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LETTER TO THE EDITOR

Metastatic melanoma in a 95 years old patient responding to treatment with talimogene laherparepvec followed by nivolumab

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Background

Talimogene laherparepvec (T-VEC) is an oncolytic virus derived from an attenuated recombinant type-1 herpes virus, genetically engineered to replicate preferentially within tumor cells. When injected directly into the tumor, it generates an antitumor immune response. This pro-immunogenic potential is orchestrated via lysis of tumor cells induced by the virus resulting in the release of tumor-associated antigens along with an enhanced expression of granulocyte macrophage colony-stimulating factor (GM-CSF) [1]. Nivolumab, a fully human immuno-globulin-4 (IgG-4) monoclonal antibody is approved as a single agent [2] and in combination with ipilimumab [3] for the treatment of metastatic melanoma. It is directed against the programed cell death-1 (PD-1) receptor and blocks its interaction with the ligands PD-L1 and PD-L2. This checkpoint blockade culminates into the release of an immunogenic response within the tumor microenvironment mainly by impeding co-inhibitory signals on effector T cells and also lowering the activation threshold for an antigen directed T-cell response [4]. Promising outcomes from an early phase-1b study have been observed with the anti-PD-1 antibody pembrolizumab in combination with T-VEC for patients with metastatic melanoma [5]. However, no cases of T-VEC in combination with nivolumab have been reported to date.

Case presentation

A 92-year-old Caucasian female was diagnosed with melanoma after noticing a change in the size and character of a skin lesion on the right calf that had been present for 10 years. A punch biopsy of the lesion revealed a 2.20 mm thick, Clark's level IV solar lentiginous melanoma positive for S-100 and MART-1 by immunohistochemistry, with both radial and vertical growth phase present. Vascular invasion was present with positive margins. She underwent a wide local excision with split thickness graft for wound coverage. No sentinel node biopsy was performed due to her advanced age. She developed recurrent in-transit disease 18 months after her initial diagnosis and subsequently underwent isolated right leg limb infusion (LI) with melphalan/dactinomycin. The patient had a second progression 8 months later and underwent repeat LI. Positron emission tomography (PET) imaging 2 months after the second LI demonstrated numerous soft tissue areas of hypermetabolic activity in the right leg and a focus in the right groin likely representing malignant adenopathy. Biopsy of right inguinal nodes confirmed *BRAF*-negative metastatic melanoma. Repeat isolated right leg LI with melphalan/dactinomycin was performed along with right superficial inguinal lymph node dissection (2 of 14 nodes were positive for melanoma). Three months postlymph node dissection when she was 95 years old, progression was noted again, with increasing number and size of nodules in the right leg. Imaging of the brain was negative. Lactate dehydrogenase was within normal range. She was started on T-VEC, injecting <4 mL of 10^6 plaque-forming units (PFU)/mL in nodal/(sub)cutaneous lesions on day 1, then 10^8 PFU/mL on day 20 and every 2 weeks subsequently. Given her advanced age and previous limb infusion therapy, the number of treatments was predefined. She completed a total of six treatments after which it was decided to monitor

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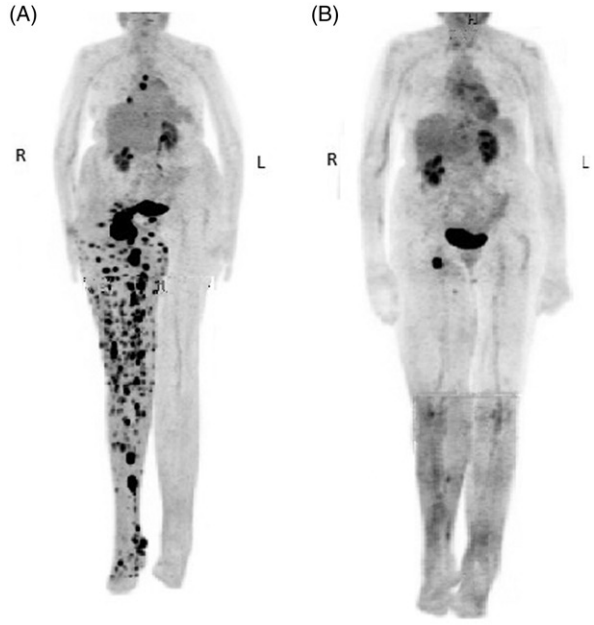

Figure 1. (A) Disease progression after T-VEC prompting consideration for sequential nivolumab. (B) Durable response of subcutaneous and nodal disease 6 months after completing 4 cycles of nivolumab.

her clinical status and disease response. However, approximately 2 months after last T-VEC, she had progressive disease (Figure 1(A)) with PET demonstrating extensive right lower extremity dermal/nodal disease with symptomatic lymphedema as well as intrathoracic adenopathy. She was started on immune therapy with nivolumab 3 mg/kg every 3 weeks and completed a total of four cycles. The dose and the dosing frequency were modified in view of her age and logistical convenience. After the four cycles, she showed dramatic clinical improvement with near resolution of the existing visible lesions and leg edema. She also had a marked improvement in performance status. Interval PET scan 1 month after nivolumab showed a significant improvement of the bulky inguinal and mediastinal adenopathy. The patient continues to be under surveillance, with repeat PET imaging 6 months post the last nivolumab treatment indicating a continued radiographic improvement (Figure 1(B)). No dose-related toxicities were observed during this period.

Discussion

The treatment landscape of metastatic melanoma has seen a tremendous change with new immunotherapies and intralesional treatments. The optimal combination and sequencing of these treatment options are unclear. This case highlights the efficacy of sequential administration of T-VEC with an anti-PD-1 in an elderly patient with metastatic melanoma.

Under physiological homeostasis, the interaction between PD-1 and its cognate ligands (PD-L1 and PD-L2) serves as a negative regulator of T-cell activation [6,7] through a diverse set of signaling mechanisms [8]. This pathway by acting as a negative checkpoint regulator maintains a balance between self-tolerance and immunopathology. However, upregulation of PD-L1 on certain cancers including melanoma [4] results in the ability of the tumor cells to evade an immune-directed attack by engaging the PD-1 on activated T-cells. This interaction leads to T-cell exhaustion and functional inactivation within the tumor microenvironment. Monoclonal antibodies directed against PD-1 or PD-L1 disrupt this engagement and restore antitumoral immunity.

The advent of immune-checkpoint blocking (ICB) antibodies has revolutionized the management of various malignancies especially melanoma [9], resulting in a paradigm shift in the form of increased response rates and survival. In patients with melanoma, the anti-PD-1 antibodies, that is, nivolumab and pembrolizumab, have both been shown to be superior when compared to ipilimumab [3,10], another checkpoint inhibitor targeting the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) receptor. Also, results from the Checkmate-067 and Checkmate-069 serve as a platform to delineate the higher potency of nivolumab/ipilimumab combination compared to ipilimumab alone [3,11–13], indirectly suggestive of the synergistic function of PD-1 and CTLA-4 in arbitrating immune escape, and hence the enhanced efficacy of the dual blockade. This combination of ICB antibodies despite its clinical effectiveness, is subject to considerable grade III/IV treatment-related adverse outcomes [14]. Hence, to some extent, this necessitates adopting improved strategies for combination/sequential immunotherapy, albeit keeping similar principles of eliciting an enhanced immunogenic antitumor response in mind.

T-VEC is derived after genetically modifying herpes simplex virus-1 (HSV-1) and has been shown to display oncolytic properties. The remodeling of HSV-1 into T-VEC involves functional deletion of genes *ICP-37.5* and *ICP-47* along with insertion of a gene-encoding GM-CSF [1]. These alterations mediate an enhanced innate and tumor-specific adaptive immunity via an array of mechanisms similar to an *in situ* vaccine [15]. The ability of this agent in priming the immune system and creating an immunologically hostile tumor microenvironment originates from studies demonstrating an increase in cytotoxic CD-8^+ T cells with a converse reduction in CD-4^+FoxP3^+ regulatory T cells from biopsy specimens of lesions showing regression [16]. This strongly bespeaks the ability of T-VEC in inducing host antitumor immunity. GM-CSF that forms an integral component of T-VEC in generating its immunogenic potential, has been shown to moderate the adverse event profile as well as potentiate the antitumor response of ICB antibdies based on preclinical studies [17]. Recent phase-II data showing that the combination of GM-CSF with ipilimumab acts synergistically with longer overall survival and lower toxicity provides affirmation of the immunomodulatory effect of GM-CSF in this setting [18]. Thus, T-VEC, by harnessing the immunomodulatory properties effectuated via GM-CSF, may achieve an amplified tumor-directed immune response when combined with ICB antibodies as well as provide an alternative strategy to overcome the side effect profile associated with anti-CTLA-4 + anti-PD-1.

T-VEC monotherapy was recently shown to have a durable response rate versus subcutaneous GM-CSF in unresectable stage III/IV melanoma [19]. Though only accessible lesions were injected with T-VEC in this study, regression of the disease was also observed in visceral sites, suggesting the role

of T-VEC in inducing a systemic immune response that promotes tumor recognition at distant sites [20]. Due to the high tolerability of this agent and its ability to foster a systemic antitumor response, combination designs utilizing T-VEC with ICB antibodies, that is, with pembrolizumab [5] or ipilimumab [21] have been employed, with early results demonstrating promising outcomes.

In our current patient model, T-VEC + anti-PD-1 combination is believed to work in a synergistic manner. We propose that the use of T-VEC driven by its oncolytic properties generates the required 'gas' in the form of tumor neoantigen release, priming the immune system to trigger a response, further enhanced by nivolumab-induced removal of PD-1/PD-L1-controlled immune 'brakes'. Honing in on the hypothesis of T-VEC primed inflamed tumor sites having an improved response rate with an anti-PD-1, we relied on sequential rather than concurrent therapy. Also, we believed that such a technique could avoid immune-related adverse events that characterize combination immunotherapies when given concurrently. Our report is the first to imply upon the efficacy of T-VEC with nivolumab, although pembrolizumab, another surrogate anti-PD-1 is being studied in combination with T-VEC

Recently presented phase 1-b data from the MASTERKEY-265 on T-VEC + pembrolizumab that enrolled 21 treatment-naïve patients with stage-3/4 melanoma showed durable efficacy and safety prompting a phase-3 trial, which is currently underway with an estimated completion in 2022 [22]. This phase-3 design aims at the concurrent administration of the anti-PD-1 and T-VEC while as the phase-1b design dispensed pembrolizumab 5 weeks after initiation of T-VEC [5]. This is similar to the T-VEC + ipilimumab study where the anti-CTLA-4 was administered at week 6 after treatment commencement [21]. One could argue that a lag time between the T-VEC and anti-PD-1 or anti-CTLA-4 rather than a concurrent approach may be vital in immune priming, although there is no data to support such a claim.

Data on optimal sequencing of combination immunotherapy is poorly defined, making it difficult to derive conclusions. Early results from a study using combination immunotherapy in melanoma examining the delivery sequence of PD-1 and CTLA-4 antagonists showed that nivolumab sequentially followed by ipilimumab achieved a higher clinical benefit in the form of overall survival compared to when the PD-1 antagonist was administered first [23]. At this point, the mechanism driving this phenomenon is not established. Extrapolating this concept by using a similar analogy, it would be interesting to see whether the sequence of anti-PD-1 followed by T-VEC versus the reverse would achieve an enhanced response. We did come across an ongoing phase-1 trial exploring the impact of sequential delivery of ONCOS-102, an adenovirus expressing GM-CSF followed by pembrolizumab for unresectable melanoma [24] that may perhaps help answer some of these questions. As of current, due to the overall paucity of data on T-VEC + ICB antibodies, the response kinetics and the efficacy/tolerability of this combination is poorly defined and hence yet to engender any significant practice changes.

Conclusions

This case demonstrates that sequential therapy with intralesional T-VEC followed by nivolumab is effective and well tolerated. Although the ideal combination or sequencing of immunotherapy in metastatic melanoma is debatable, the ongoing clinical trials with T-VEC and checkpoint inhibitors will help provide further insight to answer these questions. Thus, the understanding of combination immunotherapy has to evolve further to elucidate therapeutic strategies aimed at achieving optimal outcomes with minimal toxicities

Disclosure statement

No potential conflict of interest was reported by the authors.

Consent for publication

Consent for publication and IRB approval has been obtained from the patient as part of another study that the patient is currently enrolled in at East Carolina University (UMCIRB-15-001400), which states that the patient has consented to the reporting of any medical/clinical/laboratory and radiological data generated as part of this IRB approved study.

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LETTER TO THE EDITOR

The concept of immunocompromised district might explain the carcinogenic progression in hidradenitis suppurativa

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We read with great interest the case report recently published in Acta Oncologica by Zhang and Tan [1], which describes a 59-year-old man with a 30-years history of gluteal and perianal hidradenitis suppurativa (HS), who developed a squamous cell carcinoma (SCC). Zhang and Tan state that more than 70 cases of SCC have been documented among patients affected by chronic HS. This complication of HS is much more frequent than assumed. In fact, in the literature, we have been able to identify over 100 cases of HS patients developing SCC and the trend is on the rise.

Several authors have speculated on the pathogenic mechanisms leading to the development of SCC in HS affected areas. HPV infection has been supposed to have a role in the causation of SCC in patients with anogenital HS [2,3]. However, some authors have been unable to detect HPV DNA (genotypes 6, 11, 16, 18 and 33) using PCR, which suggests that HPV infection has a limited role in the process that leads to the development of SCC in HS affected areas [4]. Longstanding inflammation has also been suspected of promoting the development of SCC, with the release of some cytokines, such as TNF-alpha [5].

In contrast with this thesis, one must consider that TNF-alpha has an anticancer activity [6] and anti-TNF-alpha drugs may increase the risk of developing a SCC [7,8]. In our opinion, the concept of immunocompromised district (ICD) may well be the key for the comprehension of the pathogenic mechanisms leading to the development of SCC in chronic HS.

The ICD is a novel concept, delineated by Ruocco et al. [9,10] that applies to an area of diseased or injured skin where local immune control has been altered, thereby permitting the development of a dysimmune reaction, infection, or tumour confined to the diseased or injured site. The skin is an active immune organ where a pool of immune-competent cells and cytokines co-ordinately act to create and maintain a balanced immune microenvironment [11].

The crucial role played by lymph drainage in regulating skin immunity is supported to by the fact that lymph stasis, whatever the cause, may give birth to skin regions with a dysregulation of the immune control and the origin of post-mastectomy Stewart-Treves angiosarcoma is a prototypical example of this condition [12]. In this light, the outbreak of SCC in long-standing HS could be considered a typical condition of an immunocompromised district. In detail, we suggest that the outbreak of SCC in long-standing HS may well be explained by the loco-regional immune default depending on the hindered traffic of immunocompetent cells in the lymphedematous area. In fact, anogenital lymphedema due to chronic, recurrent episodes of inflammation and scarring occurring in patients with HS and causing the blockade/destruction of lymph drainage routes, has long been noted to be a common sequela of HS [13–15].

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