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Clinical Cancer Research

Molecular Pathways: Mechanism of Action for Talimogene Laherparepvec, a New Oncolytic Virus Immunotherapy

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Abstract

Oncolytic viruses are native or engineered viruses that preferentially replicate in and lyse cancer cells. Selective tumor cell replication is thought to depend on infection of neoplastic cells, which harbor low levels of protein kinase R (PKR) and dysfunctional type I IFN signaling elements. These changes allow more efficient viral replication, and with selected deletion of specific viral genes, replication in normal cells with activated PKR may not be possible. Direct tumor cell lysis, release of soluble tumor antigens, and danger-associated molecular factors are all thought to help prime and promote tumor-specific immunity. Talimogene laherparepvec (T-VEC) is a genetically modified herpes simplex virus, type I and is the first oncolytic virus to demonstrate a clinical benefit in patients with melanoma. T-VEC has also been evaluated for the treatment of head and neck cancer, pancreatic cancer, and likely other types of cancer will be targeted in the near future. T-VEC has been modified for improved safety, tumor-selective replication, and induction of host immunity by deletion of several viral genes and expression of human granulocyte-macrophage colony stimulating factor. Although the mechanism of action for T-VEC is incompletely understood, the safety profile of T-VEC and ability to promote immune responses suggest future combination studies with other immunotherapy approaches including checkpoint blockade through PD-1, PD-L1, and CTLA-4 to be a high priority for clinical development. Oncolytic viruses also represent unique regulatory and biosafety challenges but offer a potential new class of agents for the treatment of cancer. *Clin Cancer Res; 22(5); 1048–54. ©2015 AACR.*

Background

Oncolytic viruses are native or attenuated viruses that selectively replicate in cancer cells and induce host antitumor immunity (1). Many types of viruses have been tested as potential oncolytic viruses, including herpesvirus, poxvirus, picornavirus (e.g., coxsackie, polio, and Seneca Valley virus), adenovirus, paramyxovirus (e.g., measles virus), parvovirus, reovirus, Newcastle Disease virus, and rhabdovirus (e.g., vesicular stomatitis virus), among others (1). Table 1 summarizes selected oncolytic viruses being used in clinical trials and indicates the types of cancer under investigation. Each virus utilizes one or several specific cell surface receptors to gain entry, and the clinical indications will likely depend on the presence of specific viral entry receptors on the cancer cell (see Table 1). In general, oncolytic viruses are thought to mediate antitumor activity through a dual mechanism of selective replication and lysis within infected cancer cells and through induction of host antitumor immunity.

Although the potential for viruses to kill cancer cells has been recognized for nearly 65 years, only recently has therapeutic activity been demonstrated in cancer patients through prospective, randomized clinical trials. An attenuated herpesvirus encoding human granulocyte-macrophage colony stimulating factor (GM-CSF) termed talimogene laherparepvec (or T-VEC; Imlygic) was compared with recombinant GM-CSF in patients with advanced, unresectable melanoma (2). In this trial, patients treated with T-VEC showed improved overall and durable response rates with limited adverse events, largely limited to fatigue, fever, chills, nausea, and local injection site reactions. On the basis of the study outcome, T-VEC was approved for the treatment of skin and lymph node melanoma accessible for local injection. Physicians will need to become familiar with this new class of cancer therapeutics to be able to select appropriate patients, understand how the virus mediates antitumor activity, logistically integrate oncolytic virus immunotherapy into the clinic, and manage side effects. We briefly review the current understanding of how T-VEC induces tumor regression.

The dual mechanism of action for oncolytic viruses begins with the ability to preferentially replicate in tumor cells results in lysis of the cancer cells. This results in the release of new viral particles, tumor-associated antigens, and danger-associated molecular factors. The release of new viral particles allows continued infection of tumor cells and produces a bystander-type effect allowing expansion of the lytic effect and tumor debulking. Second, the local efflux of tumor antigens and danger signals can help promote an immune response, which is enhanced by viral expression of GM-CSF in the case of T-VEC. Although incompletely understood, there is increasing evidence that tumor-specific immunity is induced with oncolytic viruses, and this may allow expansion of tumor eradication to tumor cells not infected with the virus. In addition to T-VEC, numerous other types of oncolytic viruses with varying tropisms and lytic capacity against a broad array of tumor

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Table 1. Selected oncolytic viruses in clinical development

Oncolytic virus	Cancer clinical trials in progress	Cell surface entry receptor
Adenovirus	Bladder cancer, ovarian cancer, prostate cancer, head and neck cancer, sarcomas, NSCLC, glioblastoma	Coxsackie virus and adenovirus receptor (CAR)
Coxsackie virus	Melanoma, breast cancer, prostate cancer	CAR, ICAM-1, DAF
HSV-1	Melanoma, breast cancer, head and neck cancer, pancreatic cancer	HVEM, nectin 1, nectin 2
Measles virus	Ovarian cancer, glioblastoma, multiple myeloma	SLAM and CD46
Newcastle disease virus	Glioblastoma	Type I IFN and Bcl-2
Parvovirus	Glioblastoma	Sialic acid
Poliovirus	Glioblastoma	CD155
Poxvirus	Head and neck cancer, hepatocellular carcinoma, melanoma, colorectal cancer	Unknown
Reovirus	NSCLC, ovarian cancer, melanoma, head and neck cancer	Nogo receptor (NgR1) and junctional adhesion molecule A (JAM-A)
Seneca valley virus	Neuroblastoma, lung cancer	Neuroendocrine featured tumors
Vesicular stomatitis virus	Hepatocellular carcinoma	Low-density lipoprotein receptor (LDLR)

Abbreviation: NSCLC, non–small cell lung cancer.

types have been extensively reviewed elsewhere (1). For simplicity, this review focuses on T-VEC.

T-VEC is based on the herpes simplex virus, type I (HSV-1), which causes fever blister disease. T-VEC evolved from the JS-1 strain of HSV-1 originally isolated from a cold sore. HSV-1 is a double-stranded DNA virus with a large genome (~152 kb), including 30 kb that are nonessential for viral replication. HSV-1 is a highly lytic virus and human pathogen that, depending on the location of the infection, causes skin lesions and rashes and can infect peripheral nerves, where HSV-1 enters a latent state. HSV-1 infects epithelial cells, neurons, and immune cells through binding to nectins, glycoproteins, and the herpesvirus entry mediator (HVEM) on the cell surface. T-VEC has been modified by deleting the neurovirulence genes preventing fever blister development and deleting a viral gene that blocks antigen presentation. T-VEC can target and propagate in cancer cells by using surface-bound nectins to enter the cell and preferentially replicates in tumor cells by exploiting disrupted oncogenic and antiviral signaling pathways, most notably the protein kinase R (PKR) and type I IFN pathways. T-VEC also generates an immune response, which is likely enhanced by the expression of GM-CSF (3, 4). Figure 1 shows how T-VEC utilizes the PKR and IFN signaling pathways within tumor cells to promote viral replication and lysis, and also induces antitumor immunity.

T-VEC selectively replicates in tumor cells through oncogenic disruption of the PKR pathway

PKR is a 551–amino acid protein encoded on chromosome 17. PKR is composed of two subunits with distinct function: the catalytic serine/threonine kinase domain at the C-terminus and two double-stranded RNA (dsRNA)-binding motifs at the N-terminus (5, 6). PKR is a sentinel for cellular stress critical for regulating aberrant cell proliferation and intrinsic cellular antiviral responses (5). PKR can be activated by dsRNA (as a by-product of viral replication), as well as cellular stress signals, such as type I IFNs, growth factors, and Toll-like receptors (TLR; refs. 5, 7). In normal cells, activation of PKR inhibits cellular protein synthesis, which subsequently blocks cell proliferation and inhibits viral propagation. Upon binding dsRNA (or activated through other signals, i.e., type I IFNs, cellular stress, viral products), PKR undergoes a conformational shift to expose the catalytic C-terminal kinase domain resulting in autophosphorylation and activation of PKR (8). Following activation, PKR phosphorylates eIF-2α at Ser-51, increasing binding affinity (~100-fold) for eIF-2β (9, 10). eIF-2β is required for the catalytic turnover of the eIF-2 complex, which regulates protein translation by delivering Met-tRNAi to the 40S subunit of the ribosome (11). The binding of eIF-2α to eIF-2β blocks eIF-2 function and essentially inhibits cellular translation. By blocking protein translation, the PKR-eIF-2 pathway effectively halts cellular proliferation and prevents production of viral proteins precluding viral replication.

In contrast to normal cells, cancer cells have devised ways to disrupt the PKR–eIF-2 pathway, which permits continuous cell growth and allows uninhibited viral replication (see Fig. 1). Specifically, cancer cells can limit PKR activation both directly through abnormal oncogenic signaling pathways that block PKR activation and indirectly through inhibition of extracellular activators of PKR (12). Ras is an oncogenic protein commonly mutated in cancer cells where hyperactive or overexpressed protein drives tumorigenesis. Ras activates many mitogenic pathways that promote cellular proliferation. In addition, hyperactive Ras may promote tumor cell replication by blocking PKR activation, thus preventing cells from detecting the stress of aberrant proliferation and terminating protein translation (3, 13). Recently, a bovine herpes virus, BHV-1, was found to exhibit enhanced replication and lysis of tumor cells harboring mutations in K-RAS (14). Furthermore, there is some evidence that other oncogenic signaling factors may regulate PKR activity, although their role in mediating oncolytic virus replication remains speculative. For example, the MAPK kinase (MEK), which plays a key role in the MAPK signaling pathway, is frequently activated in melanoma cells and has been shown to suppress the activation of PKR and subsequently promote replication of HSV-1 in tumor cell lines *in vitro* (15). This may indicate that cancer cells with overactive MEK activity may be susceptible to T-VEC infection and lysis.

HSV-1 has also evolved ways to avoid detection by PKR that would otherwise terminate protein translation and block infection. The HSV-1 neurovirulence protein, infected cell protein 34.5 (ICP34.5), is necessary for HSV-1 infection of neurons and other healthy cells as it binds to and blocks PKR allowing for viral replication (16). ICP34.5 blocks PKR pathway activation by binding to and activating the PP1α phosphatase, which dephosphorylates eIF-2α preventing the shutdown of protein translation by eIF-2 (16, 17). In T-VEC, both copies of the *ICP34.5* gene have been deleted (18). This deletion has implications for eliminating the pathogenesis of HSV-1 and also enhances viral replication in cancer cells (19–21). ICP34.5-deficient HSV-1 infection of healthy cells activates PKR, resulting in abortive infection. In contrast, T-VEC can replicate in cancer cells because PKR activity is not activated.

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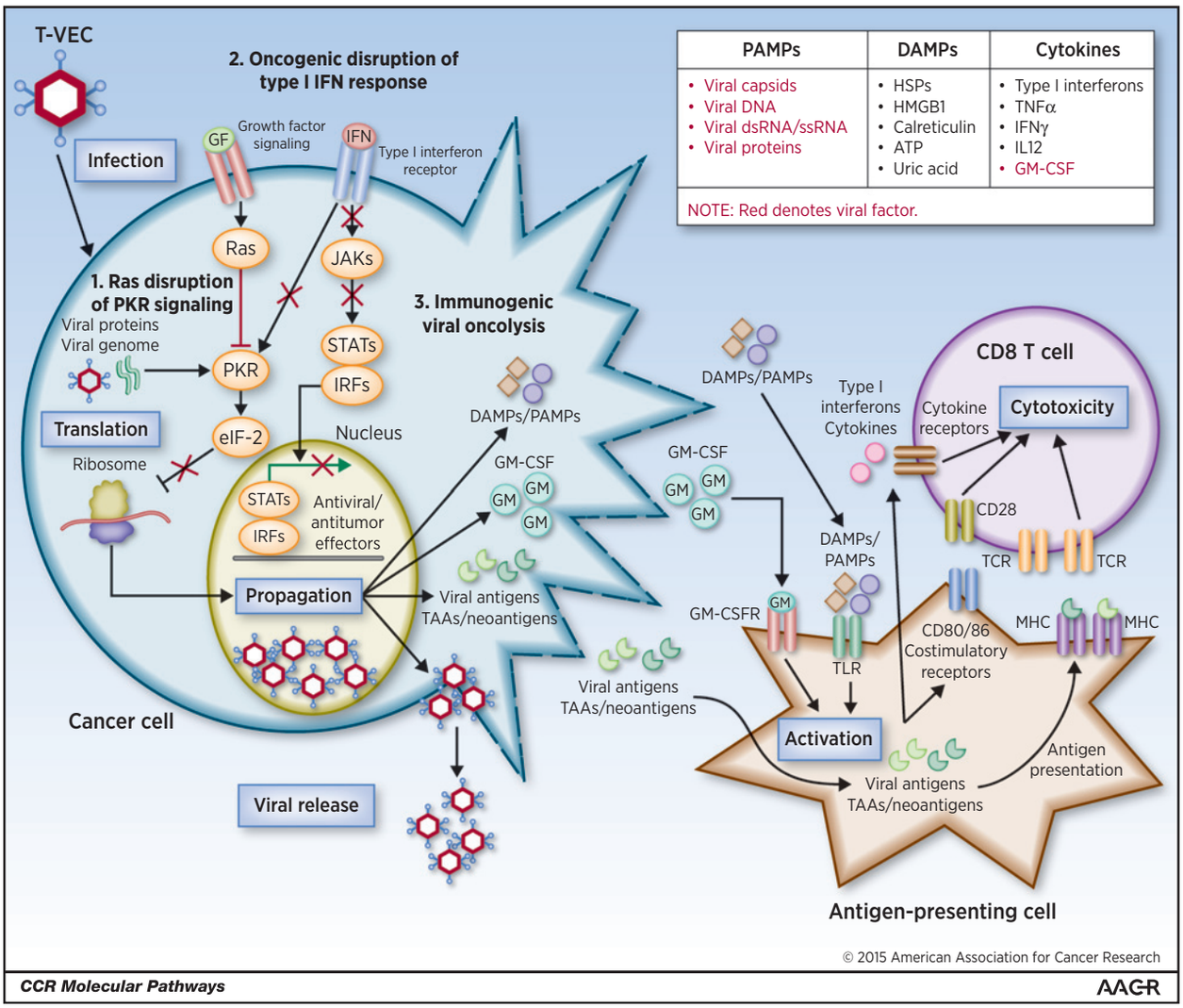

Figure 1.
Mechanism of action for T-VEC. T-VEC preferentially replicates in cancer cells because of disrupted PKR activity (1), which may be lower due to overactive Ras signaling. PKR signaling regulates cell proliferation by phosphorylating eIF-2, which prevents delivery of Met-tRNAi to ribosomes blocking protein translation. In normal cells, PKR is activated by viral infection, specifically dsRNA that blocks protein translation. Cancer cell blockade of PKR signaling through hyperactive Ras allows propagation of T-VEC because the viral infection of T-VEC no longer activates the antiviral PKR response. T-VEC also replicates in cancer cells because of disrupted type I IFN signaling (2). Type I IFN signaling activates PKR to block protein translation and induces transcription of IFN-stimulated genes, such as several IFN-related factors (IRF) that promote antitumor and antiviral responses. The disrupted IFN signaling may also result in downregulating type I IFN receptors or blocking downstream JAK–STAT signaling. Following viral replication and propagation in the nucleus, mature virions complete assembly in the cytoplasm and induce cell lysis (3) releasing new progeny virions that can infect other tumor cells and various proimmunogenic factors, such as viral-based pathogen-associated molecular patterns (PAMP), cell-derived DAMPs, and cytokines. These factors orchestrate recruitment and maturation of antigen-presenting cells, such as dendritic cells that can present tumor-associated antigens to cytotoxic $CD8^+$ T cells. The T cells, in turn, can mediate direct rejection of other tumor antigen-expressing cells. Depicted in red are factors that are directly produced by T-VEC infection and in black are factors produced as a result of an antiviral response. eIF-2, eukaryotic initiation factor 2; GM, GM-CSF; GM-CSFR, granulocyte-macrophage colony-stimulating factor receptor; HMGB1, high mobility group box 1; IRF, IFN regulatory factor; PKR, protein kinase R; TAA, tumor-associated antigen; TCR, T-cell receptor; TLR, Toll-like receptor.

To further improve the oncolytic effects of HSV-1, the original ICP34.5-deficient HSV-1 mutants were serially passaged through cancer cells to expand the lytic potential of the virus. From this, a spontaneous mutant was isolated that more potently lysed an array of different cancer cell lines. The spontaneous mutation in the HSV-1 ICP34.5$^{-/-}$ mutant was the result of the translocation of the *US11* gene following the α47 promoter that regulates expression of ICP47 (22, 23). This translocation has multiple effects that improve the lytic activity of HSV-1 ICP34.5$^{-/-}$ mutants. *US11* encodes for U_L11, which binds PKR preventing eIF-2α phosphorylation, thus permitting HSV-1 replication (24). Furthermore, *US11* is normally expressed later during infection well after ICP34.5 would inhibit PKR (25). However, the translocation in T-VEC results in the regulation of *US11* by the *α47* promoter, which causes U_L11 to be expressed as an immediate early gene, and this blocks PKR activity before PKR is able to terminate protein synthesis (23, 25).

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T-VEC infection is enhanced by disruption of type I IFN pathway in tumor cells

Type I IFNs mediate antiviral and antitumor responses by limiting cellular proliferation and promoting viral eradication. Type I IFNs are secreted during times of cellular stress, such as viral or bacterial infection. Type I IFNs bind to the type I IFN receptor alpha, which signals downstream through JAK–STAT pathways, resulting in the upregulation of IFN-regulated genes (see Fig. 1). IFN-regulated genes consist of several hundred proteins including transcription factors, cytokines, and chemokines that limit viral replication and spread (26). Type I IFNs also play a role in limiting cellular proliferation, and thus, type I IFN signaling is commonly disrupted by many different types of cancer (27, 28).

Similar to the disruption of the PKR pathway rendering cancer cells more susceptible to T-VEC replication, the disruption of type I IFN signaling pathways enhances HSV-1–selective replication (29). Cancer cells commonly downregulate expression of type I IFN receptors and inactivate downstream signaling components, including PKR and the JAK–STAT pathway (27, 28). As noted previously, HSV-1 ICP34.5 blocks the PKR pathway, and this prevents type I IFN activation and protein translation (16). Furthermore, ICP34.5 blocks the production of IFNβ by binding to TBK-1 preventing autocrine type I IFN signaling (30, 31). There is also evidence that HSV-2 proliferated more efficiently in cells with defective type I IFN signaling (29). In many cancer cells, the type I IFN signaling pathways are disrupted, and in the absence of ICP34.5, viral replication occurs in cancer cells lacking normal IFN signaling, whereas normal cells will be less permissive because IFN signaling is intact. This feature of T-VEC adds an important safety component because infection of normal cells will be aborted in the absence of PKR and type I IFN signaling defects.

Induction of host antitumor immune response by T-VEC

T-VEC infection of cancer cells induces both local antiviral inflammation and can mediate innate and tumor-specific adaptive immunity. As most established cancers exist in an immunosuppressive tumor microenvironment, the local release of IFNs, chemokines, danger-associated molecular pattern (DAMP), and pathogen-associated molecular pattern (PAMP) factors, and Toll-like receptor agonists help reverse the suppressed tumor milieu into a more proimmunogenic environment capable of promoting antitumor immune responses (see Fig. 1). PAMPs are common motifs expressed by infectious agents, such as viruses and bacteria, whereas DAMPs are often derived from host cells, and include factors such as HSPs, HMGB-1, calreticulin, ATP, and uric acid. DAMPs and PAMPs bind pattern recognition receptors (i.e., TLRs) to promote innate immune responses. Furthermore, the lysis of cancer cells releases neoantigens (antigens that were not previously presented to the immune system) that may be able to prime *de novo* antitumor $CD8^+$ T-cell responses against previously unrecognized antigens.

In addition to the natural host-derived antiviral responses, T-VEC was further modified to improve antigen presentation and T-cell priming by deleting the *ICP47* viral gene and inserting the gene for human *GM-CSF*. As mentioned, during serial passaging of HSV-1, a mutant was isolated with a translocated *US11* gene, which resulted in the deletion of *ICP47* (23). ICP47 normally limits antigen presentation by directly binding to the transporter associated with antigen processing and presentation, thereby preventing antigen loading into MHC-I molecules (32, 33). In T-VEC, the ICP47 is deleted, and this allows enhanced antigen presentation and maintains cell surface MHC-I-antigen expression on infected cancer cells (18, 32, 33). To further improve the immunogenicity of T-VEC, two copies of the human *GM-CSF* gene were incorporated into the deleted *ICP34.5* genome location (18, 34). GM-CSF is a regulatory cytokine that promotes dendritic cell accumulation at sites of inflammation, promotes antigen-presenting cell function, and can prime T-cell responses. In murine tumor studies, JS-1 viruses with *ICP34.5* and *ICP47* deletions could mediate tumor regression in injected tumors but not in contralateral tumors. When GM-CSF was incorporated into the virus design, regression of both injected and uninjected contralateral tumors was observed with a significant improvement in overall survival reported (4, 18). In summary, the deletion of *ICP34.5*, earlier expression of US_L11, deletion of *ICP47*, and expression of local GM-CSF all help improve the induction of host antitumor immunity and have been incorporated into T-VEC.

The induction of tumor-specific immune responses has been supported by clinical data demonstrating the presence of MART-1–specific $CD8^+$ T cells in tumors injected with T-VEC (35). It is possible, however, that primary $CD8^+$ T-cell responses recognizing viral antigens may also be induced and could play a role in mediating tumor clearance. Recent data from patients treated with T-cell checkpoint inhibitors have also suggested the emergence of neoantigens from established tumors as an important component of the immune response to treatment (36). The role of mutation load and neoantigen emergence with T-VEC is not established. Further studies are needed to better understand exactly how oncolytic viruses, such as T-VEC, mediate immune responses in cancer patients.

Clinical–Translational Advances

Murine syngeneic and xenogeneic preclinical models demonstrated that T-VEC was effective against many different tumor types through direct viral oncolysis and augmented antitumor immune responses (4, 18). Specifically, T-VEC showed preferential replication in a number of different types of cancer cell lines including breast cancer, colorectal adenocarcinoma, melanoma, prostate cancer, and glioblastoma (18). Furthermore, using contralateral tumor models for melanoma and lymphoma, modified HSV-1 vectors were able to induce direct lysis of injected tumors, but only when *GM-CSF* was encoded by the virus did mice exhibit rejection of uninjected contralateral tumors (4, 18). Mice that rejected tumors following treatment with the oncolytic virus appear to have immunologic memory as they are resistant to subsequent challenge with the same tumor cells, but not unrelated tumors. These observations led to phase I and II clinical trials, which confirmed the safety of T-VEC in cancer patients. The phase I clinical trial demonstrated that T-VEC was safe with generally low-grade constitutional adverse events, induced tumor necrosis, and preferentially replicated in tumor cells (37). The phase II clinical trial tested the efficacy of T-VEC in 50 patients with advanced, unresectable stage IIIC and IV melanoma (35, 38). Melanoma was selected for initial study given the immunogenicity of melanoma and the availability of accessible lesions for direct injection of T-VEC. The phase II trial confirmed the safety profile and also reported a 28% objective response rate in melanoma. The early studies also identified an accumulation of MART-1–specific $CD8^+$ T cells in the tumor microenvironment of injected lesions with an associated decrease in the number of $CD4^+FoxP3^+$ regulatory T cells and myeloid-derived suppressor cells consistent with an immune response (35, 37, 38).

The early clinical results led to the first prospective, randomized clinical trial, called OPTIM (for $Oncovex^{GM\text{-}CSF}$ Pivotal Trial in

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Melanoma; ref. 2). This trial enrolled patients with stage IIIb, IIIc, or IV melanoma with unresectable but accessible lesions in treatment-naïve and previously treated patients. The primary endpoint was durable objective response rate, defined as an objective response beginning within 1 year of treatment and maintained for 6 months or longer. In addition, data were collected on overall response rate, time to response, progression-free survival, and overall survival. The trial enrolled 439 patients from four countries, and subjects were randomized (2:1) to treatment with T-VEC ($n = 296$) or recombinant GM-CSF ($n = 141$; ref. 2). The initial dose of T-VEC was 10^6 PFU/mL injected intratumorally followed 3 weeks later by T-VEC at 10^8 PFU/mL into the tumor and then treatment at 10^8 PFU/mL every 2 weeks. Subjects assigned to recombinant GM-CSF were treated with 125 μg/mL injected subcutaneously for 14 days of a 28-day cycle for up to a year based on reports showing a possible survival advantage for this treatment regimen in stage III and IV melanoma (39).

Patients receiving T-VEC had a significantly increased durable response rate [16.3%; 95% confidence interval (CI), 12.1%–20.5%] and overall response rate (26.4%; 95%CI, 21.4%–31.5%) compared with GM-CSF ($P < 0.001$). T-VEC was also associated with a 26.4% objective response rate compared with 5.7% for GM-CSF. In this trial, T-VEC was associated with a 10.8% complete response rate, which included regression in injected and noninjected lesions compared with a 1% complete response rate for GM-CSF (2). In addition, there were no drug-related deaths, with common adverse events being low-grade fever, fatigue, nausea, chills, and injection site reactions. The only grade 3/4 adverse event reported in more than 2% of the population was cellulitis. The results of this study prompted FDA approval of T-VEC for the treatment of skin and lymph node melanoma in October 2015.

Rational T-VEC combinations and early clinical trials

The generation of a systemic antitumor immune response and tolerable safety profile supports the use of T-VEC in combination clinical trials. A high priority includes the T-cell checkpoint inhibitors that promote T-cell responses by blocking the CTL antigen 4 (CTLA-4; ipilimumab) or programmed cell death 1 (PD-1; pembrolizumab and nivolumab) receptors (40, 41). Currently, T-VEC is being evaluated in a phase IB/II clinical trial in combination with ipilimumab for patients with stage IIIb-IV melanoma (NCT01740297). Initial results from the first 18 patients with a median follow-up of 17 months showed that the median time to response was 5.3 months and the 18-month progression-free survival rate was 50%, with an overall survival rate of 67% (42). No unexpected toxicities have been associated with the combination. The phase II component includes a randomized design in which patients will receive T-VEC and ipilimumab or ipilimumab alone. A phase Ib/III clinical trial is currently enrolling patients with stage IIIb–IV melanoma for treatment with pembrolizumab (anti–PD-1) combined with T-VEC (NCT02263508). The planned enrollment for this study is 680 patients.

Although these studies will be important, further combination trials with other agents, such as IL2, adoptive T-cell therapy, radiotherapy, and targeted therapy, may also be anticipated. In addition, the success of T-VEC in melanoma has led to its testing in other types of cancer, including pancreatic cancer (NCT00402025), soft-tissue sarcomas (NCT02453191), and head and neck cancer (NCT01161498).

Safety and regulatory issues with T-VEC

T-VEC is a live replicating virus, and this presents numerous special considerations with respect to biosafety and regulatory management. In terms of T-VEC pharmacodynamics, determining the active and maximum tolerated dose will be more difficult and has, thus far, been largely empirical based on murine models. Further work to delineate dosing based on viral concentration and patient- and immune-specific variables that affect bioavailability are needed. Further investigation of both the antiviral and antitumor immune responses are needed to better understand how preexisting herpes humoral responses may affect antitumor activity and to document new combinations in terms of promoting tumor-specific immune responses.

Oncolytic viruses, including T-VEC, have been demonstrated to be safe in many clinical trials. However, because these are live-replicating viruses, there is a potential for transmission to health care workers and household contacts. Programs to ensure adherence to universal precautions in the storage, preparation, and administration of T-VEC will require additional guidelines, education, and programs for transmission monitoring. To date, no cases of close contact transmission have been reported, but several accidental exposures in health care workers have occurred. Further studies to determine the extent of viral shedding are in progress and will be important to inform future handling of the agent. The manufacturing of live viruses also requires special attention because the use of cell cultures and continuous quality control can complicate the manufacturing process. T-VEC is stored at −70°C, and this may not be practical at all medical facilities. These topics have been more thoroughly discussed in other reviews (1, 43).

Future directions

T-VEC is the first oncolytic virus to demonstrate a clinical benefit in patients with cancer. The pivotal phase III trial demonstrated an improvement in objective and durable responses in patients with unresectable melanoma. Although these findings represent significant progress in the development of oncolytic virus immunotherapy, considerable work remains to be done in defining exactly how T-VEC and related vectors kill tumor cells, commandeer cell signaling pathways, and promote host antitumor immunity. These will be goals to better identify patients likely to respond to treatment, uncover potential mechanisms of resistance, and help inform rational combination trials. Clinical trials are already in progress to extend the therapeutic benefit of T-VEC by combining it with other immunotherapy agents, such as the T-cell checkpoint inhibitors, allowing earlier administration in the neoadjuvant setting in melanoma, delivery into visceral organs, and extension to other types of cancer. Further basic and clinical research will help establish the full potential for T-VEC and other oncolytic viruses for the treatment of cancer.

Disclosure of Potential Conflicts of Interest

H.L. Kaufman reports receiving speakers bureau honoraria from Merck and is a consultant/advisory board member for Alkermes, Amgen, EMD Serono, Merck, Prometheus, and Sanofi-Aventis. No potential conflicts of interest were disclosed by the other author.

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Development of methodology: H.L. Kaufman
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.L. Kaufman

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): F.J. Kohlhapp, H.L. Kaufman
Writing, review, and/or revision of the manuscript: F.J. Kohlhapp, H.L. Kaufman
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.L. Kaufman
Study supervision: H.L. Kaufman

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