Case Reports in Dermatology

Case Rep Dermatol 2023;15:99–104
DOI: 10.1159/000530851
Received: November 4, 2022
Accepted: April 20, 2023
Published online: June 13, 2023

Single Case

Use of Talimogene Laherparepvec to Treat Cutaneous Squamous Cell Carcinoma in a Renal Transplant Patient

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Keywords

Transplant associated squamous cell carcinoma · Talimogene laherparepvec · Case report · Immunotherapy · Organ transplant recipient

Abstract

A 66-year-old female with a history of two renal transplants due to recurrent thrombotic thrombocytopenic purpura presented to clinic with multiple lesions identified to be non-metastatic cutaneous squamous cell carcinoma (CSCC). The patient previously underwent multiple Mohs procedures and radiation therapy treatment but continued to develop CSCC lesions with increasing frequency. After discussing multiple treatment options, it was elected to pursue treatment with Talimogene laherparepvec (T-VEC) given the systemic immune responses it can cause, with low theoretical risk of graft rejection. After starting intratumoral T-VEC injections, treated lesions began to decrease in size, and a reduction in the rate of new CSCC lesions was observed. Treatment was held due to unrelated renal complications during which time new CSCCs developed. Patient was restarted on T-VEC therapy with no recurrent renal issues. Upon reinitiating treatment, injected and non-injected lesions showed reduction in size, and the development of new lesions again ceased. One injected lesion was resected via Mohs micrographic surgery due to its size and discomfort. On sectioning, this demonstrated an exuberant lymphocytic perivascular infiltrate which was consistent with treatment response to T-VEC, with little active tumor. With high rates of non-melanoma skin cancer in renal transplant patients, their transplant status significantly limits treatment options, specifically with regards to anti-PD-1 therapy. This case suggests T-VEC can generate local and systemic immune responses in the setting of immunosuppression and that T-VEC may be a beneficial therapeutic option for transplant patients with CSCC.

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Introduction

Cutaneous squamous cell carcinoma (CSCC) is among the most common post-transplant malignancies resulting from immunosuppression necessary to prevent organ graft rejection [1]. Specifically, long-term renal transplant recipients have a 200-times greater incidence of non-melanoma skin cancer, 80% of which is squamous cell carcinoma, with cumulative immunosuppression and UV exposure being high contributing factors [2].

For organ transplant recipients (OTRs) with CSCC, while surgery and radiation have high cure rates for individual lesions, neither treatment modality addresses the global issues of increased risk of developing new CSCC. To address this issue and prevent new CSCCs, systemic treatments that address the cause of increased cancer risk are needed. Supplementation with oral nicotinamide and acitretin is often used preventatively in patients with high rates of CSCC development and solid OTRs. Particularly for OTRs, daily acitretin has been associated with a reduced incidence of SCC development during treatment; however, adverse events including headaches, rash, and musculoskeletal symptoms cause the treatment to be poorly tolerated [3]. Although there are many systemic options available for patients with CSCC, treatment with PD-1 immune checkpoint inhibitors including pembrolizumab or cemiplimab have proven to be of most benefit as they are able to generate anti-tumor immune responses and thus provide durable, long-term disease control [4]. OTR patients, however, are typically not eligible to receive PD-1 inhibitors due to risking acute graft rejection. A 2018 review of immunosuppressed patients receiving immunotherapy for cancer treatment cited a 41% acute graft rejection rate for OTRs [5]. The exact risk of graft rejection will be defined via prospective clinical trial (NCT04339062). Therefore, other immune based treatment options are needed for transplant patients which do not pose the same risk of graft rejection.

Talimogene laherparepvec (T-VEC) is an FDA-approved immunotherapy for the treatment of patients with advanced melanoma which does not cause similar immune-related side effects to PD-1 inhibitors [6]. T-VEC is a genetically modified type 1 herpes simplex virus (HSV-1) engineered by deleting both a gene that blocks antigen presentation and neurovirulence genes that cause fever and blisters [6]. T-VEC elicits its response by entering tumor cells and propagating using disrupted oncogenic and anti-viral pathways, leading to cell lysis [6]. The result of cell lysis is the release of soluble tumor-derived antigens into the tumor microenvironment, which when presented to CD4+ and CD8+ T-cells help the adaptive immune system form a systemic immune response [6]. While there is insufficient evidence to confirm that T-VEC is effective at preventing disease, promising results from a Phase 2 study for patients with resectable melanoma showed that neoadjuvant T-VEC extended 3-year Kaplan-Meier recurrence-free survival compared with surgical resection alone (NCT02211131), indicating a potential prophylactic effect from the immunotherapy with a biologic effect on distant sites. Although T-VEC has been FDA approved for treating patients with advanced melanoma, its safety and effectiveness are currently being investigated in non-melanoma skin cancers including SCC (NCT03714828). The main objective of this case study is to report a successful case of a renal transplant patient with multiple and rapidly developing CSCCs that was treated with intralesional T-VEC. The CARE checklist for this case report has been completed by the authors and attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530851).

Case Report

A 66-year-old female with a history of two renal transplants due to thrombotic thrombocytopenic purpura presented to clinic with numerous CSCCs. The patient had previously undergone multiple Mohs procedures and radiation treatment with good response

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to treated lesions; however, she continued to develop CSCCs with increasing frequency. Though the patient was treated with nicotinamide, no appreciable difference in the rate of CSCC formation was noted. Per nephrology, the patient was not a candidate for acitretin due to stage 4 chronic kidney disease. After discussing multiple treatment options including cetuximab, capecitabine, anti-PD-1 therapy, or intratumoral injections with 5-FU, methotrexate, or T-VEC, the patient elected to proceed with T-VEC injections on an off-label basis given its potential to generate systemic immune responses and low theoretical risk of graft rejection.

The patient began intralesional T-VEC injections on September 23rd, 2020 (timeline shown in Fig. 1) and has continued to respond to treatment through her last follow-up visit on September 21st, 2022. Due to her transplant status and as advised by nephrology, the patient was on immunosuppressive medication of 5 mg prednisone and 1.5 mg tacrolimus at the start of treatment, which was later tapered down to 0.5 mg tacrolimus daily in June 2021. By June 2022, the patient switched from tacrolimus to 1 mg sirolimus daily for the potential anti-cancer effect of sirolimus. For the first two visits, dosing was per FDA standard guidelines of 4.0 mL total injection volume per treatment session. However, due to mild fevers and chills after the initial injections, subsequent treatments were capped at 2.0 mL total per visit with a typical interval of 4 weeks between treatments. After 2–3 injections, the patient observed a reduction in the rate of new CSCC development. Injected lesions started shrinking around the 5th injection, as is common per average response time for melanoma. Due to worsening chronic kidney disease, T-VEC was held for 4 months, starting on December 23rd, 2020, to allow for a nephrology work-up. Nephrology later concluded her reduced renal function was likely not due to T-VEC injections but rather a result of reduced oral intake. During her treatment break, the patient developed new CSCCs.

T-VEC injections were restarted on April 29th, 2021, with additional IV fluids and supplementation as needed. Renal disease was stable, and no serious adverse side effects were reported. Complete regressions on some lesions were observed within 6 weeks of intralesional T-VEC injections (Fig. 2). After months of beginning treatment, an uninjected lesion on the breast began to decrease in size upon clinical observation. Photo evidence is unavailable due to patient request. Due to size and pain, one lesion was resected via Mohs surgery after 1 injection of T-VEC. Pathology from the resections showed no residual tumor and marked lymphocytic inflammation (Fig. 3). While on treatment, no lesions progressed with injection, and some degree of shrinkage was noted in all injected lesions. As of the patient's latest treatment visit on September 21st, 2022, only lesions on the arm were left to inject.

Discussion

We report in this case that T-VEC was able to generate a local and potentially systemic immune response against CSCC in the setting of immunosuppression, suggesting it may be a tolerable therapeutic option for OTRs with multiple and rapidly occurring CSCC. The results observed are notable given that under immunosuppression, T-VEC was not only effective at infiltrating injected lesions but appeared to exhibit a mild systemic response as demonstrated by the regression of an uninjected lesion on the patient's breast.

Recently, there have been several case series documenting treatment options for solid organ transplant patients. A systematic review published in 2020 found capecitabine, an oral prodrug of 5-fluorouracil, to be associated with a reduced SCC incidence rate during treatment [7]. However, a series of adverse effects including nausea, vomiting, weight loss, and anemia limited capecitabine's treatment duration in several patients [7]. Additionally, a recent

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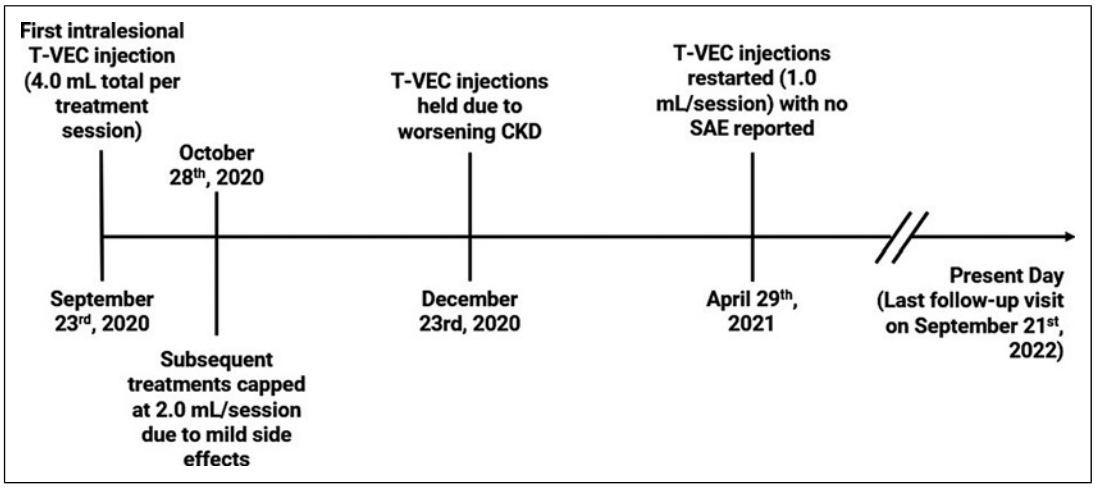

Fig. 1. Timeline illustrating schedule of treatment and dosing with T-VEC.

Fig. 2. Clinical regression of CSCC in renal transplant patient after intralesional injection of T-VEC. **a** CSCC lesion on May 19th, 2021, before intratumoral injection of 1 mL T-VEC. **b** June 30th, 2021, 6 weeks after intratumoral T-VEC injection.

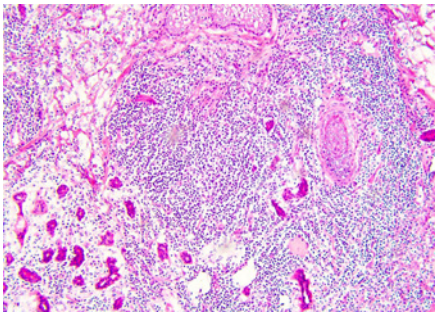

Fig. 3. Histopathologic imaging of CSCC tumor following intralesional administration of T-VEC (hematoxylin-eosin, original magnification, ×10).

review investigating 22 renal transplant patients with advanced malignancies treated with PD-1 inhibitors found patients who experienced an anti-tumor response and retained an intact graft combined treatment with either the mTOR inhibitor sirolimus or anti-VEGF medication without immunosuppression titration [8]. While it is difficult to suggest with a small patient population (n = 22) whether mTOR inhibitors and anti-VEGF medication are keys to safe PD-1 inhibitor administration in OTRs, further research is warranted. Comparatively, a phase 3 clinical study (n = 292) of patients with advanced melanoma receiving T-VEC injections saw a median exposure duration of 23 weeks with at least 26 patients receiving injections for a year, suggesting the tolerability of treatment regimen with T-VEC [9].

This case adds to a handful of published cases reporting the safe administration of T-VEC in OTRs with either metastatic CSCC or transplant associated melanoma [10, 11]. Although this patient had neither advanced disease nor inoperable lesions, the positive anti-tumor response along with the tolerability of monthly injections supports the benefit of intralesional T-VEC for patients with numerous and rapidly developing CSCCs as an alternative to the morbidity and burden of repetitive surgical procedures. While intralesional chemotherapy with methotrexate or 5-FU may be used for low-risk SCC and was considered in this case and for patients with multiple and rapidly developing CSCC, intralesional T-VEC may offer greater benefit due to its long-term tolerability and potential systemic immune response at preventing disease at distant sites. Current trials are underway determining the efficacy of T-VEC to treat CSCC (NCT03714828). However, further investigation is needed to confirm the benefit and safety of T-VEC in treating immunosuppressed patients and OTRs.

Statement of Ethics

This case study and study protocol were reviewed, and the need for approval was determined not to be required by the Internal Review Board at the HonorHealth Research and Innovation Institute. The patient has provided written informed consent to publish their case including publication of clinical photographs.

Conflict of Interest Statement

M.M., N.H.K., M.K.T., and J.C.M. have no conflicts to disclose.

Funding Sources

No funding sources were required or provided to produce this manuscript.

Author Contributions

Max Miller contributed to the chart review, literature review, inspiration, and writing/revision of the manuscript. Dr. Nancy H. Kim contributed to the diagnosis/treatment of the patient and histopathologic testing and imaging. Dr. Maya K. Thosani contributed to the diagnosis/treatment of the patient and histopathologic testing and imaging. Dr. Justin C. Moser contributed to the diagnosis/treatment of the patient, consenting the patient, chart review, inspiration, literature review, IRB clearance, and writing/revision of the manuscript.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for the manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Data Availability Statement

All data generated or analyzed during this case study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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