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Melanoma Management

Talimogene laherparepvec: overview, combination therapy and current practices

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Practice points

- Talimogene laherparepvec (T-VEC, Imlygic[®], Amgen, CA, USA) is herpes simplex virus type 1-derived oncolytic immunotherapy that selectively replicates within tumors and produces granulocyte macrophage colony-stimulating factor.
- T-VEC is an intralesional therapy indicated for advanced stage, IIIB/C and IVM1a melanoma.
- Combination therapies with T-VEC and other immunotherapies such as ipilimumab and pembrolizumab are being studied to evaluate if combination therapy may enhance the antitumor response.

Talimogene laherparepvec (T-VEC, Imlygic[®], Amgen, CA, USA) is an oncolytic herpes simplex type 1 virus used as intralesional therapy for unresectable metastatic melanoma in a cutaneous, subcutaneous or nodal location. Talimogene laherparepvec selectively replicates within and lyses tumor cells while producing granulocyte macrophage colony-stimulating factor, which may promote an immune mediated antitumor response. The US FDA approved T-VEC in late 2015 following Phase I–III trials that demonstrated safety and efficacy. Future directions for T-VEC include combination therapies with other systemic immunotherapies such as anti-CTLA-4 antibody and anti-PD-1 drugs. Current National Comprehensive Cancer Network (NCCN) practice guidelines have added T-VEC as a primary treatment for stage IIIB/C and stage IVM1a melanoma patients.

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Melanoma of the skin is the sixth most common cancer in the USA with approximately 74,000 people diagnosed with the disease in 2015 [1]. The stage of melanoma has a great impact on treatment options and prognosis. Localized melanoma is treated with surgical resection and 5-year disease-specific survival (DSS) rates for stage I and II melanoma range from 97 to 53%, respectively [2]. Prognosis is worse for patients with regionally metastatic and distant metastatic disease; stage III melanoma 5-year DSS rates range from 52 to 43% and stage IV melanoma 2-year DSS rates range from 19 to 14% [3]. Newer modalities of treatment, such as immunotherapy and targeted therapies, have recently made great advancements in increasing response rates and survival from metastatic melanoma. These new therapies have led to improvements in overall survival (OS) and prolonged progression-free survival (PFS) in patients with regional or distant metastatic disease [4].

Treatment options for stage III and IV melanoma have greatly increased over the past decade and include molecular-targeted therapies, immune checkpoint inhibitors and intralesional therapies. Molecular-targeted therapies include BRAF inhibitors; such as vemurafenib, dabrafenib alone

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or in combination with MEK inhibitors such as trametinib and cobimetinib [5–9]. Immune checkpoint inhibitors, such as ipilimumab and pembrolizumab or nivolumab, target CTLA-4 and PD-1, respectively [10–12].

Intralesional therapies are another treatment option for patients with regional and subcutaneous distant metastases that aim to locally control melanoma as well as incite a systemic anti-tumor immune response. Intralesional therapy was first developed by Coley *et al.* in 1893 when regression of a locally advanced tumor was seen after the injection of a bacterial toxin [13]. In the 1960s, intralesional bacillus Calmette–Guérin was used for intradermal lesions to activate an immune response and early studies showed response of injected and uninjected tumors [14]. However, toxicities such as skin reactions, systemic infections and even such severe reactions such as anaphylaxis and disseminated intravascular coagulation led to the disuse of bacillus Calmette–Guérin clinically. Other intralesional therapies that have shown a local response but no systemic response include IL-2, IFN- γ and IFN- α . Promising intralesional agents with the potential for specific antitumor immune response locally and systemically include PV-10 and talimogene laherparepvec (T-VEC, Imlygic®, Amgen, CA, USA) [15–19]. The objective of this article is to review T-VEC's role in the treatment of stage IIIB/C and M1a metastatic melanoma, highlight the current clinical trials that combine T-VEC with other immunotherapies and discuss T-VEC's future directions.

T-VEC overview

T-VEC, previously known as OncoVex^{GM-CSF}, is a herpes simplex virus (HSV) type 1-derived oncolytic immunotherapy that selectively replicates within tumors and produces granulocyte macrophage colony-stimulating factor (GM-CSF). In T-VEC, the HSV type 1 is modified through deletion of two nonessential viral genes, ICP47 and ICP34.5 [20]. The deletion of the ICP47 gene upregulates the *HSV US11* gene, reduces the suppression of antigen presentation and also enables the virus to grow and replicate within tumor cells [21]. Functional deletion of ICP34.5 reduces neurotoxicity and enhances tumor-selective replication [22]. The gene encoding human GM-CSF is inserted and its expression promotes dendritic cell activity and increased tumor antigen presentation, potentially inducing greater tumor-specific T-cell responses (Figure 1) [22,23].

T-VEC clinical trials

T-VEC has been evaluated in Phase I, II and III clinical trials [19–20,23–24]. The safety and clinical activity was initially established in multiple tumor types, including melanoma in a Phase I trial. The intralesional therapy had an acceptable safety profile with most common side-effects were low-grade flu-like symptoms (fever, chills, myalgias) and injection site reactions [20]. This study was followed by a single-arm Phase II clinical trial that demonstrated an overall response rate (ORR) of 26% by Response Evaluation Criteria in Solid Tumors in patients with stage IIIC and IV metastatic melanoma. Fifty patients over a 2-year period were identified and included in the study (IIIC-10, IVM1a-16, M1b-4 and M1c-20). The treatment protocol involved intratumoral injection of injectable cutaneous, subcutaneous or nodal lesions with up to 4 ml of 10^6 PFU/ml followed by up to 4 ml of 10^8 PFU/ml every 2 weeks with a maximum of 24 treatments. Patients received a median of six biweekly injections. Of the 13/50 (26%) patients who responded, five experienced a partial response (PR) and 8 had a complete response (CR). Twelve of the 13 patients experienced a response that lasted from 7 to 31 months; with responses being reported in both injected lesions and uninjected visceral lesions. The 13th patient developed brain metastasis 1 month after experiencing a response. The median follow-up was 18 months (range 11–36 months). The authors reported 1 and 2-year OS of 58 and 52% [23]. These results led the US FDA to approve a Phase III study.

The OncoVex Pivotal Trial in Melanoma (OPTiM) was a multicenter, randomized, open-label Phase III trial that compared T-VEC with GM-CSF in a 2:1 ratio, in patients with unresectable stage IIIB to IV melanoma with limited visceral disease burden [19]. The primary end point of the study was the durable response rate (DRR), which was defined as an objective response (CR or PR) lasting ≥ 6 months that began within 12 months of initiation of therapy. Overall response rate, OS and safety were secondary end points. The trial enrolled 436 patients over a 2-year period randomized in a 2:1 fashion (T-VEC:GM-CSF). 295 patients were randomized to T-VEC and 141 patients to GM-CSF. A significantly higher DRR was seen with T-VEC compared with GM-CSF, 16.3% versus 2.1% respectively, ($p < 0.001$). The ORR was also significantly higher in the T-VEC arm

Figure 1. Talimogene laherparepvec is a viral oncolytic immunotherapy designed to produce both local and systemic effect resulting in tumor lysis and death.

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being 26.4% compared with an ORR of 5.7% in the GM-CSF arm ($p < 0.001$). Antitumor effect was observed in both uninjected and visceral sites. Thirty-two patients had a CR (10.8%) with T-VEC, while only one patient had a CR with GM-CSF (<1%). The patients in the T-VEC arm had a longer median OS, 23.3 months versus 18.9 months in the GM-CSF arm with a median follow-up of 44.4 months for the trial. However, the difference was not statistically significant (HR: 0.79, $p = 0.051$).

The most common adverse events (AE) in the T-VEC arm were pyrexia, chills, fatigue, nausea and injection-site pain which was similar to those reported in the Phase II trial. No treatment-related deaths occurred. In subgroup analyses, differences in DRR were more pronounced in stage IIIB or IIIC (33 vs 0%), and IVM1a disease (16 vs 2%) versus IVM1b (3 vs 4%) and IVM1c disease (8 vs 3%). Effects of T-VEC were more pronounced in patients who were treatment-naïve receiving T-VEC as a first-line therapy (24 vs 0%) than those receiving treatment as second-line or greater therapy (10 vs 4%). OS also showed the effect of T-VEC among patients receiving T-VEC as first-line therapy and stage IIIB, IIIC or IVM1a disease. Median OS for patients receiving T-VEC as first-line therapy was 33.1 months with T-VEC versus 17.0 months with GM-CSF, compared with second-line therapy where median OS was 17.1 months with T-VEC versus 23.2 months with GM-CSF. Median OS for stage IIIB, IIIC or IVM1a disease was 41.1 months with T-VEC

versus 21.5 months with GM-CSF, compared with stage IVM1b and IVM1c disease where there was a median OS of 13.4 months with T-VEC versus 15.9 months with GM-CSF [19].

In October 2015, based on the results from the Phase III trial, T-VEC monotherapy was approved by the FDA as the first FDA-approved oncolytic viral therapy for melanoma used to treat stage IIIB, IIIC and IVM1a disease. As stated in the package insert: 'Imlygic is indicated for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery. Limitations of use: T-VEC has not been shown to improve OS or have an effect on visceral metastases' [19,24–25].

Combination therapy

Combining T-VEC to promote tumor-derived antigen release with immunotherapies to treat regional and metastatic melanoma is increasingly being studied to determine if combination therapy improves efficacy. Engeland *et al.*, demonstrated that combining oncolytic viral therapy with a measles virus and CTLA-4 or PD-1 checkpoint blockade improved therapeutic outcomes in an immunocompetent murine model of melanoma [26].

A Phase Ib multicenter trial was designed to evaluate the safety and efficacy of T-VEC + ipilimumab, a monoclonal antibody against CTLA-4 (NCT01740297). The regimen of intralesional T-VEC used consisted of 4 ml of 10^6 PFU/ml at week 1, which was increased to

4 ml of 10⁸ PFU/ml at week 4, and then every 2 weeks. Ipilimumab (3 mg/kg iv.) was given every 3 weeks for four doses starting week 6. The median duration of treatment with T-VEC was 13 weeks. Eighteen patients were assessed and the ORR was 56% with six patients reported to have a CR (33%) per immune-related response criteria. There were no dose-limiting toxicities reported during the dose-limiting toxicities evaluation period. Grade 3/4 treatment-emergent adverse events (AEs) occurred in 32% and ipilimumab was attributed to cause two grade 3/4 adverse events. One patient had grade 3 hypophysitis, grade 3 adrenal insufficiency and grade 3 diarrhea; and one patient had grade 4 elevated amylase and lipase. One grade 5 event was observed with progression of disease and CNS metastasis [27,28]. The Phase II portion of the study with a primary end point of ORR is currently enrolling patients to receive T-VEC + ipilimumab vs. ipilimumab alone (NCT01740297).

Another combination therapy currently being studied, combines pembrolizumab with T-VEC in stage IIIB/IIIC and IV melanoma. The multicenter Phase Ib/III trial is designed to assess the safety profile and dose-limiting toxicities of T-VEC with pembrolizumab as well as PFS and OS (NCT02263508) [29]. Patients were given T-VEC injection doses up to 4 ml per treatment (10⁶ PFU/ml, then 10⁸ PFU/ml every 2 weeks) then started pembrolizumab 200 mg iv. on day 36 every 2 weeks until CR or progressive disease (per immune-related response criteria) or for up to 2 years. Twenty one patients were enrolled in the Phase Ib trial. The median treatment duration was 13.1 weeks and seven T-VEC infusions and 10.1 weeks and five pembrolizumab infusions. No treatment-related grade 4 AEs were reported, six patients had grade 3 AEs (anemia, hyperglycemia, macular rash, headache and generalized rash). The secondary objectives will include assessing the DRR, overall response and AEs [29].

Current practices

Following the OPTiM study and FDA approval, interest in T-VEC intralesional therapy is increasing. The 2016 National Comprehensive Cancer Network clinical practice guidelines list T-VEC as an option for intralesional injection in stage IIIB/C, in-transit melanoma and stage IVM1a disease [25]. Treatment protocols involve intratumoral injection of injectable cutaneous, subcutaneous or nodal lesions with up to 4 ml of 10⁶ PFU/ml for the initial injection. Three weeks later, up to 4 ml of 10⁸ PFU/ml is injected intralesionally every 2 weeks for a suggested minimum of 6 months, or until there is no residual tumor to inject. The volume of T-VEC that is injected is based on the lesion diameter (Table 1). Priority is given to the largest lesion first based on the diameter and then smaller lesions are injected until the total injectate (4 ml max) has been given or there are no more lesions to inject. Subsequent injections are prioritized by injecting new lesions first, followed by the largest lesions until all lesions are injected or the total volume of 4 ml has been used.

Conclusion & future perspective

T-VEC is an HSV type 1-derived oncolytic immunotherapy designed to selectively replicate within tumors and lyse tumor cells while promoting regional and systemic antitumor immunity. T-VEC has been evaluated in Phase I, II and III clinical trials. Following results of a Phase III trial demonstrating a significantly higher DRR of 16.3% in patients treated with T-VEC versus 2.1% in those treated with GM-CSF, T-VEC is now the only FDA approved oncolytic virus therapy for treatment of stage IIIB/C and IVM1a melanoma. Combination therapies with T-VEC and immunotherapies such as ipilimumab and pembrolizumab are currently under investigation to evaluate if combination therapy enhances the antitumor response

Table 1. Recommended dosing volume of talimogene laherparepvec.

Lesion size (longest dimension)	Talimogene laherparepvec injection volume	Dose (concentration: 10 ⁶ PFU/ml)	Dose (concentration: 10 ⁸ PFU/ml)
>5 cm	Up to 4 ml	Up to 4 million PFU	Up to 400 million PFU
>2.5–5 cm	Up to 2 ml	Up to 2 million PFU	Up to 200 million PFU
>1.5–2.5 cm	Up to 1 ml	Up to 1 million PFU	Up to 100 million PFU
>0.5–1.5 cm	Up to 0.5 ml	Up to 500,000 PFU	Up to 50 million PFU
≤0.5 cm	Up to 0.1 ml	Up to 100,000 PFU	Up to 10 million PFU

Dosing volume depends on lesion size and dosing stage/ dose concentration. Per Imlygic instructions for use/package insert (Amgen).

compared with monotherapy in metastatic melanoma. The use of T-VEC in the future may continue to expand as the prevalence of patients with melanoma increases and as we better understand its efficacy in combination treatment with immunotherapies.

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