Safe and Effective Standards of Care

Supporting the administration of T-VEC for patients with advanced melanoma in the outpatient oncology setting

Lisa M. Wail, PhD, RN, CNS, AOCNS®, and Abigail Baldwin-Medsker, MSN, RN, OCN®

BACKGROUND: Talimogene laherparepvec (T-VEC) is the first oncolytic virus (OV) to demonstrate therapeutic benefit for the treatment of advanced melanoma. As a live virus, the use of T-VEC in medical and surgical outpatient clinics posed challenges.

OBJECTIVES: The purpose of this article is to describe the challenges faced when introducing an OV treatment into outpatient clinics and the processes implemented to ensure safety for patients, caregivers, and staff across the care continuum.

METHODS: An interdisciplinary team of experts developed and implemented new practices and workflows to support the administration of T-VEC in the outpatient setting. Clinical staff were educated on this new treatment, its indications and side effects, and the practice standards created to support its use.

FINDINGS: T-VEC posed safety and logistical challenges that were successfully addressed and implemented. To date, 16 patients with locoregionally advanced melanoma have been treated with T-VEC. No adverse events occurred related to preparation or administration, which opens the door for similar therapies in the future.

KEYWORDS
talimogene laherparepvec; T-VEC; oncolytic viruses; virus therapy; cancer

DIGITAL OBJECT IDENTIFIER
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MELANOMA IS SKIN CANCER THAT ARISES FROM THE MELANOCYTES in the epidermis. Its incidence has risen since 1980; an estimated 87,110 new melanomas will be diagnosed in 2017 (American Cancer Society, 2017; Howlader et al., 2013). Surgery cures most early-stage melanoma, but five-year survival rates for late-stage melanoma are as low as 15%–20% (American Cancer Society, 2017). Traditional treatment options for unresectable or metastatic melanoma include palliative surgery, radiation therapy, systemic chemotherapy, and immunotherapy with interleukin-2 (IL-2) (Dummer et al., 2015). Unfortunately, these treatments have had little impact on overall survival, leaving patients with no effective first-line treatment options.

Since 2011, new and more effective immunotherapies have been approved for treating advanced melanoma and have changed clinical management of this disease (Eggermont et al., 2016; Hodi et al., 2010; Ribas et al., 2016). Each of these immunotherapies has a unique mode of action. Immune checkpoint inhibitors use the immune system to attack cancer cells while ignoring healthy cells. Common checkpoint inhibitors used to treat melanoma are cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitors, such as ipilimumab (Yervoy®), and programmed cell death protein 1 (PD-1) inhibitors, such as pembrolizumab (Keytruda®) and nivolumab (Opdivo®). CTLA-4 and PD-1 inhibitors induce antitumor immune responses by regulating T-cell activation and proliferation (McDermott et al., 2014; Papaioannou, Beniata, Vitsos, Tsitsilonis & Samara, 2016). As single agents, ipilimumab and pembrolizumab have each shown increased overall survival (Hodi et al., 2010; Robert et al., 2015; Schadendorf et al., 2015). Studies examining combination treatments using ipilimumab and nivolumab, a PD-1 inhibitor, and ipilimumab with dacarbazine, a chemotherapy, resulted in longer progression-free survival and higher response rates, but patients experienced higher incidences of grade 3 or 4 adverse events (Larkin et al., 2015; Postow et al., 2015; Robert et al., 2011). For patients with advanced disease, the risk of enduring severe side effects may outweigh the survival benefit that these treatments offer.

Oncolytic Viruses

Oncolytic viruses (OVs) are emerging as vital agents in cancer treatment. Because of their intrinsic characteristics, viruses can be capitalized on to
create safer and more effective cancer therapies. They are not independent life forms; rather, they are dependent on a host to multiply (Sze, Reid & Rose, 2013). Viruses are cultivated to recognize a particular cancer cell type as their host and modified to improve safety. Viruses that are designed to target cancer cells are called OVs (Pol et al., 2015).

OVs are naturally occurring or engineered to target specific cancer cells’ signaling pathways as they undergo a malignant transformation while leaving healthy tissue intact (Keller & Bell, 2016). Although the mechanism of cell death varies in different viruses, the debris released during cell lysis stimulates an immune response in which viral and tumor antigens are emitted into the tumor’s microenvironment (Lawler, Speranza, Cho, & Chiocca, 2017). The release of these antigens into the microenvironment allows the OV to infect more cancer cells and expand tumor lysis (Alvarez-Breckenridge, Choi, Suryadevara, & Chiocca, 2015; Kohlhapp & Kaufman, 2016; Pol et al., 2015). In addition, OVs produce a tumor-specific immunity, which expands tumor destruction beyond the infected sites (Kohlhapp & Kaufman, 2016). OVs infect endothelial cells within the tumor and induce a vascular breakdown, which results in necrosis of uninfected tumor cells. These two distinct mechanisms may create a double-edged sword and inhibit the potential of OVs to fight cancer. A robust immune system may respond to limit the spread of the virus into the tumor environment and diminish the effectiveness of the OV. To maximize the anticancer efficacy of OVs, future treatments need to target therapies that enhance the replication and lytic activity of the OV while promoting the stimulation of specific immune responses (Marchini, Scott, & Rommelaere, 2016).

**Talimogene Laherparepvec**

Talimogene laherparepvec (T-VEC) (IMLYGIC®) is the first OV to demonstrate a therapeutic benefit (Andtbacka et al., 2015). T-VEC is a genetically modified oncolytic viral therapy engineered from herpes simplex virus 1 (HSV-1), the virus that causes cold sores (Amgen, Inc., 2016). It destroys cancer by directly attacking cancer cells and helps the immune system recognize and destroy cancer cells. T-VEC has demonstrated promise as an intratumor therapy for unresectable, advanced melanoma (Andtbacka et al., 2015; Kaufman et al., 2016; Senzer et al., 2009). In 2015, the U.S. Food and Drug Administration (FDA) approved its use as a treatment for unresectable, cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after initial surgical resection (Amgen, Inc., 2016). Satellite metastases are locoregional tumors that are located less than 2 cm from the primary tumor; tumors that are located greater than 2 cm from the primary site are called in-transit metastases (Sloot, Rashid, Sarnaik, & Zager, 2016). Although six new agents for melanoma have been approved since 2011, none of them are specific to the local treatment of the small melanoma lesions found in patients with locoregionally advanced melanoma (Eastman, 2015). The addition of T-VEC fills a void in treatment options for this subset of patients.

T-VEC’s efficacy has been demonstrated in studies. Senzer et al. (2009) conducted a phase 2 trial assessing overall tumor response and survival in 50 patients with stage IIIIC or IV melanoma receiving intratumor injections with T-VEC. Overall survival was 58% at one year and 52% at two years. T-VEC was well tolerated with flu-like symptoms, such as fever (52%) and chills (48%).

In the OPTiM trial, a phase 3 study examining the efficacy of intrallesional T-VEC versus subcutaneous recombinant granulocyte-macrophage colony–stimulating factor (GM-CSF), 436 patients with unresectable stage IIIIB or IV melanoma were randomized to receive T-VEC or GM-CSF (Andtbacka et al., 2015). Durable response rate (DRR) was the primary endpoint. DRR was significantly higher in the T-VEC group (16.3%, 95% confidence interval [CI] [12.1%, 20.5%]) as compared with the GM-CSF group (2.1%, 95% CI [0%, 4.5%]) (odds ratio = 8.9,

<table>
<thead>
<tr>
<th>TABLE 1. T-VEC TREATMENT SCHEDULE</th>
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<td><strong>TREATMENT</strong></td>
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| Initial | Not applicable | 4 ml | 10⁶ (1 million) PFU per ml | ▪ Inject largest lesion(s) first.  
▪ Prioritize injection of lesion(s) based on size until maximum injection volume is reached or all injectable lesions have been treated. |
| Second | 3 weeks after initial treatment | 4 ml | 10⁷ (100 million) PFU per ml | ▪ Inject any new lesion(s).  
▪ Prioritize injection of lesion(s) based on size until maximum injection volume is reached or all injectable lesions have been treated. |
| All subsequent treatments | 2 weeks after previous treatment | 4 ml | 10⁷ (100 million) PFU per ml | ▪ Inject any new lesion(s).  
▪ Prioritize injection of lesion(s) based on size until maximum injection volume is reached or all injectable lesions have been treated. |

PFU—plaque-forming unit; T-VEC—talimogene laherparepvec

Note. Used and adapted with permission of Amgen, Inc.
p < 0.001). Responses were observed in injected and un.injected lesions, including a greater than 50% decrease in the size of 15% of un injected, visceral lesions. Patients receiving T-VEC had a median overall survival of 23.3 months (95% CI [19.5, 29.6]) as compared with those receiving GM-CSF whose overall survival was 18.9 months (95% CI [16.2, 23.7]) (hazard ratio = 0.79; 95% CI [0.62, 1], p = 0.051). T-VEC was well tolerated, with less than 2% of patients reporting grade 3 or worse adverse events. Kaufman et al. (2016) conducted a one-arm study of 50 patients with stage IIIIC or IV melanoma. Each participant received as many as 8 doses during 15 weeks in 1 or more skin or subcutaneous tumors for a total of 128 treated tumors. To assess systemic response, at least one tumor, visceral or nonvisceral, per patient (N = 146) was not treated. Patients were treated until a complete response was achieved or clinically significant disease progression or unacceptable toxicity occurred. Findings suggest a local and systemic benefit of T-VEC. Of the 128 lesions injected directly with T-VEC, 86 (67%) decreased in size by greater than 30%, and 59 (46%) resolved completely. Of the untreated tumors, 146 were nonvisceral, and 32 were visceral. Sixty (41%) nonvisceral tumors decreased in size by greater than 30%, with a complete response seen in 44 lesions. Four of 32 visceral tumors decreased in size by greater than 30%, of which a complete response was seen in three lesions. T-VEC was well tolerated and demonstrated efficacy in this subset of patients with advanced melanoma.

**Considerations for T-VEC Administration**

As a first-time live virus treatment, the use of T-VEC posed unique concerns related to patient care and safety, staff safety, and workflows. At Memorial Sloan Kettering Cancer Center, a National Cancer Institute–designated cancer center in New York, New York, an interdisciplinary team was convened to develop a comprehensive plan to ensure the safe and seamless delivery of T-VEC treatments. The team consisted of clinical nurses, nurse leaders, infection control nurses, medical and surgical oncologists, pharmacists, and administrators who developed optimal workflows and coordinated care across the continuum. The purpose of this article is to describe the challenges overcome by this team in response to the introduction of T-VEC into the outpatient clinics. Since January 2016, 16 patients with locoregionally advanced melanoma have been treated with T-VEC, for a total of 77 doses at this comprehensive cancer center.

**Safety**

The team’s primary focus was safety. In accordance with the manufacturer’s recommendations, the hospital’s pharmacy and therapeutics committee and infection control group developed guidelines for storage, preparation, dosing, and administration of T-VEC (Amgen, Inc., 2016). No reports have been made of secondary transmission of the HSV-1 virus from patients receiving T-VEC; however, T-VEC poses a small and finite risk of accidental exposure and transmission of the herpes virus to those who may come in contact with the treated site. For this reason, T-VEC is contraindicated in immunocompromised individuals, pregnant women, or those with a history of primary or acquired immunodeficient states, leukemia, or lymphoma (Amgen, Inc., 2016). In immunocompromised individuals, HSV-1 infection can be devastating. For example, oral lesions may be larger or last longer; keratoconjunctivitis or cutaneous lesions by skin abrasions or cuts may develop. The most serious risk is the development of encephalitis (Rechenchoski, Faccin-Galhardi, Linhares, & Nozawa, 2017).

The manufacturer of T-VEC recommends that healthcare providers, caregivers, pregnant women, and newborns avoid direct contact with an injected lesion, dressings, or body fluids of a treated patient (Amgen, Inc., 2016). To accommodate this requirement, each clinic was outfitted with specialized personal protective equipment (PPE) suitable for handling chemotherapy and proper disposal units. The PPE required includes a protective, disposable gown made of lint-free, low-permeability fabric with a closed front, long sleeves, and knit closed cuff; nitrile, nonsterile, powder-free gloves; and a face shield. Staff who are pregnant or immunocompromised are advised to avoid direct contact with treated lesions and dressings and assisting with administration of the drug. Under the guidance of infection control nurses, the examination room cleaning procedures were updated. A pharmacist prepares all treatments under a dedicated hood that requires special cleaning and drying time after preparation. Special precautions are taken when transporting the drug from the pharmacy to the patient’s treatment room. The syringes containing T-VEC are double-bagged and placed in a rigid container. The donning of nitrile, nonsterile, powder-free gloves is required when handling the plastic bags and rigid container used to transport chemotherapy.

A physician or an advanced practice provider administers T-VEC into the tumor via a series of injections, beginning with the lower concentration and proceeding to the higher concentration.
on subsequent treatments (see Table 1). The drug is administered evenly throughout each lesion using a single insertion point along multiple tracks. The injection needle should be changed when injecting different lesions. The total amount of drug or injection volume administered per clinic visit is not to exceed 4 ml (Amgen, Inc., 2016). Treated sites should be covered with a nonpermeable, occlusive dressing for one week after injection or until no weeping or oozing occurs. Because many patients interface with multiple departments and healthcare providers, precautions to prevent inadvertent exposure across the care continuum were implemented. Dressing sets with a specialized label indicating the patient received a live virus were developed to place over the treated site. In addition, the nurse enters an alert into the clinical information system that the patient requires special precautions.

To promote safety and compliance with the plan of care, the nurse views the rationale for treatment and care precautions

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**FIGURE 1.**
NURSE COMPETENCY FOR ASSISTING WITH INTRATUMOR BIOLOGIC TREATMENTS

**DIRECTIONS**
Evaluator must validate competency on two occasions and document the method of verification and outcome after staff successfully demonstrates competency. Methods of verification must include discussion and at least one of the other methods listed. Evaluator must sign and date next to the appropriate title in the verification box.

**SPECIAL CONSIDERATIONS**
When assisting with talimogene laherparepvec (T-VEC) procedure, healthcare providers who are immunocompromised or pregnant should not prepare drug or be in the room when drug is administered.

<table>
<thead>
<tr>
<th>METHOD OF VERIFICATION</th>
<th>OUTCOME</th>
<th>VERIFICATION</th>
<th>SIGNATURE AND DATE</th>
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<tr>
<td>Discussion (required)</td>
<td></td>
<td>Nurse professional development specialist</td>
<td></td>
</tr>
<tr>
<td>Return demonstration</td>
<td>Satisfactory</td>
<td>Clinical nurse specialist</td>
<td></td>
</tr>
<tr>
<td>Simulation</td>
<td></td>
<td>Nurse leader</td>
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<tr>
<td>Performance</td>
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<td>Preceptor</td>
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**UPON COMPLETION OF TRAINING PROGRAM, THE NURSE WILL BE ABLE TO DO THE FOLLOWING:**

- Discuss the process for obtaining insurance authorization for the drug prior to procedure.
- Discuss knowledge of drug indications, dosage, administration, and side effects.
- Ensure that a pregnancy test has been ordered and resulted for all female patients of childbearing age two weeks prior to initiation of treatment.
- Assess pregnancy status of all female patients prior to each subsequent treatment.
- Demonstrate patient identification process.
- Demonstrate two-person process for chair- or bedside checks of agent.
- State rationale for the need to don necessary personal protective equipment when caring for patients receiving live virus.
- Demonstrate proper use of personal protective equipment.
- Discuss need for premedication.
- Demonstrate knowledge of handling and waste procedures of a live virus.
- Obtain vital signs before and after treatment.
- Monitor patient treatment tolerance.
- Demonstrate discharge teaching for patients and families.
- Perform patient and family education related to treatment, dressing care, and documents in patient education documentation form.
- Demonstrate use of the following:
  - Electronic adult treatment order (eATO)
  - Electronic medication administration record (eMar)
  - Clinical documentation note

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with the patient and caregiver, and educates both on how to care for injection site dressings. They are instructed to avoid touching the injection sites and dressings because doing so can lead to the inadvertent transfer of T-VEC to other parts of the body. If the dressing must be changed, patients and caregivers are instructed to wear gloves, dispose of the dressing in a sealed plastic bag, and perform hand hygiene.

Coordination of Care and Financial Concerns
T-VEC treatments produce scheduling and workflow challenges because of the short stability of the recommended first dose. A pharmacist prepares T-VEC under a dedicated hood to minimize exposure. Close coordination between pharmacy and patient scheduling is necessary to avoid interfering with overall high chemotherapy demands. High drug cost is another issue. Because T-VEC is expensive, insurance preauthorization needs to be ensured before initiating treatment. Treatments can last for six months or more, which translates into a significant financial burden. The high cost of T-VEC also requires a finely tuned process of collaboration between the clinical staff and those securing financial clearance. The physician orders T-VEC at least 48 hours before the scheduled administration date to ensure time for insurance approval and coordination with the pharmacy. A verification process is initiated immediately after the order is placed, which involves an independent check of the order by a verification nurse, pharmacist, and the treating clinician at the chairside.

Implications for Nursing Practice
New standards of care were created for the administration of T-VEC. The clinical nurses were educated on the care of the patient receiving T-VEC and demonstrated their competency as outlined in the Nurse Competency for Assisting with Intratumor Biologic Treatments (see Figure 1). A nurse assesses the patient prior to and after the procedure and educates the patient and caregiver on postinjection care to the site, precautions to minimize exposure, and potential side effects.

During the patient assessment, the nurse obtains pre- and postadministration vital signs. OV treatment is commonly followed by an expected viral syndrome that may include tachycardia, fever, chills, fatigue, and a change in blood pressure (Burke, Nieva, Borad, & Breitbach, 2015). Supportive care with antipyretics and analgesics is indicated for the management of symptoms after OV treatment. Patients are educated that a low-grade fever is common in the first 48 hours after treatment and advised to still report any temperature greater than 100.5°F.

T-VEC increases the risk of impaired healing in patients with underlying risk factors (e.g., previous radiation at the injection site or lesions in poorly vascularized areas). Necrosis or ulceration of tumor tissue may occur during T-VEC treatment (Amgen, Inc., 2016). Prompt assessment of and intervention for these issues are essential. The nurse needs to provide meticulous wound care and infection precautions, particularly if tissue necrosis results in open wounds. The following case study illustrates the nurse’s role in caring for a patient undergoing this treatment.

Case Study
Mrs. T is a 52-year-old Russian-speaking woman with in-transit metastases to the midback area. She has a history of type 2 diabetes treated with metformin and diet. She speaks some English, but her primary language is Russian. Mrs. T lives alone. Her daughter lives nearby and is pregnant with her fourth child. She is the frequent caregiver of her daughter’s children, ages 10, 7, and 3 years. Mrs. T presents with three tumors located about 4 cm proximal to her primary tumor site where she had a melanoma tumor resected four years ago. She recurred about a year ago and was treated with IL-2 injections. The tumors responded initially but then began to grow. At this point, her physician decides to initiate T-VEC injections. In planning her care, the primary nurse identifies the individualized needs of Mrs. T. The first challenge is Mrs. T’s language barrier. In educating Mrs. T about her disease and treatment, the nurse secures a Russian translator to ensure that Mrs. T and her caregiver understand the plan of care, potential side effects of T-VEC, and self-care measures. At every visit, a translator is provided.

The second issue is Mrs. T’s social situation. She lives alone and depends on her pregnant daughter for support. She also has contact with her young grandchildren. Because the location of her disease is in a difficult area to see and care for, home care is arranged. The primary nurse educates the homecare nurse on safe handling of the treated sites and dressings to avoid inadvertent exposure of virus to the homecare nurse or family.

A third concern is Mrs. T’s diabetes, which places her at risk for poor wound healing. Her risk for tumor ulceration is increased further with T-VEC. At all nurse encounters, at home and in the clinic, a skin assessment is performed to note changes in skin color and integrity.

Discussion and Recommendations
As the first OV of its kind, T-VEC has demonstrated promise as an effective treatment for unresectable advanced melanoma (Andtbacka et al., 2015; Kaufman et al., 2016; Senzer et al., 2009). As a genetically modified live virus, the administration of T-VEC in the authors’ outpatient clinics posed unique challenges. The absence of literature to support the creation of standards of care was a barrier. Employing a comprehensive, interdisciplinary team

IMPLICATIONS FOR PRACTICE
- Develop and implement interdisciplinary workflows that support the safe delivery and administration of talimogene laherparepvec (T-VEC) in outpatient medical and surgical clinics.
- Educate patients about T-VEC, its mechanism of action, and the precautions that need to taken to prevent inadvertent exposure of live virus to unaffected areas and caregivers.
- Assess and monitor patients receiving T-VEC therapy for side effects, particularly in adults who are at increased risk.
of experts helped overcome these obstacles. Careful consideration by the team in developing new workflows and practices that supported patient, caregiver, and staff safety across the care continuum was essential. Education of the staff regarding management of the patient receiving T-VEC therapy, dissemination of the new workflows, and the provision of onsite support from nursing leadership facilitated the introduction of this treatment into the institution. It also opened the door for similar therapies in the future.

Since January 2016, this comprehensive cancer center has treated 16 patients with T-VEC for a total of 77 doses in the outpatient clinics. The workflows described in this article have proven to be successful as evidenced by no adverse patient or employee events have occurred related to inadvertent exposure. In addition, the rigorous preparatory processes have prevented drug waste. The nurses and physicians who care for patients undergoing treatment for advanced melanoma have verbalized positive feedback regarding the implementation process and sustaining the practices outlined in this article. Maintenance of competencies has been demonstrated through peer review and annual observations.

Conclusion
Coinciding with the FDA approval of T-VEC, efforts continue to be dedicated to the development and clinical research of OV's with improved specificity and potency in solid tumor disease (Pol et al., 2015). As the cancer community continues to embrace viruses as a form of treatment, nurses and other healthcare providers face the challenge of implementing safe and efficient operating procedures that mitigate potential liabilities and promote safe, effective treatments.

Lisa M. Wall, PhD, RN, CNS, AOCNS®, is a clinical nurse specialist and Abigail Baldwin-Medsker, MSN, RN, OCN®, is a nurse leader, both in the Department of Nursing at the Memorial Sloan Kettering Cancer Center in New York, NY. Wall can be reached at walli@mskcc.org, with copy to CJONEditor@ons.org. (Submitted December 2016. Accepted March 20, 2017.)

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REFERENCES


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