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Research Progress and Future Prospects of Three Oncolytic Viruses in the Treatment of Melanoma

Lizhou Fang *

School of pharmacy, Chengdu university of Traditional Chinese Medicine, Chengdu, 611137, China

* Corresponding Author Email: 20201034@stu.hebmu.edu.cn

Abstract. Melanoma is one of the more common tumors among young people, and the number of deaths caused by melanoma is increasing year by year. How to find efficient and safe treatment methods is currently a problem that needs to be solved. At present, most melanoma patients are treated through surgical resection, but the recurrence rate is higher and the effect is poor. Research has found that oncolytic virus therapy alone or in combination with other methods (radiotherapy, cell therapy, immunotherapy) not only has a high acceptance rate for patients, but also has a lower recurrence rate due to better healing. The three viruses that are currently being studied extensively are herpes simplex virus, Coxsackie virus, and vesicular stomatitis virus. In the future, it may become a first-line treatment method. This article mainly discusses the current research progress and therapeutic effects of three viruses, as well as the research on their corresponding variants. Provide corresponding suggestions for future development direction.

Keywords: Melanoma; Oncolytic virus; Immune checkpoint inhibitor.

1. Introduction

Melanoma is a common malignant tumor of the skin in humans. According to data from the World Health Organization, there were a total of 325000 new cases of melanoma (174000 males and 151000 females) and 57000 deaths (32000 males and 25000 females) worldwide in 2020[1]. Although the incidence rate and mortality of melanoma are lower than other types of tumors, the overall trend is increasing year by year. Melanoma is one of the most common cancers among young people, concentrated between the ages of 20 and 30, which hinders their growth and development. There are also some differences in incidence rate among different countries: the incidence rate of eastern countries is lower than that of western countries, but the mortality rate is higher and the harm is greater. Therefore, attention should be paid to prevention and treatment in areas with high incidence rate. How to find efficient and safe treatment methods is also an urgent problem that needs to be solved at present.

The occurrence of melanoma is related to factors such as ultraviolet radiation, sunburn, and familial inheritance. At present, the main treatment method for solid melanoma is surgical resection, supplemented by radiotherapy, chemotherapy, and targeted therapy. The patient has a poor prognosis and a high rate of tumor metastasis. Recent studies have shown that oncolytic viruses can target and infect cancer cells. Viruses that reproduce and spread within cancer cells without damaging normal cells. They have three anti-cancer mechanisms: directly cleaving cancer cells, attracting the immune system to attack them, and carrying natural immune stimuli through genetic modification, thereby further promoting the anti-cancer immune response. Coxsackie virus A21 (V937), herpes simplex virus (HSV), and vesicular stomatitis virus (VSV) are the three most extensively studied viruses in recent years. The current research mainly focuses on using virus therapy alone. Alternatively, viruses can be used as carriers to introduce human derived genes and recombine to form more efficient viral variants for the treatment of melanoma. The three viruses can also be combined with other treatment methods (immunotherapy, cell therapy, radiotherapy) to reduce cancer progression and improve the objective response rate of patients.

This article mainly summarizes the clinical data and future development directions of different oncolytic viruses in the treatment of melanoma in the past five years.

2. Coxsackie Virus A21 (V937)

Coxsackie virus is a ribonucleic acid enterovirus, divided into two categories: A and B, usually infecting the host through the respiratory and digestive tracts. At present, 23 types of Coxsackie viruses (A1-22, 24) have been discovered, with only A21, abbreviated as V937, which can be used as oncolytic viruses and have limited applications. Gebasaxturev (V937, CAVATAK) is a proprietary formulation of the common cold Coxsackie virus A21 (CVA21), which binds to highly expressed specific receptor proteins on various types of cancer cells, killing local and metastatic cancer cells through cell lysis and potential immune responses to cancer cells. V937 can also increase the levels of serum CXCL10 and CCL22, which are two pro-inflammatory chemokines secreted by various cells and can enhance the body's anti-tumor immunity [2]. The human body has weak tolerance to V937 and will not affect the body's immune response. The treatment of unresectable melanoma patients deserves further research.

PD-1 is a receptor on the surface of immune cells. When combined with programmed death ligand 1, it inhibits the activity of immune cells, allowing tumor cells to evade immune system attacks. PD-1 monoclonal antibody can inhibit this process and enhance anti-tumor activity. Research has shown that the use of V937 alone and combined use of PD-1 monoclonal antibody (one of the immune checkpoint inhibitors) can significantly improve the objective response rate (ORR) of advanced melanoma patients. A total of 50 patients received treatment. The ORR of patients treated with V937 alone was 47%, while patients treated with PD-1 monoclonal antibody before V937 had an ORR of 21% [3]. The results indicate that although both treatment methods have higher objective response rates in patients, the ORR of V937 alone is higher than that of combined immune checkpoint inhibitors (ICIs). However, the persuasiveness of the results is weak, as some patients who have received PD-1 monoclonal antibody treatment in the early stages and then used V937 may have weaker immune responses. It may also be related to the disease progression and further development of cancer after patients use monoclonal antibodies. Even with subsequent treatment with V937, the ORR will still be relatively low. So more clinical data on individual treatment and simultaneous combination therapy are needed to prove which one has the best therapeutic effect. Whether treated alone or in combination with ICIs, the overall disease progression of patients can be better alleviated.

The usual treatment method for V937 is injection therapy at the tumor site, and both the injection site and non-injection site show significant regression of the tumor. In another experiment, 11 patients were enrolled, receiving an average of 6 injections of V937 and 3.5 injections of ICIs. Three patients have stable conditions, and eight patients are progressing. 10 patients experienced treatment-related adverse events (AEs), mainly diarrhea (55%), fatigue (45%), and muscle pain (36%). There is no dose limited toxicity associated with V937, nor is there any level 5 AE related to treatment. Some patients received intravenous injection therapy, with AE increasing to levels 3-5, but only a few experienced symptoms such as fever, muscle pain, and difficulty breathing. The incidence of AE using V937 alone is lower than that of PD-1 monoclonal antibody combination therapy, and the level is lower [4]. So, although most patients with combination therapy experience treatment-related AEs, most AEs are associated with PD-1 monoclonal antibodies and have a relatively small correlation with V937. Although the therapeutic effect of V937 is not as significant as other oncolytic viruses, its toxic side effects are small and the level of AE is low.

At present, there are relatively few research reports on V937, only discussing oncolytic virus therapy alone and combined therapy with some ICIs. In the future, more clinical data should be collected by combining other methods (radiotherapy, chemotherapy) to better analyze the effectiveness of V937. Other human recombinant genes should also be transferred to viral vectors for experiments to discover new V937 variants that make the therapeutic effect more significant.

3. Herpes Simplex Virus (HSV)

Two types of herpes simplex virus have been discovered, namely HSV-1 and HSV-2. The main site of infection for HSV-1 is above the waist, while HSV-2 mainly infects below the waist.Most of them use HSV-1 as a viral vector and human derived gene protein recombinant viruses to improve tumor lysis and immune activity. Herpes simplex virus is currently the most widely used virus in clinical practice. Due to the weak pathogenicity of HSV to the human body and its high biological safety, it is not only possible to treat solid tumors through local injection, but also metastatic tumors through intravenous injection.

3.1. Talimogene Laherparepvec(T-VEC)

In 2015, with the approval of the US Food and Drug Administration, HSV for the treatment of melanoma was officially launched and named as Talimogene Laherparepvec (T-VEC), marking a significant breakthrough in the clinical application of oncolytic viruses. T-VEC is an effective therapeutic drug formed by the introduction of HSV-1 through human genetic modification. At present, it has been found that the combination of T-VEC and other treatment methods can significantly improve the objective effective rate of patients and prolong their survival.

T-VEC can be combined with ICIs to treat advanced melanoma. Panaprizumab is an ICIs and a targeted drug, also known as monoclonal antibody, which is widely used in cancer treatment. The mechanism of pembrolizumab is to inhibit the secretion of immunosuppressive molecules, restore the activity of immune cells, increase the secretion of cytokines, and promote the phagocytosis and dissolution of tumor cells. Among 692 selected patients, the objective effective rate of T-VEC combined with perbrolizumab treatment was 48.6%, while the objective effective rate of perbrolizumab alone was 41.3%. And only about 20% of the patients in both groups experienced treatment-related adverse events greater than level 2 [5].

Ipilimumab is also a type of immune checkpoint inhibitor and a monoclonal antibody. Cytotoxic T cell antigen-4 (CTLA-4) is a type of immunosuppressive molecule that can inhibit the human immune system and ultimately reduce the killing power of immune cells against cancer cells. Ipilimumab can effectively weaken the content of CTLA-4 in vivo, thereby increasing anti-tumor activity. Among 198 selected patients, the ORR of T-VEC combined with ipilimumab treatment was 35.7%, while the ORR of ipilimumab alone treatment was 16.0%. And there was no new safety signals reported during the subsequent treatment process [6]. The combination of T-VEC and ICIs has a better therapeutic effect on melanoma compared to using ICIs alone. And the combined treatment is also relatively safe.

However, compared to using ICIs alone, combination therapy is more expensive. The cost of enabling patients to have no cancer progression within one year and have the same quality of life as healthy individuals is approximately $1.6 million [7]. Compared to individual treatment, combination therapy requires a higher economic cost and is only suitable for personalized treatment. In the future, we should consider how to reduce the cost of combined T-VEC treatment and meet social needs.

When some ICIs have poor therapeutic effects, T-VEC combined with immune cells can be used to treat advanced melanoma. After T-VEC treatment alone, the cellular immunity in the body is activated, and a large number of CD8+T cell populations are summoned, ultimately secreting a large number of cytokines (IFN, protease granule B). Not only can T cells exert cellular immunity to phagocytose tumor cells, but cytokines can also synergistically kill cancer cells. So, T-VEC can increase the immune activity of the whole body and recruit immune cells and cytokines to heat up the tumor microenvironment. On this basis, combined with cell therapy, it can effectively enhance the therapeutic effect. Studies have shown that injecting modified T cells and T-VEC into the lesion site can improve the disease progression of early melanoma, and patients can tolerate it [8]. This method has strong feasibility and is expected to be developed as a drug for the treatment of advanced melanoma in the future.

T-VEC can also be combined with radiotherapy to treat advanced melanoma. Compared with patients receiving radiation therapy alone, patients receiving combination therapy have higher levels of caspase-3 in their tissues. This indicates that combination therapy can significantly enhance the body's immune function and promote tumor cell apoptosis. And during the combined treatment process, no patient developed herpes infection due to treatment, and no dose limited toxicity was observed. This indicates that this combination therapy is a safe and well tolerated approach.

3.2. OrientX010

At present, an oncolytic virus called OrientX010 has been discovered. This virus is carried by HSV-1 as a vector and carries GM-CSF genes of human or mouse origin. Experimental results have shown that among the 26 selected melanoma patients, the objective effective rate of treatment is approximately 20%, while the disease control rate is approximately 54%. Among all patients, only a small proportion of them experienced AEs, and most of them exhibited fever and pain at the injection site. All patients did not experience any toxic reactions with increasing treatment dose [9]. The experimental results indicate that low-dose OrientX010 has tolerable safety and anti-tumor effects in the treatment of early and late-stage melanoma. Although the objective effective rate is lower compared to T-VEC, increasing the treatment dose may enhance the treatment effect and further experiments are needed to verify.

Whether it is combination therapy or individual treatment, the treatment-related adverse reactions experienced by patients are not greater than level 2. The most common symptoms are fever, discomfort, chills, decreased appetite, itching, and skin ulcers [10]. Compared to other oncolytic viruses, HSV is safer and more effective. In the future, it is possible to consider combining more treatment methods to enhance the application value of HSV.

4. Vesicular Stomatitis Virus (VSV)

Vesicular stomatitis virus (VSV) is a viral disease of cattle, horses, and pigs, characterized by blisters and erosion on the oral mucosa, nipple skin, and hoof crown skin, but rarely resulting in death. Although there are few reports on the use of vesicular stomatitis virus as an oncolytic virus to treat melanoma, this virus has minimal toxic side effects and deserves further research and development.

VSVs generally lack pre-existing immunity, can rapidly grow to high titers in cancer cells, and their genomes are easy to operate, so most research is based on novel recombinant VSVs. VSV can be combined with cytokine therapy to enhance the body's anti-tumor immune activity. However, systemic injection of cytokines can lead to various uncertain inflammatory and toxic reactions in the body, so targeted drug delivery is necessary to improve the specificity of treatment. VSV can not only recombine with cytokines, but also with the genetic components of other viruses to form chimeric oncolytic viruses.

4.1. VSV+ Immune Stimulating Cytokines

VSV combines with cytokines (IL-2, GM-CSF) to form a new variant VSV (rVSV). Mice were selected as the experimental subjects and rVSV was injected into the cancerous site. The results indicate that rVSV can effectively inhibit the growth of melanoma and prolong the survival cycle of mice [11]. The experiments of rVSV are only limited to animal experiments, and more clinical trials are needed in the future to prove the safety and effectiveness of rVSV.

VSV can also interact with interferonβ(IFN-β) Co expression with tyrosinase associated protein 1 (TYRP1) to form a novel recombinant VSV (VSV-IFNβ- TYRP1). 12 melanoma patients were treated with a single intravenous injection every day. Only one patient experienced dose limiting toxicity, while the remaining patients did not experience dose limiting toxicity. Four patients have stable conditions, and eight patients have made progress. Three patients later received treatment with ICIs, and two patients experienced persistent reactions [12]. Research has shown that VSV-IFNβ-TYRP1 can be safely administered in patients and has good potential for combined treatment with

ICIs. Especially in combination with immune checkpoint blockers of CD200 activated receptor ligand (CD200AR-L) peptide [13]. However, there are more patients with disease progression treated alone than those with stable conditions. In the future, it is expected to be treated together with other immunotherapies rather than single therapy.

4.2. VSV+Newcastle Disease Virus

VSV can recombine with Newcastle disease virus (NDV) to form a new oncolytic virus (VSV-NDV). VSV-NDV treatment of melanoma in mouse experiments. The results showed that the tumor growth time of mice was prolonged and the survival time was improved. VSV-NDV can also be used in combination with ICIs (anti CTLA-4), ultimately further improving therapeutic efficacy [14]. Similar to rVSV, VSV-NDV only has animal experiments and lacks clinical experimental data.

4.3. VSV+Severe Acute RespiratorySyndrome Coronavirus Type 2

VSV can bind to the receptor binding domain (RBD) of severe acute respiratory syndrome coronavirus type 2 spike protein to enhance its oncolytic activity. In vitro cell experiments have shown that compared with ordinary VSVs, variant VSVs can significantly increase the concentration and infection area of the virus in cells. This indicates that this new variant of VSV can enhance its oncolytic activity in vitro [15]. However, the experiment only stays at the cellular level, and more in vivo experiments are needed to prove its effectiveness.

5. Conclusion

At present, the application of oncolytic viruses has become a hot topic. The application and exploration of oncolytic viruses will not stop. The three viruses discussed in this article have certain therapeutic effects on melanoma patients, whether treated alone or in combination with other treatment methods. The patient has a lower level of adverse reactions and a better prognosis. Compared to the other two viruses, HSV is currently the most researched and widely used virus. Represented by T-VEC, it has not only been approved by the FDA, but also has excellent therapeutic effects in combination with other treatment methods (chemotherapy, immune checkpoint inhibitor therapy, cell therapy). Whether it is solid tumors or advanced metastatic tumors, T-VEC has good therapeutic effects. However, the cost of combination therapy is relatively expensive. Although other variants of HSV have been discovered, the objective efficacy rate is not as high as T-VEC. In the future, consideration should be given to finding other low-cost and more efficient variants of HSV to replace T-VEC treatment. V937 has lower adverse reactions compared to other viruses. When used in combination with ICIs, patients have a poorer prognosis and stronger toxic side effects. V937 is suitable as a single treatment method or in combination with other treatment methods (chemotherapy, radiotherapy) to demonstrate its toxic side effects. In the future, V937 should be recombined with more human derived genes to improve its efficacy. Most VSVs are recombinant oncolytic viruses, combined with cytokines and other viral genes, which increase the body's immune response and anti-tumor range. However, currently most of the experiments are only at the animal or cellular level, and more clinical trials are needed to prove the safety and effectiveness of VSV. There are few reports on the combination of VSV with other treatment methods, and it is expected to expand the scope of treatment with more treatment methods in the future. In addition to these three viruses, other oncolytic viruses (reovirus, oncolytic adenovirus) are also gradually being developed and utilized. It is believed that in the future, viruses are not just negative effects that lead to diseases. It can also be developed and utilized to treat more cancer (breast cancer, rectal cancer, gastric cancer) patients.

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