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REVIEW ARTICLE

A Review Of PVSRIPO As a Treatment for Glioblastoma

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ABSTRACT: Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor that is highly aggressive with a dismal prognosis. It infiltrates into the surrounding tissue, making complete surgical extirpation impossible.

Furthermore, the blood-brain barrier limits the delivery of effective chemotherapy. All available treatments are limited by inevitable recurrence, making the cure of this tumor a nearly impossible reality. Therefore, a new treatment is being tested using a genetically engineered poliovirus, PVSRIPO, a non-neurovirulent rhinovirus poliovirus chimera. A recent groundbreaking study revealed that in patients injected with doses of PVSRIPO, the treated group exhibited longer median and overall survival rates and reduced tumor progression. While brain cancers often escape the immune response, injection of PVSRIPO into the tumor activates an anti-tumor immune response. This advantageous mechanism has the potential to be used in many different cancers. While the use of PVSRIPO should be tested further, the increase, albeit small, in survival rate and reduced tumor progression in patients injected with PVSRIPO is still monumental, given that GBM is one of the most challenging diseases to treat.

KEYWORDS: Biomedical and Health Sciences; Cancer; Immunology; Brain Cancer; Glioblastoma; Treatments; Immunotherapy; Poliovirus; PVSRIPO.

Introduction

Glioblastoma multiforme is the most common malignant primary brain tumor classified as grade IV glioma by WHO.[1] It accounts for 54% of all gliomas and 16% of all primary brain cancers.[2] The annual incidence of GBM is 3.19 per 100,000 individuals in the United States.[3] It is more common in males than females and Caucasians than in African Americans.[4] The mean age of occurrence for primary or *de-novo* GBM is 64 years. At the same time, while secondary *GBM* arises from lower-grade astrocytoma and presents at a mean age of 45.[5] GBM is incurable cancer despite the current standard of care with surgical resection, radiotherapy, and chemotherapy. Despite multimodal therapy, the median overall survival of patients is 10-16 months, and only 10% of the patients are alive five years from the diagnosis.[6,7]

More recently, the development of TTF (tumor treating fields) for the treatment of GBM showed mild improvement, but the survival remained under two years.[8] The poor response and high recurrence of GBM have been attributed to the location and behavior of the tumor. The blood-brain barrier prevents the delivery of effective chemotherapy to the tumor. The GBM is chemo-resistant, and tumor cells develop tolerance quickly. These tumors are highly infiltrative and located in functionally important areas precluding their curative resection. Furthermore, the cancer stem cells have been identified in these tumors, which regenerate and resist chemoradiation therapy.[9-11] Due to these factors, the recurrence of these tumors is high, and overall survival continues to be dismal despite continuous efforts made over the past four decades. Therefore, there is a dire need to develop novel treatments to achieve disease control and improve overall survival. One such treatment is a genetically altered version of the poliovirus called PVSRIPO.

PVSRIPO is a genetically engineered polio rhinovirus chimera that contains a combination of both polio- and rhinoviruses. The chimerism and genetic modifications of PVSRIPO make it nonpathogenic- it does not cause polio and does not harm healthy cells. When PVSRIPO is injected into the tumor using a catheter, PVSRIPO recognizes and attaches to the poliovirus receptor (CD155) as shown in the figure (Figure 1).[1]

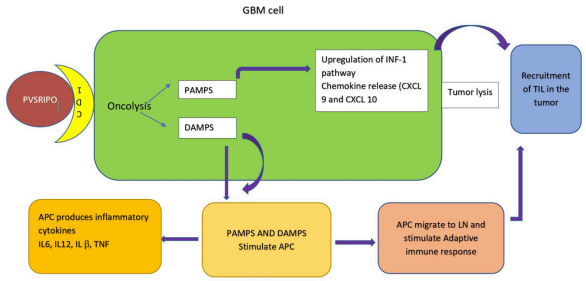

Figure 1: Mechanism of action of PSVRIPO in a GBM cell
The PSVRIPO attaches to the CD1-55 receptor, which causes direct viral-mediated oncolysis. As a result of this, pathogen-associated molecular patterns (PAMPS) and damage associated moleculer patterns (DAMPS) are releases and stimulate an adaptive lymphocytic immune response. As a result, tumor-infiltrating lymphocytes (TIL) are activated. which causes tumor lysis. The PAMPS further augments recruitment of the TIL through upregulation of the INF-1 pathway and chemokine release.

CD155 is expressed at low levels in healthy human tissues but is over-expressed in human cancerous tumors, including glioblastoma. The over-expression of CD155 helps tumor cells hide from the immune system and escape an anti-tumor immune response.[13] The immune system tries to avoid immune over-activation, which could destroy healthy tissues. Cancer uses immune escape mechanisms initially developed to prevent autoimmunity (the immune system accidentally attacking the body's tissues) to its advantage. Therefore, the tumor cells can be undetected by the immune system.[13]

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Although CD155 is evolutionarily advantageous for GBM, researchers have created a new treatment called PVSRIPO that takes advantage of the over-expression of the CD155 receptor and uses this receptor to facilitate the infection of tumor cells. In GBM, PVSRIPO generates an anti-tumor immune response, an immune response against cancer cells. Infecting the tumor with PVSRIPO causes inflammation, and immune cells recognize and attack tumor cells. PVSRIPO- infected tumor cells recruit macrophages (which destroy pathogens through phagocytosis, engulfing the tumor cells) and dendritic cells (which present antigens, or cancer targets, to immune cells) that can become activated by tumor antigens (proteins expressed by the tumor cell). This instigates an immune response, which destroys these infected cells. PVSRIPO does not promote cell death directly but stimulates the immune system to recognize the tumor as a virally infected cell and initiates an anti-tumor immune response.[14] Tumors grow and accumulate in environments because of a weakened immune response. Therefore, anti-tumor immunity is imperative to fight off cancer.[15]

These viral therapies have been established to be safe in treating glioma. Furthermore, the recent success of the Herpes Simplex virus armed with granulocyte-macrophage colony-stimulating factor (GM-CSF) in metastatic melanoma that led to its FDA approval has stimulated interest and raised hopes for the success of viral therapy in malignant tumors.[16] Moreover, there are many ongoing trials where oncolytic viruses are used to treat different cancers. Hence, based on these observations and the fact that there is no durable treatment for GBM that leads to a long-lasting response and a stable disease-free or overall survival, we were stimulated to investigate the role of PVSRIPO as a potential therapeutic agent for GBM.

Methods

A systematic search of PubMed was conducted to identify the articles used in this review. The Medical Subject Headings (MeSH)-related English words that were used in the databases include "*PVSRINO*" and "*Glioblastoma*." The study also used the snowballing method to extract relevant articles considered for analysis. First, the primary researcher performed reference searching to identify the articles on the essential outcomes. In the second stage, title and abstract screening of the database and snowballed sources was completed. Finally, a review of the full-text version of the studies was performed, and the relevance and quality of the sources were evaluated. Twelve articles published between 2014 and 2021 were generated from the database search and were included in this review.

Furthermore, *Clinical trials.gov* was searched for registered clinical trials in different phases on the subject matter. First, the search was conducted using the terms '*PVSRIPO*" AND "*Glioblastoma*." Then, all the trials were evaluated for the outcomes like median survival and overall survival.

Results

A total of six clinical trials on the use of PVSRIPO in primary or recurrent glioblastoma were found to be registered on clinical trials.gov. All these studies are in phase I or II. Most of the trials are active except one in the planned re-submission process, as shown in the table (Table 1) below. The results are available for the NTC01491893 trial.

Table 1: Clinical trials for the use of PVSRIPO in GBM

Clinical Trails.gov identifier	Study Title	Indications	Interventions	Phase	Status	Location
NCT04599647	Expanded Access Protocol for the Treatment of Glioblastoma With PVSRIPO	Glioblastoma	Biologic: **PVSRIPO**		Available	USA
NCT01491893 *	PVSRIPO for recurrent Glioblastoma	Glioblastoma multiforme Glioblastoma Glioma Malignant Glioma	Biologic: **PVSRIPO**	1	Active, not recruiting; has results	USA
NCT04479241	LUMINOS-101: Lerapolturev (PVSRIPO) and Pembrolizumab in Patients with Recurrent Glioblastoma	Glioblastoma Recurrent Glioblastoma Supratentorial Glioblastoma Brain tumor	Biologic: **PVSRIPO** Biologic: Pembrolizumab	2	Active, not recruiting	USA
NCT03043391	Phase 1b Study PVSRIPO for Recurrent Malignant Glioma in Children	Malignant glioma Anaplastic Astrocytoma Anaplastic Oligoastrocytoma and 8 more	Biologic: **PVSRIPO**	1	Active; not recruiting.	USA
NCT02986178	PVSRIPO in Recurrent Malignant Glioma	Malignant glioma	Biologic: **PVSRIPO**	2	Active; not recruiting	USA
NCT03973979	Combination of PVSRIPO and Atezolizumab for Adults with Recurrent Malignant Glioma	Malignant glioma	Biologic: **PVSRIPO** Drug: Atezolizumab	1 2	Withdrawn; Resubmission planned	USA

PVSRIPO: Chimeric polio rhinovirus
ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine: * Results available

Under the trial conducted by Desjardins *et al.*,[12] the survival rate of GBM patients that were given a dose of PVRISPO and compared to GBM patients that were not treated with PVSRIPO. In this study, 61 patients diagnosed with World Health Organization (WHO) grade IV malignant gliomas were treated with PVSRIPO. In the results of this study, the median and overall survival rates were determined. The median survival rate represents when half the patients diagnosed with a disease are still alive. In contrast, the overall survival rate measures the total percentage of patients alive in a study after a specific time. For example, the median survival rate of the GBM patients in the historical control group (not given PVSRIPO) was 11.3 months. In comparison, the survival rate of patients injected with PVSRIPO was 12.5 months, which was 1.2 months longer. Furthermore, among the patients not given PVSRIPO (historical control group), the overall survival rate decreased significantly from 24 months to 36 months, going from 14% to 4%.

In contrast, the patients treated with PVSRIPO had an overall survival rate of 21% (at both 24 and 36 months).[12] While the overall survival rate of the patients injected with PVSRIPO was maintained between 24 and 36 months, the historical control group decreased drastically. Therefore, PVSRIPO effectively increased the overall and median survival rates of GBM patients.

Main Challenges/ Side Effects:

Just over two-thirds of all patients who received PVSRIPO had a grade 1 or 2 adverse event (mild side effects of the treatment that were not considered dangerous). Some patients that were injected with PVSRIPO had symptoms including headaches (experienced by 52% of the patients), muscle weakness on one side of the body (hemiparesis), difficulty swallowing foods and liquids (dysphasia), and seizures. Others had mild symptoms, including confusion, fatigue, nausea,

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and changes in gait. Approximately one-fifth of the patients (during the dose-expansion phase) had severe side effects during the treatment (grade 3 or higher). These side effects directly resulted from brain inflammation due to the injected PVSRIPO.[12]

Long-term Survival:

Nevertheless, after treatment with PVSRIPO, eight patients had a robust anti-tumor response, as seen by magnetic resonance imaging (MRI). Two of these eight patients had a complete response and survived 15.1 months after getting the dose of PVSRIPO. Another three patients had tumors that either shrunk or did not progress after treatment. Some patients injected with PVSRIPO underwent a round of chemotherapy after the treatment. At least 11 of these patients had a reduced tumor size.[12]

Discussion

The results of this study suggest that PVSRIPO may be an effective treatment for glioblastoma. In this study, patients treated with PVSRIPO had increased overall and median survival rates compared to patients treated with standard care alone. The median survival rate of GBM patients injected with PVSRIPO was 1.2 months longer than patients in the historical control group. In addition, the overall survival rate of GBM patients infused with PVSRIPO was 21% (at both 24 and 36 months post-treatment). In comparison, the overall survival rate of the historical control group decreased by 10% from 24 to 36 months.

The outcome of the comprehensive review of the available literature on the subject reiterates the fact that GBM is a complex disease to treat and one for which there is no cure. Therefore, any increase in survival, even a slight increase, is impressive. This increased longevity gives GBM patients more time with their families and lets them live their lives to the fullest before passing away. Furthermore, a negative relationship exists between increased age in GBM patients and survival rate. Therefore, it is integral for patients to be treated effectively so that age does not play a huge factor in causing a shorter survival rate.[17] In some patients, PVSRIPO slowed tumor progression. Decreased tumor progression means that the tumors do not grow as quickly and, therefore, are smaller. In addition, size is a factor in the severity of the symptoms a GBM patient experiences.[18] If the tumors are smaller, there are chances that patients may exhibit less severity in symptoms. Therefore, not only would these GBM patients live a prolonged life, but they may also attain an increased quality of life, which is essential for their mental health.

Given the overexpression of CD155 in various human tumors, not just GBM, using PVSRIPO as a treatment may also be effective in other cancers. In addition, it can be used to enhance anti-tumor immunity.[19] More multicentric trials of PVSRIPO in GBM patients need to be conducted worldwide to analyze the efficacy of this chimeric virus in GBM so that a durable treatment can be found. In addition, PVSRIPO can be tested with other drugs to see if these provide an even more significant patient benefit.

Conclusion

More effective standard-of-care options are essential to treat GBM, and PVSRIPO is a promising treatment that should be further studied. PSVRIPO is an emerging treatment modality on the horizon and one of the innovative treatments and has been accorded breakthrough drug therapy by FDA. More patients should have the chance to be part of future clinical trials that include PVSRIPO, and this opportunity should be widely available to GBM patients that are willing to be part of these trials. Finally, not only can PVSRIPO be used to treat GBM, but it may be effective in other cancers and should be studied in those contexts.

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