

Systematic Review of the Safety of Immune Checkpoint Inhibitors Among Kidney Transplant Patients



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Introduction: Kidney transplant (Ktx) recipients are excluded from clinical trials of immune checkpoint inhibitors. The aim of this systematic review was to assess the safety of immune checkpoint inhibitors among Ktx patients.

Methods: A literature search was conducted using MEDLINE, EMBASE, and Cochrane Database from inception through April 2019. We included studies that reported outcomes of Ktx recipients who received immune checkpoint inhibitors for cancer treatment. Outcomes of interest were allograft rejection and/or allograft failure.

Results: Twenty-seven articles with a total of 44 Ktx patients treated with immune checkpoint inhibitor were identified. Of 44 Ktx patients, 18 were reported to have acute rejection. Median time from immune checkpoint inhibitors to acute rejection diagnosis was 24 (interquartile range, 10–60) days. Reported types of acute allograft rejection were cellular rejection (33%), mixed cellular and antibody-mediated rejection (17%), and unspecified type (50%). Fifteen (83%) had allograft failure and 8 (44%) died. Three patients had a partial remission (17%), 1 patient achieved cancer response (6%), and 5 patients had stable disease (28%).

Conclusion: The findings of our study raise awareness of the increased risk for acute allograft rejection/failure following immune checkpoint inhibitors for cancer treatment among Ktx patients, in particular with programmed cell death 1 (PD-1) inhibitors. Future large-scale clinical studies are required to appraise the pathogenesis and plan optimal balanced therapy that helps sustain graft tolerance.

Kidney Int Rep (2020) 5, 149–158; <https://doi.org/10.1016/j.ekir.2019.11.015>

KEYWORDS: allograft rejection; immune checkpoint inhibitors; immunosuppressants; kidney transplant; PD-1 inhibitor; systematic review

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Kidney transplantation is a life-saving therapy for patients with end-stage kidney disease with overall improved survival and quality of life.^{1,2} Despite this, kidney transplant recipients remain at high risk of fatal cardiovascular disease events as compared with the general population and this accounted for approximately 40% to 55% of all deaths.³ However, in the past 30 years, there has been a decline in deaths from cardiovascular disease and a rise in malignancy-related deaths,⁴ which now accounts for approximately 30% of all deaths. Solid organ transplant patients are at a 2-fold higher risk of malignancy compared with the

general population.⁵ The overall incidence of malignancies is markedly higher in patients who receive a Ktx compared with those who stay on dialysis.⁶ Immunosuppression, oncogenic viruses, and age are considered a few of the risk factors. The most common cancers are the carcinomas of the skin and lip, anogenital cancers, and non-Hodgkin's lymphoma.⁷ Melanoma represents approximately 5% of posttransplant skin cancers compared with 2.7% in the general population.⁸

The advent of immunotherapy, especially immune checkpoint inhibitors (ICIs) changed the cancer treatment landscape, initially for metastatic melanoma and since then for many other cancer types, and its use has quickly moved to the frontline therapies. However, cancer trials have excluded transplant patients. The core principle of checkpoint inhibitors is to stimulate the immune system to destroy the cancer cells, which

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Received 28 August 2019; revised 11 November 2019; accepted 25 November 2019; published online 7 December 2019

contradicts a transplant patient's need to suppress the immune system to prevent allograft rejection. There are currently no guidelines for the transplant community for the use of ICIs, and in the end, when the question becomes of a life versus graft, mutual discussion between the patient and provider is crucial, and the graft is in many circumstances the one to be sacrificed. Experiences reported in the literature have been mixed, and the objective of our study was to systematically review the literature for safety of ICIs in Ktx patients.

METHODS

Search Strategy

The protocol for this study is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42019126777). A systematic search of the published literature was conducted in MEDLINE (1946 to April 2019), EMBASE (1988 to April 2019), and the Cochrane Database of Systematic Reviews (2005 to April 2019) from inception of databases through April 2019. We also obtained pertinent references via manual review of these retrieved references. Review of the abstracts and full text was conducted independently by the investigators SM and CT using the search approach that incorporated the terms of "pembrolizumab" OR "nivolumab" OR "ipilimumab" OR "cemiplimab" OR "atezolizumab" OR "avelumab" OR "durvalumab" AND "kidney transplantation" OR "kidney graft" OR "kidney graft rejection" OR "acute graft rejection" OR "organ transplantation" which is provided in [Supplementary Item S1](#). Differing decisions were solved by mutual consensus. We conducted this systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.⁹ The PRISMA checklist is shown in [Supplementary Item S2](#).

Inclusion Criteria

Our intended patient populations were all Ktx patients who received checkpoint inhibitor for cancer therapy. The included studies fulfilled the following criteria: (i) Ktx recipient with an active functioning graft, (ii) received a checkpoint inhibitor therapy like cytotoxic T-lymphocyte-associated-antigen 4 inhibitor (ipilimumab) or PD-1 inhibitor (pembrolizumab or nivolumab) or programmed cell death ligand 1 (PDL-1) inhibitor (avelumab, atezolizumab or durvalumab). We included conference abstracts and observational studies. We excluded any reports that did not fit our inclusion criteria.

Outcomes of Interest

Clinical outcomes of interest were renal allograft rejection and/or failure, cancer outcome, and mortality after treatment with checkpoint inhibitors.

Data Extraction

We used a standardized data collection template to extract the following information: last name of the first author, article title, study type, year of publication, sample size, name of checkpoint inhibitors, indication of treatment (tumor type), age, sex, baseline graft function, year after transplant, lag time from checkpoint inhibitor initiation and development of allograft rejection, renal biopsy features, follow-up time after treatment, cancer, and patient outcome as reported in the study.

Outcome Measures

The outcome terminology "allograft rejection" was used to define any renal adverse event reported by authors as a rejection either by clinical criteria alone or after histological confirmation of rejection based on criteria followed at their individual institutions. The outcome terminology allograft failure was used to define a complete loss of graft requiring the initiation of dialysis.

Statistical Analysis

Descriptive statistics were performed. Continuous variables were reported as mean \pm SD. Categorical variables were reports as count and percentage. The differences in patient and cancer characteristic, management, and outcomes between patients who developed and did not develop rejection after ICIs were tested using Wilcoxon rank-sum test for continuous variables, and Fischer's exact test for categorical variables. All analyses were performed using JMP statistical software (version 10; SAS Institute, Cary, NC).

RESULTS

Our search strategy yielded 247 articles. Of these, 198 articles were excluded based on relevance and eligibility criteria after the review of the title and abstract. The remaining 49 articles underwent full-length review. Subsequently, 11 articles were excluded because they were review articles and another 11 articles were excluded because they were not Ktx patients (liver,^{10–16} heart,^{17,18} and hematopoietic stem cell transplantation^{19,20}). Finally, 27 articles with a total of 44 Ktx patients were enrolled in our systematic review.^{21–47} [Figure 1](#) outlines the search methodology used.

Among these 44 Ktx patients, the average age at the time they received the ICIs was 64 years (SD \pm 10).

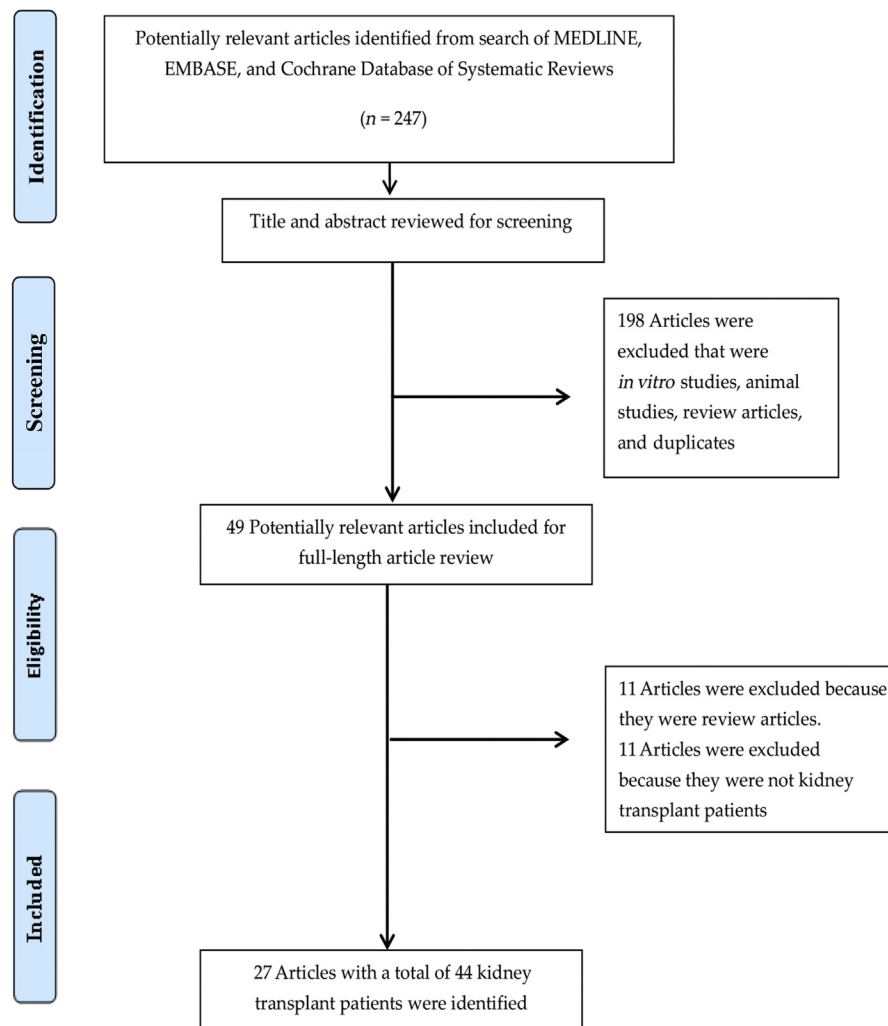


Figure 1. Outline of our search methodology.

Thirty-five of the 44 patients (80%) were male. The predominant underlying cancer being treated was dermatological, with 30 cases (68%) being melanoma and 5 cases (11%) presenting with metastatic squamous cell carcinoma of the skin. Lung cancer was the next most common cancer in 11% (5 of 44) of cases. The other cancers noted were Merkel cell carcinoma (5%), urothelial carcinoma (2%), and duodenal cancer (2%). Patients had developed cancer an average of 107 months (98) after kidney transplantation.

Thirty-six (81%) patients received a single ICI with nivolumab in 15 (34%) cases, pembrolizumab in 11 (25%), ipilimumab in 9 (20%), and avelumab in 1 (2%) patients. Among the different classes, the PD1 inhibitor was the most commonly chosen drug, with use in 26 (59%) patients. Combination checkpoint blockade was conducted in a sequential manner in 8 (18%) patients in the following patterns: ipilimumab followed by pembrolizumab in 2 (5%) or nivolumab in 4 (9%) cases, or pembrolizumab followed by nivolumab in 1 (2%) or ipilimumab in 1 (2%) case. [Table 1](#) summarizes the

demographic characteristics and outcomes of Ktx patients with ICIs for cancer treatment.

Acute Rejection Following ICIs

Of 44 Ktx patients, 18 (41%) were reported to have acute rejection of renal allograft. Median time from ICI to acute rejection diagnosis was 24 (interquartile range, 10–60) days. Cancer types treated were melanoma (66%), lung cancer (17%), and metastatic squamous cell carcinoma of skin (12%), respectively. There were 83% men with a mean age of 62 ± 13 years ([Table 2](#)). Eight (44%) patients received nivolumab, 3 (17%) received pembrolizumab, 2 (11%) received ipilimumab, 2 (11%) received ipilimumab followed by pembrolizumab, 2 (11%) received ipilimumab followed by nivolumab, and 1 (6%) received pembrolizumab followed by nivolumab.

Reported types of acute allograft rejection were cellular rejection (33%), mixed cellular and antibody-mediated rejection (17%), and unspecified type (50%). Eventually, 15 (83%) of the 18 patients had

Table 1. Demographic characteristics and outcomes of kidney transplant patients with immune checkpoint inhibitors for cancer treatment

Variable	Total (N = 44)
Age, yr	64±10
Male sex	35 (80)
Immune checkpoint inhibitor	
- Nivolumab	15 (34)
- Pembrolizumab	11 (25)
- Ipilimumab	9 (20)
- Avelumab	1 (2)
- Ipilimumab followed by pembrolizumab	2 (5)
- Ipilimumab followed by nivolumab	4 (9)
- Pembrolizumab followed by nivolumab	1 (2)
- Pembrolizumab followed by ipilimumab	1 (2)
Cancer	
- Melanoma	30 (68)
- Lung cancer	5 (11)
- Metastatic squamous cell carcinoma of skin	5 (11)
- Merkel cell carcinoma	2 (5)
- Urothelial carcinoma	1 (2)
- Duodenal cancer	1 (2)
Rejection	18 (41)
Graft failure	16/43 ^a (37)
Cancer outcomes	
- Complete response	5 (11)
- Partial response	8 (18)
- Stable disease	8 (18)
- Progressive disease	21 (48)
- Not available	2 (5)
Death	18 (41)
Follow-up time	
- Less than 1 yr	15
- 1–3 yr	5

^aOne patient was excluded because he had graft failure due to transplant nephrectomy.

allograft failure with subsequent mortality in 8 (44%) patients. From a cancer standpoint, progressive disease was seen in 7 (40%) of these patients. Complete response, partial response, and stable disease was reported in 1 (6%), 3 (17%), and 5 (28%) of patients respectively.

Graft Tolerance Following ICIs

Out of the 44 Ktx patients, 25 (59%) patients did not have a rejection. One of the patients had a transplant nephrectomy (Boyle *et al.*⁴⁴) before the use of ICI, as he had donor-derived melanoma. All patients were followed for an average of 9.6 months after receiving ICI. Most of these patients had received a PD-1 inhibitor (57%) with pembrolizumab or nivolumab in 8 (3.07%) and 7 (26.9%) cases, respectively. The predominant cancer indication was noted to be melanoma (69% of patients). From a cancer standpoint, 14 (53%) of them had progressive disease, whereas a favorable response, including complete response, partial response, and stable disease, was noted in 4 (15.3%), 5 (19.2%), and 3 (11.5%) of the patients, respectively. From a renal

Table 2. Demographic characteristics and outcomes of kidney transplant patients who developed acute rejection following immune checkpoint inhibitors

Variable	Total (N = 18)
Age, yr	62 ± 13
Male sex	15 (83)
Immune checkpoint inhibitor, n (%)	
- Nivolumab	8 (44)
- Pembrolizumab	3 (17)
- Ipilimumab	2 (11)
- Ipilimumab followed by pembrolizumab	2 (11)
- Ipilimumab followed by nivolumab	2 (11)
- Pembrolizumab followed by nivolumab	1 (6)
Cancer	
- Melanoma	12 (67)
- Lung cancer	3 (17)
- Metastatic squamous cell carcinoma of skin	3 (17)
Time from immune checkpoint treatment to rejection, d	24 (10–60)
Type of rejection	
- Acute cellular rejection	6 (33)
- Acute mixed rejection	3 (17)
- Unspecified	9 (50)
Graft failure	15 (83)
Cancer outcomes	
- Complete response	1 (6)
- Partial response	3 (17)
- Stable disease	5 (28)
- Progressive disease	7 (39)
- Not available	2 (11)
Death	8 (44)

standpoint, only 2 (7.6%) patients had a graft failure (Table 3).

Immunosuppression Management

Immunosuppression data were missing in multiple studies. At the time of cancer diagnosis, baseline immunosuppression regimen data were available in 31 of the 44 patients. Of these patients, 15 (48%) were on a triple regimen with a calcineurin inhibitor (CNI), such as tacrolimus or cyclosporine, mycophenolate mofetil (MMF), and a low-dose steroid. A CNI-based regimen was used in 30 of 31 patients, which included the following: CNI alone in 1 (3.2%), CNI/steroid in 6 (19.3%), CNI/MMF in 5 (16.1%), CNI/MMF/steroid in 15 (48.3%), CNI/azathioprine/steroid in 3 (9.6%) of the patients. One patient was on a mammalian target of rapamycin inhibitor with steroids.

The data were again limited on the changes in immunosuppression for allograft after the cancer diagnosis, which was available only in 21 of the 44 patients. Of these, interestingly, 42% (9 patients) had no change done to their immunosuppressive therapy. Nine patients of 21 had their CNI discontinued. Of these, 7 of them were replaced with a mammalian target of rapamycin inhibitor like sirolimus or everolimus, and 3 of them, in addition, also had discontinuation of

Table 3. Characteristics of kidney transplant patients that developed an acute rejection with those that did not develop rejection after immune checkpoint inhibitor therapy

Variable	Rejection (N = 18)	No rejection (N = 25) ^a	P value
Age	61.6 (12.6)	66 (6.28)	0.13
Sex, male	15 (83.3)	20 (76)	0.6
Drug class			
CTLA-4	2 (11.1)	7 (26.9)	0.27 ^b
PD-1	11 (61)	15 (57)	0.8
PDL-1	—	1 (3.8)	—
Combination CTLA-4 and PD-1	4 (22.2)	3 (11.5)	0.41 ^b
Sequential PD-1	1 (5.5)	—	—
Drug name			
Ipilimumab	2 (11.1)	7 (26.9)	0.2 ^b
Pembrolizumab	3 (16.6)	8 (30.7)	0.2 ^b
Nivolumab	8 (44.4)	7 (26.9)	0.22
Avelumab	—	1 (3.8)	—
Ipilimumab followed by pembrolizumab	2 (11.1)	1 (3.8)	^c
Ipilimumab followed by nivolumab	2 (11.1)	2 (7.6)	^c
Pembrolizumab followed by nivolumab	1 (5.5)	—	—
Cancer type			
Melanoma	12 (66.6)	18 (69)	0.85
Metastatic Squamous cell carcinoma of skin	3 (16.6)	2 (7.6)	^c
Lung cancer	3 (27)	2 (7.6)	^c
Duodenal cancer	—	1 (3.8)	—
Urothelial cancer	—	1 (3.8)	—
Merkel cell carcinoma	—	2 (7.6)	—
Follow-up time after immune checkpoint inhibitor therapy, mo	11.3 (10.3)	9.6 (8.1)	—
Graft failure	15 (83.3)	2 (7.6)	<0.0001
Cancer outcome			
Favorable response			0.52
Complete response	1 (5.5)	4 (15.3)	—
Partial response	3 (16.6)	5 (19.2)	—
Stable disease	5 (27.7)	3 (11.5)	—
Progressive disease	7 (38.8)	14 (53.8)	0.32
Not available	2	—	—
Patient mortality			
Dead	8 (44.4)	10 (38.4)	0.88
Not available	2	5	—

CTLA-4, cytotoxic T-lymphocyte-associated-antigen 4; PD-1, programmed cell death 1; PDL-1, programmed cell death ligand 1.

^aOne patient excluded as he had a nephrectomy before immune checkpoint blockade.

^bNonparametric test was used for statistical analysis.

^cToo few patients for any clinically meaningful statistical analysis.

P value < 0.05 was considered statistically significant and is in bold.

their MMF. Overall, 4 of 21 patients had their MMF discontinued.

We also reviewed the changes in immunosuppression done at the time of ICI therapy initiation. Data were incomplete for interpretation in 16 patients. Of the remaining 28 patients, interestingly, 5 patients had no change in their immunosuppression both at the time of cancer diagnosis and checkpoint inhibitor therapy initiation. Three of those 5 patients had melanoma and they ended up with progressive disease, whereas the other 2 of 5 patients had other underlying cancers (1 squamous cell carcinoma and 1 urothelial cancer) and they had complete response. On the other hand, 11 (39%) of the 28 patients

Table 4. Immunosuppression management in kidney transplant patients around the time of immune checkpoint inhibitor therapy

Variable	Rejection (N = 18)	No rejection (N = 25) ^a
Time from kidney transplantation to cancer development, mo	135 (103)	91 (92)
Baseline creatinine at the time of immune checkpoint inhibitor therapy, mg/dl	1.3 (0.56)	1.4 (0.4)
Baseline eGFR at the time of immune checkpoint inhibitor therapy, mL/min	63.8 (15.4)	53.2 (16.7)
Maintenance immunosuppression at the time of cancer diagnosis		
CNI	1 (7.6)	—
CNI/MMF	3 (23)	2 (11.7)
CNI/steroid	2 (15.3)	4 (23.5)
CNI/MMF/steroid	4 (30.7)	10 (23.5)
CNI/AZA/steroid	3 (23.0)	—
mTOR/steroid	—	1 (5.8)
Not available	5	8
Change in immunosuppression at the time of cancer diagnosis		
No change	3 (33.3)	6 (50)
Reduction in dose alone	2 (22.2)	—
Stop CNI alone	1 (11.1)	1 (8.3)
CNI to mTOR alone	1 (11.1)	3 (25)
CNI to mTOR + stop MMF	2 (22.2)	1 (8.3)
Not available	9	13
Planned change in immunosuppression at the time of immune checkpoint inhibitor therapy		
No change	—	8 (34.7)
Reduction in dose alone	2 (11.7)	1 (4.3)
Stop MMF	—	1 (4.3)
CNI to mTOR	2 (11.7)	1 (4.3)
CNI to mTOR + stop MMF	1 (5.8)	1 (4.3)
Steroid alone	8 (47)	3 (13.0)
Baseline immunosuppression data not available for comparison	—	8 (34.7)
Missing data	1	2

AZA, azathioprine; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin inhibitor.

^aOne patient excluded due to nephrectomy before immune checkpoint blockade.

were tapered down to steroids alone for graft preservation at the time of checkpoint inhibitor initiation and 8 of them subsequently ended up with a rejection. For the 9 patients whose CNI had already been stopped at the time of cancer diagnosis, 6 patients underwent further reduction in therapy, which ranged from overall reduction in dose of other immunosuppressant ($n = 2$), discontinuation of MMF ($n = 1$), regimen of steroid alone ($n = 3$). In the 9 patients described earlier who had undergone no change in immunosuppression at the time of cancer diagnosis, 4 of them were rapidly tapered to steroid-alone regimen at the time of checkpoint inhibitor therapy initiation. Three of the 4 were on triple immunosuppression with CNI/MMF/steroid and 2 of these had a rejection with graft failure (Table 4).

Cancer Outcomes

Overall, details regarding cancer outcome was reported in 42 of the 44 patients. Complete response, partial

response, and disease stability was noted in 5 (11%), 8 (18%), and 8 (18%) of the patients, respectively. Progressive disease was reported in 21 (48%) of the patients. Three patients had a partial remission (17%), 1 patient achieved cancer response (6%), and 5 patients had stable disease (28%).

Patient Outcomes

Overall, of the 44 Ktx recipients, survival data were reported in 37 patients. Nineteen of 37 (43%) were reported to be alive at the end of follow-up. Among the 18 patients who had a rejection, 8 (44%) were reported alive and the remaining died of various etiologies. The median age of those who were reported alive was lower than those who died (60, interquartile range, 50.5–72.5; vs. 68, interquartile range, 47.5–73.0) but not statistically significant. Both groups had predominantly melanoma patients, but information regarding the stage of cancer and associated comorbidities was not available for review.

Among those who did not have a rejection, data were missing in 6 patients, but interestingly, 9 (36%) of the patients were reported alive at last follow-up. Eighteen patients were reported deceased at the time of last follow-up, and of these, progressive disease was noted in 14 (77.8%) of them, but interestingly only 6 (28%) of them had graft failure. Of the 18 patients who were reported alive at the time of last follow-up, 15 of them had a favorable cancer outcome with complete response in 4, partial response in 4, and stable disease in 7, and this was despite the fact that half of them had allograft failure (1 of whom was the patient with donor-derived melanoma who underwent a nephrectomy).

DISCUSSION

In our systematic review of 27 articles, we found 44 Ktx patients who had received ICI therapy, with 18 of the 44 (41%) culminating in a renal allograft rejection. Of these, 15 (83%) patients eventually had complete graft failure. Evidence of rejection was noted early with an average of 24 days (10–60 days). Management of immunosuppression around the time of ICIs is crucial in balancing the delicate yin-yang of cancer therapy and allograft protection with the multitude of regimen changes reported in literature is a testament to the need for expert consensus guidance to the transplant community.

In immunology, the concept of co-stimulatory signals was a major milestone.⁴⁸ The immunoglobulin superfamily of co-stimulatory receptors is crucial in the adaptive immune system's ability to create a destructive response to an antigenic target. The role of the "stimulatory" members of this family is the generation

of the signal 2, typically CD28 on T cell with CD80 or CD86 of the antigen-presenting dendritic cell, which along with T-cell receptor and peptide major histocompatibility complex trigger (signal 1) this immune cascade. Moreover, to regulate this system, it is critical to have negative regulatory members. This is to be able to restrain an activated immune system and hence induce a tolerance. The inhibitory members of the immunoglobulin superfamily can be either "T-cell intrinsic," as are cytotoxic T-lymphocyte-associated-antigen 4 and PD-1. CD4 regulatory T cells, T follicular helper cells, memory cells, and exhausted CD8 cells typically have high levels of PD-1 expression.⁴⁹ The inhibitors that are T-cell extrinsic are present on the tissue (e.g., macrophages), like the ligand of PD-1, PDL-1.⁵⁰

In organ transplantation, the PD-1:PDL-1 pathway plays a critical role in regulation of peripheral tolerance as well as protective immunity.⁴⁹ PDL-1 is expressed by human renal tubular epithelial cells and suppresses T cell cytokine production. Major histocompatibility complex class II-expressing renal tubular epithelial cells can function as antigen-presenting cells for T cells.⁵¹ Renal tubular epithelial cells can regulate T-cell activation and suppress alloreactivity and immunopathology in the kidney, but with the blockade of this PD1:PDL-1 pathway, the kidney allograft is at a higher risk of rejection.⁵² The immunosuppressive drugs that could be used to alter this balance by generating an environment of graft tolerance, unfortunately, dampen the immune system's ability to detect and destroy cancer cells. Furthermore, immunogenic cancers, such as melanoma, also induce immunosuppression around it to be able to grow and metastasize. It does this by various mechanisms: downregulation of surface antigens, secretion of immunosuppressive cytokines, and lack of co-stimulatory signals, which in the end induce tolerance and evade immune system detection.⁵³ ICIs take away these tolerance "brakes" and are very effective in cancer therapy but can be detrimental to the allograft.

The use of ICI in organ transplant patients is uncommon, and evidence is limited. De Bruyn *et al.*,⁵⁴ in their systematic review, found 48 cases of liver and Ktx recipients who had received ICI. Of the 29 Ktx patients, 45% (13 of 29) had rejection after receiving ICI. Six of them had received dual ICI with a cytotoxic T-lymphocyte-associated-antigen 4 and PD-1 inhibitor, but only 3 had experienced a rejection within 2 to 4 weeks of receiving the second agent. Most of their immunosuppression, around the time of immunotherapy, had been reduced to steroid monotherapy.⁵⁴ From a cancer outcome standpoint, 7 of 13 (53%) patients who had a rejection had a favorable outcome.⁵⁴

Abdel-Wahab *et al.*⁵⁵ noted in their systematic review, 39 solid organ transplant patients (including 9 from their institution) who had received ICI therapy. This included cardiac ($n = 5$), liver ($n = 11$), and kidney ($n = 23$) recipients. Rejection was highest in the Ktx group reported in 48% of the patients compared with liver (36%) and cardiac (20%). Of those who had histology obtained, approximately 50% of them were T-cell-mediated rejection, and the rest was a combination of cellular and antibody-mediated rejection. They noted that 20 patients had preemptive baseline immunosuppression modifications before ICI use. Patients who were on prednisone <10 mg/d had the highest rate of graft rejection but were also the ones with the best tumor response, with 63% having disease either in remission or stabilization. Those on calcineurin inhibitors had the least rejection rates, at 11%, but also had the lowest tumor response rate at 25%.⁵⁵ In our study, we noted similar results: 61% of the patients who had a rejection were on a steroid-alone regimen at the time of ICI use and those who had no significant change to their immunosuppression regimen had allograft preservation. Among those who had a favorable cancer outcome, 9 (52%) patients were on a steroid-alone regimen. More recently, Venkatachalam *et al.*⁵⁶ reported another case series of 6 Ktx patients receiving ICIs (2 patients with squamous cell cancers, 2 with melanoma, 1 with adenocarcinoma of the lung, and 1 with renal cell cancer). In this case series with a longer follow-up, 3 of 6 patients developed acute kidney injury. Two had biopsy-proven acute allograft rejections and subsequently had allograft loss. The third case had probable acute rejection, which fortunately recovered following the discontinuation of the checkpoint inhibitor. In this case series, 5 of 6 patients died within a year of being on ICI.⁵⁶

Regardless of the cancer type Abdel-Wahab *et al.*⁵⁵ noted that the median overall survival was lower in patients who had a rejection (5 months; 95% confidence interval, 1–9 months) compared with those who did not have a rejection (12 months; 95% confidence interval, 8–16 months). It is important to note that in this study, the authors included liver, kidney, and cardiac transplant patients, which differs from our study that was restricted to Ktx recipients alone. Therefore, we believe the transplant patient overall survival was more closely linked with the cancer outcome rather than the allograft failure because these patients could be transitioned to dialysis in the case of renal allograft failure unlike other solid organ transplant patients. We found 83% of those who were alive at the last follow-up showed evidence of favorable cancer outcome. This highlights the importance of understanding the underlying cancer biology and its

aggressiveness and the need for close communication among the patients, their families, oncologists, and transplant nephrologists.

The level of reduction in immunosuppression after a cancer diagnosis alone depends on many factors, for instance, the patient's age, HLA match, prior history of rejection, allograft source, time after transplantation, prior kidney transplants received, and the medication types and levels. In melanoma, expert consensus guidelines by International Transplant Skin Cancer Collaborative and the Skin Care in Organ Transplant Patients Europe give recommendations of the level of reduction in immunosuppression to consider based on the allograft type and stage of melanoma.⁵⁷ For Ktx recipients, a mild reduction in immunosuppression is recommended for stage 1A–1B melanoma, moderate reduction for stage 2A–2B, and a severe reduction for those with stage $\geq 2C$ melanoma.⁵⁷ Although not ideal, a more aggressive approach may be needed in some patients with discontinuation of all immunosuppressive agents with a return to dialysis, as a life-saving measure, a life support option that is only possible in Ktx patients as opposed to other solid organ transplant recipients. This would need to be a careful informed mutual decision among the patients, oncologists, hematologists, and transplant nephrologists.

So what immunosuppressant drugs should we consider stopping? In our review, we found that CNIs were the most common drug to be discontinued at the time of cancer diagnosis (42.8%) and at the time of ICI initiation (17.8%). When the CNI was switched, it was typically to the mammalian target of rapamycin agent. MMF was stopped in 19% of patients at the time of cancer diagnosis and again in 10% of patients at the time of ICI initiation.

CNIs changed the allograft survival paradigm in organ transplantation; however, these are also the drugs that have the strongest evidence of heightened cancer risk. Hojo *et al.*⁵⁸ demonstrated in their mice model study using noninvasive adenocarcinoma cell lines that exposure to cyclosporine made these cells acquire an invasive nature with the development of metastasis. They also showed that this is related to cyclosporine-induced transforming growth factor-beta production by tumor cells,⁵⁸ and that when transforming growth factor-beta was blocked, metastatic lesions were prevented. Similar effects have been reported with tacrolimus,⁵⁹ and some even report that the risk of posttransplant lymphoproliferative disease is higher with tacrolimus than cyclosporine.⁶⁰ Interestingly, in a recent randomized trial of Ktx recipients, Dantal *et al.*⁶¹ showed that the incidence of cancer in cyclosporine patients might be dose-dependent. The patients who were randomized to receive maintenance

immunosuppression after 1 year with cyclosporine at a lower trough (75–125 ng/ml) had a lower incidence of any type of cancer (20% vs. 32%) compared with their standard trough (150–250 ng/ml) group.⁶¹ One of the older immunosuppressive drugs, azathioprine, is also known for its cytotoxic and mutagenic potential with an increased risk of posttransplant lymphoproliferative disease.^{60,62}

On the other hand, mammalian target of rapamycin inhibitors, such as rapamycin and sirolimus, have been shown in animal model studies to prevent tumor growth and progression.⁶³ They are also noted to reduce vascular endothelial growth factor levels.⁶⁴ Subsequent studies by Kauffman *et al.*⁶⁵ have shown this to be clinically appreciable as well. In their study, they reported that in 33,249 Ktx recipients, the incidence rate of any *de novo* malignancy was lowest in sirolimus/everolimus groups at 0.6% compared with 1.8% with cyclosporine/tacrolimus.⁶⁵ Also, one must not forget that immunosuppression begins with the initial induction regimen and that the risk of malignancies like posttransplant lymphoproliferative disease rose with the use of OKT3 and anti-thymocyte globulin.⁶⁰ It has also been shown that treatment of rejection episodes with these drugs only has an additive effect on their risk.⁶⁰ Unfortunately, data regarding this in our review were incomplete and hence unable to make any sufficient conclusions.

The major limitation of our systematic review was that the included articles were case reports and case series, which may have precluded the real evaluation of the acute allograft rejection following the ICI therapy. Certain cases of successful treatment of ICI without allograft rejection/failure among Ktx recipients might not have been published, leading to potential publication bias. We were also limited by the short-term follow-up available to be able to determine the impact of the allograft rejection on overall patient and cancer outcome. Thus, our statistical analysis was limited to descriptive, because of potential significant bias in the reporting source. Further, large cohort studies are required to evaluate the incidence of ICI-associated allograft rejection/failure among Ktx recipients, and the impacts of different immunosuppression regimens around the time of ICI use on patient/outcomes.

In summary, we present a systematic review of all reported Ktx patients who received immune checkpoint inhibitor therapy. Allograft rejection following immune checkpoint inhibitor therapy has been increasingly reported. The time to allograft rejection is rapid and necessitates close follow-up by the nephrologists. The management of immunosuppression around the time of ICI use is difficult and a close

collaboration with the treating hematologist/oncologist as well as the goals of the patient are critical while caring for these complex cases.

DISCLOSURE

SMH is supported by National Institutes of Health K08 DK118120 from the National Institute of Diabetes and Digestive and Kidney Diseases and by a Mary Kathryn and Michael B. Panitch Career Development Award. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

An abstract of this paper was presented as an oral presentation at the American Society of Nephrology conference 2019. All authors had access to the data and had a role in writing the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1. Search terms and strategy for systematic review.

Item S2. PRISMA Checklist.

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