Administration and Handling of Talimogene Laherparepvec: An Intralesional Oncolytic Immunotherapy for Melanoma

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Purpose/Objectives: To describe the administration and handling requirements of oncolytic viruses in the context of talimogene laherparepvec (Imlygic™), a first-in-class oncolytic immunotherapy.

Data Sources: Study procedures employed in clinical trials, in particular the OPTiM study.

Data Synthesis: Evaluation of nursing considerations for administration of talimogene laherparepvec.

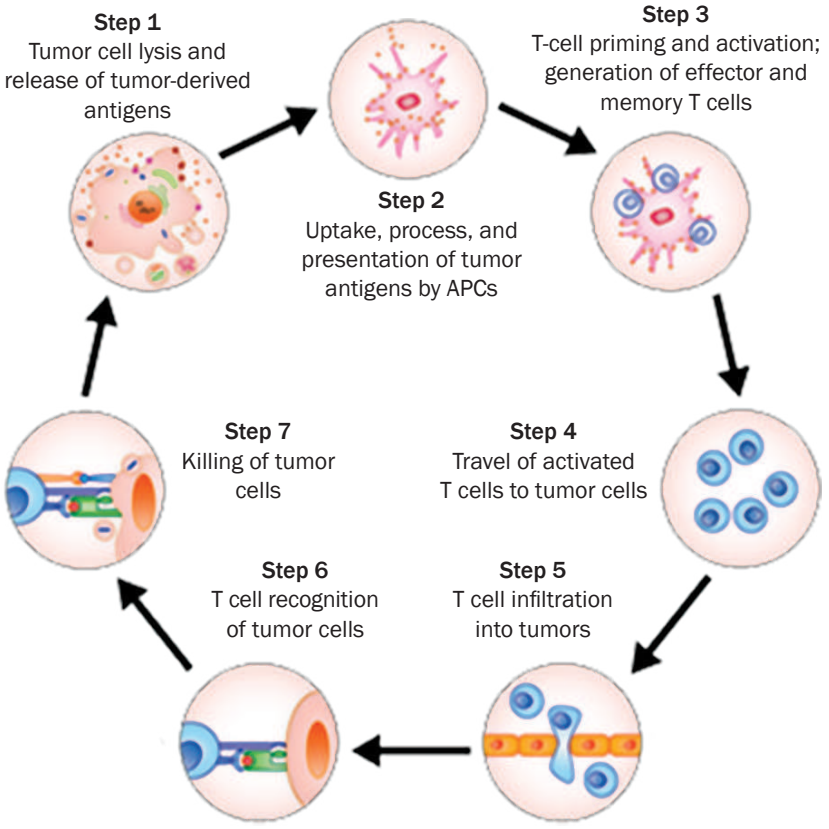
Conclusions: Talimogene laherparepvec is administered through a series of intralesional injections into cutaneous, subcutaneous, or nodal tumors (with ultrasound guidance as needed) during an outpatient clinic visit. A single insertion point is recommended; however, multiple insertion points are acceptable if the tumor radius exceeds the needle's radial reach. Talimogene laherparepvec must be evenly distributed throughout the tumor through each insertion site. Talimogene laherparepvec requires storage at −90°C to −70°C and, once thawed, should be administered immediately or stored in its original vial and carton and protected from light in a refrigerator (2°C to 8°C).

Implications for Nursing: Because talimogene laherparepvec can be administered in the outpatient setting, nurses will be pivotal for appropriate integration and administration of this unique and effective therapy.

The development of cancer immunotherapies, which employ the immune system to promote antitumor activity, has resulted in significant changes in the treatment of cancer (Mellman, Coukos, & Dranoff, 2011). Treatment with immunotherapies has resulted in durable responses and long-term benefit in patients with a variety of different tumor types, including advanced melanoma (Brahmer et al., 2015; Garon et al., 2015; Hamid et al., 2013; Herbst et al., 2013; Hodi et al., 2010; Postow et al., 2015; Robert et al., 2015; Topalian et al., 2012).

The Cancer-Immunity Cycle proposed by Chen and Mellman (2013) has become the model for cancer immunotherapy research (see Figure 1). In this model, tumor-derived antigens (TDAs), which are released through cancer cell death, are processed and presented by dendritic cells to T cells in the lymph nodes. In subsequent steps, activated cytotoxic T cells traffic systemically and infiltrate distant tumor sites. If the activated T cell encounters cancer cells with a matching antigen profile, the target cancer cell is killed, resulting in immunogenic cell death. TDAs are subsequently released, resulting in a vicious cycle (Chen & Mellman, 2013).

The Cancer-Immunity Cycle does not act appropriately in patients with cancer: (a) tumor antigens may go unpresented by dendritic cells or be identified as self rather than foreign by dendritic cells or T cells; (b) T cells may not be properly activated; (c) T cells may not accurately localize or infiltrate tumors; and/or (d) the



APC—antigen-presenting cell

Note. From "Oncology Meets Immunology: The Cancer-Immunity Cycle," by D.S. Chen and I. Mellman, 2013, *Immunity,* p. 2. Copyright 2013 by Elsevier Inc. Adapted with permission.

FIGURE 1. The Cancer-Immunity Cycle

activity of effector cells may be impeded by the tumor microenvironment (e.g., expression of programmed death–ligand 1 [PD-L1] by cancer cells) (Chen & Mellman, 2013).

The goal of cancer immunotherapy is to restore the Cancer-Immunity Cycle while avoiding the development of autoimmune adverse outcomes. A variety of different and novel approaches to cancer immunotherapy have been employed in metastatic melanoma, including checkpoint inhibitors against cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) (e.g., ipilimumab [Yervoy®], pembrolizumab [Keytruda®], nivolumab [Opdivo®]), which restore the effector function of T cells (Hodi et al., 2010; Robert et al., 2014; Topalian et al., 2012, 2014); adoptive T-cell transfer using modified T cells to induce anticancer immunity (Garfall et al., 2015; Rosenberg & Restifo, 2015); and oncolytic immunotherapies, which use oncolytic viruses to prime the immune system (Andtbacka, Kaufman, et al., 2015; Cripe et al., 2015; Kaufman, Ruby, Hughes, & Slingluff, 2014). This review focuses on the oncolytic immunotherapy approach and, in particular, its potential role in the treatment of melanoma.

Oncolytic Immunotherapy

Oncolytic immunotherapy is a novel treatment strategy that employs wild-type, mutated, or genetically modified viruses to infect and lyse cancer cells (oncolysis), promoting tumor-specific immunity (Nguyen, Ho, & Wan, 2014; Rini, 2014).

In contrast to other systemic immunotherapies that act in the later stages of the Cancer-Immunity Cycle (e.g., checkpoint inhibitors), oncolytic immunotherapies affect the first steps of the cycle, the release of TDAs and presentation by dendritic cells. Tumor antigen release through oncolysis can stimulate a local (Pol, Rességuier, & Lichty, 2012) and systemic antitumor immune response that may include responses at distant uninjected sites. After infection of the tumor cells, these viruses replicate within, and subsequently rupture, cancer cells (oncolysis); newly released viruses then infect other surrounding cancer cells (Mullen & Tanabe, 2002). This step can be repeated over and over, decreasing the tumor mass (Liu, Galanis, & Kirn, 2007).

A number of different oncolytic immunotherapies are in development for advanced melanoma, including talimogene laherparepvec (Imlygic™), a genetically modified recombinant herpes simplex virus type 1 (HSV-1); HF-10, a spontaneously occurring oncolytic mutant HSV-1; and CVA21, a bio-selected immunotherapeutic strain of the Coxsackievirus A21 (Andtbacka, Curti, et al., 2015; Andtbacka, Kaufman, et al., 2015; Gildener-Leapman et al., 2013). Oncolytic immunotherapy represents a novel therapeutic modality for which administration, handling, and storage requirements differ from other approved cancer immunotherapies.

The goal of this article is to describe these requirements in the context of talimogene laherparepvec, the only oncolytic immunotherapy to have been evaluated in a phase 3 randomized, controlled trial to date. Talimogene laherparepvec was approved in 2015 by the U.S. Food and Drug Administration and is indicated for the local treatment of unresectable, cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery (Amgen Inc., 2015). However, talimogene laherparepvec has

not been shown to improve overall survival or have an effect on visceral metastases.

Talimogene Laherparepvec

Genetically Altered Herpes Simplex Virus Type 1 as an Oncolytic Virus

HSV-1 can be genetically modified to selectively destroy tumor cells while sparing normal tissues. These viruses replicate in tumors and mediate oncolysis through a variety of different mechanisms (Russell, Peng, & Bell, 2012). Preclinical studies have shown that genetically modified HSV-1 could elicit antitumor activity against tumor xenografts implanted in mice; subsequently, genetically modified viral strains were developed to enhance antitumor potency, drive host immune antitumor responses, and reduce clinical risk (Martuza, Malick, Markert, Ruffner, & Coen, 1991; Russell et al., 2012). In particular, the *ICP34.5* gene is the primary mediator of HSV-1 neurovirulence (Bolovan, Sawtell, & Thompson, 1994; Chou, Kern, Whitley, & Roizman, 1990) and, when it was deleted, subsequent infection was found to result in the lysis of many tumor types while sparing normal tissues. This observation resulted in the investigation of a number of *ICP34.5*-deficient HSV-1 strains as potential oncology therapeutics (Campadelli-Fiume et al., 2011).

The interferon–protein kinase R (PKR) pathway is a critical host defense mechanism that evolved to protect cells against viral infection. After HSV-1 infection, cellular activation of the PKR response typically decreases protein synthesis, promotes apoptosis, and activates autophagy to contain viral replication and proliferation. Consequently, HSV-1 relies on the ICP34.5 protein to circumvent this response and promote replication. Preferential tumor cell elimination by *ICP34.5*-deficient HSV-1 appears to result from PKR pathway defects and inhibited autophagy that may occur in tumors. These changes allow *ICP34.5*-deficient HSV-1 to efficiently propagate in tumor cells. Non-tumor cells that contain an intact interferon–PKR response are able to efficiently suppress viral replication and eliminate the *ICP34.5*-deficient virus (Campadelli-Fiume et al., 2011). *ICP34.5*-mediated neurovirulence appears to be similarly linked to the effects of *ICP34.5* on the PKR response, and the potential for induced autophagy, apoptosis, and other antiviral responses that protect against viral replication in the nervous system.

Genetic Modifications and Mechanisms of Action

Talimogene laherparepvec is a recombinant oncolytic virus created by genetic modification of a clinical isolate of HSV-1, the causative agent of the common fever blister or cold sore, that demonstrates enhanced oncolytic activity toward tumor cells (Liu et al., 2003). Viruses encode their own genes but use the host cellular machinery for replication after infection. To facilitate selective replication of talimogene laherparepvec in tumor cells and to maintain patient safety, the wild-type virus was genetically modified (see Figure 2). These modifications were as follows:

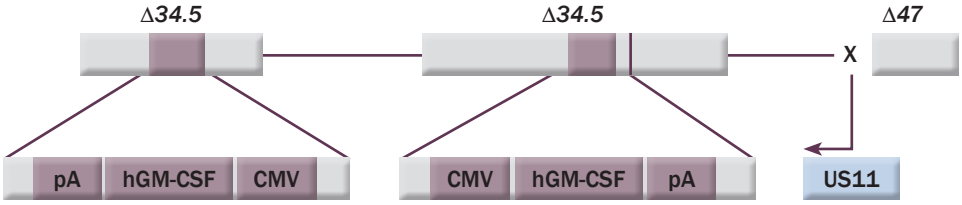
- Deletion of the *ICP34.5* gene promotes preferential killing of tumor cells, and selective talimogene laherparepvec replication in various tumors (but not normal tissue) has been confirmed in nonclinical pharmacology and toxicology studies (Bolovan et al., 1994; Chou et al., 1990).
- Insertion of a gene cassette encoding human granulocyte macrophage–colony-stimulating factor (GM-CSF) in both of the *ICP34.5*-deleted regions. Local GM-CSF expression following intratumoral injection is intended to increase the influx and activation of antigen-presenting cells, which process and present TDAs from tumor cells during cell death (Dranoff et al., 1993; Huang et al., 1994).
- Deletion of the *ICP47* gene to permit proper antigen presentation for both virus and tumor antigens and to increase replication efficiency in tumors.

The susceptibility of talimogene laherparepvec to anti-HSV therapeutics has been maintained via retention of the viral thymidine kinase gene, which is responsible for converting common anti-herpes virus pro-drugs (e.g., acyclovir [Zovirax®]) to their

FIGURE 2. Talimogene Laherparepvec Genome

CMV—cytomegalovirus; hGM-CSF—human granulocyte macrophage–colony-stimulating factor; pA—polyadenylation

Note. The talimogene laherparepvec genome is shown with the positions of the *ICP34.5* and *ICP47* deletions, marked as Δ34.5 and Δ47, respectively; immediate early expression of *US11* is driven by the *ICP47* promoter. The site of the hGM-CSF cassette insertion is shown in purple and expanded to show the composition of the hGM-CSF expression cassette, the CMV promoter, hGM-CSF cDNA, and a bovine growth hormone pA signal.



active forms. The proposed mechanism of action of talimogene laherparepvec is two-fold (see Figure 3). First, the virus produces a direct oncolytic effect in injected lesions by replication in tumor cells, resulting in cell lysis (oncolysis) and the release of TDA. Second, the virus produces systemic anti-tumor immune response, which is enhanced by production of virally derived human GM-CSF.

Clinical Studies With Talimogene Laherparepvec

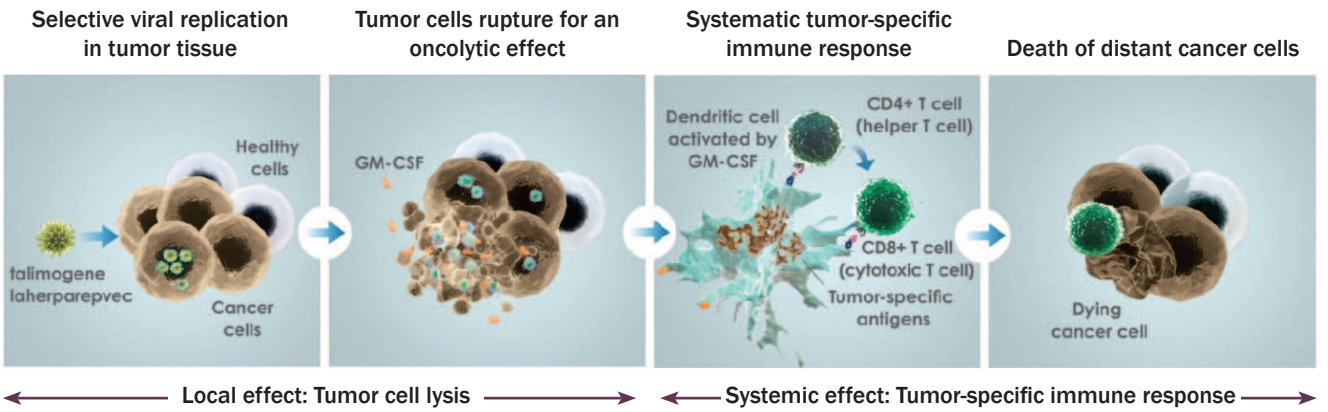
Early-phase clinical trials have demonstrated that talimogene laherparepvec produced an intratumoral response with an acceptable safety and tolerability profile (Hu, Coffin, & Davis, 2006; Senzer et al., 2009). Biologic activity was evidenced in a phase 1 study by tumor flattening, shrinkage, and necrosis (Hu et al., 2006). Data reported from a single-arm phase 2 study indicated that treatment with talimogene laherparepvec elicited a 26% overall response rate (ORR) in patients with stage IIIC/IV melanoma; responses were seen in injected and uninjected lesions, including visceral lesions (Senzer et al., 2009). A one-year survival rate of 58% was seen in all patients; one-year response rates of 58% and 40% were seen in all patients with stage IV melanoma and all patients with stage IV M1c melanoma, respectively (Senzer et al., 2009). Characterization of the tumor microenvironment of some patients treated during the phase 2 study indicated a significant increase in melanoma-associated antigen recognized by T cells (MART-1)-specific T cells in a patient who had a complete response after talimogene laherparepvec treatment (Kaufman et al., 2010). Evidence of MART-1–specific T cells could be detected in both local and distant lesions, which is consistent with the induction of systemic antitumor immunity (Kaufman et al., 2010). Common adverse events (AEs) experienced included mild influenza-like symptoms (e.g., fever, chills, nausea, fatigue), local reactions at the injection site, and low-grade (grade 1/2) anorexia (Hu et al., 2006; Senzer et al., 2009).

In a randomized, open-label, phase 3 study (OPTiM), patients with histologically confirmed and surgically unresectable stage IIIB, IIIC, or IV melanoma suitable for direct or ultrasound-guided injection were randomized 2:1 to receive intralesional talimogene laherparepvec or subcutaneous GM-CSF (Andtbacka, Kaufman, et al., 2015). GM-CSF was selected as a comparator because of preliminary evidence that it provided clinical benefit in resectable stage III/IV melanoma (Lawson et al., 2010; Spitler et al., 2009), its safety profile, and putative immune-mediated mechanism of action. Talimogene laherparepvec was delivered by intratumoral injection into cutaneous, subcutaneous, or nodal lesions on day 1, at three weeks after the first dose, then once every two weeks; injection into visceral tumors was not permitted. GM-CSF was administered subcutaneously once daily for 14 days in 28-day cycles. The primary endpoint, durable response rate (DRR), was significantly higher after talimogene laherparepvec administration (16%, 95% CI [12%, 21%]) than with GM-CSF treatment (2%, 95% CI [0%, 5%]; unadjusted odds ratio, 8.9, 95% CI [2.7, 29.2], $p < 0.001$). ORR also was significantly higher after talimogene laherparepvec injection than with GM-CSF treatment (26%, 95% CI [21%, 32%] versus 6%, 95% CI [2%, 10%]; descriptive $p < 0.001$) (Andtbacka, Kaufman, et al., 2015). Responses could be seen in injected nonvisceral lesions and noninjected visceral lesions after talimogene laherparepvec treatment, indicating local administration could evoke a systemic response at distant metastases. At the primary analysis of overall survival (OS), median OS was 23.3 months (95% CI [19.5, 29.6]) with talimogene laherparepvec treatment and 18.9 months (95% CI

FIGURE 3. Talimogene Laherparepvec Proposed Mechanism of Action

GM-CSF—granulocyte macrophage–colony-stimulating factor

Note. Image courtesy of Amgen Inc. Used with permission



[16.0, 23.7]) with GM-CSF treatment (hazard ratio [HR] = 0.79, 95% CI [0.62, 1.00], p = 0.051) (Andtbacka, Kaufman, et al., 2015). Differences in DRR and ORR after treatment with talimogene laherparepvec compared with GM-CSF alone were larger for patients with treatment-naive disease (DRR, 24% versus 0%; ORR, 38% versus 5%) compared with patients receiving treatment with second-line or greater therapy (DRR, 10% versus 4%; ORR, 17% versus 7%). Compared with GM-CSF alone, the effect of talimogene laherparepvec on OS was also more distinct for patients with stage IIIB/IIIC and IV M1a disease (HR = 0.57, 95% CI [0.40, 0.80]) and patients receiving first-line treatment (HR = 0.50, 95% CI [0.35, 0.73]) (Andtbacka, Kaufman, et al., 2015).

AEs that occurred more frequently during talimogene laherparepvec treatment than with GM-CSF treatment included chills, fever, injection-site pain, nausea, influenza-like illness, and fatigue (Andtbacka, Kaufman, et al., 2015). The incidence of grade 3 or greater AEs was 36% for patients who received talimogene laherparepvec and 21% for patients who received GM-CSF. The only grade 3 or greater AE occurring in 2% or more of the patients was cellulitis (talimogene laherparepvec, 2% [n = 6]; GM-CSF, less than 1% [n = 1]). Few patients discontinued because of AEs (talimogene laherparepvec, 4%; GM-CSF, 2%), and disease progression was the most common reason for discontinuation. No treatment-related fatal events occurred (Andtbacka, Kaufman, et al., 2015).

Administration and Handling Considerations

As an oncolytic virus administered by intralesional injection, talimogene laherparepvec has unique administration and handling requirements. Information on these requirements was drawn from the U.S. prescribing information for Imlygic, the pivotal phase 3 OPTiM study clinical trial protocol (Andtbacka, Kaufman, et al., 2015), and additional information provided by the manufacturer.

Intralesional Injection

Talimogene laherparepvec can be injected in the ambulatory/outpatient setting using universal biohazard precautions. Talimogene laherparepvec is administered as a series of intralesional injections using two different concentrations: an initial dose of 10^6 plaque-forming units per milliliter (PFU/ml) to seroconvert HSV-seronegative patients, and second and subsequent doses of 10^8 PFU/ml. Talimogene laherparepvec is measured in PFU/ml to account for the functional viruses only (i.e., defective viral particles that will fail to infect cells are not counted). Talimogene laherparepvec should be administered by appropriately qualified and trained healthcare professionals (including nurses) and in accordance with institutional policies. Protective equipment (e.g., gown, safety glasses, gloves) should be worn when preparing or administering talimogene laherparepvec. Talimogene laherparepvec is administered intralesionally into cutaneous, subcutaneous, and/or nodal tumors that are palpable or detectable by ultrasound guidance. Injection into visceral lesions (e.g., liver) has not been allowed in previous talimogene laherparepvec trials, but is now being explored in clinical studies (ClinicalTrials.gov identifier NCT02509507). Before talimogene laherparepvec injection, a topical or local anesthetic may be applied to the injection site, if necessary. Local anesthetic should not be directly injected into lesions and should be injected around the periphery of the lesions; otherwise, the altered pH in the microenvironment may impact the stability of talimogene laherparepvec. After administration of anesthetic, the lesion should be swabbed with alcohol.

Talimogene laherparepvec is injected evenly in the lesion using a single insertion point along multiple tracks as far as the radial reach of the needle allows. A single insertion point is recommended; however, multiple insertion points may be used if the tumor radius exceeds the radial reach of the needle. The needle should be changed every time when administering into a new lesion to avoid bacterial infection. The total volume of talimogene laherparepvec administered is as much as 4 ml per visit; the volume delivered to each tumor is contingent on the longest diameter of the lesion (Andtbacka, Kaufman, et al., 2015) (see Figure 4). Different lesions could be injected at different visits based on prioritization of injection of any new lesions and largest lesions, which should be injected first.

After injection of talimogene laherparpvec, pressure should be applied with a sterile gauze for at least 30 seconds. After swabbing the injection site with alcohol, gloves should be changed and the injection site covered with an absorbent pad and dry occlusive dressing. In addition, the exterior of the occlusive dressing should be swabbed with alcohol to minimize the risk of secondary transmission. Patients should be educated to keep the injection sites covered for at least the first week after each treatment visit—or longer if the injection site is weeping or oozing—and to replace the dressing if it falls off. Patients should also be advised that used dressings and cleaning materials should be sealed in a plastic bag and disposed of in household waste. Patients, caregivers, and healthcare professionals should wash their hands before and after accessing sites injected with talimogene laherparepvec.

Distribution and Storage

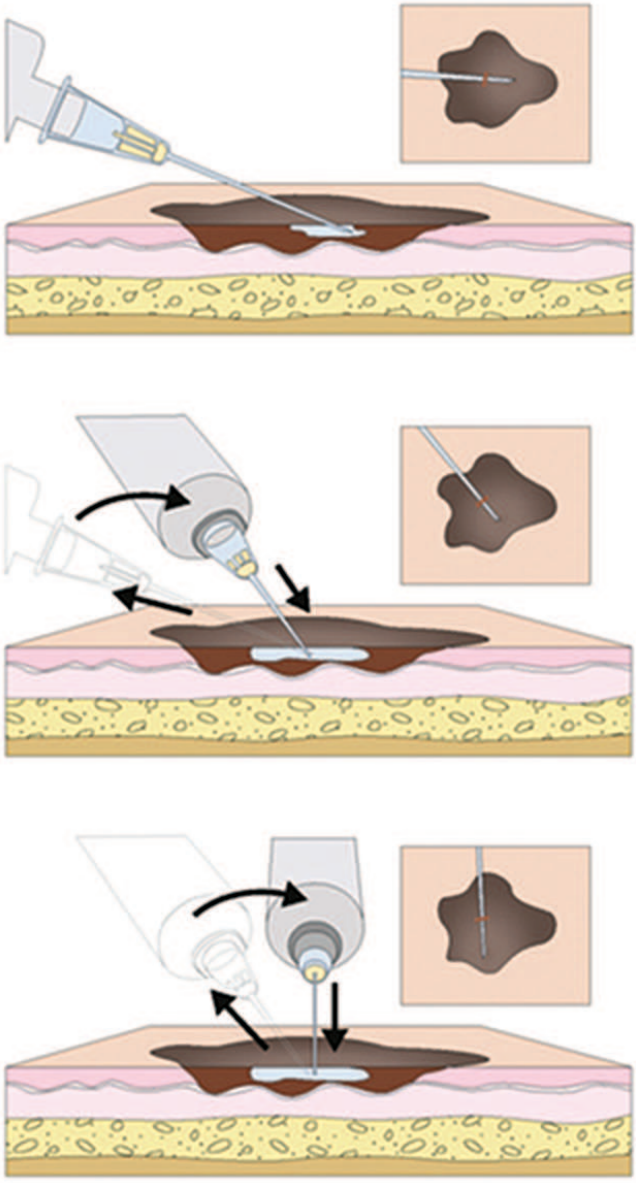
As an attenuated, live-replicating virus therapy, a number of aspects of talimogene laherparepvec

administration and handling differ from current therapies; however, these procedures are no more complex than those for other locally delivered cancer therapeutics, such as bacillus Calmette–Guérin. Unlike chemotherapy agents and monoclonal antibodies, which can be stored at room temperature and under refrigeration (2°C to 8°C [36°F to 46°F], respectively), unopened vials of talimogene laherparepvec should be securely stored and transported at –90°C to –70°C (–130°F to –94°F). Exposure of frozen virus to temperatures exceeding –70°C must be limited because the virus will begin to thaw after 60 seconds. Frozen talimogene laherparepvec should be thawed at room temperature until talimogene laherparepvec is liquid (about 30 minutes). After thawing, talimogene laherparepvec should be administered immediately or stored in its original vial and carton and protected from light in a refrigerator for no longer than 12 hours for the 10^6 PFU/ml vial and 48 hours for the 10^8 PFU/ml vial. It should not be refrozen/rethawed once it becomes liquid.

FIGURE 4. Method for the Intralesional Injection of Talimogene Laherparepvec

Note. Talimogene laherparepvec is administered via intralesional injection into cutaneous, subcutaneous, or nodal lesions using a needle and must be evenly distributed throughout the tumor through each insertion site using the radial reach of the needle in multiple directions. The volume of talimogene laherparepvec to be injected is dependent on the dimensions of the lesion. For lesions with longest diameters of ≤ 0.5 cm, > 0.5 cm to ≤ 1.5 cm, > 1.5 cm to ≤ 2.5 cm, > 2.5 cm to ≤ 5 cm, and > 5 cm, injection volumes are ≤ 0.1 ml, ≤ 0.5 ml, ≤ 1 ml, ≤ 2 ml, and ≤ 4 ml, respectively. The maximum injection volume on any treatment day is 4 ml.

Note. Image courtesy of Amgen Inc. Adapted with permission.



Secondary Transmission

Although talimogene laherparepvec has been periodically detected in the blood or urine of injected patients, a secondary transmission to household contacts has not been reported. However, although remote, a theoretical possibility exists of live virus transmission from patients receiving treatment to individuals who have open skin lesions or who are immunocompromised or immunosuppressed; therefore, universal biohazard precautions (e.g., biosafety level 1 or 2) are recommended when administering talimogene laherparepvec and when changing occlusive dressings. Laboratory coats, protective gowns or uniforms, safety glasses, and gloves should be worn while preparing or administering talimogene laherparepvec. Any exposed wounds should be covered before administering talimogene laherparepvec, and contact with skin, eyes, or mucous membranes should be avoided. Healthcare professionals who are pregnant or who have immunosuppressive conditions should not prepare or administer talimogene laherparepvec and should not come into direct contact with injection sites or bodily fluids of treated patients.

In the event of accidental exposure through the eyes or mucous membranes, the exposed area should be flushed with clean water for 15 minutes or longer. In the event of exposure via a skin break or needle stick, the site should be cleaned thoroughly with soap and water or with a skin disinfectant. The exposed person should see a physician for monitoring of any signs of infection. Any possible infections may be treated with standard drugs. If a spill occurs, the contaminated area should be treated with a virucidal agent (e.g., ethanol or bleach) and absorbent materials. Any materials that come into contact with talimogene laherparepvec should be disposed of in accordance with institutional procedures. Systemic treatment with antiviral

Knowledge Translation

- The oncolytic immunotherapy talimogene laherparepvec (Imlygic™) is a potential new treatment option for the local treatment of unresectable, cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. Talimogene laherparepvec has not been shown to improve overall survival or have an effect on visceral metastases.
- As a viral therapy administered by intralesional injection, talimogene laherparepvec has administration and handling procedures that differ from current therapies.
- Nurses and nurse administrators will be vital for the appropriate integration and administration of this unique and effective therapy in the clinical setting.

therapies (e.g., acyclovir) also can be considered in the event of an accidental exposure.

Implications for Nursing

The authors' experience with the use of talimogene laherparepvec treatment in clinical trials has provided a number of insights on practical considerations related to implementation of talimogene laherparepvec in the clinical setting. Given that talimogene laherparepvec must be thawed immediately before use and cannot be prepared in advance, ensuring that the drug is available when the patient is at the clinic for his or her administration requires close coordination with the pharmacy. Consequently, administration by nurses (rather than physicians) can provide greater flexibility in timing and ensure that patients are not unduly inconvenienced.

Although healthcare professionals (including nurses) understand that the likelihood of secondary transmission of talimogene laherparepvec is remote, patients do ask whether there are risks, particularly for their close family members. Nurses are well placed to educate patients on the potential risk of secondary transmission, the precautions that can be taken (e.g., covering of exposed wounds; avoidance of contact with skin, eyes, or mucous membranes), and procedures to take should contact occur (e.g., flush or wash area with clean/soapy water, treat with antiviral therapies, ensure monitoring by a physician).

Conclusion

Talimogene laherparepvec is a novel oncolytic virus immunotherapy that improves DRR in metastatic melanoma and has demonstrated systemic antitumor effects, inducing responses in uninjected lesions including some visceral lesions. In the phase 3 OPTiM trial, talimogene laherparepvec demonstrated a statistically significant improvement in DRR compared with GM-CSF (16% versus 2%, $p < 0.0001$) and median OS of 23.3 months versus 18.9 months with GM-CSF ($p = 0.051$) (Andtbacka, Kaufman, et al., 2015). In addition, the benefits of talimogene laherparepvec treatment were observed across all substages of the disease. AEs related to talimogene laherparepvec treatment are generally mild to moderate in severity; therefore, talimogene laherparepvec offers patients a tolerable treatment option. These results indicate that talimogene laherparepvec is a potential new treatment option for patients with metastatic melanoma with regionally or limited visceral disease that is injectable and not surgically resectable.

Talimogene laherparepvec can be administered by intralesional injection in the outpatient setting. As an attenuated virus therapy, talimogene laherparepvec has administration and handling procedures that differ from current therapies. These procedures are required to minimize the risks of contamination or possible exposure to healthcare personnel and family members. Nurses and nurse administrators are vital to the appropriate integration and administration of this unique and effective therapy in the clinical setting. Consequently, the need for associated nursing education becomes essential.

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