VIEWPOINT

# Immunotherapy for Advanced Skin Cancer in Kidney Transplant Recipients—The High-Risk Balancing Act

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**Solid organ transplant recipients** are at significantly higher risk for development of skin cancer compared to immunocompetent patients. Cutaneous malignancies in solid organ transplant recipients are commonly characterized by high-risk pathologic features, increased rates of recurrence, metastasis, and rapid progression, with worse outcomes leading to significant mortality.[1]

Immuno-oncology has drastically transformed the management of advanced melanoma and now keratinocyte cancers in immunocompetent patients. However, in solid organ transplant recipients, immunotherapy is considered a high-risk or salvage option due to the possibility of allograft rejection. The newly published results of the first 2 prospective clinical trials involving immune checkpoint inhibitors in kidney transplant recipients contribute important information to this risk-benefit ratio and may enable more successful use of immunotherapy.[2,3]

In the study by Hanna et al,[2] 12 kidney transplant recipients with locally advanced and metastatic cutaneous squamous cell carcinoma (cSCC) were cross-tapered to an mTOR inhibitor (mTORi), from their existing immunosuppressive regimen within 7 to 10 days prior to starting the programmed cell death 1 (PD-1) inhibitor (PD-1i), cemiplimab. In addition, patients received a pulsed prednisone taper each cycle. The pulsed prednisone comprised 40 mg on days −1 to +3, 20 mg on days 4 to 6, and 10 mg on days 7 to 20, relative to each cemiplimab dose given 3 times weekly. The response rate was 46% in the 11 evaluable patients, with 3 complete responses (CRs) and 2 partial responses (PRs). Remarkably, no kidney allograft rejections occurred. Disease progression rate was 36% (4 of 11 patients).

The study by Schenk et al[3] enrolled 12 kidney transplant recipients, of which 8 were evaluable and carried the diagnosis of cSCC, Merkel cell carcinoma or cutaneous melanoma. Patients were transitioned to low-dose tacrolimus (serum trough goal 2-5 ng/mL) and prednisone (5 mg/daily) at enrollment and started taking the PD-1i, nivolumab, within 11 days. All patients experienced disease progression, and 1 allograft rejection occurred. Six patients then received ipilimumab (a CTLA-4 inhibitor) in addition to nivolumab while maintaining low-dose tacrolimus and prednisone. The response rate was 33% with 2 patients achieving CRs. Four of 6 patients experienced disease progression with allograft rejection occurring in 2 additional patients (**Table**).

These 2 small trials, with dramatically different outcomes, have important lessons for multidisciplinary teams caring for kidney transplant recipients with advanced skin cancers. First, immunotherapy can potentially be given without allograft rejection, and second, a response to therapy is indeed possible in this patient population. The combination of sirolimus, pulsed-dose steroids, and cemiplimab appears to be a promising strategy for not only treating locally advanced and metastatic cSCC, but also for preserving allograft function. However, closer scrutiny raises important questions.

## Patient Populations

Hanna et al[2] enrolled kidney transplant recipients with cSCC, while Schenk et al[3] included kidney transplant recipients with heterogeneous skin cancers. Although the concept of "all comers" may be more generalizable, the variety of tumor types may have influenced the lower response rate. Only cSCC achieved CRs in the study by Schenk et al,[3] and CRs was only observed with dual checkpoint inhibition.

The study by Schenk et al[3] showed a lack of tumor response to single-agent nivolumab; however, the very small number of patients and absence of head-to-head data make it difficult to speculate on this apparent difference in response to nivolumab compared with cemiplimab. Future studies in kidney transplant recipients are needed to provide information on single vs combination checkpoint inhibitors, or checkpoint inhibitors combined with other agents.

**Table. Comparison of Studies**

| Variable | Hanna et al[2] (n = 11) | Schenk et al[3] (n = 8) |
|---|---|---|
| Cancer type | cSCC | cSCC, cMel, MCC |
| Immunosuppression | Sirolimus; pulsed-dose prednisone | Low-dose tacrolimus; low-dose prednisone |
| Immune-oncologic regimen | Cemiplimab | Nivolumab[a]; nivolumab + ipilimumab[b] |
| Overall response rate[c] | 5/11 (45%) | 0/8 Taking nivolumab; 2/6 (33.3%) taking nivolumab + ipilimumab |
| Allograft rejection | 0/11 | 1/8 Taking nivolumab; 2/6 taking nivolumab + ipilimumab |
| Progressive disease | 4/11 (36%) | 8/8 Taking nivolumab; 4/6 taking nivolumab + ipilimumab |
| Disease-specific death[d] | 0/11 | 2/8 Taking nivolumab; 2/6 taking nivolumab + ipilimumab |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; cMel, cutaneous melanoma; MCC, Merkel cell carcinoma.

[a] Nivolumab was dosed 480 mg intravenously once every 4 weeks.

[b] Ipilimumab (1 mg/kg) was added to nivolumab (3 mg/kg) intravenously once every 3 weeks for 4 doses after progression in 6 of 8 patients. This was then followed by nivolumab 480 mg intravenously once every 4 weeks for a total of 96 weeks.

[c] Partial and complete responses were observed only in cSCC.

[d] MCC (n = 1), cMel (n = 1), and cSCC (n = 2).

## Allograft Rejection and the Role of Pulsed-Dose Prednisone

The trials differed in management of immunosuppression. Hanna et al[2] converted all patients to mTORi and used pulsed-dose prednisone with each cycle of cemiplimab, while Schenk et al[3] treated patients with low-dose tacrolimus and prednisone throughout. Whether it was the pulsed-dose prednisone or the mTORi that helped maintain stable allograft function is unknown. However, acute tubule-interstitial nephritis is the most common type of kidney immune-related adverse event attributed to checkpoint inhibitors, and early initiation of corticosteroids has been shown to be independently associated with higher rate of kidney recovery.[4] In the study by Schenk et al,[3] allograft rejection occurred in 3 patients. Rejections were observed after initiation of nivolumab, after addition of ipilimumab and after discontinuation of all immunotherapies. The expression of PD-1/programmed death-ligand 1 on kidney tubular cells of rejected allografts raises questions regarding the role of this pathway in allograft tolerance.

## mTORi vs Calcineurin Inhibitor–Based Immunosuppression in the Setting of Immune Checkpoint Inhibition

Histologic analysis of tumor samples from both trials revealed moderate infiltration of CD8+ T lymphocytes after the start of PD-1i and only in responders.[2,3] The higher response rate in the cemiplimab study may have been influenced by the switch to an mTORi or by other variables including patient/tumor factors, pulsed-dose prednisone, or the immunotherapy itself. Plausibly, sirolimus may support greater antitumor activity of the checkpoint inhibitor due to decreased ability to interfere with acute expression of inflammatory cytokines[5] than even a low dose of tacrolimus. It is also possible that sirolimus exerts an inherent antineoplastic effect[6] creating positive synergism with cemiplimab. However, the decreased incidence in keratinocyte cancers in kidney transplant recipients switched to sirolimus could be driven more by lack of cyclosporine than by a direct antiproliferative effect of sirolimus.[7] Regardless, these data demonstrate that minimizing immunosuppression is not necessary for achieving adequate antitumor immune responses and indeed may risk compromising allograft function.

## Importance for Dermatologists

These 2 trials reveal potential benefits and means for reducing immunotherapy risks for kidney transplant recipients with locally advanced or metastatic cSCC. Clear lines of communication between dermatology, transplant nephrology, and medical oncology in anticipation of any such patient are crucial, as there is a narrow window of opportunity for successful intervention. Delay in starting immunotherapy due to fear of allograft rejection may result in progression and death from disease. Death from locally advanced cSCC is a devastating posttransplant complication, and dermatologists have a responsibility both to alert the transplant nephrologist and to ensure timely referral to medical oncology. We encourage our colleagues to consider early referral for patients with high-risk tumor features. A multidisciplinary approach with transplant team, medical oncology, dermatology, and importantly active involvement of the patient, is crucial. Upcoming clinical trials (ETCTN 10614 and CONTRAC-2) will hopefully elucidate the optimal immunotherapy and immunosuppressive regimens to successfully balance strong checkpoint antitumor activity with preservation of allograft function.

ARTICLE INFORMATION

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