Use of Immune Checkpoint Inhibitors in End Stage Kidney Disease Patients, Single Center Experience and Review of the Literature

Jamie S. Hirsch,1,2,3 Rimda Wanchoo,1 Jia H. Ng,1 Yuriy Khanin,1 and Kenar D. Jhaveri1

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Introduction

Immune checkpoint inhibitors (ICIs), immunomodulatory antibodies that are used to enhance the immune system, have substantially improved the prognosis of patients with advanced malignancy. Although we are aware that there is no renal clearance of these agents (1), the data on the use of ICIs in patients with ESKD on hemodialysis (HD) as well as those on peritoneal dialysis (PD) is sparse. Published reports on the use of ICIs in patients with ESKD are limited to case reports and case series: one from Korea (2) and the second from Italy (3). We describe our single-center experience of ICI use in patients with ESKD and summarize the current literature of ICI use in this population.

Materials and Methods

We used data from a large health system in the state of New York comprising 23 hospitals and 700 ambulatory facilities. Data for this study were obtained from the enterprise inpatient electronic health record (Sunrise Clinical Manager; Allscripts, Chicago, IL), which covers 13 of the hospitals, including the oncology infusion centers. Using an analytics database, we identified all patients with a minimum of one ESKD diagnosis code (Insertional Classification of Diseases 10th Edition, N18.6) who received at least one of the following agents between 2012 and 2019: ipilimumab, nivolumab, pembrolizumab, or atezolizumab. We included both prevalent patients on dialysis (those already receiving dialysis during the time of ICI initiation) and incident patients on dialysis (those who started dialysis after ICI initiation). Charts were reviewed manually to confirm that patients were on HD or PD during the ICI therapy. Clinical details such as demographics, comorbidities, cancer type, immune-related adverse events (irAEs), cancer disease status, and patient survival were reviewed. Further literature search was performed for all published cases of ICI use in patients with ESKD and was summarized as part of the Methods. This study was determined to be exempt by the Northwell Health Institutional Review Board.

Results

In total, eight patients with ESKD were initiated on ICIs. The baseline characteristics of the patients undergoing dialysis before initiating ICIs are shown in Table 1. A variety of malignancies were identified: four patients had genitourinary cancers, two had gastrointestinal cancers, one had Hodgkin lymphoma, and one had neuroendocrine tumor. Four patients received pembrolizumab, two received nivolumab, one received both ipilimumab and nivolumab, and the last received the programmed death-ligand 1 inhibitor atezolizumab. All eight patients were receiving proton pump inhibitors. The mean duration on dialysis (dialysis vintage) before ICI therapy was 15.8 months (range, 3–60 months). Two patients had an immunotherapy-related adverse event: dermatitis (confirmed via tissue biopsy) and transplant kidney rejection, respectively. In both cases, the physicians discontinued the offending ICI biopsy and started the patients on systemic steroid therapy. Both patients subsequently suffered from cancer progression. The remaining patients tolerated the ICIs well, without significant complication or side effect. No dose adjustments were required in any of the patients undergoing treatment with the ICI. In regards to cancer status, the cancer did not progress in three patients but progressed in the remaining five. At the time of this writing, four patients had died.

Two patients are highlighted because their clinical courses appear exceptional. The first, a 65-year-old male with a history of renal transplantation (2010) and subsequent allograft failure (2016), was on HD for 3 years and weaned off maintenance transplant immunosuppression by 2018. He subsequently developed hepatocellular carcinoma in 2018 and was initiated on nivolumab. Several cycles into therapy, he developed abdominal pain at the graft site and acute gross hematuria. Although the patient declined kidney biopsy or transplant nephrectomy, acute rejection due to ICI therapy was clinically suspected, steroids were initiated, and the patient’s pain and hematuria resolved. Further ICI was held due to progression of disease and he was transitioned to hospice care.
The second patient, a 79-year-old male with cholangiocarcinoma and known CKD stage 4 was treated with pembrolizumab, which was complicated by AKI after the second cycle. A kidney biopsy confirmed oxalate nephropathy, with the cause being attributed to prior gastric surgeries. Given the progressive renal failure, he was initiated on HD. ICI therapy was continued without any adverse events. This case was included to illustrate an alternate cause of renal failure unrelated to acute interstitial nephritis from ICI therapy, underscoring the importance of a kidney biopsy in the diagnosis of AKI during ICI therapy.

Three additional patients developed dialysis-dependent ESKD as a result of ICI therapy (Table 2). All three patients were on proton pump inhibitors. Two of the patients had ICI-associated amyloid A amyloidosis (based on kidney biopsy); the detailed report has been published separately (4). The other patient developed ESKD after the initiation of atezolizumab, however, a kidney biopsy was not performed. His long-term outcome was unclear because he was lost to follow-up.

Review of the Literature
Table 3 summarizes all currently published cases and outcomes of using ICIs in patients with ESKD. A total of 26 patients have previously been described in the literature (5–18), with the majority of them from two centers, (2,3) and mostly receiving HD (92%). A variety of malignancies were treated (35% for melanoma; 54% for renal cell carcinoma; with the remainder composed of squamous cell skin cancer, urothelial cancer, and nonsmall cell lung cancer). Interestingly, 27% of these patients were on dialysis as a result of a rejected kidney transplant due to ICI therapy, and then continued to receive ICI. Over 80% of the patients had either partial or complete response to treatment. Aside from the kidney transplant rejection preceding dialysis, a minimal number of patients had a grade 2, 3, or 4 adverse immunotherapy-related event (15%).

Conclusion
Immunotherapy has changed the paradigm of treatment in several solid malignancies. The incidence and type of irAEs vary with the immunotherapeutic agent and duration of therapy (19). The reported incidence of any grade irAEs ranges from 60% to 70% in patients treated with ipilimumab as compared with 39%–41% on programmed cell death protein 1 inhibitors, and the incidence of grade 3–4 irAEs is higher with ipilimumab (15%) compared with non-cytotoxic T-lymphocyte-associated protein 4 checkpoint inhibitors (5%–6%) (20–22). In a recent single-center retrospective study, 98 of 290 patients (34%) experienced any grade irAEs. Among the 15 (5%) patients with grade ≥3 irAEs, the most common irAEs were dermatitis and enterocolitis (23). These studies were not inclusive of patients with severe kidney disease or those receiving dialysis. Further, the data on event rate of irAEs in patients with ESKD are scarce. Although limited to a small number of patients at

Table 1. Clinical details of eight patients with ESKD who received immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Gender (M/F)</th>
<th>Cancer Diagnosis</th>
<th>Dialysis Type</th>
<th>Months on Dialysis before ICI Therapy</th>
<th>ICI Given</th>
<th>irAE</th>
<th>Cancer Status</th>
<th>Death (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>M</td>
<td>Urothelial cancer</td>
<td>HD</td>
<td>60</td>
<td>Atezolizumab</td>
<td>None</td>
<td>Did not progress</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>M</td>
<td>Hepatocellular cancer</td>
<td>HD</td>
<td>36</td>
<td>Nivolumab</td>
<td>Rejection of the failed transplanted kidney</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>M</td>
<td>Urothelial cancer</td>
<td>HD</td>
<td>3</td>
<td>Pembrolizumab</td>
<td>None</td>
<td>Did not progress</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>79</td>
<td>M</td>
<td>Cholangiocarcinoma</td>
<td>HD</td>
<td>5</td>
<td>Pembrolizumab</td>
<td>None</td>
<td>Progressed</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>F</td>
<td>Hodgkin lymphoma</td>
<td>HD</td>
<td>5</td>
<td>Pembrolizumab</td>
<td>None</td>
<td>Progressed</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>F</td>
<td>Neuroendocrine tumor</td>
<td>PD</td>
<td>8</td>
<td>Nivolumab + ipilimumab</td>
<td>Dermatitis</td>
<td>Progressed</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>M</td>
<td>Renal cell cancer</td>
<td>HD</td>
<td>3</td>
<td>Pembrolizumab</td>
<td>None</td>
<td>Progressed</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>76</td>
<td>M</td>
<td>Urothelial cancer</td>
<td>HD</td>
<td>6</td>
<td>Nivolumab</td>
<td>None</td>
<td>Did not progress</td>
<td>No</td>
</tr>
</tbody>
</table>

M, male; F, female; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; HD, hemodialysis; PD, peritoneal dialysis.

Table 2. Clinical summary of patients who developed ESKD from immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Gender (M/F)</th>
<th>Cancer Diagnosis</th>
<th>Time to ESKD after ICI (mo)</th>
<th>Kidney Biopsy Findings</th>
<th>Months to Dialysis after ICI Was Started</th>
<th>ICI Given</th>
<th>Cancer Status</th>
<th>Death (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>M</td>
<td>Colorectal cancer</td>
<td>3</td>
<td>AA amyloidosis</td>
<td>4</td>
<td>Pembrolizumab</td>
<td>In remission</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>M</td>
<td>Melanoma</td>
<td>10</td>
<td>AA amyloidosis</td>
<td>11</td>
<td>Nivolumab</td>
<td>In remission</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>M</td>
<td>Bladder cancer</td>
<td>4</td>
<td>No kidney biopsy done</td>
<td>5</td>
<td>Atezolizumab</td>
<td>Progressed</td>
<td>Lost to follow-up</td>
</tr>
</tbody>
</table>

M, male; F, female; ICI, immune check point inhibitor; AA amyloidosis, amyloid A amyloidosis.
In a single center, our data suggest that ICIs can be safely administered in ESKD without dose adjustments. In addition, based on our series and previously published literature, the rate of irAEs appears similar to patients with non-ESKD (15%–25%). ESKD may not be a contraindication to the use of ICIs.

More data and further analysis is necessary to better understand tolerance as well as malignancy outcomes in patients receiving both dialysis and ICI. The oncology literature is sparse in terms of studies in patients with cancer with CKD and ESKD (24). We believe that this brief report adds to the ongoing literature of ICIs use in patients with ESKD.

Author Contributions

J. Hirsch and K Jhaveri were responsible for formal analysis; J. Hirsch and K Jhaveri conceptualized the study and were responsible for data curation; J Hirsch wrote the first draft of the manuscript; and K Jhaveri, Y. Khanin, J. Ng, and R. Wanchoo reviewed and edited the manuscript.

Disclosures

K. Jhaveri reports consultant fees from Astex Pharmaceuticals during the conduct of the study. J. Hirsch, Y. Khanin, J. Ng, and R. Wanchoo have nothing to disclose.

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References


