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LETTER TO THE EDITORS

Impact of corticosteroids on allograft protection in renal transplant patients receiving anti-PD-1 immunotherapy

Melissa J. Danesh[1] · Patrick M. Mulvaney[1] · Naoka Murakami[2] · Leonardo V. Riella[2] · Ann W. Silk[3] · Glenn J. Hanna[3] · Chrysalyne D. Schmults[1]

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To the Editor,

Immune checkpoint inhibitors (ICIs) are an effective treatment for metastatic malignancies. Renal transplant recipients (RTRs) have a higher risk of developing advanced malignancy over time, however, ICI use comes with potential risk for acute allograft rejection through immune activation [1, 2]. Due to exclusion from clinical trials, the safety profile and ICI response outcomes among RTRs are largely unknown. We add to this evolving literature with a case series of RTRs with advanced malignancy treated with ICIs.

Patients treated between 1/1/2011 and 11/15/2019 were identified from electronic health records at Brigham and Women's Hospital and Massachusetts General Hospital using International Classification of Diseases codes (Ninth and Tenth Revisions) for renal transplantation* and free text search for ICIs FDA-approved for treatment of malignancy**. Inclusion criteria were (1) RTR, (2) post-transplant advanced malignancy treated with ICI, and (3) functioning allograft at ICI initiation.

We identified eight patients who met aforementioned criteria (Table 1). Malignancy type included cutaneous squamous cell carcinoma ($n=5$), melanoma ($n=1$), tonsillar squamous cell carcinoma ($n=1$), and gastric adenocarcinoma ($n=1$). All patients were treated with pembrolizumab or cemiplimab.

Four patients suffered acute allograft rejection observed at 5 ($n=2$), 34 ($n=1$) and 35 weeks ($n=1$) following ICI initiation. All rejection episodes were treated with high-dose corticosteroids (methylprednisolone 250–500 mg) resulting in either preservation of allograft function and no dialysis requirements ($n=2$), ongoing rejection ($n=1$) or death ($n=1$; patient declined further care and discontinued dialysis). Among four patients who received peri-infusional prednisone mini-pulses (40–20 mg over 1–2 weeks, beginning the day of or prior to ICI infusion) followed by 10 mg daily for maintenance, only one experienced acute rejection which occurred 34 weeks after ICI initiation following prednisone discontinuation. Of four patients on mTOR inhibitors, three had no acute rejection episodes, all of whom were also on prednisone 10 mg daily.

Malignancy treatment outcomes were: complete response ($n=3$; one with disease relapse after 12 months), symptomatic deterioration ($n=2$), progression of disease ($n=1$; subsequently developing complete response on cetuximab), mixed response ($n=1$) and stable disease ($n=1$). Survival following treatment initiation ranged from 1 to 19 months. Patients with any tumor response to ICI was similar between those who did and did not develop acute graft rejection (2/4 vs. 3/4, respectively). Of those receiving peri-infusional prednisone mini-pulses, one complete response was observed, one maintained stable disease, one experienced progressive disease, and one had a dramatic partial response shortly after discontinuing cemiplimab and starting cetuximab (Table 2). During that time, she developed progressive cellular and antibody-mediated rejection during the 6 months following the last dose of cemiplimab.

This case series adds to the growing literature on ICI use in RTRs. Previous reports cite acute renal allograft rejection risk from anti-PD-1 of 52% [2], which is similar to the 50% reported herein. Use of higher maintenance and

Melissa J. Danesh and Patrick M. Mulvaney contributed equally to this manuscript

✉ Melissa J. Danesh
mdanesh@mgh.harvard.edu

[1] Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[2] Division of Nephrology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[3] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Table 1 Characteristics and clinical course of RTRs receiving ICIs for advanced malignancy ($n=8$)

Case	Age at ICI initiation (years)/sex	Immunosuppression regimen at diagnosis of malignancy	Malignancy type/stage at diagnosis[a]	Stage at ICI initiation	Prior treatments	ICI and dose	Immunosuppression at time of ICI initiation	Number of ICI treatments before rejection or to date
1	65/male	1. Mycophenolate 2. Sirolimus	Cutaneous squamous cell carcinoma (CSCC, left cheek)/T2b	IV	1. Wide local excision (WLE), adjuvant radiation 2. Mohs micrographic surgery (MMS), adjuvant radiation 3. WLE with orbital exenteration/maxillectomy, adjuvant radiation 4. MMS	Pembrolizumab 200 mg every 3 weeks	1.Mycophenolate 2. Tacrolimus	11
2	77/male	1. Mycophenolate 2. Tacrolimus 3. Prednisone	Melanoma (nose)/IIIC	IV	1. WLE 2. Lymph node dissection, adjuvant radiation to left cervical lymph nodes	Pembrolizumab 200 mg every 3 weeks	1.Mycophenolate 2.Sirolimus 3.Prednisone 5 millig (mg)	2
3	53/male	1. Azathioprine 2. Tacrolimus 3. Prednisone	CSCC (right forehead)/T2a	IV	1. MMS × 3, adjuvant radiation × 2 2. Cetuximab, cisplatin 3. WLE 4. Gefitinib 5. Carboplatin, paclitaxel	Pembrolizumab 200 mg every 3 weeks	1. Prednisone 40 mg × 5 days (beginning day before immunotherapy), 20 mg × 10 days, then increased daily maintenance dose from 7.5 to 10 mg 2. Everolimus 3. Azathioprine	18
4	64/male	Azathioprine	CSCC (right elbow)/IV	IV	WLE, salvage radiation to primary site and involved right axillary lymph nodes	Pembrolizumab 200 mg every 3 weeks	1. Prednisone 10 mg daily 2. Sirolimus 1 mg daily	13
5	47/male	1. Azathioprine 2. Belatacept 3. Prednisone	Gastric adeno-carcinoma/IV	IV	FOLFIRI	Pembrolizumab 200 mg every 3 weeks	Prednisone 5 mg daily	2
6	62/male	1. Tacrolimus 2. Prednisone	CSCC (left cheek)/T3	IV	1. MMS 2. WLE, lymph node dissection with adjuvant chemoradiation (carboplatin/taxol) 3. Partial maxillectomy	Cemiplimab 350 mg every 3 weeks	1.Prednisone 40 mg day (beginning day before infusion), 20 mg × 5 days, then 10 mg daily 2.Tacrolimus	5

Table 1 (continued)

Case	Age at ICI initiation (years)/sex	Immunosuppression regimen at diagnosis of malignancy	Malignancy type/stage at diagnosis[a]	Stage at ICI initiation	Prior treatments	ICI and dose	Immunosuppression at time of ICI initiation	Number of ICI treatments before rejection or to date
7	51/female	1. Tacrolimus 2. Mycophenolate	CSCC (R 4th finger)/at least T2a	IV	1. MMS 2. Brachytherapy 3. Lymph node dissection, adjuvant radiation to right axillary and supraclavicular lymph nodes	Cemiplimab 350 mg every 3 weeks	1.Prednisone 40 mg day before infusion, 20 mg × 5 days, then 10 mg daily 2.Tacrolimus 3.Mycophenolate	4
8	42/male	1. Mycophenolate 2. Tacrolimus 3. Prednisone	Tonsillar SCC/IV	IV	1. Definitive chemoradiation (cisplatin) 2. Palliative carboplatin, 5-fluorouracil, cetuximab	Pembrolizumab 200 mg	1. Prednisone 40 mg × 5 days (beginning day of immunotherapy), 20 mg × 10 days, then increased daily maintenance dose from 5 to 10 mg 2. Everolimus	1

Case	Creatinine at ICI initiation (mg/dL)	Type of allograft rejection	Management of allograft rejection	Discontinuation of ICI	Outcome of allograft	Tumor response to ICI	Follow-up after ICI initiation (months)
1	1.89	Antibody mediated rejection (AMR) and acute cellular rejection (ACR)	Acute: Methylprednisolone 250 mg × 3 days, then 500 mg × 3 days 2 months later and IVIG (both treatments) Maintenance: Prednisone 10 mg daily	Yes	Stable function	Complete response × 12 months, followed by disease relapse	19
2	1.36	ACR	Acute: Methylprednisolone 500 mg × 3 days, then 500 mg × 3 days 2 weeks later with prednisone taper Maintenance: Mycophenolate increased from 1000 to 2000 mg daily	Yes	Stable function	Mixed response	14
3	0.56	None	N/a	No	Stable function	Complete response	14
4	1.63	None	N/a	No (Cycle 12 held due mild AKI)	Stable function	Complete response	12
5	2.33	Acute kidney injury (AKI; no biopsy performed)	Acute: Methylprednisolone 125 mg × 5 days (patient made comfort measures only thereafter)	Yes	Loss of graft	Symptomatic deterioration	2 (death)
6	1.10	None	N/a	No (Cycle 6 held due mild AKI)	Stable function	Stable disease	4

Table 1 (continued)

Case	Creatinine at ICI initiation (mg/dL)	Type of allograft rejection	Management of allograft rejection	Discontinuation of ICI	Outcome of allograft	Tumor response to ICI	Follow-up after ICI initiation (months)
7	1.80	AMR and ACR	Acute: Methylprednisolone 500 mg × 1 day, 250 mg × 2 doses (spaced 20 h apart), 100 mg × 2 days, 50 mg × 2 days + IVIG + therapeutic plasma exchange × 5 doses + bortezomib × 4 doses	Yes (due to disease progression)	Ongoing rejection	Progression of disease[c]	9
8	0.58	None	N/a[b]	Yes (due to symptomatic deterioration)	Stable function	Symptomatic deterioration	1 (death)

NB; Cases 1 and 2 have been previously described in the published literature [7]

[a]Staging was performed using the Brigham and Women's Hospital Tumor Staging for Cutaneous Squamous Cell Carcinoma for CSCCs and American Joint Committee on Cancer (edition current at time of diagnosis) for non-CSCCs

[b]Patient developed anti-PD-1-induced pneumonitis 3 weeks after first infusion and was treated with intravenous methylprednisolone 50 mg daily. AKI developed in the setting of hypovolemia, contrast dye exposure and sepsis

[c]Patient had disease progression after 4th dose of cemiplimab and was thus transitioned to cetuximab. She subsequently developed partial response of her malignancy after six doses of cetuximab

Table 2 Allograft rejection and response to ICI therapy in relation to peri-infusional prednisone mini-pulse and mTOR inhibitor use ($n = 8$)

Case	Peri-infusional prednisone Mini-pulse	Use of mTOR inhibitor as part of immunosuppressive regimen	Allograft rejection	Response to ICI therapy (includes complete response, partial response, and stable disease)
1			✓	✓
2		✓	✓	✓
3	✓	✓		✓
4		✓		✓
5			✓	
6	✓			✓
7	✓		✓	
8	✓	✓		

mini-pulsed corticosteroids appeared to provide a positive impact on maintenance of allograft function while permitting anti-tumor effect of PD-1 blockade. In five patients treated with either maintenance prednisone 10 mg daily or peri-infusional mini-pulses, only one experienced a rejection episode. In contrast, all three patients on maintenance prednisone doses < 10 mg daily suffered a rejection episode. Similarly, Abdel-Wahad et al. previously reported higher risk of allograft rejection in patients on prednisone ≤ 10 mg daily alone compared to those on other immunosuppressive regimens [1]. Addition of peri-infusional prednisone in conjunction with mTOR inhibitors in preventing ICI-related rejection has been reported previously [3]. In addition to providing allograft protection, mTOR inhibitors also provide anti-tumor effect which may be beneficial in balancing treatment response with immune suppression [3, 4]. Whether certain anti-rejection regimens or peri-infusional prednisone mini-pulses can mitigate rejection risk is the subject of current clinical trials [5, 6].

*International Classification of Diseases (Ninth and Tenth Revision codes) for renal transplantation: ICD-9: V42.0, ICD-10: Z94.0.

**Immunotherapies included: "pembrolizumab", "keytruda", "nivolumab", "opdivo", "ipilimumab", "yervoy", "atezolizumab", "tecentriq", "avelumab", "bavencio", "durvalumab", "imfinzi", "cemiplimab", and "libtayo".

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Compliance with ethical standards

Conflict of interest CS is a steering committee member for Castle Biosciences; a steering committee member and consultant for Regeneron Pharmaceuticals; a consultant for Sanofi; has received research funding from Castle Biosciences, Regeneron Pharmaceuticals, Novartis, Genentech, and Merck, and is a chair for NCCN. AWS reports advisory board participation (with honorarium) from Merck and EMD Serono, and consulting with Bristol-Myers-Squibb. The remaining authors have no conflicts of interest to declare.

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