Clinicopathologic Features of Acute Kidney Injury Associated with Cyclin-Dependent Kinase 4/6 Inhibitors

Shruti Gupta, MD, MPH,¹ Tiffany Caza, MD, PhD,² Sandra M. Herrmann, MD,³ Vipulbhai C. Sakhiya, MBBS,⁴ Kenar D. Jhaveri, MD⁴

¹Division of Renal Medicine, Brigham and Women’s Hospital, Boston, MA
²Arkana Laboratories, Little Rock, Arkansas, USA
³Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN
⁴Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine, Hofstra/Northwell, NY

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Address correspondence to:
Shruti Gupta MD, MPH
Division of Renal Medicine
Brigham and Women’s Hospital
75 Francis Street, Boston MA 02115, USA
Phone: 617-732-7482
Email: sgupta21@bwh.harvard.edu
Twitter Handle: @ShrutiGKidney

Kenar D. Jhaveri, MD
Division of Kidney Diseases and Hypertension
Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
Northwell Health, Hempstead, NY
Phone: 516-465-8200
Email: Kjhaveri@northwell.edu
Twitter Handle: @kdjhaveri
INTRODUCTION

Selective estrogen receptor inhibitors and aromatase inhibitors are the mainstay of therapy for hormonal receptor-positive (HR+) breast cancer; however, most metastatic HR+, human epidermal growth factor receptor 2-negative (HER2-) progress and acquire resistance to endocrine therapies.\(^1\) Cyclin-dependent kinase 4/6 inhibitors (CDK4/6 inhibitors) comprise a new class of drugs that overcome this resistance by blocking the transition from the G1 to S phase of the cell cycle, thereby preventing cell-cycle progression and cancer growth.\(^2\) Three CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—have been approved for HER2-negative metastatic breast cancers, usually in combination with hormone therapy. Multiple clinical trials have demonstrated that CDK4/6 inhibitors increase progression-free survival.\(^3\)–\(^6\)

The most common adverse events associated with CDK4/6 inhibitors are neutropenia, leukopenia, and fatigue.\(^3\)\(^,\)\(^4\)\(^,\)\(^6\) Acute kidney injury (AKI) is not a well-described complication, with pharmacologic studies suggesting that patients may have a rise in serum creatinine (SCr) without true renal injury.\(^7\) Here, we present the first series of patients with biopsy-proven AKI associated with CDK4/6 inhibitors, with a focus on clinical features and pathologic findings.

BRIEF METHODS

All protocols were approved by each hospital’s Institutional Review Board. Cases were obtained by querying nephrology and pathology departments at 2 academic centers (Massachusetts General Hospital, Mayo Clinic) and Arkana Laboratories.

Data Collection

Data on age, gender, race, type of malignancy, concomitant medications and chemotherapy, type of CDK4/6 inhibitor, SCr trend before, during, and after AKI, urinalysis findings, urine sediment (if available), renal ultrasound findings, pathology reports and images, and outcomes (e.g., need for renal replacement therapy [RRT], vital status at last follow-up) were collected on each patient by manual chart review.

Definitions

AKI was defined and staged according to modified Kidney Disease Improving Global Outcomes criteria as a ≥1.5-fold rise in SCr from baseline any time after the drug was started or the need for RRT.\(^8\) Baseline SCr was defined as the closest SCr prior to CDK4/6 inhibitor initiation. If baseline SCr was unavailable, AKI was defined as a new rise in SCr to >3 mg/dl. The AKI was directly attributed to the CDK4/6 inhibitors by the treating nephrologist, and the patient must have undergone a kidney biopsy because of the AKI. Renal recovery was defined as a nadir SCr ≤1.5 times the baseline value within 90 days following AKI.

Reporting of Renal Adverse Events

The Federal Drug Enforcement Adverse Event Reporting System (FAERS) was queried for kidney adverse events associated with CDK4/6 inhibitors (palbociclib, abemaciclib, and ribociclib) between 2010 and 2020 using these search terms: hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypocalcemia, hypercalcemia, hyperkalemia, hypernatremia, hyperphosphatemia, proteinuria, renal failure acute, acute kidney injury, elevated creatinine, hypercreatinemia, hypertension and nephritis.
RESULTS

Baseline Characteristics

We identified 6 patients from Massachusetts General Hospital (n=1), Mayo Clinic (n=1), and Arkana Laboratories (n=4) who had AKI associated with the CDK4/6 inhibitor and underwent a kidney biopsy. Baseline characteristics of each patient are shown in Supplementary Table 1. Four of 6 patients were above the age of 65. Most patients were White (4 out of 6). Two patients had baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². All had metastatic disease at the time of treatment with the CDK4/6 inhibitor.

The most common underlying malignancy was breast adenocarcinoma in 5 of 6 patients (patient 6 had glioblastoma multiforme). Three of 6 were treated with palbociclib, two were treated with abemaciclib, and 1 received ribociclib.

Concomitant Medications and Chemotherapy

There were two patients who were using proton pump inhibitors (PPIs), and one patient who reported occasional non-steroidal anti-inflammatory drug (NSAID) use (patient 6) (Supplementary Table 2). Two patients were prescribed concomitant hormonal therapy (e.g., letrozole) and 2 patients received fulvestrant.

Clinical Features at the Time of AKI

The median time from CDK4/6 initiation to AKI was 278 days (IQR 183-430) (Table 1). Patients 2, 4, and 5 each had stage 3 AKI, and patient 5 required RRT. The median SCR at the time of AKI was 2.9 (interquartile range [IQR] 1.9-5.3). Nephrology was consulted in all cases. None of the patients had hypotension within 72 hours of the AKI event.

At the time of AKI, all patients with urinalyses available were dipstick positive for protein. Renal ultrasound demonstrated cortical echogenicity in three patients. Serologic workup (e.g., antinuclear antibody, double-stranded DNA, antinuclear cytoplasmic antibodies, C3, C4, rheumatoid factor, and serum protein electrophoresis) were normal in all patients.

Pathologies

Representative images of kidney biopsies are shown in Figure 1. Acute tubular necrosis (ATN) was the predominant lesion in Patients 2 through 6. Patient 5 had marked and widespread tubular injury, characterized by dilation and loss of brush borders, flattened epithelium, focal tubular rupture and many intratubular casts in the medulla. Patient 1 had acute tubulointerstitial nephritis (ATIN), which was neutrophil-rich. A urine culture was performed, and was positive for Candida species. However, the pathology was not suggestive of pyelonephritis; a Grocott’s methenamine silver stain was performed on the biopsy and was negative for fungal elements. The ATIN was attributed to the CDK4/6 inhibitor by the treating nephrologist.

Treatment and Outcomes

The CDK4/6 inhibitor was discontinued in patients 1 and 5, and dose-reduced in patients 4 and 6. Patient 5 was subsequently liberated from RRT 6 months after the AKI event. Patient 1 was
not treated with corticosteroids as she was transitioned to comfort care and died. Patient 5 was also transitioned to comfort care and passed away. Patient 6 had incomplete recovery of SCr to a nadir of 1.6 approximately 50 days after the AKI event. Patient 4 similarly had incomplete recovery with a nadir SCr of 2.4 within 90 days of the AKI event, and had progression of disease with liver involvement. Patients 2 and 3 had limited treatment and follow-up data. No patients received any immunosuppressive treatment for the AKI event.

Reporting of Renal-Related Adverse Events

There were 783 adverse events reported for all 3 agents (palbociclib, abemaciclib, and ribociclib) (Table 2), most commonly renal injury. Palbociclib had the largest number of adverse events, and these were most frequently reported among females. Metabolic disturbances were reported with all 3 agents, usually hypokalemia, though hyponatremia and hypocalcemia were also observed.

DISCUSSION

While CDK4/6 inhibitors have transformed the landscape of therapy for hormonal receptor-positive advanced breast cancer, here we describe 6 patients who had biopsy-proven AKI that was directly attributed to the CDK4/6 inhibitor. AKI had major repercussions, requiring dose reduction and or discontinuation of therapy in 4 of 6 patients. Additionally, based on a search of the FAERS database, AKI is a reported complication of CDK4/6 inhibitors, as are metabolic disturbances like hypokalemia, hyponatremia, and hypocalcemia. Supplementary Table 3 summarizes prior data, as well as our findings of adverse renal events reported with CDK4/6 inhibitors.

Existing data on AKI from CDK4/6 inhibitors are scant. Several early trials of palbociclib and ribociclib did not describe the incidence of AKI, whereas clinical trials of abemaciclib have reported that up to 25% of patients experienced a rise in SCr. In vitro studies of abemaciclib have shown that the drug and its major metabolites inhibit renal transporters like organic cation transporter-2, multidrug and toxin extrusion-1 (MATE-1), and MATE2-K, potentially leading to a reversible rise in SCr without actually changing GFR. However, in our series, 3 of 6 patients had severe stage 3 AKI with 1 requiring RRT, and each of the 6 patients had biopsy-proven AKI. Differentiating “pseudo-AKI” from true AKI can be challenging. Simultaneous measurement of SCr, kidney iothalamate clearance, and/or estimated glomerular filtration rate based on a cystatin C level (with the caveat that this might be elevated in the setting of inflammation) may help distinguish between the two entities. Furthermore, patients with true AKI may have cortical echogenicity on renal ultrasound, though 2 of the patients had normal renal ultrasounds.

The time of onset of AKI was prolonged in relation to use of CDK4/6 inhibitors. It is therefore possible that there was a “second-hit” that predisposed to the development of AKI; however, there was no other identifiable trigger in any of the cases, aside from the CDK4/6 inhibitor. Additionally, there are other cancer therapies (e.g., immunotherapy, vascular endothelial growth factor inhibitors), where there is often a lag time between initiation of the treatment and the onset of AKI.

The most common histopathologic finding on biopsy was ATN, in the absence of an alternative explanation, such as hypotension, recent intravenous contrast use, or sepsis. The mechanism behind the ATN is unclear, but may be due to off-target effects of the CDK4/6 inhibitors, with
tubular cell damage from the inhibition of cell-cycle progression. Patient 1 had ATIN, which suggests that there is also the possibility of hypersensitivity reactions to these drugs. Paradoxically, there are preclinical data that suggest that CDK4/6 inhibitors may have a nephroprotective effect. Induction of G0/G1 cycle arrest through CDK4/6 inhibition has been shown to protect proximal tubular epithelial cells following exposure to nephrotoxins like cisplatin, etoposide, and antimycin A.\textsuperscript{S7,S8} It is therefore possible that the duration of exposure to CDK4/6 inhibition matters, whereby transient exposure to cell cycle inhibitors may be protective, yet prolonged exposure may lead to AKI. Additionally, in advanced breast cancer, mutations can accumulate, with mismatch repair defects that could result in anti-tumor immune responses driving increased cytokine production and/or leukocyte infiltration.

A search of the FAERS database revealed that, in addition to AKI, metabolic disturbances like hypokalemia, hyponatremia, and hypocalcemia may occur while on CDK4/6 inhibitors. Hyponatremia has been reported with ribociclib and with abemaciclib\textsuperscript{S9,S10} and grade 2 hypokalemia was reported in 20.8% of patients taking abemaciclib.\textsuperscript{S10} Given that CDK4/6 inhibitors are associated with QT prolongation, particularly ribociclib,\textsuperscript{S11} it is imperative that patients undergo frequent monitoring of serum electrolytes prior to therapy and with each cycle.

While our study is the first to describe clinical features and histopathology associated with CDK4/6 inhibitors, there were limitations. We had incomplete follow-up data for two patients. Additionally, we cannot exclude the possibility that the AKI event was caused by a concomitant medication rather than the CDK4/6 inhibitor. Use of the FAERS database has its limitations as well; it includes all provider and patient-reported adverse events, and may therefore may not capture true AKI. Furthermore, demographic and comorbidity information is not readily available to determine whether other nephrotoxic risk factors may be contributing.

While CDK4/6 inhibitors may lead to a reversible rise in SCr without actually changing GFR in some cases, we now show that they can also cause true renal tubular toxicity. Given the relative novelty of CDK4/6 inhibitors, there is much that remains unknown about the mechanism behind AKI associated with these drugs. Larger, prospective studies are needed to understand and characterize the incidence of and risk factors for AKI in patients receiving CDK4/6 inhibitors.
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TC and VCS have no disclosures.
SUPPLEMENTARY MATERIAL

Supplementary Table 1: Baseline Characteristics (PDF)

Supplementary Table 2: Medications at the time of CDK4/6 Inhibitor-Associated AKI (PDF)

Supplementary Table 3: Summary of Renal Adverse Events Associated with CDK4/6 Inhibitors (PDF)

Supplementary information is available at KI Report's website
REFERENCES


Figure 1. Histopathology of cyclin-dependent kinase inhibitor-associated acute kidney injury.
(A) Interstitial fibrosis and disproportionate tubular atrophy throughout cortex, Jones Methenamine Silver, 100x, scale bar = 10 µm. (B) Normal glomeruli without matrix expansion or proliferative changes, Periodic Acid Schiff, 200 x, scale bar = 50 µm.
(C) Interstitial edema and mixed interstitial inflammation, Hematoxylin + Eosin, 200x, scale bar = 50 µm.
(D) Neutrophil-rich inflammation and tubulorrhesis, Hemoxylin + Eosin, 400x, scale bar = 20 µm.
(E) Mild lymphocytic interstitial inflammation and acute tubular injury (apical cytoplasmic blebbing, epithelial cell simplification, and ectasia of tubular profiles), Hemoxylin + Eosin, 400x, scale bar = 20 µm.
(F) Interstitial edema separating tubular profiles and acute tubular injury with epithelial cell simplification, reactive and regenerative nuclear changes, and dilation, Hemoxylin + Eosin, 400x, scale bar = 20 µm.
Table 1: Clinical Features of CDK4/6 Inhibitor-Associated AKI

<table>
<thead>
<tr>
<th>Pt</th>
<th>Peak SCr&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Time to AKI&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Admission</th>
<th>UA/Sediment</th>
<th>Albuminuria&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Renal US</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.0</td>
<td>NA</td>
<td>Yes</td>
<td>+Protein, +Blood, 100 WBCs</td>
<td>1.5</td>
<td>Cortical echogenicity</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>NA</td>
<td>Yes</td>
<td>+LE, +Protein</td>
<td>4.5</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>210</td>
<td>No</td>
<td>+Protein, +Blood</td>
<td>0.3</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>5.9</td>
<td>346</td>
<td>Yes</td>
<td>NA</td>
<td>0.3</td>
<td>Cortical echogenicity</td>
</tr>
<tr>
<td>5</td>
<td>11.2</td>
<td>683</td>
<td>Yes</td>
<td>+Blood, +Protein, Granular Casts</td>
<td>1.6</td>
<td>Cortical echogenicity</td>
</tr>
<tr>
<td>6</td>
<td>1.9</td>
<td>102</td>
<td>No</td>
<td>+Blood, +Protein, Hyaline and Muddy Brown Casts</td>
<td>5</td>
<td>Normal</td>
</tr>
</tbody>
</table>

<sup>1</sup>Peak SCr during AKI episode, in mg/dl
<sup>2</sup>Days from CDK4/6 initiation to AKI
<sup>3</sup>Albuminuria at the time of AKI, g/g

Abbreviations: AKI, acute kidney injury; LE, leukocyte esterase; NA, not available; SCr, serum creatinine; UA, urinalysis; US, ultrasound; WBCs, white blood cells
Table 2: Renal Adverse Events Associated with CDK4/6 Inhibitors from the Food and Drug Administration Adverse Event Reporting System

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Reaction</th>
<th>Male (N=5) n/N (%)</th>
<th>Female (N=195) n/N (%)</th>
<th>Missing (N=10) n/N (%)</th>
<th>Overall (N=210) n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIBOCICLIB (N=210)</td>
<td>Renal Injury</td>
<td>3 (60)</td>
<td>82 (42)</td>
<td>8 (80)</td>
<td>93 (44)</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>1 (20)</td>
<td>29 (15)</td>
<td>1 (10)</td>
<td>31 (15)</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
<td>1 (20)</td>
<td>29 (15)</td>
<td>0 (0)</td>
<td>30 (14)</td>
</tr>
<tr>
<td></td>
<td>Hyponatremia</td>
<td>0 (0)</td>
<td>31 (16)</td>
<td>1 (10)</td>
<td>32 (15)</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td>0 (0)</td>
<td>9 (5)</td>
<td>0 (0)</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia</td>
<td>0 (0)</td>
<td>7 (4)</td>
<td>0 (0)</td>
<td>7 (3)</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
<td>0 (0)</td>
<td>6 (3)</td>
<td>0 (0)</td>
<td>6 (3)</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Reaction</th>
<th>Male (N=1) n/N (%)</th>
<th>Female (N=77) n/N (%)</th>
<th>Missing (N=6) n/N (%)</th>
<th>Overall (N=84) n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABEMACICLIB (N=84)</td>
<td>Renal Injury</td>
<td>1 (100)</td>
<td>45 (58)</td>
<td>4 (67)</td>
<td>50 (60)</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>0 (0)</td>
<td>16 (21)</td>
<td>2 (33)</td>
<td>18 (21)</td>
</tr>
<tr>
<td></td>
<td>Hyponatremia</td>
<td>0 (0)</td>
<td>10 (13)</td>
<td>0 (0)</td>
<td>10 (12)</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td></td>
<td>Acidosis</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
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<tr>
<td></td>
<td>Hyperkalemia</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Reaction</th>
<th>Male (N=14) n/N (%)</th>
<th>Female (N=470) n/N (%)</th>
<th>Missing (N=5) n/N (%)</th>
<th>Overall (N=489) n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALBOCICLIB (N=489)</td>
<td>Renal Injury</td>
<td>7 (50)</td>
<td>279 (59)</td>
<td>4 (80)</td>
<td>290 (59)</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>3 (21)</td>
<td>62 (13)</td>
<td>0 (0)</td>
<td>65 (13)</td>
</tr>
<tr>
<td></td>
<td>Hyponatremia</td>
<td>3 (21)</td>
<td>39 (8)</td>
<td>0 (0)</td>
<td>42 (9)</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
<td>1 (7)</td>
<td>34 (7)</td>
<td>0 (0)</td>
<td>35 (7)</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
<td>0 (0)</td>
<td>25 (5)</td>
<td>1 (20)</td>
<td>26 (5)</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td>0 (0)</td>
<td>20 (4)</td>
<td>0 (0)</td>
<td>20 (4)</td>
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<tr>
<td></td>
<td>Hypomagnesemia</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>0 (0)</td>
<td>4 (1)</td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>0 (0)</td>
<td>4 (1)</td>
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<tr>
<td></td>
<td>Hyponatremia</td>
<td>0 (0)</td>
<td>3 (1)</td>
<td>0 (0)</td>
<td>3 (1)</td>
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</table>

There are limitations to the Food and Drug Administration Adverse Event Reporting System. The events are reported by providers and/or patients and may therefore be subject to reporting bias. In addition, not all demographic and comorbidity information is available to help identify whether other nephrotoxic risk factors are present (e.g., use of nonsteroidal anti-inflammatory agents, history of hypertension or diabetes mellitus, known chronic kidney disease, recent use of contrast agent, and recent use of chemotherapy with nephrotoxic potential). It is not possible to
determine whether an event is truly caused by the drug as opposed to the underlying disease, concomitant medications, or prior chemotherapies administered to these patients. Finally, there is no denominator for the number of patients who received these agents, and therefore a percent risk of the adverse outcome cannot be computed.

1 Renal Injury comprises proteinuria, renal failure acute, acute kidney injury, elevated creatinine, hypercreatinemia, and nephritis.