca, Astellas (Medivation), Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Calithera, Clovis, Eisai, Exilixis, Genentech (Roche), Johnson & Johnson (Janssen), Merck, Novartis, Pfizer, Seattle Genetics, Tesaro, X4Pharmaceuticals

• Stockholder:
  • None

• Expert Witness
  • None

• Miscellaneous/Editorial:
  • Cancer (ACS), Up-To-Date
WHAT HAS CHANGED IN ONCOLOGY: BIG PICTURE

• We keep sub-dividing cancers based on molecular phenotyping
• We increasingly recognize cancer genomic predisposition syndromes
• Smoking is decreasing, weight/metabolic syndrome is increasing
• We have an increasingly large therapeutic armamentarium
  • Many more drugs and targets
  • Much more imaging technology
  • More sophisticated minimally invasive surgical and radiotherapy techniques
• The vast majority of care is in the outpatient setting
• We are increasingly conducting chronic disease management
THE ONCOLOGISTS VIEW OF THE KIDNEY

• Purpose
  • To appropriately excrete anti-cancer drugs
  • To appropriately excrete products from killed cancer cells

• Pathophysiology
  • Pre-renal: is there an appropriate pump
  • Intra-renal: all those parts that nephrologists think about
  • Post-renal: is there something blocking the plumbing
EXCRETING PRODUCTS FROM KILLED CANCER CELLS

• The tumor lysis problem

• We wish this were a bigger issue

• Most oncologists are reasonably cognizant of methods for treatment and prevention
EXCRETING ANTI-CANCER DRUGS: THE DRUGS WE USE

• DNA/RNA interfering
  • Alkylating agents: e.g. busulfan, cyclophosphamide
  • Platining: e.g. cisplatin, oxaliplatin
  • Topoisomerase inhibitors: e.g. doxorubicin, daunorubicin, topotecan
  • Nucleotide metabolism: e.g. 5FU, hydroxyurea
  • Tubule inhibitors: e.g. paclitaxel, vinblastine
  • PARP inhibitors: e.g. olaparib, rucaparib

• Growth factor signalling interfering
  • Cell surface receptors: e.g. EGFR, BTK, HER2, VEGFR inhibitors
  • Signal transduction: e.g. RAF, mTOR inhibitors

• Nuclear Hormone Receptor Interacting
  • Androgen receptor: e.g. castration, enzalutamide, abiraterone
  • Estrogen receptor: e.g. oophorectomy, tamoxifen, faslodex
  • Glucocorticoid receptor: e.g. prednisone, dexamethasone
EXCRETING ANTI-CANCER DRUGS: THE DRUGS WE USE

• Other Protein interfering
  • Protein degradation: e.g. bortezomib, lenolidomide

• Immunotherapy
  • Cytokines: e.g. IL2, IFNA
  • PD1 pathway inhibitors: e.g. pembrolizumab, atezolizumab
  • CTLA4 pathway inhibitors: e.g. ipilimumab

• Cell Surface Recognition Markers
  • CD20: e.g. rituximab
  • CD30: brintuximab
  • PSMA & others: emerging

• Cellular Therapy
  • Allogeneic stem cell transplant
  • CAR-T cells: CD19 interacting, others emerging
  • Other cellular therapy emerging
**Excreting Anti-Cancer Drugs: Some Pharmacology**

- **Large Molecules**
  - Naked antibodies: e.g. CD20, EGFR, PD1, CTLA4, HER2
  - Conjugated antibodies: e.g. CD30, CD20, HER2, emerging
  - Large peptides: e.g. mTOR inhibitors
  - IV or sub-cutaneous administration
  - Metabolism & renal excretion typically minimal

- **“Small” Molecules**
  - Natural product derived: e.g. taxanes, doxorubicin
  - Endogenous ligand derived: e.g. growth factor, testosterone
  - Nucleoside analogues: e.g. 5FU, azacitidine
  - Everything else that medicinal chemists make
  - IV, subcutaneous and oral administration
  - Variable metabolism & renal excretion
EXCRETING ANTI-CANCER DRUGS: SOME PHARMACOLOGY

• Thinking about dosing
  • We tend to not think carefully about
    • Absorption, half-life, clearance, volume of distribution, etc
    • Metabolites
  • We don’t have good ways to assess hepatic function
  • We tend to be over-reliant on: Cockroft-Gault and MDRD equations

• Thinking about renal function
  • eGFR > 60: “normal”
  • eGFR 40-60: pretend its normal
  • eGFR 10-40: look up dosing in some app or online
  • eGFR <10 or dialysis: (expletive deleted)
**RENAL PATHOPHYSIOLOGY: IMPACT OF THE CANCER**

- **Pre-renal**
  - Hospital/ICU care

- **Post-renal**
  - Ureteral obstruction from mass
  - Urethral obstruction from mass
  - Intratubular obstruction: uric acid, hypercalcemia, light chain disease in MM

- **Intra-renal**
  - Tumor infiltration: e.g. lymphoma, renal cancer
  - Protein deposition: e.g. MM immunoglobulin deposition
  - Thrombotic microangiopathy
  - (Electrolyte imbalance: e.g. SIADH)
RENAL PATHOPHYSIOLOGY: IMPACT OF CANCER THERAPY

• Pre-renal
  • Things we do that land patients in the hospital
  • Things we do that lead to anorexia/nausea/vomiting/diarrhea

• Post-renal
  • Intratubular obstruction: e.g. Methotrexate crystallization

• Intra-renal
  • Surgeon: e.g. renal cancer
  • Radiation: rare, but relevant in Wilms
  • Drugs
    • Methotrexate
    • CDDP
    • Ifosfamide
    • VEGF pathway inhibitors
    • PD1/CTLA4 directed immunotherapy
    • Imaging IV contrast/NSAID’s
**OncoNephrology: The Oncologist’s Questions**

- What is the best way to educate nephrologists regarding the large number of new cancer therapies?
  - Rapid pace of therapeutic advances is difficult even for oncologists
  - Most large academic centers don’t even have a nephrologist interested in these aspects
  - Recognition of drug associated renal toxicities is typically delayed
  - Many drug associated toxicities are rare
ONCO-NEPHROLOGY: THE ONCOLOGIST’S QUESTIONS

• What is the best way to educate oncologists on nephrology care aspects
  • Methods and limitations of assessing renal function
  • Predicting renal toxicity
  • Drug dosing with renal dysfunction
  • Drug dosing in dialysis and does method matter
  • When to obtain formal consultation
ONCO NEPHROLOGY: THE ONCOLOGIST’S QUESTIONS

- What is the best way to investigate mechanisms and prevention of renal toxicity from cancer therapy?
  - Most large academic centers don’t even have a nephrologist interested in these aspects
  - Many of the toxicities are rare or delayed
  - Therapy associated toxicities are typically multi-factoral
ONCONEPHROLOGY: THE ONCOLOGISTS PERSPECTIVES

• We tend to have a simplistic view of the kidney
• We are developing novel therapeutic approaches at an unprecedented pace
• We need help thinking about prevention and treatment of renal toxicity
• We need help thinking about appropriate drug dosing
• There are opportunities for collaborative care, research, and education