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CKJ REVIEW

Immune checkpoint inhibitor use in patients with end-stage kidney disease: an analysis of reported cases and literature review

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ABSTRACT

Immune checkpoint inhibitors (ICIs), immunomodulatory antibodies that are used to enhance the immune system, have substantially improved the prognosis of patients with advanced malignancy. As the use of ICI therapy becomes increasingly widespread across different types of cancer, their use in patients receiving dialysis is likely to increase. In this review we summarize the current literature on the use of ICIs in end-stage kidney disease (ESKD) patients and provide aggregate data from reported cases and series. Based on available pharmacological information, ICIs require no dosing adjustment in ESKD patients. Analysis of the reported cases in the literature demonstrates a similar incidence of immune-related adverse events in patients with ESKD receiving dialysis as compared with the general population (49%). Severe reactions graded as 3 and 4 have been seen in 15 patients (16%). As such, it is important that these patients are monitored very closely for immune-related adverse events; however, the risk of these adverse events should not preclude patients on dialysis from receiving these therapies. Cancer remission (complete and partial) was seen in close to 30% of patients, stable disease was seen in 28% and progression of disease in ∼36%. One-third of the patients died. Urothelial and renal cell cancer represented approximately half of all treated cancers and accounted for ∼50% of all deaths reported. Additional data in the dialysis population with the use of ICIs and involvement in prospective studies are needed to better assess outcomes, particularly within specific cancer types.

Keywords: cancer, dialysis, ESKD, immunotherapy, pembrolizumab, nivolumab

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Clinical Kidney Journal

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 there is no renal clearance of these agents, the data on the use of ICIs in end-stage kidney disease (ESKD) patients on hemodialysis (HD) as well as peritoneal dialysis (PD) patients is sparse [1]. Initial reports of the use of ICI therapy in dialysis patients were limited to patients who had rejected a transplanted kidney and were resumed on dialysis with continued ICI therapy [2, 3]. In the last year, several single-center case reports and series from around the world have emerged suggesting their safe use in both HD and PD patients [4–6]. In this review we summarize the pharmacology of ICI therapy and then systematically review all published cases of the use of ICI therapy in patients on dialysis (both incident dialysis patients due to allograft rejection as well as prevalent dialysis patients).

Pharmacology of ICIs

ICIs are humanized or human immunoglobulin (Ig) antibodies of the IgG1 isotype (except nivolumab, which is of the IgG4 isotype) with pharmacokinetic properties similar to other therapeutic monoclonal antibodies (mAbs) [1, 7]. They have a small volume of distribution following intravenous administration and are for the most part confined to the vascular space [1, 7]. Their distribution is determined by rates of extravasation out of the vascular space through convective transport and transcytosis, distribution in the interstitial space via diffusion, convection and antibody binding, followed by intracellular degradation or recycling by the neonatal Fc receptor (FcRn) [8, 9]. Removal of ICIs from the interstitial space is dependent on convection into the lymph. The time to reach drug steady state varies for each ICI and ranges from 4 to 18 weeks [1, 7]. mAbs are too large to be eliminated by the kidneys, except possibly in the setting of high-grade non-selective proteinuria [10]. Hepatic elimination of these agents is negligible. Intracellular catabolism by lysosomal degradation following pinocytosis or receptor-mediated endocytosis is the main route of elimination. Receptor-mediated endocytosis of IgG molecules occurs after binding of their Fc domain to cell surface receptors or after binding of their Fab domains to their target antigen, so-called target-mediated drug disposition (TMDD). Catabolic degradation of IgG following pinocytotic uptake occurs throughout the body, particularly in organs and tissues that are rich in endothelial cells.

The rate of elimination through TMDD is dependent on the availability of the target antigen (tumor type and burden), the affinity of the ICI for the antigen, the dose of the ICI, the rate of internalization and the rate of catabolism within the target cell. The elimination of ICI is time dependent (changing clearance over time after the start of treatment) and this is probably due to a change in the availability of their tumor antigen during the disease process [11–13]: reduced tumor burden results in a lower availability of available antigens and lower TMDD. The elimination of ipilimumab is not time dependent, possibly because of the small amount of target cells in comparison with other ICIs. To prevent excessive degradation of IgG after pinocytosis, there is a salvage pathway through binding to the FcRn. The FcRn is present in the endosome and binds IgG. FcRn–IgG complexes are returned to the cell surface and IgG is released back into the extracellular space. It is estimated that two-thirds of ICIs are recycled in this manner [14], resulting in extended half-lives of ICIs (6–27 days) [9]. Further highlighting the importance of the FcRn salvage pathway is the observation that a genetic variant in the *FCGRT* gene encoding for FcRn results in decreased expression of FcRn and is associated with increased mAb clearance and decreased systemic exposure [15, 16].

Finally, ICI clearance can also occur through the formation of antidrug antibodies, which facilitate endocytic degradation of these drugs [1, 7]. The percentage of patients developing antidrug antibodies, as well as its impact on clearance, is considered limited for most ICIs, as they are either human or humanized antibodies [17, 18]. Interestingly, the development of antidrug antibodies might be more frequent in patients receiving ICI combination therapy (e.g. ipilimumab + nivolumab) [19]. Figure 1 summarizes the pharmacokinetics of ICIs. No registry or large database exists on the use of ICIs in ESKD patients. Hence we performed a detailed literature review to assess the use of these agents in ESKD patients from published case reports and case series.

Literature search

We performed a descriptive literature review of ICI use in ESKD patients receiving HD or PD. Case series and reports with at least one ESKD patient receiving ICIs were included. Manuscripts were required to report individual-level data for patients. A similar descriptive study design as previously used for outcomes of myeloma patients with kidney transplants was utilized [20].

Literature search methodology. We performed a structured search (developed by a health information specialist) of the MEDLINE and Embase databases from inception to February 2021. We sought to identify case reports, case series, observational studies and clinical trials that described the use of ICI therapy for cancer in patients receiving dialysis (either HD or PD). We included cases in which kidney transplant recipients received ICI, provided that they continued on ICI therapy following graft failure and received dialysis. The search strategy and terms can be found in the Supplementary Appendix. Citations retrieved from the search underwent title and abstract review for inclusion. Articles identified from the search were then reviewed in full for relevance and inclusion. We then reviewed the references of included articles for additional relevant citations not identified by the search strategy. All authors were involved in data abstraction of clinical information from the search strategy.

Data abstraction and descriptive statistical analysis. For each included study we performed a standardized patient-level data abstraction using prespecified parameters of interest: patient demographics, cancer diagnosis, ICI treatment characteristics, dialysis modality, immune-related adverse events (irAEs), cancer outcomes and survival. We reported descriptive statistics related to the prespecified parameters of interest. We expressed continuous variables as the mean [standard deviation (SD)] or median (25th–75th percentile) and categorical variables as a percentage.

The structured search yielded 136 citations for title and abstract screening. Of these, 31 articles were reviewed in full and 28 articles met inclusion criteria. Review of the reference lists identified 5 additional articles, resulting in a total of 33 articles for inclusion [2–6, 21–49]. From these 33 articles, 98 cases with patient-level data were included. A summary of each included citation is shown in Table 1. Aggregate data summarizing

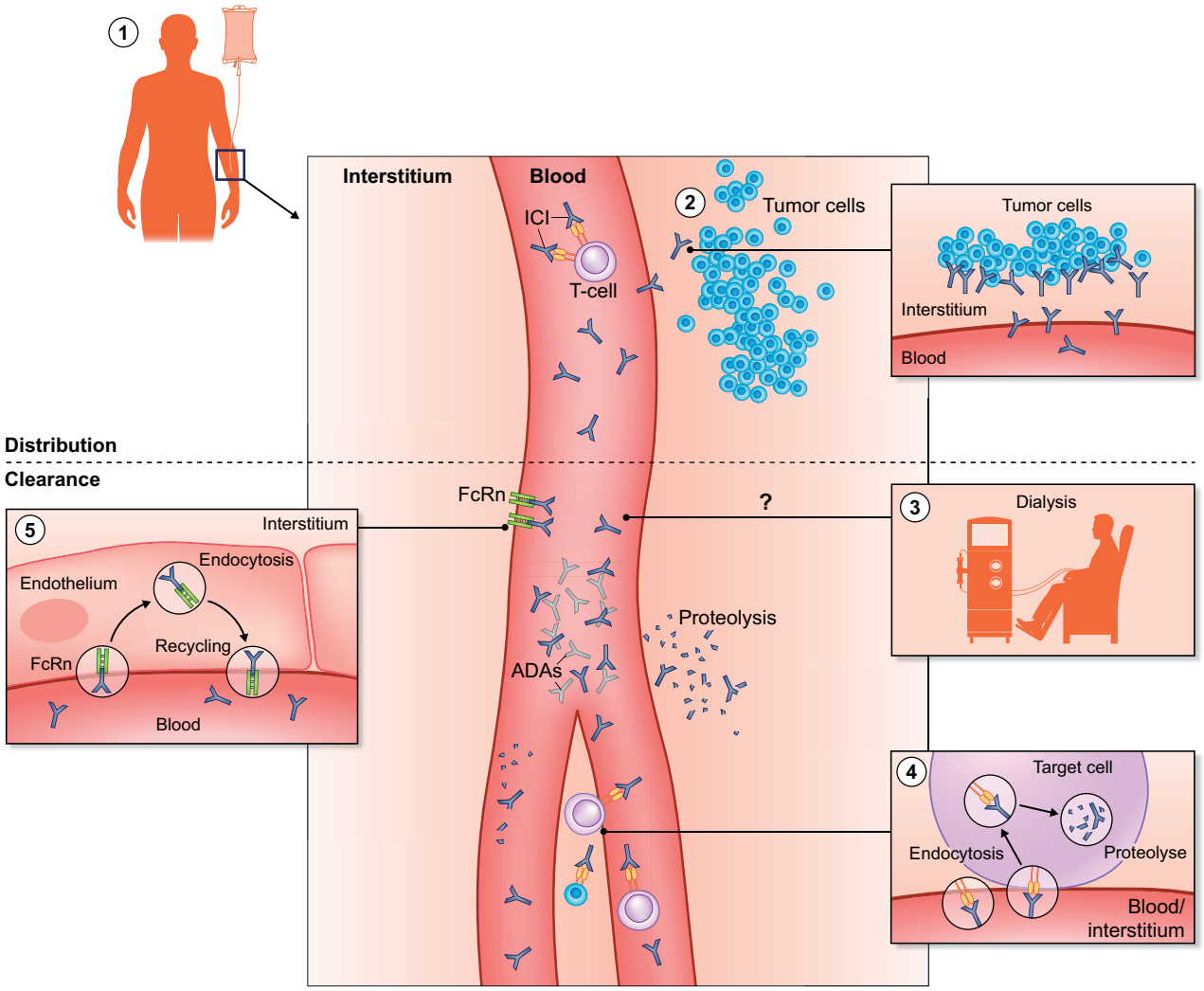

FIGURE 1: Pharmacology of ICIs. (1) After intravenous administration, ICIs are distributed in the vascular space and the interstitial space. (2) Distribution in the interstitial space is determined via diffusion, convection and antibody binding followed by intracellular degradation. Receptor-mediated endocytosis of IgG occurs after binding of their Fc domain to cell surface receptors or by TMDD, which is dependent on the availability of the target antigen (tumor type and burden). (3) mAbs are too large to be eliminated during dialysis, although adherence to the dialysis filter is a theoretical possibility. (4) Intracellular catabolism by lysosomal degradation following pinocytosis or receptor-mediated endocytosis is the main route of elimination. Endocytic degradation can be facilitated by antidrug antibodies. (5) To prevent excessive degradation of IgG after pinocytosis, there is a salvage pathway through binding to the FcRn.

patient characteristics (stratified by previous kidney transplant status) are shown in Table 2. Tables 3 and 4 report these characteristics among recipients of nivolumab and pembrolizumab (the two most commonly used ICIs in the cohort) and those with urothelial cancers and renal cell carcinoma (RCC; the two most common cancer diagnoses in the cohort), respectively.

Demographics of ESKD patients receiving ICI

Among the 98 patients with ESKD receiving ICI, 80 patients had a diagnosis of ESKD preceding the administration of ICI and an additional 18 were kidney transplant patients who rejected their allograft with the use of ICI and initiated dialysis with continued use of these drugs. The median age at ICI initiation was 66 years [interquartile range (IQR) 58–73]. The most frequent cancers reported were RCC (33%), genitourinary (GU; 24%) and melanoma (17%). It should be noted that ICIs were initially approved for melanoma; however, over the years they have shown considerable promise in the treatment for various other cancers [50]. In our patient population, more than half of the patients (56%) treated with these agents had RCC or GU cancer. This is likely reflective of the increased incidence of these types of cancers seen in the ESKD population as reported previously in the literature [51, 52]. Nivolumab and pembrolizumab were the most common ICI agents used, representing 46% and 32% of initial therapy, respectively. HD recipients comprised 91% of reported dialysis patients.

Safety data and irAEs

As patients with CKD and ESKD have been largely excluded from trials of cancer therapy, including ICI [53], estimating the risk of safety events and irAEs is challenging. From our literature search we observed that there were 75 irAEs reported among 98 patients. In total, 49% of patients (48/98) experienced any irAE. The majority of the adverse events were Grades 1 and 2, seen in 33 patients (34%). Fifteen patients experienced Grades 3 and 4 adverse events (15%). The most common adverse events

Table 1. Published case reports and series of ICI therapy in patients with ESKD on dialysis

References	Patients (*n*)	Cancer(s)	ICI(s)	Grades 3/4 irAEs (nonrenal)	Summary of cancer outcomes
Cavalcante *et al.* [40]	2	Melanoma	Ipilimumab	Pemphigoid rash and bullous lesions	PR (1), CR (1)
Alhamad *et al.* [44]	1	Melanoma	Ipilimumab, pembrolizumab	None	PDS
Boils *et al.* [3]	1	Lung	Nivolumab	None	N/A
Carlo and Feldman [41]	1	RCC	Nivolumab	None	PR
Chang and Shirai [39]	1	Melanoma	Pembrolizumab	None	CR
Jose *et al.* [54]	1	Melanoma	Ipilimumab	None	PDS
Lipson *et al.* [2]	1	Skin SCC	Pembrolizumab	None	PR
Ong *et al.* [28]	1	Melanoma	Nivolumab	None	PR
Spain *et al.* [48]	1	Melanoma	Ipilimumab, nivolumab	None	SD
Boyle *et al.* [42]	1	Multiple myeloma	Nivolumab	None	PR
Park	4	RCC (2), skin SCC (2)	Nivolumab (2), pembrolizumab (2)	Grade 3 penumonitis, Grade 4 encephalitis/death (1)	PDS (1), PR (2), death (1)
Tabei *et al.* [24]	1	RCC	Nivolumab	None	PR
Akturk *et al.* [45]	1	Melanoma	Pembrolizumab, nivolumab	Hypothyroidism	PR
Ansari *et al.* [55]	1	RCC	Nivolumab	None	PR
Ishizuka *et al.* [37]	1	Lung	Pembrolizumab	None	PR
Cheun *et al.* [6]	3	RCC (2), urothelial (1)	Nivolumab (2), atezolizumab (1)	None	PR (1), SD (1), PDS (1), death (1)
Fernandez-Diaz *et al.* [38]	1	Melanoma	Nivolumab	None	SD
Ito *et al.* [47]	1	RCC	Nivolumab	None	CR
Morinaga *et al.* [30]	1	RCC	Nivolumab	None	PDS
Osa *et al.* [27]	1	Lung	Pembrolizumab	None	SD
Parisi *et al.* [25]	1	Urothelial	Atezolizumab	None	PDS
Tachibana *et al.* [23]	7	RCC	Nivolumab	Grade 3 fatigue	PR (1), SD (4), PDS (2), death (2)
Vitale *et al.* [21]	8	RCC	Nivolumab	Grade 3 diarrhea, Grade 3 asthenia, Grade 3 anorexia	PR (1), SD (5), PDS (2), death (3)
Hirsch *et al.* [4]	8	Cholangiocarcinoma (1), hepatocellular carcinoma (1), Hodgkin's lymphoma (1), NET (1), RCC (1), urothelial (3)	Atezolizumab (1), nivolumab (2), ipilimumab + nivolumab (1), pembrolizumab (4)	Dermatitis (grade unspecified)	SD (3), PDS (5), death (4)
Jain *et al.* [35]	8	Angiosarcoma (1), lung (1), melanoma (2), retroperitoneal sarcoma (2), RCC (1), urothelial (1)	Nivolumab (3), pembrolizumab (5)	Pneumonitis (grade unspecified)	SD (3), PDS (5), death (2)
Kuo *et al.* [33]	11	Urothelial	Atezolizumab (3), nivolumab (2), pembrolizumab (6)	Grade 3 anemia (3), Grade 4 anemia (1), Grade 4 neutropenia (1), Grade 4 TEN (1)	PR (6), SD (1), PDS (4), death (3)
Osmán-García *et al.* [26]	3	RCC	Nivolumab	None	PR (2), PDS (1)
Mejia *et al.* [31]	1	RCC	Ipilimumab + nivolumab	None	PR
Murakami *et al.* [46]	3	Skin SCC (2), melanoma	Cemiplimab, pembrolizumab, ipilimumab + nivolumab	None	PR (1), SD (2)
Strohbehn *et al.* [1]	19	GU (6), melanoma (4), Merkle cell (3), head and neck (3), lung (2), GI (1)	Avelumab (1), atezolizumab (2), ipilimumab (1), ipilimumab/nivolumab (2), nivolumab (5), pembrolizumab (8)	Grades 3–4 myocarditis (1), pneumonitis (1)	SD (4), PDS (9), death (13)
Duni *et al.* [49]	1	RCC	Nivolumab	None	SD
Tan *et al.* [22]	1	Melanoma	Nivolumab	None	CR

NET, neuroendocrine tumor; SCC, squamous cell carcinoma; PDS, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

Table 2. Summary data from published cases of ICI therapy in patients with ESKD on dialysis stratified by prior kidney transplant status[a]

Variable	Total reported cases	ESKD without prior kidney transplant	ESKD with prior kidney transplant
Patients, *n*	98 (100)	80 (81.6)	18 (18.4)
Age at ICI initiation (years), mean (SD)	64.2 (12.1)	65.6 (12.1)	59.4 (11.1)
Age at ICI initiation (years), median (IQR)	66 (58–73)	67 (63–73)	60.5 (53.3–67.5)
Male, *n* (%)	69 (70.4)	60 (75.0)	9 (64.3)
Female, *n* (%)	29 (29.6)	20 (25.0)	5 (35.7)
Cancer site, *n* (%)			
RCC	32 (32.6)	30 (37.5)	2 (11.1)
Melanoma	16 (17.3)	9 (11.3)	8 (44.4)
Urothelial/GU NOS	23 (23.5)	23 (28.8)	0 (0.0)
Lung	6 (6.1)	5 (6.3)	1 (7.1)
Skin SCC	5 (5.1)	3 (3.8)	2 (11.1)
Head and neck	3 (3.1)	2 (2.5)	1 (5.6)
Merkle cell	3 (3.1)	3 (3.8)	0 (0.0)
Other[b]	9 (9.6)	5 (6.3)	4 (22.2)
ICI initial therapy, *n* (%)			
Atezolizumab	8 (8.2)	8 (10.0)	0 (0.0)
Avelumab	1 (1.0)	1 (1.3)	0 (0.0)
Cemiplimab	1 (1.0)	0 (0.0)	1 (5.6)
Ipilimumab	6 (6.1)	3 (3.8)	3 (16.7)
Nivolumab	45 (45.9)	38 (47.5)	7 (38.9)
Pembrolizumab	31 (31.6)	26 (32.5)	5 (27.8)
Combination (ipilimumab + nivolumab	6 (6.1)	4 (5.0)	2 (11.1)
Dialysis modality, *n* (%)			
Hemodialysis	89 (90.8)	76 (95.0)	13 (72.2)
Peritoneal dialysis	9 (9.2)	4 (5.0)	5 (27.8)
Treatment duration (months), median (IQR)	6.1 (4.4–9.7)	6 (2.8–9.0)	4.2 (1.0–6.0)
irAEs (nonrenal), *n* (%)			
irAEs	76	–	–
Grade 1/2 irAEs	53	–	–
Grade 3/4 irAEs	23	–	–
Patients experiencing any irAE	48 (49.0)	45 (56.3)	3 (16.7)
Patients experiencing Grade 1/2	33 (33.7)	30 (37.5)	3 (16.7)
Patients experiencing Grade 3/4	15 (15.3)	15 (18.8)	0 (0.0)
irAEs by type, *n*			
Cutaneous	8	–	–
Encephalitis	1	–	–
Endocrine	4	–	–
GI/diarrhea	2	–	–
Hematologic	12	–	–
Hepatitis	3	–	–
Myocarditis	1	–	–
Pneumonitis	5	–	–
Cancer outcomes, *n* (%)			
Complete remission	4 (4.1)	3 (3.8)	1 (5.6)
Partial remission	25 (25.5)	19 (23.8)	5 (33.3)
Stable disease	27 (27.5)	23 (28.8)	4 (22.2)
Progressive disease	35 (35.7)	30 (37.5)	5 (27.8)
Not available	7 (7.1)	5 (6.3)	2 (11.1)
Death	30 (30.6)	27 (33.8)	3 (16.7)

[a]Values and proportions reported for each characteristic among those patients in whom individual (patient-level) data were available.
[b]Sarcoma (3), GI (1), cholangiocarcinoma (1), hepatocellular (1) Hodgkin's lymphoma (1), multiple myeloma (1), neuroendocrine (1).
SCC, squamous cell cancer.

reported were hematologic, seen in 12 patients. These manifested as anemia, thrombocytopenia and neutropenia. The next most common adverse effect was dermatologic (seen in eight patients), including pruritus, dermatitis, toxic epidermal necrolysis and pemphigoid rash. Gastrointestinal (GI) toxicity was seen in five patients, presenting as hepatitis, ascites, ileus, abdominal pain and diarrhea. Pulmonary toxicity presenting as pneumonitis was seen in four patients. Tuberculosis reactivation was described in one patient. Other irAEs described in dialysis patients but occuring at a low frequency include asthenia, anorexia, fatigue and endocrine (thyroid dysfunction).

With respect to severe (i.e. Grade 4) irAEs, notable reported events included one death in the context of encephalitis, one (nonfatal) episode of myocarditis and two (nonfatal)

Table 3. Summary data from published cases of nivolumab and pembrolizumab in patients with ESKD on dialysis[a]

Variable	Total reported cases	Nivolumab	Pembrolizumab
Patients, *n* (%)	76 (100)	45 (59.2)	31 (40.8)
Age at ICI initiation (years), mean (SD)	64.2 (12.1)	65.8 (9.2)	59.4 (11.1)
Age at ICI initiation (years), median (IQR)	66 (58–73)	67 (63–73)	60.5 (53.3–67.5)
Male, *n* (%)	42 (76.4)	29 (76.3)	13 (76.5)
Female, *n* (%)	13 (29.6)	9 (23.7)	4 (23.5
Cancer site, *n* (%)			
RCC	30 (39.5)	29 (64.4)	1 (3.2)
Melanoma	10 (13.2)	5 (11.1)	5 (16.1)
Urothelial/GU NOS	15 (19.7)	5 (11.1)	10 (32.3)
Lung	5 (6.5)	2 (4.4)	3 (9.7)
Skin SCC	4 (5.2)	0 (0.0)	4 (12.9)
Head and neck	3 (3.9)	0 (0.0)	3 (9.7)
Merkle cell	1 (1.3)	1 (2.2)	0 (0.0)
Other	8 (10.5)	3 (6.7)	5 (16.1)
Dialysis modality, *n* (%)			
Hemodialysis	73 (96.1)	43 (95.6)	30 (96.8)
Peritoneal dialysis	3 (3.9)	2 (4.4)	1 (3.2)
Treatment duration (months), median (IQR)	6.1 (4.4–9.7)	8.0 (4.6–14.0)	6.5 (2.9–7.7)
irAE (non-renal), *n* (%)			
irAEs	47	–	–
Grade 1/2 irAEs	38	–	–
Grade 3/4 irAEs	14	–	–
Patients experiencing any irAE	40 (52.6)	21 (46.7)	19 (61.3)
Patients experiencing Grade 1/2	26 (34.2)	14 (31.1)	12 (38.7)
Patients experiencing Grade 3/4	14 (18.4)	7 (15.6)	7 (22.5)
irAEs by type, *n*			
Cutaneous	5	–	–
Encephalitis	1	–	–
Endocrine	4	–	–
GI/diarrhea	0	–	–
Hematologic	9	–	–
Hepatitis	2	–	–
Myocarditis	1	–	–
Pneumonitis	3	–	–
Cancer outcomes, *n* (%)			
Complete remission	3 (3.9)	2 (4.4)	1 (3.2)
Partial remission	20 (26.3)	13 (28.9)	7 (22.5)
Stable disease	22 (28.9)	15 (33.3)	7 (22.5)
Progressive disease	26 (34.2)	12 (26.7)	14 (45.2)
Not available	5 (6.6)	3 (6.7)	2 (6.4)
Death	21 (27.6)	12 (26.7)	9 (29.0)

[a]Values and proportions reported for each characteristic among those patient in whom individual (patient-level) data were available.
SCC, squamous cell cancer.

pneumonitis events [5]. The death associated with encephalitis was the only reported fatal event attributed to therapy.

The frequency of irAEs has been estimated to be in the range of 56% in a large meta-analysis of multiple cancer sites [31, 56]. Other large analyses assessing individual cancer types have estimated the incidence of irAEs to range between 39% and 59%, depending on the malignancy and ICI [29, 57, 58]. As such, the observed frequency of irAEs among patients receiving dialysis does not appear substantially different from that of the nondialysis general population, although definitive conclusions cannot be drawn from a review of reported literature alone. As in the general population, the skin and GI systems were among the most commonly observed sites for irAEs [56, 59]. Regarding the severe irAEs noted in this review, including encephalitis and myocarditis, these events are similar and occur infrequently in the general population, with incidence estimates of 1.3% [60, 61] and <1% [60], respectively. Given these findings, along with the nonrenal excretion and metabolism of ICI described above, it is plausible that the overall risk for irAEs and severe events is unlikely to differ from that of nondialysis patients. Of note, no particular elevated risk for irAEs has been noted among elderly patients, and drug tolerance appears similar [62]. Also, there were no apparent major differences in overall rates of irAEs between nivolumab and pembrolizumab.

It should be noted that the relatively high frequency of hematologic adverse events among reported patients with ESKD differs from the general population, in which hematologic adverse events are comparatively infrequent [63]. Of the 12 cases of hematologic adverse events noted in this review, 11 were reported in the series by Kuo *et al.* [33] and predominantly reflective of anemia. In their report, immune-mediated anemia was not specifically distinguished from other potential causes of low hemoglobin, including malignancy and ESRD-associated

Table 4. Summary data from published cases of ICI therapy in patients with urothelial cancers and RCC and ESKD on dialysis[a]

Variable	Total reported cases	Urothelial cancers	RCC
Patients, *n* (%)	55 (100)	23 (41.8)	32 (58.1)
Age at ICI initiation (years), mean (SD)	65.3 (11.2)	62.3 (13.4)	62.3 (11.1)
Age at ICI initiation (years), median (IQR)	67 (63–73)	67 (61–75)	67 (64–73)
Male, *n* (%)	36 (65.5)	10 (58.8)	26 (81.3
Female, *n* (%)	13 (23.6)	7 (41.2)	6 (18.8)
ICI (initial therapy), *n* (%)			
Atezolizumab	7 (12.3)	7 (30.4)	0 (0.0)
Avelumab	0 (0.0)	0 (0.0)	0 (0.0)
Cemiplimab	0 (0.0)	0 (0.0)	0 (0.0)
Ipilimumab	0 (0.0)	0 (0.0)	0 (0.0)
Nivolumab	33 (60.0)	5 (21.7)	28 (87.5)
Pembrolizumab	12 (21.8)	10 (43.5)	2 (6.3)
Combination (ipilimumab + nivolumab)	3 (5.4)	1 (4.3)	2 (6.3)
Dialysis modality, *n* (%)			
Hemodialysis	44 (90.8	17 (73.9)	27 (84.3)
Peritoneal dialysis	3 (9.2)	0 (0.0)	3 (9.4)
Unavailable	7 (12.7)	6 (26.0)	1 (3.1)
Treatment duration (months), median (IQR)	6.0 (2.1–8.3)	2.1 (1.7–3.5)	6.1 (3.2–8.3)
irAE (non-renal), *n* (%)			
irAEs	50	–	–
Grade 1/2 irAEs	36	–	–
Grade 3/4 irAEs	16	–	–
Patients experiencing any irAE	35 (63.6)	19 (82.6)	26 (81.3
Patients experiencing Grade 1/2	21 (38.2)	10 (43.5	21 (65.6)
Patients experiencing Grade 3/4	14 (25.5)	9 (39.1)	5 (15.6)
irAEs by type, *n* (%)			
Cutaneous	5	–	–
Encephalitis	0	–	–
Endocrine	0	–	–
GI/diarrhea	0	–	–
Hematologic	11	–	–
Hepatitis	3	–	–
Myocarditis	1	–	–
Pneumonitis	3	–	–
Cancer outcomes, *n* (%)			
Complete remission	1 (1.8)	0 (0.0)	1 (3.1)
Partial remission	17 (30.9)	6 (26.1)	11 (34.4)
Stable disease	17 (30.9)	6 (26.1)	11 (34.4)
Progressive disease	20 (36.4)	11 (47.8)	9 (28.1)
Not available	0 (0.0)	0 (0.0)	0 (0.0)
Death	17 (30.9)	9 (39.1)	8 (25.0)

[a]Values and proportions reported for each characteristic among those patients in whom individual (patient-level) data were available.
SCC, squamous cell cancer.

anemia. As anemia and other hematologic abnormalities may be multifactorial in patients receiving dialysis, careful monitoring of these parameters (with appropriate investigations as to etiology) is warranted during ICI therapy in this population.

Lastly, management of irAEs among patients receiving dialysis was broadly reported to be similar as in nondialysis patients. The mainstays of treatment remain corticosteroids for most irAEs and endocrine replacement therapy, in keeping with American Society of Clinical Oncology and European Society of Medical Oncology guidelines [64, 65]. None of the reported cases describe the use of other forms of immunosuppression for management of irAEs. However, given the predilection of patients with ESKD for other potentially steroid-adverse medical comorbidities, including diabetes mellitus, heart failure, etc., there should be consideration for limiting corticosteroid exposure in this population (where required and permitted by the indicating irAE). Since immune senescence is known to correlate with dialysis vintage, the relationship between dialysis vintage and irAEs is a subject for future study [66, 67].

Dialysis patients with prior kidney transplants

Eighteen of the reported dialysis patients had prior kidney transplants. Of these, 11 (61%) initiated dialysis after ICI-related rejection of their kidney allografts [31]. Unfortunately, data on specific modifications of immunosuppressive regimens were often not reported. Caution is warranted when prescribing ICIs in a patient on dialysis with a failed kidney allograft. Hirsch *et al.* [4] described a series of eight patients on dialysis receiving ICIs in which one of the patients who had a previous history of kidney allograft failure on HD for 3 years developed hepatocellular cancer and received nivolumab. He subsequently experienced

acute rejection of his allograft immediately after starting ICI therapy and also suffered from cancer progression. Likewise, Mejia *et al.* [31] recently reported the case of a 66-year-old patient with a failed kidney allograft undergoing HD who received combination immunotherapy with anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) for metastatic papillary renal and urothelial cancer. The patient's clinical course was complicated by development of gross hematuria and pain over the allograft, necessitating removal of the allograft. Histopathological evaluation following transplant nephrectomy revealed chronic active T-cell-mediated rejection. Another similar report by Duni *et al.* [49] describes a single case of kidney graft rejection of a long-term nonfunctioning graft 14 days after the first cycle of therapy with PD-1 inhibitor (nivolumab) in a patient receiving PD for >3 years. On the other hand, a report of 19 dialysis patients who received ICI therapy between 2013 and 2019 showed that although 32% of the patients experienced diverse irAEs, none of the 4 patients with prior failed kidney allografts included in the study demonstrated clinical evidence of rejection [5]. Rejection of the old allograft can occur with initiation of ICI in dialysis patients. One might consider a 'mini-pulse' steroid protocol in the first 6–10 weeks of initiation of ICIs to prevent this occurrence [46, 68]. A recent multicenter retrospective cohort study of kidney transplant patients with cancer receiving ICIs showed that 42% of patients developed acute graft rejection, of which 65.5% progressed to ESKD requiring dialysis [46]. Continuing ICI therapy in patients who recently failed their allograft has been done safely without dose alterations, as noted in some of the cases reviewed above in our analysis.

Cancer and patient outcomes

Survival of patients receiving ICI is largely dependent on the tumor type. Real-world outcomes seen with these agents are different from those in clinical trials. This is likely due to patients with a lower comorbidity index being enrolled in these studies [69–71]. In a large Veterans Affairs study with 11 888 (non-ESKD) patients with different types of cancer receiving ICI, the overall survival ranged between 6.7 and 25.5 months [72]. This was largely dependent on the tumor type, with the longest survival seen in melanoma patients (25 months) and the shortest in patients with urothelial cancer receiving second-line ICI (6 months). Although this study reported outcomes worse than those seen in clinical trials, these patients still did better than the historical controls. There are also data that show that development of irAEs is associated with treatment response and improved survival in patients with cancer treated with ICI [73]

Mortality on dialysis remains unacceptably high in various situations, including cardiac surgery [74], influenza [75] or severe acute respiratory syndrome coronavirus 2 infection [76]. In a broad population-based cohort study in Canada, men treated with dialysis had worse adjusted 5-year survival than men with prostate or colorectal cancer and women on dialysis had worse adjusted 5-year survival than women with breast or colorectal cancer [77]. The 5-year cumulative incidence of any cancer in ESKD patients is ~9.5%, much higher than the incidence expected in the general population. The risk for kidney cancer is four times higher than the risk of bladder cancer [51, 78]. The mortality risk is also high when patients receiving dialysis are diagnosed with cancer [79]. Patient and cancer outcomes of immunotherapy use in cancer patients on dialysis are not well known.

In our literature review, cancer outcomes in these patients were divided into three categories: remission (complete and partial), stable disease and progressive disease. No data were available for seven patients. Remission (complete and partial) was seen in 29 patients (29.6%). Of note, partial remission was more common than complete remission (25.5% versus 4.1%). Stable disease was seen in 27 patients (27.5%). There was progression of disease in a total of 35 patients (35.7%). Of the 98 patients, there were 30 deaths recorded (31%). Urothelial and renal cell cancer accounted for 56% of cases and 50% of all deaths. When comparing urothelial and renal cell cancers, outcomes appeared similar overall within the categories assessed.

Of all the patients studied, more than half (57%) had evidence of remission or stable disease. We are unable to comment on the overall and progression-free survival of these patients as all our studies were limited to case reports and case series not reporting this specific outcome. Most trials reporting on the efficacy of these agents are limited to their use in specific cancer types [69–71]. In our analysis, different cancer types were included, making it impossible to directly compare to non-ESKD patients and comment on these outcomes within individual cancer types. Figure 2 summarizes our findings.

Future directions

Most clinical trials exclude patients with advanced kidney disease on dialysis. Due to limited data, these patients are excluded from potential lifesaving drugs. On reviewing the literature, it appears that ICI is reasonably well tolerated in this population, with modest survival benefit. Although our analysis has several limitations, it is the largest review to date looking at the outcomes of these patients. The safety signal of these drugs and the modest survival benefit seen should encourage oncologists to use these drugs in dialysis patients with close monitoring. Additional larger studies enrolling dialysis patients in early clinical trials are needed to define the incidence and outcomes of the irAEs.

CONCLUSIONS

As ICI therapy becomes increasingly widespread across the spectrum of cancer, its use in patients receiving dialysis is likely to increase. Based on available pharmacological information, ICIs require no dosing adjustment in ESKD patients. Our review demonstrates a similar incidence of irAEs in patients with ESKD receiving dialysis as compared with the general population (49%). Severe reactions graded as 3 and 4 were seen in 15 patients (16%). As such, it is important that these patients are monitored very closely for irAEs; however, the risk of these adverse events should not preclude patients on dialysis from receiving these therapies. The three most common groups of organ toxicities reported were hematologic, dermatologic and GI. Caution is warranted when prescribing ICIs in a patient on dialysis with a failed renal allograft, as there is a heightened risk for rejection and need for possible transplant nephrectomy. Cancer remission (complete and partial) was seen in close to 30% of patients. Stable disease was seen in 26% and progression of disease in ~36% of patients. One-third of the patients died. Urothelial and renal cell cancer represented approximately half of all cases and accounted for ~50% of the deaths reported. At present, comparison with general population outcomes on mortality and cancer progression cannot be definitively made.

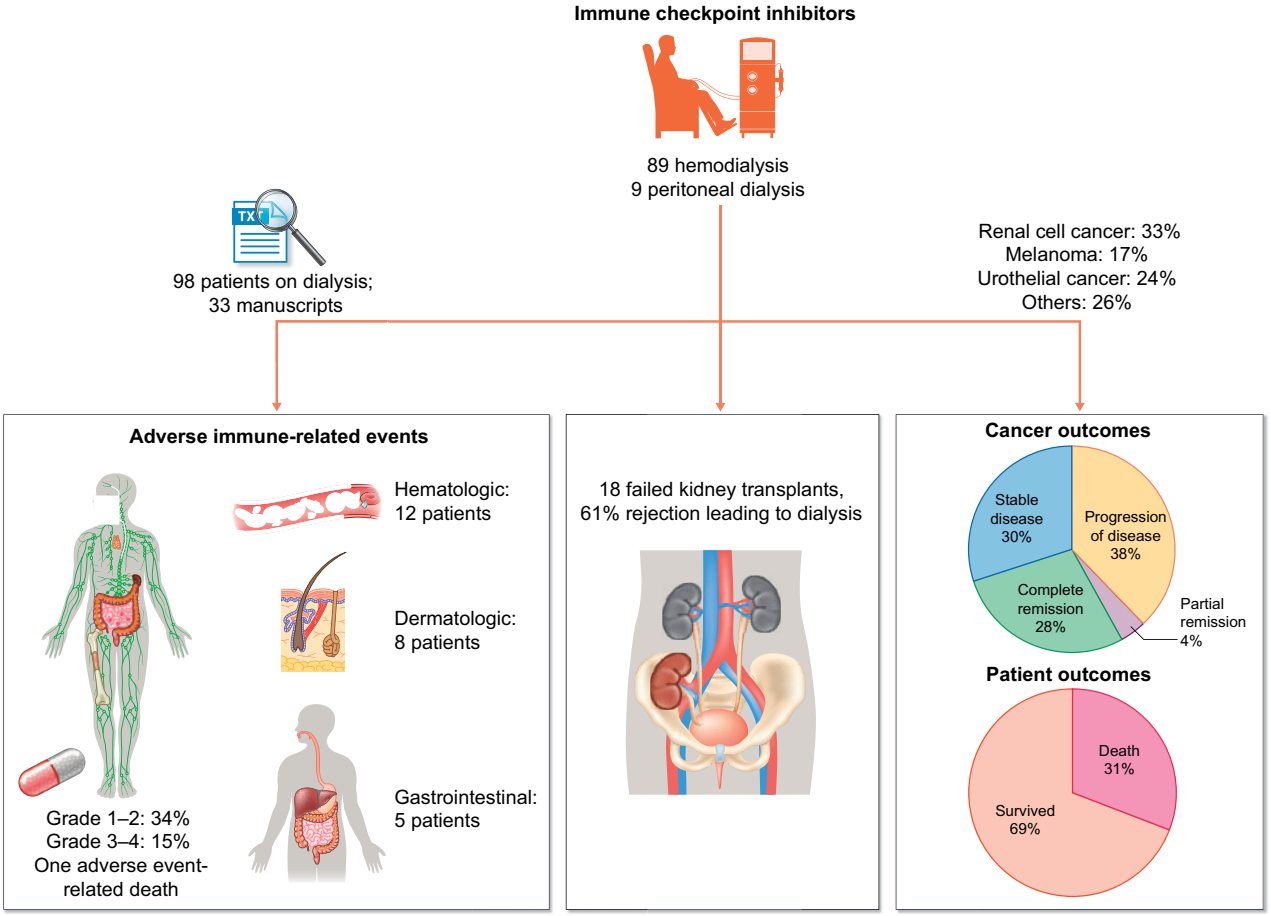

FIGURE 2: Summary of review of ICI use in dialysis patients, immune related Adverse Event(irAE) rate and patient outcomes. Figure created using biorender.com.

Additional data in the dialysis population and involvement in prospective studies are needed to better assess outcomes, particularly within specific cancer types.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

K.D.J. is a consultant for Astex Pharmaceuticals, GlaxoSmithKline, ChemoCentryx, Chinook and Natera. K.D.J. receives honorarium from the International Society of Nephrology and American Society of Nephrology and is a paid contributor to UptoDate.com. M.Y. received grants from Kyowa Kirin, Chugai, Tanabe Mitsubishi Pharma and Boehringer Ingelheim. B.S. is a senior clinical investigator of the Research Foundation Flanders (1842919N) and received funding from the Foundation Against Cancer (Stichting tegen Kanker; C/2020/1380).

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