Real-World Outcomes of Talimogene Laherparepvec Therapy: A Multi-Institutional Experience

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BACKGROUND: Talimogene laherparepvec (TVEC) is an FDA-approved oncolytic herpes virus used to treat unresectable stage IIIB to IV metastatic melanoma via intralesional injection. This study aims to characterize the efficacy TVEC in patients with unresectable stage IIIB to IV melanoma.

METHODS: We performed a multi-institutional, IRB-approved review of all patients who received TVEC at 3 centers from October 2015 to October 2018. Clinicopathologic characteristics, TVEC treatment data, and outcomes were assessed.

RESULTS: One hundred and twenty-one patients received TVEC, of which 80 patients had available treatment response data with at least 3-month follow-up. Anatomic sites treated were 19 (24%) head and neck, 9 (11%) upper extremity, 12 (15%) torso, and 40 (50%) lower extremity. Thirty-four (42.5%) patients did not receive therapy before TVEC. Side effects were mild and self-limited, most commonly flu-like symptoms seen in 22 (28%) patients. Median follow-up was 9 months (range 3 to 28 months), with complete local response in 31 (39%) and partial response in 14 (18%) patients. Of complete responders, 29 (37%) had no evidence of disease at last follow-up and received a median of 6 (range 2 to 12) cycles of therapy.

CONCLUSIONS: Talimogene laherparepvec is a well-tolerated, durable treatment option for patients with unresectable locoregional melanoma, particularly in stage IIIB/C disease. Additionally, we found that TVEC can be administered safely across anatomic sites that are otherwise not amenable to other local therapies. (J Am Coll Surg 2019;228:644–651. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Historically, locoregional recurrences of melanoma, including in-transit disease, account for 6% to 10% of all recurrences,[1,2] with a 5-year overall survival rate of 44%.[3] Locoregional treatment options were limited to surgical resection, isolated limb infusion, isolated limb perfusion, and external beam radiation therapy because there were no efficacious systemic therapies. In the past decade, advances in targeted systemic therapies[4,5] and intralesional therapies[6] have provided additional therapeutic options to treat locoregional and metastatic melanoma.

In 2015, the FDA approved the use of talimogene laherparepvec (TVEC) (Imlygic; Amgen Inc) for the

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treatment of unresectable stage IIIB to IV melanoma based on the results of the Oncovex (granulocyte macrophage colony-stimulating factor) Pivotal Trial in Melanoma (OPTiM).[6] Talimogene laherparepvec is a modified oncolytic herpes virus in which its neurovirulence factor has been removed by deleting both copies of the γ34.5 gene, and has been augmented to express human granulocyte macrophage colony-stimulating factor[7] by inserting that gene at one of the γ34.5 locations. The OPTiM trial,[6] a phase III prospective randomized trial comparing TVEC with granulocyte macrophage colony-stimulating factor, reported a statistically significant durable response (defined as continuous partial or complete response ≥6 months) in the TVEC arm compared with the control arm (16.3% vs 2.1%) and demonstrated an improvement of the overall response rate of 26.4% vs 5.2%. Additionally, in patients with a clinical response to TVEC, this study found a durable response of 80% at the time of last follow-up.[6]

The purpose of the current study is to evaluate the effectiveness and durability of TVEC administration in unresectable stage IIIB to IV melanoma patients since the drug became commercially available.

METHODS

We performed an IRB-approved retrospective chart review at Emory University, Moffitt Cancer Center, and University of North Carolina, of patients treated with TVEC from October 1, 2015 to October 1, 2018. We included patients 18 years old or older treated with TVEC at 1 of the 3 study centers. Exclusion criteria included patients treated before October 1, 2015 and/or patients enrolled in TVEC clinical trials. Patient characteristics including age at diagnosis, sex, Eastern Cooperative Oncology Group functional status, and race were collected. Primary tumor characteristics, including depth of primary tumor, mitotic rate, microsatellite instability, ulceration, BRAF status, RAF status, and tumor-infiltrating lymphocytes, were collected. Surgical management, including time to initial operation, type of operation, and lymph node operation was captured, including final pathology. Additional therapies before TVEC were recorded.

Talimogene laherparepvec was administered according to a well-defined process[8] and manufacturer-recommended doses. All injections were performed in the outpatient setting at 1 of the 3 study sites. Technical details have been published previously.[6] The initial concentration of the first dose of TVEC was 10^6 plaque-forming units/mL. The second dose was administered 3 weeks after the initial administration, at a higher concentration of 10^8 plaque-forming units/mL. For both concentrations, a maximum volume of 4 mL was used. The amount injected per lesion was based on the diameter of the lesion to be injected, varying from 0.1 mL to 4 mL. The 10^8 plaque-forming units/mL injection dose was repeated every other week until completion of therapy. The administrating physician determined completion of therapy, clinical evidence of complete response (which was confirmed by punch biopsy if pigmented or palpable lesions remained), progression of disease, stable disease, or the development of an adverse event.

At the time of TVEC initiation, TNM data were collected. All patients were staged according to the American Joint Committee on Cancer (AJCC) staging, 8th edition,[9] even when treatment was initiated before adoption of this staging version. Concurrent systemic therapies were also recorded. The duration, including number of cycles, time of first treatment effect, and local tumor response were recorded. Side effects to TVEC were also documented. Patients with at least 3 months of follow-up were included in the analysis. Follow-up data included duration of follow-up, evidence of recurrence, duration of disease-free survival from TVEC (in months), and subsequent therapies. Descriptive statistics Fisher's exact test, and Cox regression were calculated using STATA (Stata Corp).

RESULTS

From October 1, 2015 to October 1, 2018, we identified 121 patients that received TVEC therapy for advanced melanoma and met inclusion criteria. Fourteen patients were still receiving active treatment and 27 patients had fewer than 3 months of follow-up and were excluded from analysis. Median time of follow-up of the remaining 80 patients was 9 months (range 3 to 28 months). Median age at diagnosis for this cohort was 68.8 years (range 33 to 94 years); 52% of the patients were male (n = 41) and 99% of patients were non-Hispanic Caucasian (n = 79). The BRAF status was known in 58% of the patients, with 11 patients positive for a BRAF mutation. The primary sites of disease at the time of diagnosis were distributed as follows: 36% head and neck (n = 21), 11% upper extremity (n = 9), 14% torso (n = 14%), and 49% in the lower extremity (n = 39). Six patients did not undergo resection. Disease-free interval was defined as the time from surgical excision of the primary tumor to the time of clinical diagnosis of recurrent disease. Median disease-free interval was 13 months (range 1 to 175 months) (Table 1).

The majority of patients (n = 46 [57.5%]) did undergo systemic or regional therapy before TVEC, 4 patients

Table 1. Patient Characteristics

Characteristic	Data
Age at diagnosis, y, median (range)	68.8 (33–94)
Sex, n (%)	
Male	41 (52)
Female	39 (48)
Race, n (%)	
Non-Hispanic Caucasian	79 (99)
Black	1 (1)
BRAF status	
Negative, n (%)	35 (44)
Positive, n (%)	11 (11)
Unknown, n	34
No upfront resection, n	6
Disease-free interval, mo, median (range)	13 (1–175)
Therapy before talimogene laherparepvec	
None, n (%)	34 (42.5)
Received before therapy, n (%)	46 (57.5)
Adjuvant therapy, n	4
1 to 2 lines of therapy, n	24
3 to 4 lines of therapy, n	12
≥5 lines of therapy, n	3

received adjuvant therapy (systemic therapy after initial wide local excision), 27 patients received 1 to 2 lines of systemic therapy, 12 patients received 3 to 4 lines of systemic therapy, and 3 patients with 5 or more lines of systemic therapy. The most common therapy selected was checkpoint inhibition, accounting for 55% (n = 43) of therapies received. The second most common form of therapy was isolated limb infusion/perfusion, accounting for 13% (n = 10) of patients. Additional therapies included external beam radiation, interferon, interleukin-2, BRAF-MEK inhibition, and temozolomide (Table 2).

Clinical stage at the time of TVEC initiation was obtained and staged according to the AJCC 8th edition

Table 2. Distribution of Pre-Talimogene Laherparepvec Therapy

Pre-talimogene laherparepvec therapy	n	%
Checkpoint inhibitor	43	55
BRAF-MEK inhibitor	4	5
Isolated limb infusion/perfusion	10	13
External beam radiation therapy	7	9
Interferon therapy	5	6
Interleukin-2	3	4
Temozolomide	4	5
Other	2	3

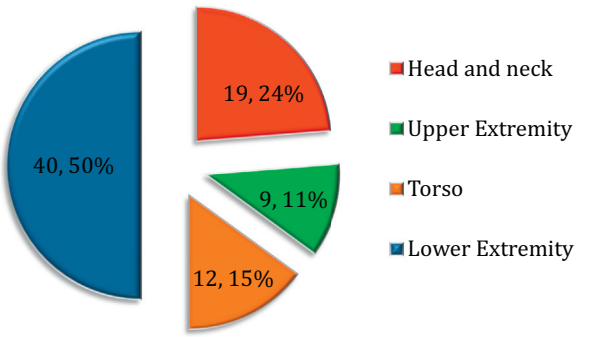

Figure 1. Location of talimogene laherparepvec treatment (n, %). Distribution of anatomic sites treated with talimogene laherparepvec. Number of patients and percent reported.

definitions.[9] One patient was staged as a clinical stage IIA and was administered TVEC, as the patient had persistently positive margins despite multiple resections to the point of unresectability. We excluded this patient from our analysis, as the patient did not meet FDA-approved indications for use of TVEC. Thirty-seven patients had clinical stage IIIB disease (46%), 25 patients had clinical stage IIIC disease (31%), 1 patient had clinical stage IIID disease (1%), and 16 patients also had distant metastatic disease at the time of treatment (20%). Patients received a median of 5 cycles of TVEC (1 to 14 cycles). Anatomic distribution of treatment included 24% in the head and neck region (n = 19), 15% in the torso (n = 12), 11% in the upper extremity (n= 9), and 50% in the lower extremity (n = 40) (Fig. 1). Twenty-nine (37%) patients experienced a complete response. Six (8%) patients had partial response at the end of treatment, 15 (19%) patients had stable disease, and 25 (30%) patients had disease progression. When evaluating only locoregional response, there was a 57% overall response rate (n = 45), with 39% patients

Table 3. Talimogene Laherparepvec Treatment Details

TVEC therapy	n	%
Reason for stopping talimogene laherparepvec		
No evidence of disease/complete remission	29	37
Partial response	6	8
Stable disease	15	19
Systemic progression	24	30
Other	5	6
Local response		
Complete response	31	39
Partial response	14	18
Stable disease	20	25
Local progression	14	18

Table 4. Complications

Symptom	n	%
None	46	58
Constitutional/flu-like (fever, fatigue, nausea, syncope)	22	28
Injection site (pain, bleeding, itching, redness)	6	8
Cold sore	1	1
Infection	4	5

exhibiting complete response (n = 31) and 18% with partial response (n = 14). Stable disease was noted in 20 (25%) patients and there was local disease progression in 14 (18%) patients (Table 3).

Talimogene laherparepvec was relatively well tolerated, as 46 (58%) patients did not experience any adverse events. Constitutional, flu-like symptoms, including fatigue, fevers, nausea, and syncope, developed in 22 (28%) patients. Transient injection-site side effects, including pain, bleeding, itching, and redness developed in 6 (8%) patients. Five (6%) patients had treatment terminated early due to the development of cold sores (n = 1) and infection (n = 4), which included osteomyelitis in 1 patient and sepsis in another patient (Table 4).

We examined the durability of TVEC treatment in the complete response cohort. Median number of cycles received was 6 (range 2 to 12) cycles, and patients had a median follow-up of 12 (range 3 to 28) months. At the time of last follow-up, 83% (n = 24) of patients remained disease-free, and 4 (14%) patients had recurrent disease, and 1 (3%) patient died without evidence of disease. All 4 recurrences occurred distant to the TVEC treatment sites.

DISCUSSION

To date, this multi-institutional retrospective review is the largest published series assessing the efficacy and safety of the use of TVEC in locoregional advanced melanoma patients since the drug become commercially available in October 2015. Fifty-seven percent of patients in our cohort had local response to treatment and 39% had a complete local response. Our multi-institutional response data were similar to the single institutional data published by Perez and colleagues,[10] where they reported a complete response rate of 43.5% and an overall response rate of 56.5%. Both studies had a higher complete response rate than the OPTiM trial.[6]

To review, patients in the OPTiM trial had surgically unresectable stage IIIB to IV clinical disease and demonstrated overall response rate of 26.4%.[6] However, nearly half of these patients (44%) were staged as M1b or M1c according to the AJCC, 7th edition.[6,11] M1b disease was characterized as patients with metastatic lung disease and M1c disease as metastatic visceral disease compared with M1a disease, which included in-transit and locoregional metastatic disease. Following the new AJCC 8th edition staging guidelines published in 2017,[12] we performed a subset analysis according to stage at the time of TVEC treatment (Tables 5 and 6). The majority of our patients had stage IIIB to IVM1a disease (67%), a much higher percentage than seen in the OPTiM trial. More importantly, we found that patients with stage IIIB disease were more likely to have a complete local response (68%) compared with stage IIIC, IIID, and IV disease (26%, 0%, and 6%, respectively). In the post-FDA era of TVEC use, it appears that the drug is being used preferentially in stage IIIB to D and IVM1a patients. In addition, these findings neared statistical significance (p = 0.057). These findings demonstrate that response rates are reproducible across different academic practice settings, as our findings were consistent with the Moffitt single-institution experience.[10] Additionally, these patients also demonstrated a durable response, as 59% of patients with stage IIIB disease treated with TVEC had no evidence of disease at a median follow-up of 12 months (range 3.4 to 28.1 months) (Table 5). When compared across all stage III and IV disease, this was statistically significant (p = 0.003). This mirrors the

Table 5. Outcomes According to Stage at the Time of Talimogene Laherparepvec

		No evidence of disease		Alive with disease		Dead with disease		Died, no evidence of disease	
Stage	Total, n	n	%	n	%	n	%	n	%
IIIB	37	22	60	12	32	2	5	1	3
IIIC	25	13	52	8	32	4	16	0	0
IIID	1	0	0	1	100	0	0	0	0
IV	16	1	6	10	63	3	19	2	12
Total	79	37	—	31	—	9	—	3	—

p = 0.003.

Table 6. Local Response to Talimogene Laherparepvec According to Stage at the Time of Talimogene Laherparepvec

		Complete response		Partial response		Stable disease		Progressive disease	
Stage	**Total, n**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
IIIB	37	21	57	4	11	7	19	5	13
IIIC	25	8	32	5	20	7	28	5	20
IIID	1	0	0	0	0	0	0	1	100
IV	16	2	12	5	31	6	38	3	19
Total	79	31	—	14	—	20	—	14	—

$p = 0.057$.

findings of the OPTiM trial, in which patients with stage IIIB and IIIC disease had improved durable response rates compared with patients with stage IV disease (33% vs 16%).[6]

Although the majority of our patients received therapy before TVEC (57.5%), we found that patients treated with TVEC as first-line therapy for unresectable locoregional metastatic melanoma had improved durable response. Thirty-three patients received TVEC as first-line therapy, with 72.7% (n = 24) with no evidence disease at last follow-up. Based on Kaplan-Meier survival estimates and Cox regression analysis, this was statistically significant when compared to patients that received 1 to 2 lines or ≥3 lines of pre-TVEC therapy ($p = 0.025$) (Fig. 2).

This study confirms the safety profile of TVEC seen previously.[6,10] Patients tolerated the treatment with minimal side effects. The majority of patients (86%) reported no side effects or mild constitutional symptoms (fevers, fatigue, nausea, and/or light-headedness). Only 5 patients had significant adverse events in which therapy was terminated early (cold sores, cellulitis, sepsis, and osteomyelitis).

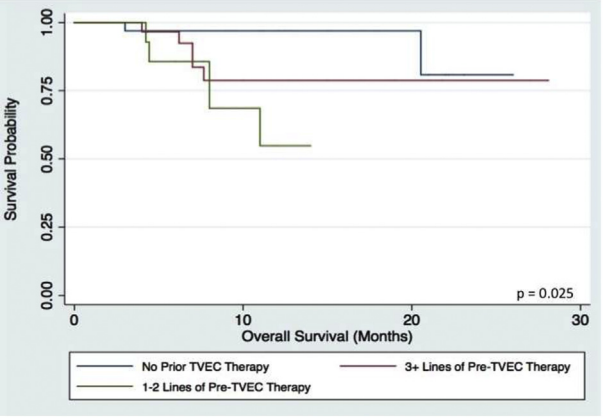

Figure 2. Kaplan-Meier survival estimates according to earlier talimogene laherparepvec (TVEC) therapies.

As evident in in this study, TVEC is well tolerated and can be used across anatomic locations, including the treatment of locally advanced head and neck melanomas with good response. Our study included 19 cases of head and neck stage IIIB to IV melanomas. Twelve patients had a complete response, of which 10 patients had remained disease free at the time of last follow-up. Recurrent and intransit head and neck melanomas in particular prove to be a challenging location to treat, as infusion and perfusion therapies are not feasible and external beam radiation can be technically challenging. Talimogene laherparepvec provides a well-tolerated locoregional treatment option in an otherwise difficult anatomic location.

As with any retrospective study, there are inherent limitations. Specifically, selection bias holds true. Although this is a limitation, this also reflects the real world application of TVEC, in which appropriate patient selection allows the maximal benefit of using TVEC. Our study also demonstrated the variability in treatment progression with the use of systemic therapy and other modes of local therapy. More than half of the patient cohort underwent earlier therapies to TVEC, which included external beam radiation therapy, isolated limb infusion, isolated limb perfusion, check point inhibitor therapy, and targeted BRAF-MEK therapy.

With improved systemic therapies for advanced melanoma, there will be a role to assess the synergistic effect of intralesional therapies in combination with targeted therapies (BRAF-MEK inhibitors) and immunotherapies, such as checkpoint inhibitors. Combination therapy continues to hold promise for both locoregional and distant metastatic disease, as a phase II randomized study compared TVEC plus ipilimumab vs ipilimumab alone.[13] Chesney and colleagues[13] found that combination therapy had and improved local overall response rate (39% vs 18%) as well as response in visceral lesions (52% vs 23%). More recently, a phase I study evaluating concurrent TVEC with pembrolizumab therapy demonstrated that the combination therapy was well tolerated with promising results demonstrating augmentation of

the microenvironment, specifically an increase in the presence of $CD8^+$ and PDL-1 expression.[14]

CONCLUSIONS

In summary, TVEC is a well-tolerated, durable treatment option for patients with unresectable locoregional melanoma, particularly in stage IIIB/C disease. Additionally, we found that TVEC can be administered safely across anatomic sites that are otherwise not amenable to other local or regional therapies.

Author Contributions

Study conception and design: Zager, Ollila
Acquisition of data: Louie, Perez, Jajja, Sun, Collichio, Delman, Lowe, Sarnaik, Zager, Ollila
Analysis and interpretation of data: Louie, Zager, Ollila
Drafting of manuscript: Louie, Zager, Ollila
Critical revision: Louie, Sun, Collichio, Delman, Lowe, Sarnaik, Zager, Ollila

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Discussion

DR PERRY SHEN (Winston-Salem, NC): Melanoma is a neoplasm for which the treatment of advanced stage disease has literally exploded due to increased understanding of the molecular underpinnings of this malignancy and the role of the immune system in cancer. New treatment approaches include immunotherapy using immune system checkpoint inhibitors against cytotoxic T-lymphocyte antigen 4 and programmed death-1 and molecular targeted therapy using BRAF inhibition, using BRAF inhibitors alone or in combination with MEK inhibitors for the 40% to 50% of patients with metastatic melanoma who have BRAF V600 mutation.

The authors present outcomes of patients with stage IIIB to IV melanoma treated with talimogene laherparepvec (TVEC) at 3 institutions with high-volume melanoma programs. They report a complete response rate of almost 40% and a partial response rate of almost 20%.

The overall response rate in your study was much higher than in the randomized trial comparing TVEC with granulocyte macrophage colony-stimulating factor (GM-CSF) that you described in your presentation. Their overall response rate, complete and partial, is about 26%. Can you comment on this and what you observed in terms of response rates in noninjected sites?

At this point, you did point out that your follow-up is short, so it is difficult to know the long-term outcomes of patients treated with this modality. You did mention that some of your partial response rate patients were down-staged so they could undergo resection. Can you tell us a little more about the type of patients? Who was able to be down-staged and what type of resections were there in those patients who were able to undergo resection after downstaging with TVEC? And then you mentioned a Phase I trial. There are preliminary data about the use of TVEC with checkpoint inhibitors such as ipilimumab or pembrolizumab to increase overall response. Did any patients in your current cohort receive any concomitant therapy with checkpoint inhibitors, or were they all TVEC alone in this current cohort of patients?

When I was looking over a bit of the history of injectional intralesional therapy, I remember when I was a fellow at the John Wayne Cancer Institute, hearing Dr Donald Morton discussing bacille Calmette-Guerin (BCG) injections for recurrent melanoma. And we did some when I was a fellow. He first proposed the use of this BCG when he was at the National Cancer Institute Surgery Branch, with initially pretty amazing results, but also considerable