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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. Jhaveri[1]

[1]Division of Kidney Diseases and Hypertension, Donald and Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY

[2]Institute of Health Innovations and Outcomes Research, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, New York, USA.

[3]Department of Information Services, Northwell Health, New Hyde Park, New York

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Correspondence:

Kenar D. Jhaveri, MD
Division of Kidney Diseases and Hypertension, Donald and Zucker School of Medicine at Hofstra/Northwell, 100 Community Drive, Great Neck, NY
kjhaveri@northwell.edu or kdj200@gmail.com

Introduction

Immune checkpoint inhibitors (ICI), immunomodulatory antibodies that are used to enhance the immune system, have substantially improved the prognosis of patients with advanced malignancy. While we are aware that there is no renal clearance of these agents(1), the data on the use of ICI in end stage kidney disease (ESKD) patients on hemodialysis (HD) as well as peritoneal dialysis (PD) patients is sparse. Published reports on the use of ICI in ESKD patients 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 ESKD patients and summarize the current literature of ICI use in this population.

Methods

We used data from a large health system in New York State, comprised of 23 hospitals and over 700 ambulatory facilities. Data for this study was obtained from the enterprise inpatient electronic health record (EHR; 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 (ICD-10 N18.6) who received at least one of the following agents between 2012 and 2019: ipilumumab, nivolumab, pembrolizumab, or atezolizumab. We included both prevalent dialysis patients (those already receiving dialysis during the time of ICI initiation) and incident dialysis patients (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 ESKD patients 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 ICI. The baseline characteristics of the patients undergoing dialysis prior to initiating ICI are shown in **Table 1**. A variety of malignancies were identified: four patients had genitourinary cancers, two had gastro-intestinal cancers, one had Hodgkin's lymphoma, and one had neuro-endocrine tumor. Four patients received pembrolizumab, two received nivolumab, one received both ipilumumab and nivolumab, and the last received PD-L1 inhibitor atezolizumab. All eight patients were receiving proton pump inhibitors. The mean duration on dialysis (dialysis vintage) prior to 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 agent 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 as 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 was transitioned to hospice care.

The second patient, a 79-year-old male with cholangiocarcinoma and known chronic kidney disease stage IV 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 AA 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 as he was lost to follow-up.

Review of the literature

Table 3 summarizes all currently published cases and outcomes of using ICI in ESKD patients. 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 (melanoma 35%, and renal cell carcinoma 54%, with the remainder composed of squamous cell skin cancer, urothelial cancer, and non-small 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 60-70% in patients treated with ipilimumab as compared to 39-41% on PD-1 inhibitors, and the incidence of grade 3-4 irAEs is higher with ipilimumab (15%) compared to non-CTLA-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 (5.2%) 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 ESKD patients is scarce. Although limited to a small number of patients at 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 iRAE appear similar to non-ESKD patients (15-25%). ESKD may not be a contraindication to the use of ICI.

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 oncologic patients with CKD and ESKD(24). We believe that this brief report adds to the ongoing literature of ICI use in ESKD patients.

Disclosures

K Jhaveri reports other from Astex Pharmaceuticals during the conduct of the study; other from Astex Pharmaceuticals outside the submitted work. The coauthors have nothing to disclose.

Author Contributions

Jamie Hirsch: Conceptualization; Data curation; Formal analysis

Rimda Wanchoo: Writing - review and editing

Jia Hwei Ng: Writing - review and editing

Yuriy Khanin: Writing - review and editing

Kenar Jhaveri: Conceptualization; Data curation; Writing - review and editing

Table 1: Clinical details of 8 ESKD patients who received immune checkpoint inhibitors

Legend: M: male, F: female, HD: hemodialysis, PD: peritoneal dialysis, ICI: immune checkpoint inhibitor, irAE: immune related adverse events

Case #	Age	Gender (M/F)	Cancer diagnosis	Dialysis type	Months on dialysis prior to ICI therapy	ICI given	irAE	Cancer status	Death (yes/ no)
1	83	M	Urothelial cancer	HD	60	Atezolizumab	None	Did not progress	No
2	65	M	Hepatocellular cancer	HD	36	Nivolumab	Rejection of the failed transplanted kidney	Progressed	Yes
3	65	M	Urothelial cancer	HD	3	Pembrolizumab	None	Did not progress	No
4	79	M	Cholangio-carcinoma	HD	5	Pembrolizumab	None	Progressed	Yes
5	37	F	Hodgkin's lymphoma	HD	5	Pembrolizumab	None	Progressed	No
6	35	F	Neuro-endocrine tumor	PD	8	Nivolumab+ ipilumumab	Dermatitis	Progressed	Yes
7	74	M	Renal cell cancer	HD	3	Pembrolizumab	None	Progressed	Yes
8	76	M	Urothelial cancer	HD	6	Nivolumab	None	Did not progress	No

Table 2: Clinical summary of patients who developed end-stage kidney disease from immune checkpoint inhibitors

Legend: M: male, F: female, ESKD: end-stage kidney disease, ICI: immune check point inhibitor

Case #	Age	Gender (M/F)	Cancer diagnosis	Time to ESKD after ICI (months)	Kidney biopsy findings	Months to dialysis after ICI was started	ICI given	Cancer status	Death (yes/no)
1	42	M	Colorectal cancer	3	AA amyloidosis	4	Pembrolizumab	In remission	No
2	81	M	Melanoma	10	AA amyloidosis	11	Nivolumab	In remission	Yes
3	71	M	Bladder cancer	4	No kidney biopsy done	5	Atezolizumab	Progressed	Lost to follow up

Table 3: Summary of patient data from 26 published cases of the use of immunotherapy in dialysis patients

Legend: ICI: immune check point inhibitor, HD: hemodialysis, PD: peritoneal dialysis; irAEs: immune related adverse events, SCC: squamous cell cancer; RCC: renal cell cancer; NSCLC: non-small cell lung cancer; NA: not available.

***The patient had a transplant rejection due to immunotherapy leading to dialysis-dependent kidney failure; immunotherapy was continued while the patient was on dialysis**

No. of patients	Age	ICI type	Cancer	Dialysis modality	Cancer response(Full, partial, none)	irAEs	Reference #
1*	74	Nivolumab	Melanoma	HD	Full	Rejected transplant on dialysis	6
1*	76	Nivolumab	Melanoma	HD	Full	Rejected transplant on dialysis	7
1*	57	Pembrolizumab	Skin SCC	HD	Full	Rejected transplant on dialysis	10
1*	48	Ipilumumab+ nivolumab	Melanoma	HD	Full	Rejected transplant on dialysis	11
1*	68	Ipilumumab+ pembrolizumab	Melanoma	HD	Full	Rejected transplant on dialysis	12
1*	40	Ipilumumab	Melanoma	HD/PD	None	Rejected transplant on dialysis	13
1*	57	Nivolumab	Melanoma	HD	Full	Rejected transplant on dialysis	15
1	77	Nivolumab	RCC	HD	Full	None	8
1	NA	Pembrolizumab	Melanoma	HD	Full	None	9
1	49	Nivolumab	RCC	HD	Full	None	14
2	56,69	Ipilumumab(2)	Melanoma	HD	Full, partial	One patient had dermatitis	5
1	66	Pembrolizumab	NSCLC	HD	Partial	None	16
1	72	Nivolumab	RCC	HD	Partial	None	17
3	64,65,68	Nivolumab(2), Atezolizumab	RCC(2), Urothelial cancer(1)	HD	Full, partial, none	Pneumonitis in 1 patient	2

8	51-77	Nivolumab	RCC	7 HD, 1 PD	6 with partial response, 2 with none	2 patients with grade 3 toxicities	3
1	NA	Atezolizumab	RCC	HD	Partial response	None	18

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