

T-VEC for Cancer Therapy: Applications, Limitations, and Potentials

Zixuan Zhen *

Department of Life Science, Nankai University, Tianjin, China

* Corresponding Author Email: 2010365@mail.nankai.edu.cn

Abstract. Cancer is a great threat to human health, and immunotherapy has become an important means to treat cancer in recent years. Talimogene laherparepvec (T-VEC), as an oncolytic virus, is one of the immunotherapy for melanoma. This article explains its mechanism, and then summarizes its clinical applications, including the effects and safety of monotherapy and combination therapy. Current limitations and potentials of T-VEC are also analyzed, in order to provide guidance for the further development of it and even other oncolytic viruses.

Keywords: Talimogene Laherparepvec, Melanoma, Cancer Immunotherapy.

1. Introduction

Cancer is a leading cause of death worldwide. The most common treatments for cancer today include surgery, radiotherapy, and chemotherapy, but these methods have severe side effects that can damage healthy cells. Vaccine is another option for cancer with significantly fewer side effects, including autologous tumor cell vaccines, allogeneic tumor cell vaccines, peptide vaccines, dendritic cell vaccines, and oncolytic virus vaccines. Oncolytic virus is a category of virus that can specifically replicate in and kill tumor cells without damaging normal cells, as well as induce an anti-tumor immune response. Because of its unique advantages, the research on the oncolytic virus has become one of the focuses of cancer immunotherapy in recent years.

Few viral vaccines have been licensed for use in the treatment of cancer as of yet, and the majority of them are currently undergoing clinical studies. T-VEC is a genetically engineered oncolytic virus suggested for the local treatment of melanoma that recurs after an initial surgery and is the only oncolytic virus vaccination licensed by the FDA. This article summarizes the principles, applications, challenges, and prospects of this representative vaccine, in the hope of helping the future development of it and other cancer vaccines.

2. Mechanism of T-VEC

As an oncolytic virus with gene editing, T-VEC can infect most cells, including blood cells, and doesn't need a high multiplicity of infection to kill tumor cells effectively. T-VEC is based on HSV-1, with deletion of 2 nonessential viral genes, RL1, encoding ICP34.5, and US12, encoding ICP47, and insertion of GM-CSF. These edits allow it to selectively replicate in tumor cells and kill them through an immune response.

ICP34.5 of HSV-1 can bind to protein phosphatase 1 of the host and relieve the antiviral effect of protein kinase R (PKR). In normal cells, HSV-1 without ICP34.5 is unable to block the antiviral action of phosphorylated PKR and is unable to replicate. However, in tumor cells, the virus can still replicate due to the low PKR content [1]. Besides, the deletion of ICP34.5 can also weaken the pathogenicity of HSV-1.

As for ICP47, it can inhibit antigen presentation by inhibiting antigen presentation-related proteins [2]. In addition to stimulating the body to develop a particular anti-tumor immune response that further strengthens the therapeutic impact, T-VEC also reduces ICP47 to boost viral antigen presentation. The virus also destroys the tumor cells while continuing to infect the surrounding tumor cells with its freshly produced daughter virus.

Additionally, the insertion and production of GM-CSF trigger the activation and recruitment of antigen-presenting cells and the generation of T-cell responses specific to tumors [3].

As shown in Figure 1, T-VEC specifically infects and replicates in tumor cells, releasing viral particles to infect neighboring cells and perform local anti-tumor effects. At the same time, the lysed tumor cells release molecules such as tumor-specific antigens and GM-CSF, triggering innate immunity and recruiting dendritic cells, which in turn activate tumor-specific CD8⁺ T cells and initiate a systemic anti-tumor response.

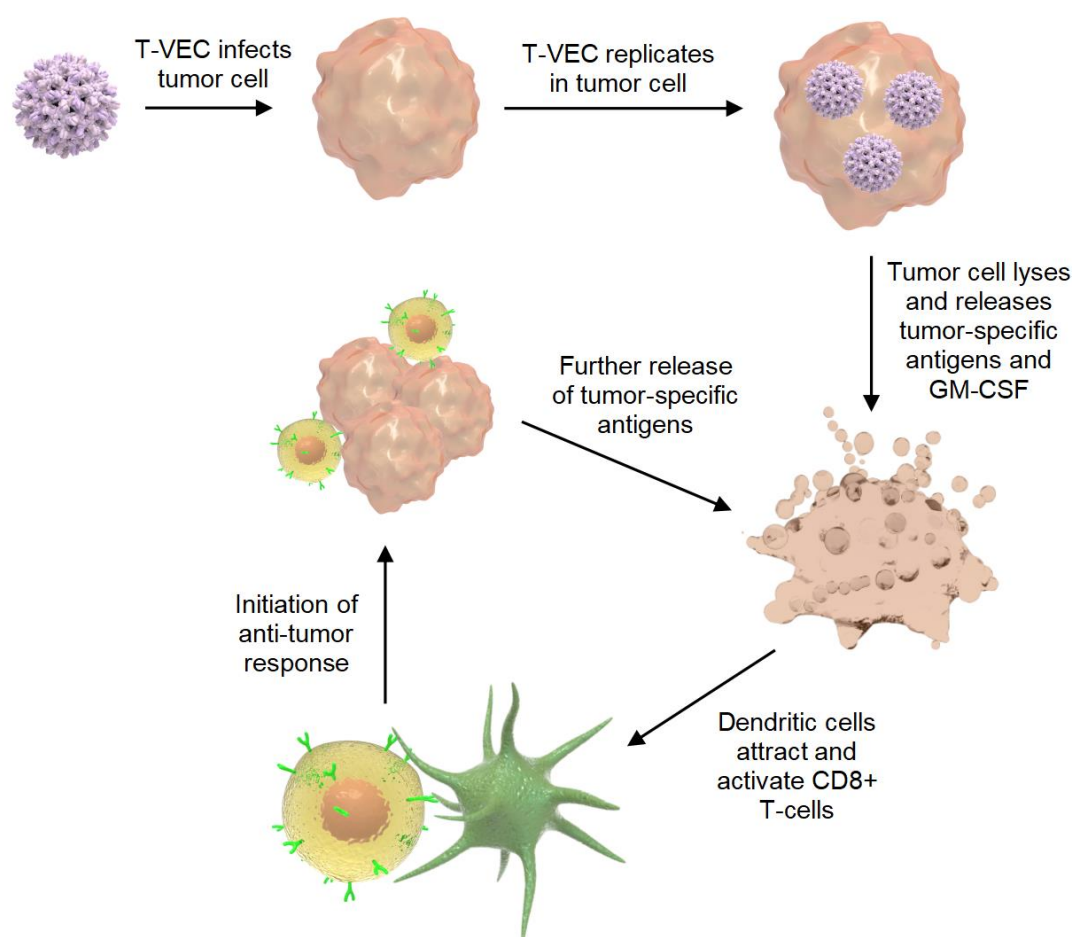


Figure 1. T-VEC oncolytic mechanism and immune response

3. Current applications

3.1. Monotherapy

T-VEC can induce systemic immunotherapeutic effects and is mainly used for melanoma. In a phase III study [4], 436 patients received T-VEC or GM-CSF, and each patient received treatment for at least 6 months. According to this study, among the injected lesions, 64% were reduced by $\geq 50\%$ in size, and 47 % were completely resolved. Meanwhile, the size of 15% to 34% of uninjected lesions decreased by $\geq 50\%$, and complete resolution occurred in 9% to 22%. Administration of T-VEC not only resulted in an anti-tumor response of injected lesions but also had an effect on uninjected lesions, suggesting that T-VEC induced the establishment of the systemic immune response. However, despite the significant effect of T-VEC on local melanoma, the efficacy of monotherapy in clearing the lesion remains suboptimal.

This study also demonstrated that T-VEC enhances the effect of GM-CSF. According to it, the durable response rate (DRR) of T-VEC was observably higher than that of GM-CSF (16.3% v 2.1%).

Overall response rate and median overall survival of T-VEC were also higher. However, response rates with monotherapy are still suboptimal, which is why the combination therapies mentioned in the next section have been explored.

Treatment with T-VEC is usually safe. The majority of T-VEC-related adverse effects were mild or moderate and often went away within 72 hours. Cellulitis was the most typical grade 3 adverse response and commonly reported adverse drug reactions to include fatigue, chills, pyrexia, etc. Besides, herpetic infections also appeared in some patients. Immunocompromised patients, such as those with a history of immunodeficiency, leukemia, lymphoma, or AIDS, as well as those receiving immunosuppressive therapy, are also susceptible to developing a disseminated herpetic infection. Even if this infection can be controlled by drugs, it is still necessary to evaluate the patient's immune level before injection.

HSV-1 can infect a variety of tumor cells with high infection efficiency and a short replication cycle, so T-VEC monotherapy may also be effective for other cancers. Some relevant clinical trials are underway, as shown in Table.1.

Table 1. Monotherapy of T-VEC in other cancers

Cancer Type	Phase	ClinicalTrials.gov Identifier
Pancreatic cancer	I	NCT03086642
Advanced non-CNS tumors	I	NCT02756845
Malignant chest wall neoplasm, recurrent breast carcinoma	II	NCT02658812

3.2. Combination

The combination of different mechanisms is expected to improve the efficacy of cancer therapy. T-VEC can be combined with radiotherapy, chemotherapy, and surgery, and the most promising combination is the administration of it with immune checkpoint inhibitors.

Ipilimumab is a monoclonal antibody that blocks CTLA-4, and CTLA-4 can weaken the immune system's ability against cancer cells. T-VEC, as described before, can attract dendritic cells to activate CD8+ T cells, while Ipilimumab assists T-VEC by enhancing T cell recruitment and preventing the depletion of activated T cells. In a clinical trial that enrolled 217 patients and lasted for 3 years (NCT01740297), T-VEC was injected into the tumor, and ipilimumab was injected into the vein. In phase Ib, the objective response rate (ORR) was 52.6%; in phase II, ORR was 38.8%, and DRR was 29.6%. In addition, the median overall survival in phase II was 84.9 months. These outcomes are superior to the T-VEC monotherapy described in the previous section. However, 26.3% of patients had grade 3+ adverse events in phase Ib, which is more serious than monotherapy.

Pembrolizumab, a PD-L1 antibody, is another promising checkpoint inhibitor. A 7-year, 713-person clinical study was conducted to examine the effectiveness of T-VEC in combination with the therapy (NCT02263508). In phase Ib, ORR was 61.9% and DRR was 57.1%; in phase III, ORR was 49.1% and DRR was 45.7%. ORR and DRR are both significantly higher than those in monotherapy of T-VEC, indicating the high efficiency of this combination.

T-VEC combination therapy has also been explored in other cancers by some clinical trials, as shown in Table 2. In general, combination therapy with T-VEC can improve efficacy and broaden application but may be accompanied by new side effects.

Table 2. Combination of T-VEC in other cancers

The combination treatment	Cancer type	Phase	ClinicalTrials.gov identifier
Anastrozole, exemestane, fulvestrant, letrozole, paclitaxel, tamoxifen, nab paclitaxel, gemcitabine, carboplatin	Breast cancer	I	NCT03554044
Pembrolizumab	Sarcoma, epithelioid sarcoma, cutaneous angiosarcoma	II	NCT03069378
Melphalan, tumor necrosis factor	Melanoma, sarcoma	I/II	NCT03555032
Paclitaxel	Breast cancer, ductal carcinoma	I/II	NCT02779855
Radiotherapy	Soft tissue sarcoma	Ib/II	NCT02453191
Pembrolizumab	Hepatocellular carcinoma, liver metastases, liver tumors	Ib/II	NCT02509507

4. Limitations and expectations

Compared with targeted therapy and other immunotherapy, T-VEC does not need mutation targets and has fewer adverse reactions, which are the main advantages of it. Even though, there are still several aspects to be improved.

Since intravenous injection of T-VEC induces the body to produce antibodies that remove it rapidly, T-VEC is administered by intratumoral injection. However, the intratumoral injection can only be applied to tumor types that are close to the body surface or can be imaged to guide injection, and there are problems of difficult administration and incomplete treatment for many non-superficial solid tumors and metastatic tumors. As mentioned before, ipilimumab can enhance T cell recruitment and prevent activated T cell depletion. In the combined treatment of T-VEC and ipilimumab, ipilimumab was administered intravenously at the later stage. The curative effect of combination therapy is better than that of a single drug, suggesting that the effect of ipilimumab can make up for the incomplete clearance of migrated tumors by T-VEC. In addition, it is also possible to make the intravenous injection of T-VEC work effectively through some modifications.

Another problem is the limited clearance of tumors after injection of T-VEC because physical factors such as extracellular matrix can limit the spread of oncolytic viruses [5]. Therefore, two potential solutions have been explored with other oncolytic viruses: using new vectors to deliver viruses or genetically modifying viruses. First, stem cells are promising vectors for oncolytic viruses to reduce the immunogenicity of the virus [6]. In addition, the use of polymers to shield oncolytic viruses can also reduce their immunogenicity and prolong their circulation in the blood [7]. As for modifying the virus itself, one study has shown that oncolytic adenoviruses expressing relaxin selectively degrade aberrant ECM components to induce apoptosis [8]. Therefore, the combination therapy of oncolytic virus and other drugs that can reconstruct ECM is an improvement strategy. Clinical research still needs to verify if these methods enhance T-VEC.

Besides, the mechanism of its combination therapy is not fully known. Therefore, extensive clinical trials are needed to explore the optimal dose, administration time, and combination regimen, as well as improve the tolerance and efficacy.

Biosafety is also a factor to consider. T-VEC rarely causes serious adverse reactions and these reactions are generally controllable. Herpetic infection is one of them have been reported in some patients following inoculation with T-VEC [9]. It could be due to the presence of wild-type HSV-1 or the reacquisition of T-VEC infectious capacity, and this symptom can be treated with anti-herpes drugs, such as acyclovir [10].

The above problems are not only with T-VEC but also with other solid oncolytic viruses. Therefore, T-VEC, as the most mature representative among them, is necessary to be explored these aspects.

5. Conclusions

T-VEC can specifically infect and lyse tumor cells, triggering a systemic immune response. It has been widely used in the clinical treatment of melanoma, and the effect of combined therapy with other drugs is significantly better than that of a single drug. However, there are still many limitations of T-VEC, such as the problem of subcutaneous injection, and hindered intratumoral spread. These aspects are expected to improve with the development of immunological mechanisms and biotechnology. As the representative of the oncolytic virus, T-VEC not only has a significant curative effect on melanoma but also is expected to be applied to other cancers.

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