Immune Checkpoint Inhibitor-Associated Acute Kidney Injury

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Medicine Residency @Columbia
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MMSc (Clinical Investigation) @HMS
Associate Professor of Medicine @HMS

- Clinical focus: ICU Nephrology
- Research focus: AKI
Disclosures

I have no financial disclosures
Outline and Key Learning Objectives

Overview of ICPI-AKI and immune-related adverse events

Incidence of ICPI-AKI

Histologic features

Risk factors, clinical features, renal recovery, safety of rechallenge, and treatment

Use of ICPIs in kidney transplant recipients

Role of kidney biopsy

Recently published data from our multicenter studies
ICPis prevent inhibitory receptors from binding to their ligands, resulting in unopposed T-cell activation

Evans et al., Pharm J, 2018
“What we needed to do was to release the brakes of the immune system to fight cancer”

James P. Allison, Ph.D.
U. Texas MD Anderson Cancer Center
Nobel Prize Laureate in Physiology or Medicine 2018
Timeline of FDA Approvals of ICPis

Maritaz et al., Journal of Hematology & Oncology, 2022
Immune-related Adverse Events (irAEs)

Postow et al., N Engl J Med, 2018
Connolly et al., Frontiers in Oncology
Incidence of ICPi-AKI

Meta-analysis of all phase II and III clinical trials that treated >100 patients with an ICPi and provided data on ICPi-AKI (total of n=3695 patients)

[Bar chart showing incidence of any AKI and grade 3 or 4 AKI for Ipi Alone (N=1244), Nivo Alone (N=1489), Pembrolizumab Alone (N=555), Ipi + Nivo (N=407), and Overall (N=3695).]

AKI definitions

- **Any AKI**: increase in SCr >0.3 mg/dl within 48h or >50% above baseline
- **Grade 3 AKI**: increase in SCr >3-fold above baseline or an increase to a level >4.0 mg/dl
- **Grade 4 AKI**: KRT

Cortazar et al., Kidney Int, 2016
Incidence of ICPI-AKI

doi: 10.1093/ndt/gfy105
Advance Access publication 11 May 2018

Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis

Sandhya Manohar1, Panagiotis Kompotiatis1, Charat Thongprayoon2, Wisit Cheungpasitporn3, Joerg Herrmann4 and Sandra M. Herrmann1

\( n=11,482 \)

(48 Clinical Trials)

Manohar et al., Nephrol Dial Transplant, 2019
Incidence of ICPI-AKI

4.19-fold ↑ risk of AKI in patients receiving ICPIs compared to controls receiving non-nephrotoxic chemotherapy

Manohar et al., Nephrol Dial Transplant, 2019
Incidence of ICPI-AKI

The Incidence, Causes, and Risk Factors of Acute Kidney Injury in Patients Receiving Immune Checkpoint Inhibitors

Harish Seethapathy, Sophia Zhao, Donald F. Chute, Leyre Zuhiri, Yas Oppong, Ian Strohleben, Frank B. Cortazar, David E. Leaf, Meghan J. Mooradian, Alexandra-Chloé Villani, Ryan J. Sullivan, Kerry Reynolds, and Meghan E. Stiel

Patients who received ICPI therapy at MGH between 2011 and 2016 with baseline and follow-up SCr available (N=1016)

3% incidence of ICPI-AKI

‘Sustained AKI’ (N=82 patients)
110 episodes of sustained AKI

ICPI-related (41 episodes; N=30 patients)

Hemodynamic AKI/ATN (57 episodes)

AKI of undetermined cause (9 episodes)

Urinary tract obstruction (3 episodes)

Seethapathy et al., Clin J Am Soc Nephrol, 2019
Histologic Features of ICPi-AKI: Initial Case Reports

ATIN with granulomatous features
Histologic Features of ICPI-AKI: Subsequent Case Series

Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors

Frank B. Cortazar¹, Kristen A. Marrone², Megan L. Troxell³, Kenneth M. Ralto⁴, Melanie P. Hoenig⁵,
Julie R. Brahmer⁶, Dung T. Le⁷, Evan J. Lipson⁸, Ilya G. Glezerman⁹, Jedd Wolchok⁸, Lynn D. Cornell⁹,
Paul Feldman¹⁰, Michael B. Stokes¹¹, Sarah A. Zapata¹², F. Stephen Hodi¹¹, Patrick A. Ott¹¹,
Michifumi Yamashita¹² and David E. Leaf¹²

AJKD
Case Report

Association of Acute Interstitial Nephritis With Programmed Cell Death 1 Inhibitor Therapy in Lung Cancer Patients

Anushree C. Shirali, MD,¹ Mark A. Perazella, MD,¹ and Scott Getlinger, MD²

n=13 (ATIN in 12/13)

n=6 (ATIN in 6/6)

18/19 (95%) with ATIN
Histologic Features of ICPi-AKI: Beyond ATIN

Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience

Omar Mamlouk, Umut Selamet, Shana Machado, Meen Abdelrahim, William F. Glass, Amanda Tchakarov, Lillian Gaber, Amit Lahof, Biruh Workeneh, Sheldon Chen, Jamie Lin, Noha Abdel-Wahab, Jean Tayar, Huifang Lu, Maria Suarez-Almazor, Nizar Tannir, Cassian Yee, Adil Diab and Ala Abudayyeh

Retrospective study of all patients treated with ICPis at MD Anderson Cancer Center between 2008–2018 who were biopsied for AKI (n=16 out of 6412 treated patients)

Mamlouk et al., J Immunother Cancer, 2019
Histologic Features of ICPi-AKI: Beyond ATIN

**ATIN (n=14)**

- Pauci-immune GN (n=3; only 1 had +ANCA)
- AA amyloid (n=1)
- IgAN (n=2)
- MN (n=1; anti-PLA2R neg)
- C3GN (n=1)
- Secondary FSGS (n=1)

Mamlouk et al., J Immunother Cancer, 2019
Many questions about ICPi-AKI remain unanswered: Until Now!

**Risk factors** for ICPi-AKI

**Clinical features** associated with ICPi-AKI

- Timing
- Clinical findings
- Frequency of extrarenal irAEs

**Renal recovery**

**Risk of recurrent ICPi-AKI with ICPi rechallenge**

**Treatment** – Steroids, but for how long?
Acute kidney injury in patients treated with immune checkpoint inhibitors

Multicenter international study
429 patients with ICPI-AKI
429 control patients
30 sites
10 countries

Shruti Gupta,1,2 Samuel A P Short,3 Meghan E Sise,4 Jason M Prosek,4 Sethu M Madhavan,5 María Jose Soler,6 Marlies Ostermann,5 Sandra M Herrmann,7 Ala Abdussyyeh,7 Shuchi Arain,7 Illya Glezerman,10 Olivet S Motsani,11 Yoaka Murokami,12 Rimda Wanchoo,12 David I Ortiz-Melo,12 Arash Rashid,12 Ben Sprangers,13,14 Vikram Aggarwal,15 A Bilal Malik,16 Sebastian Loew,16 Christopher A Carlos,17 Wei-Ting Chang,11,12,23 Pazit Beckerman,24 Zain Mithani,25 Chintan V Shah,26 Amanda D Renaghan,27 Sophie De Selgheux,28 Luca Campedel,27 Abhijat Kitchlu,29 Daniel Sanghoon Shin,31 Sunil Rangarajan,32 Priya Deshpande,30 Gaa Coppel,28 Mark Eijgelsheim,33 Ganish Seethapathy,34 Meghan D Lee,35 Ian A Stroehlein,36 Dwight H. Owen,36 Varun Husain,34,35 Clara Garcia-Carro,37,38 Sheila Bermejo,39 Nuttha Lumtertug,26,39 Yina Seylanova,37,38 Lucy Flanders,37 Busra Isik,1 Omar Mamlok,6,37 Jamie S Lin,6 Pablo Garcia,3 Aydin Kaghazchi,35 Yury Khranik,4 Sheru K Kansal,41 Els Wauters,41,44 Sunandana Chandras,41 Kai M Schmid-Ott,41,42 Raymond K Hsu,43 Maria C Tio,1 Suraj Sarvode Mothi,1 Harkaran Deep Singh,1 Deborah Schrag,1 Kenar D Jhaveri,17 Kerry L Reynolds,48 Frank B Cortazar,69 David E Leaf,69 ICPI-AKI Consortium Investigators
Definition of ICPi-AKI

**Criteria 1:** Increase in SCr ≥100% from baseline OR treatment with KRT

**Criteria 2:** Increase in SCr ≥50% from baseline AND at least one of the following:

1) ATIN on biopsy
2) ICPi held for at least one cycle
3) Treated with corticosteroids

Gupta et al., J Immunother Cancer, 2021
Severity of IC Pi-AKI

- 77 patients (18%) had stage 1
- 144 (34%) had stage 2
- 208 (49%) had stage 3, including 33 who received KRT (8% overall)

Gupta et al., J Immunother Cancer, 2021
### Risk Factors for ICPI-AKI

#### Lower baseline eGFR, PPI use, and extrarenal irAEs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.17 (1.04-1.31)</td>
<td>1.05 (0.92-1.21)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.16 (0.88-1.52)</td>
<td>1.15 (0.86-1.53)</td>
</tr>
<tr>
<td>Combination ICPI therapy</td>
<td>1.42 (1.01-1.98)</td>
<td>1.30 (0.90-1.87)</td>
</tr>
<tr>
<td><strong>Baseline eGFR (ml/min/1.73m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90 (REF)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>60-89</td>
<td>1.54 (1.13-2.10)</td>
<td>1.36 (0.95-1.94)</td>
</tr>
<tr>
<td>45-59</td>
<td>2.48 (1.59-3.87)</td>
<td>2.23 (1.35-3.68)</td>
</tr>
<tr>
<td>&lt;45</td>
<td>1.92 (1.74-4.89)</td>
<td>2.62 (1.47-4.65)</td>
</tr>
<tr>
<td><strong>PPI use</strong></td>
<td>2.55 (1.92-3.40)</td>
<td>2.40 (1.79-3.23)</td>
</tr>
<tr>
<td>Prior or concomitant extrarenal irAEs**</td>
<td>2.19 (1.65-2.91)</td>
<td>2.07 (1.53-2.78)</td>
</tr>
</tbody>
</table>

Gupta et al., J Immunother Cancer, 2021
Timing of ICPI-AKI

ICPI-AKI developed at a median of 16 weeks (IQR, 8-32) after ICPI initiation

Gupta et al., J Immunother Cancer, 2021
Frequency of Urinary Abnormalities in Patients with ICPi-AKI?

- Proteinuria
- Pyuria
- Hematuria
Proteinuria in Patients with ICPi-AKI

59% had a UPCR ≥0.3 g/g

Gupta et al., J Immunother Cancer, 2021
41% had $\geq 1+$ leukocyte esterase on UA

Gupta et al., J Immunother Cancer, 2021
Hematuria in Patients with ICPi-AKI

40% had ≥1+ blood on UA

Gupta et al., J Immunother Cancer, 2021
Extrarenal immune-related Adverse Events (irAEs)

57% had a prior or concomitant extrarenal irAE

Gupta et al., J Immunother Cancer, 2021
Histopathology: ATIN in 125/151 (83%) of biopsied patients

Gupta et al., J Immunother Cancer, 2021
82% of patients were treated with steroids, of whom 29% initiated treatment with IV pulse-dose steroids

Gupta et al., J Immunother Cancer, 2021
## Predictors of Renal Recovery after ICPI-AKI

Renal recovery occurred in 64% of patients
**Stage 3 AKI** associated with ↓chance of recovery
Treatment w/steroids associated with ↑chance of recovery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>Lower Odds of Recovery</th>
<th>Higher Odds of Recovery</th>
</tr>
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<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.10 (0.92-1.34)</td>
<td>0.92 (0.71-1.18)</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.80 (1.18-2.75)</td>
<td>1.43 (0.86-2.38)</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>White</td>
<td>1.57 (0.93-2.67)</td>
<td>1.22 (0.64-2.30)</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>1.65 (0.98-2.77)</td>
<td>0.94 (0.50-1.75)</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Baseline eGFR (per 10 points)</td>
<td>0.74 (0.66-0.82)</td>
<td>0.79 (0.69-0.91)</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>0.38 (0.25-0.60)</td>
<td>0.51 (0.29-0.87)</td>
<td>■</td>
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</tr>
<tr>
<td>Concomitant ATIN-causing medication</td>
<td>1.50 (0.98-2.29)</td>
<td>1.70 (1.03-2.82)</td>
<td>■</td>
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<tr>
<td>Concomitant extrarenal irAEs</td>
<td>2.01 (1.20-3.39)</td>
<td>1.60 (0.88-2.90)</td>
<td>■</td>
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<td>≥2+ Blood on urinalysis</td>
<td>0.49 (0.26-0.90)</td>
<td>0.58 (0.26-1.28)</td>
<td>■</td>
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</tr>
<tr>
<td>≥2+ Leukocyte esterase on urinalysis</td>
<td>0.42 (0.24-0.73)</td>
<td>0.58 (0.31-1.12)</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>≥1 g/g UPCR</td>
<td>0.40 (0.20-0.81)</td>
<td>0.54 (0.22-1.32)</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Stage 3 AKI</td>
<td>0.30 (0.20-0.47)</td>
<td>0.33 (0.19-0.57)</td>
<td>■</td>
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</tr>
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<td>Treated with corticosteroids</td>
<td>2.27 (1.48-3.48)</td>
<td>2.64 (1.58-4.41)</td>
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Among Patients Treated with Steroids, those treated **EARLY** (within 3 days) had ↑Odds of Renal Recovery

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<tr>
<td>Combination Therapy</td>
<td>2.81 (1.50-5.26)</td>
<td>1.81 (0.85-3.89)</td>
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<td>eGFR (per 10 points)</td>
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<tr>
<td>≥1 g/g Urine protein:Cr ratio</td>
<td>0.44 (0.21-0.94)</td>
<td>0.70 (0.26-1.91)</td>
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<td>Stage 3 AKI</td>
<td>0.26 (0.16-0.42)</td>
<td>0.31 (0.17-0.58)</td>
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<tr>
<td><strong>Corticosteroids within 3 days of ICPI-AKI</strong></td>
<td>2.24 (1.38-3.64)</td>
<td>2.09 (1.16-3.79)</td>
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Gupta et al., J Immunother Cancer, 2021
**Low Incidence of Recurrent ICPI-AKI after ICPI Rechallenge**

Of 121 patients rechallenged, only 20 (16.5%) developed recurrent ICPI-AKI

Gupta et al., J Immunother Cancer, 2021
Ancillary Studies from the ICPI-AKI Consortium

Risk of AKI with ICPIs when used in combination with nephrotoxic chemotherapy (Gupta et al., Kidney Int, In Press)

Optimal Duration of Steroid Taper (Gupta et al., J Immunother Cancer, In Press)
**Objective**: To examine AKI severity and renal recovery in patients with lung cancer receiving pembrolizumab versus combination therapy with pemetrexed from 2 cohorts.

**Results**

- No difference in overall AKI or therapy-related AKI incidence in the MGB cohort.
- No difference in AKI severity or renal recovery in either cohort.

**Conclusion**

AKI incidence, severity, recovery, and treatment does not significantly differ between patients receiving triplet therapy vs pembrolizumab monotherapy.

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Gupta and Strohbehn*, 2022
*equal contribution
Visual Abstract by Ian Strohbehn
Corticosteroid Duration and Recurrent ICPI-AKI

429 Patients with ICPI-AKI

264 Excluded from analysis
77 Initiated CS >14 d after ICPI-AKI
76 Not treated with CS for ICPI-AKI
48 CS duration >84d
21 Treated with low-dose CS (<40mg)
14 Missing/incomplete data
13 Already receiving CS (>10mg)
8 Primary lesion other than ATIN on biopsy
4 Died within 28d of initiating CS
3 Treated with non-CS immunosuppression

165 Included in the analysis

56 Shorter Duration of CS (≤28 d)
109 Longer Duration of CS (29–84 d)

Gupta et al., J Immunother Cancer, In Press
Important Questions Remaining on ICPI-AKI

1) Non-invasive biomarkers
   - Urine
   - Plasma/serum
   - Imaging

2) Treatment for refractory/atypical disease
   - CS-resistant ATIN
   - Glomerular disease

3) Additional data on safety and risk/benefit ratio of ICPIs in organ transplant recipients

Moledina et al., JCI Insight, 2019

Manohar & Albright, Kidney Int, 2019
Personalized Treatment Algorithm for irAEs

Esfahani et al., Nat Rev Clin Oncol, 2020
8 Take Home Points on ICPI-AKI

1) Estimated incidence is 2–5%

2) ATIN is the most common histopathologic lesion

3) Risk factors include lower baseline eGFR, PPI use, and extrarenal irAEs

4) Latency period is variable and often prolonged

5) Proteinuria and pyuria are common (~40-60% of patients) but not sensitive

6) Corticosteroids are first-line treatment, and most patients recover

7) Low risk of recurrent ICPI-AKI with ICPI rechallenge

8) Shorter durations of steroids (4 weeks) may be similarly effective as longer durations
Collaborators

Shruti Gupta, MD, MPH
References

- Seethapathy et al., Clin J Am Soc Nephrol, 2019
- Mamlouk et al., J Immunother Cancer, 2019
- Gupta et al., J Immunother Cancer, 2021
- Gupta et al., Kidney Int, In Press
- Gupta et al., J Immunother Cancer, In press
Thank you!

deleaf@bwh.harvard.edu
Extra Slides
Which Patients should be Biopsied vs. Treated Empirically?
Cancer patients receiving ICPI therapy

AKI

AKI Stage 1

AKI resolves; continue ICPI therapy

AKI Stage 2 or 3

AKI persists or progresses: stop ICPI therapy

Nephrology consult; stop ICPI therapy

AKI potentially due to ICPI-related nephrotoxicity

Plausible alternative etiology for AKI (e.g., other nephrotoxins, ATN, GN) and no contraindication to biopsy

Kidney biopsy

Treat with steroids if ATIN; Non-ATIN lesions (e.g., GN) may require addition IS therapy; Consider ICPI rechallenge when AKI resolves

Treat underlying cause of AKI; restart ICPI therapy

Absence of an alternative plausible etiology for AKI or kidney biopsy contraindicated*

AKI progresses or AKI does not recover

Treat with steroids

AKI due to non-ICPI toxicity (e.g., urinary obstruction)

Adapted from Gupta et al., Kidney360, 2020
Potential Mechanisms of ICPI-AKI

1) Generation of autoantibodies pathogenic to the kidney

2) Formation of new or reactivated T cells against tumor antigens that cross-react with kidney tissue

3) Binding of drug directly to kidney tissue (e.g., PD-L1 is expressed by renal tubular epithelial cells)

4) Reactivation of drug-specific T cells, resulting in loss of tolerance

5) Increase in proinflammatory cytokines

Perazella & Shirali, J Am Soc Nephrol, 2018