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PRACA POGLĄDOWA
REVIEW

# The use of viruses in anti-cancer therapies – new achievements and challenges

## Wykorzystanie wirusów w terapiach przeciwnowotworowych – nowe osiągnięcia i wyzwania

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## ABSTRACT

Viruses are gaining pivotal significance in innovative therapeutic strategies, underscoring their growing role in the field of oncology. The utilization of oncolytic viruses for the selective recognition and effective elimination of cancerous cells has captured the interest of scientists for many years. Due to the unique features of their application, such as greater patient comfort compared to the use of conventional therapies alone, a positive response of the body to treatment, and improved patient survival rates, virus-based therapies may become a pivotal pillar of modern oncology in future, particularly when integrated into combination therapies. It is assumed that further research into the specifics of viruses and their interactions will enable the development of more precise and effective immunotherapies targeted at cancers. However, considering the dynamic nature of these strategies, simultaneous rigorous monitoring of the potential hazards associated with virus application is imperative to ensure patient safety and further advancements in oncology. This review focuses on the analysis of virus application in cancer therapy and the emerging challenges related to clinical studies, placing particular emphasis on their specificity, versatility, and the direction in which modern forms of therapy are heading.

KEYWORDS

oncolytic viruses, cancer, immunotherapy, oncology, medicine

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## STRESZCZENIE

Wirusy odgrywają coraz większą rolę w nowatorskich strategiach terapeutycznych, co podkreśla ich rosnącą rolę w dziedzinie onkologii. Wykorzystanie wirusów onkolitycznych do selektywnego rozpoznawania ognisk i skutecznej likwidacji chorych komórek od wielu lat cieszy się rosnącym zainteresowaniem wśród naukowców i lekarzy. Ze względu na unikalne cechy ich zastosowania, takie jak większy niż w przypadku stosowania wyłącznie terapii konwencjonalnych komfort pacjentów, pozytywna odpowiedź organizmu na leczenie oraz lepsze wskaźniki przeżywalności pacjentów, terapie z zastosowaniem wirusów mogą w przyszłości stać się kluczowym filarem nowoczesnej onkologii, szczególnie w połączeniu z terapiami skojarzonymi. Zakłada się, że dalsze badania nad specyfiką wirusów oraz ich interakcjami pozwolą na rozwinięcie bardziej precyzyjnych i skutecznych terapii immunologicznych ukierunkowanych na leczenie nowotworów. Jednak zważywszy na dynamiczny charakter tych strategii, konieczne staje się równoczesne ścisłe monitorowanie potencjalnych zagrożeń związanych z zastosowaniem wirusoterapii, aby zapewnić bezpieczeństwo pacjentów. W pracy skupiono się na analizie zastosowania wirusów w onkologii i pojawiających się nowych wyzwaniach związanych z badaniami klinicznymi, kładąc szczególny nacisk na ich specyficzność, wszechstronność oraz kierunek, w jakim zmierzają nowoczesne formy leczenia.



SŁOWA KLUCZOWE

wirusy onkolityczne, nowotwory, immunoterapia, onkologia, medycyna


## Introduction

The presence of viruses in the environment have intrigued biologists and medical professionals for a long time. Although they are an integral part of the microscopic world, their origin has not been fully clarified. Viruses form a distinct group, unclassified in any of the five kingdoms. These biological entities, capable of infecting and multiplying in diverse cells due to their ability and unique mechanisms of altering the host's genetic information, have been considered in the development and design of gene therapies. The effective utilization of virus-based therapies would have unimaginable significance in the field of oncology, where, owing to the specificity of the disease and its treatment methods, systemic approaches prevail, rarely targeted exclusively at the tumor.

The application of virotherapy could improve not only the comfort of cancer patients but also impact their survival rates through integration with traditional methods. For nearly three decades, research on the introduction of safe therapeutic methods has been ongoing [1], while the idea of potentially using viruses was first proposed in the 1960s and 1970s. From that time, the noteworthy clinical studies are the investigation of oncolytic APC (adenoid-pharyngeal--conjunctival) viruses in the treatment of cervical cancer in 1956 and the application of a modified mumps virus in 1974 [2].

Over the years, scientists have made significant progress in this field, focusing not only on the utilization of oncolytic viruses (OVs) but also on their supporting role in therapy utilizing modified T lymphocytes (chimeric antigen receptor T-cell therapy – CAR-T). Both methods are part of immuno--oncology, whose main premise is to harness the individual's immune system to combat cancer. There are several different methods of oncologic immunotherapy, each working in a different way, including blocking immune checkpoints (ICI), NK cell therapies, or those based on cytokine action within the immunosuppressive tumor environment [3].

Many immunotherapies have been approved by the European Medicines Agency (EMA) and national regulatory agencies for treating various types of cancers. The approval of immunotherapy signifies an expansion of available treatment options for oncology patients. Despite intensive research in vitro, in vivo, and clinical studies, new challenges continue to arise, which may severely limit the accessibility of the developed methods or even completely preclude their application in specific medical cases.

## Statistics

Every year, millions of people worldwide receive a cancer diagnosis. In Poland, there are annually over 160,000 new cases of malignant tumors and approximately 100,000 recorded deaths [4]. Statistics show a constant increase in the number of cases [5], which may result from societal stress, unhealthy lifestyles, and the pollution of urban areas with carcinogenic factors, as well as improved diagnostics and an increasing number of available screening tests. Despite advances made in the cancer therapy field, the disease still remains one of the deadliest among civilization diseases, characterized by a significant rate of incidence. Given the heterogeneity of tumors in terms of the types, sources, and dynamics of disease evolution, there are various therapeutic strategies.

The majority of the employed treatment procedures significantly impact patient comfort and the overall integrity of health. This is due to the specificity of cancer, where the pathogenic factor consists of mutated cells. Cytostatic agents and radiotherapies, commonly used in treatment, can rarely be targeted solely at the proliferative tumor, resulting in systemic effects. Anticancer therapies encompass a wide range of methods, from surgical tumor removal to the application of radiotherapy and chemotherapy. The

most common choice in oncology involves combining two or three forms of therapy to maximize the chances of curing the patient. Modern immunological therapies and experimental therapeutic approaches are in the process of being improved, aiming to enhance their specificity towards cancer cells, and by that, patient safety.

The interest in using viruses for therapeutic purposes is primarily because of their impact on the human genotype and phenotype. Retroviruses, for example, illustrate the serious influence of these factors on the human genome and their role in triggering cancer foci in infected cells activated by exposure to external factors. An example is the human papillomavirus (HPV), associated with the development of cervical epithelial neoplasia (almost 99% of cervical cancer cases have an etiology related to HPV [6]). The modification and application of viruses to selectively distinguish pathological cells from healthy ones represent notable advancement in improving cancer therapy. Their use will have a direct impact on increasing the survival rate of patients being treated [7].

## Application of *herpes simplex virus* in oncology

The first type of virus utilized for oncological purposes was the *herpes simplex virus* (oncolytic HSV – oHSV). Due to its well-documented lytic replication cycle and the ability to produce multiple molecules in the host cell, HSV became an attractive subject for research into new therapy. In the 1990s, using the biotechnological achievements of the time, a variant of the virus was isolated with silenced or deleted genes regulating nucleotide metabolism in cells remaining in the G0 phase of the cell cycle, preventing oHSV replication in healthy cells [8,9]. The virus would only replicate in dividing cancer cells, leading to their breakdown and death, consequently inducing remission of the tumor focus. The deletion of, among others, *UL23* in the virus DNA, which is responsible for encoding thymidine kinase, was deemed necessary in each of the used recombinant genotypes to enable the use of acyclovir in situations of uncontrolled virus replication in the body [10].

Similar safeguards against infecting the patient's entire organism include gene silencing within *UL39*, responsible for encoding the viral large subunit of ribonucleotide reductase, and the removal of the $\gamma_1 34.5$ gene involved in combating the host cell's defense response. Although the deletion of these genes makes oHSV more focused on destroying cancer cells, it simultaneously weakens its ability to produce new progeny viruses compared to the wild-type *herpes simplex virus*. This is particularly evident in the absence of gene $\gamma_1 34.5$ expression. This potentially affects the overall effectiveness of the therapy, given that the primary action of oHSV is to destroy cancer cells in a lytic cycle [11,12]. A prospective solution was to use different strategies to complement the primary idea of the method.

## Role of activators in OVs gene expression

The primary importance is to safeguard against the excessive spread of the virus in patients undergoing therapy. Therefore, achieving effective removal of tumor foci needs to be accomplished in a different manner. One of the proposed methods to achieve this is by activating gene expression previously silenced upon contact with stimuli presented only in diseased cells. An exemplary activator of gene expression is the protein nestin, present and active during embryogenesis [13]. Nestin is a filamentous protein in the cytoskeleton structure, and it takes an essential role during cell differentiation and migration. After this period, biosynthesis in adult neurons ceases. However, its presence has been observed in dividing glioma cells, making nestin an excellent distinguishing factor between astrocytes and the tumor. It is worth noting that glioma, which develops in the tissues of the brain and spinal cord, is one of the most aggressive cancers and the most challenging to treat.

The immune system, responsible for the monitoring and early elimination of abnormal cells, does not penetrate the brain tissues. Therefore, cancer cells proliferate undisturbed, exerting pressure on structures and causing pathological neurological symptoms. The detection of glioma often occurs when it is already at an advanced stage. Owing to the blood-brain barrier and the delicate nature of neuronal connections, chemotherapy, radiotherapy, or oncological surgery often remain ineffective, and traditional treatments do not guarantee positive results.

In 2005, an experiment was conducted to identify the effectiveness of OVs. Animals with glioma were injected with modified HSV, in which the expression of a gene responsible for evading the cell's defense reaction (*ICP34.5* gene) occurred only under the presence of nestin. The trial yielded phenomenal results. Compared to the control group, the use of OVs allowed the tested mice to survive 50% longer [14]. Conducting further research on the topic of improving the expression of silenced genes could result in a safe and patient-centered therapy that is superior to existing treatments. Although gliomas remain a challenge, the development of oncolytic therapies and those targeting the distinctive molecular features of tumors revive hope for more effective treatment of this deadly disease [15].

## The effectiveness of OVs

OVs are fascinating tools in cancer treatment. Although they have been perceived in medicine solely as pathogenic factors, now are being introduced into the battle against tumors as an ally. All OVs share similar characteristics: the ability to penetrate human cancer

cells and release viral progeny, which lead to the lysis of infected cells. For example, adenoviruses, with the capacity for targeted attack on neoplasm cells, are now finding an application in breast cancer therapy [16], while *herpes simplex viruses* have become an attractive subject of research resulting from their effectiveness in combating pancreatic cancer [17,18].

The key is to understand that the selection of a specific virus for therapy mainly depends on the unique molecular features of a given tumor. The precise customization allows the action of OVs to be more focused and specific. Nevertheless, the effectiveness of the virus is only one side of the coin. Another influential aspect is the injection process itself; after all, precise placement of the virus can improve the success of the treatment. Direct injection into the tumor area enables a more concentrated response on neoplasm cells. Moreover, when administered systemically (intraperitoneal or intravenous), this helps reach metastatic tumors and is useful in situations where the tumor consists of several small nodules distributed over a large area or is located in an anatomical site inaccessible by direct approach (e.g. in the brain) [19,20]. Nonetheless, central administration may result in the fast recognition and elimination of OVs by the complement system and antibodies of the humoral immune response, the same way, in the tumor vicinity.

One way to bypass this phenomenon is the simultaneous administration of pharmacological agents that prolong the survival of viruses. In models demonstrating the increased effectiveness of OVs compared to control attempts, the following were used: histone deacetylase (HDAC) inhibitors, immunomodulatory drugs, or genes blocking internal cell defense mechanisms [21]. It is suggested that upon the discontinuation of pharmacological agents, the destroyed cancer cells and OVs could induce a long--lasting secondary immune response, leading to the creation of memory cell generation. The OVs would then act as a specific in situ vaccine. Precise balancing between immunosuppressive and immunostimulatory agents would contribute to more effective oncological treatment, and at the same time, as a "vaccination" of the patient against a specific type of cancer, reducing the risk of disease recurrence and metastasis.

Current research on oncological vaccines is based on the use of characteristic monoclonal antibodies often directed against tumor markers, but also in the case of tumors induced by oncogenic viruses, viral protein antibodies are used [21,22]. Further clinical and experimental studies are needed to explore the mechanisms of action of OVs to optimize treatment protocols and provide solid evidence of their efficacy and safety in long-term use. This exciting prospect in oncology necessitates collaboration among scientists, physicians, and geneticists.

**CAR-T and OVs**

The application of OVs activators finds particular use in immunologically privileged tissue cancers where the immune system is physically separated, e.g. by the blood-brain barrier. In the case of other organs, there has been increased interest in utilizing the patient's immune cells for fighting disease. The human body is not entirely defenseless against cancer. Through perforin, tumor necrosis factor (TNF), TNF-α-related apoptosis-inducing ligand (TRAIL), NK cells, and cytotoxic T lymphocytes, it targets and eliminates selected diseased cells, thereby preventing the tumor from progressing to a dangerous stage [23]. However, mutated cells are provided with various mechanisms facilitating their growth and protection against immune responses. Immunosuppression of the tumor microenvironment (TME), biosynthesis of membrane receptors, infiltration into healthy tissues, angiogenesis, T-cell suppression, and the induction of tolerance, are only a few from many.

Oncologists have been conducting research for many years to identify the specifics of these mechanisms, which would certainly result in more effective therapies. Despite decades of study, challenges still persist. The proliferation of each tumor progresses differently, and it is dependent on the type of mutation, their location in DNA material, the microenvironment and factors which are individual to an organism [24].

CAR-T represents a novel method approved in 2017, primarily used for patients diagnosed with acute lymphoblastic leukemia. Clinical trials have shown significant efficiency, leading to remission in many patients who were unresponsive to traditional treatments. In a study of 75 participants receiving the innovative therapy, an overall remission rate was observed at 81% after a minimum 3-month follow-up. Of these, 60% achieved complete remission, and 21% achieved complete remission with concurrent, incomplete hematologic recovery [25]. These discoveries marked a turning point in the field of immunotherapy, paving the way for further trials improving the idea behind the method. With its application, the challenge appeared to be the tumor microenvironment.

As a consequence of uncontrolled tumor growth, parts of diseased tissue develop under hypoxic conditions, with cells tightly adhering, hindering blood and lymph from penetration into the tumor core [26]. Limitations also arise from the immunosuppressive nature of TME, characterized by unique cytokine and chemokine profiles, promoting the selective attraction of immunosuppressive cells such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). Tregs can effectively suppress the cytotoxic functions of T cells, promoting an immunosuppressive environment.

In preclinical models, chimeric T cells have displayed a significant reduction in efficacy due to the presence of cancer-associated fibroblast (CAF) cells. Under the influence of the chemokine TGF-β, CAFs demonstrate the ability to produce a dense mitochondrial matrix, limiting the contact between immune and tumor cells [27]. As a result, the destruction of cancer cells occurs only at the edges of the tumor, allowing unrestricted growth of the core.

Other limiting factors of CAR-T therapy include the immunosuppressive nature of TME with a distinctive profile of cytokines and chemokines. This environment favors the selective attraction of immunosuppressive cells, such as Tregs, MDSCs, and TAMs. Tregs exhibit the ability to effectively suppress the cytotoxic functions of T cells by releasing immunosuppressive cytokines, the competitive uptake of IL-2, inhibition of antigen-presenting cells (APCs) through CTLA-4 (cytotoxic T-lymphocyte antigen 4), and by preventing the activation of T cells [27,28]. For these and many other reasons, it was decided to investigate the combination of CAR-T immunotherapy with OVs to analyze their mutual impact on therapy efficacy. Recent discoveries indicate that the post-injection of OVs can induce the production of type I interferon (I-IFN) in TME, a cytokine necessary for stimulating the antitumor responses of T lymphocytes. Additionally, it has been shown that I-IFN enhances the cytolytic activity of T lymphocytes, promotes clonal proliferation, and most importantly, promotes the differentiation of T lymphocytes towards memory cells. These findings suggest a potentially positive impact of OVs utilization on the efficiency and safety of therapy [29].

In a study involving melanoma-afflicted mice, there was an attempt to combine CAR-T cells and the oncolytic vesicular stomatitis virus (oVSV). The animal group was divided and then cancer cells were injected with virals, transforming them into a ‘hot tumor’, which demonstrated an initiated immune response in the microenvironment. Unexpectedly, after CAR-T cell administration, there was a significantly smaller population of chimeric lymphocytes in the OV-infected tumors than in the control group. The authors of the study suggested that the high concentrations of I-IFN produced under viral influence might have immunosuppressive effects on CAR-T cells and it might promote the apoptosis of memory T cells, ultimately reducing the treatment’s effectiveness. Nevertheless, the complexity of cytokine actions makes it challenging to correctly attribute the trial’s failure to the proposed hypothesis or other phenomena [30].

Other studies have demonstrated a positive impact of the simultaneous application of OVs and CAR-T in a modified method known as tumor-tagging. The main assumption of the method is to express proteins and receptors absent on the cell membrane so that the immune system (including CAR-T cells) would locate them easier and faster to initiate apoptosis [31]. For example, when using OVs capable of expressing CD19 on diseased cells, chimeric T cells remarkably more effectively located and eliminated diseased B cells [32,33]. This phenomenon could have applications in the treatment of lymphomas, where current prognoses, particularly for non-Hodgkin lymphomas, are low because of a high metastasis rate. Examples of other expressions in tumor-tagging include the glycoprotein (FRα) [34] and Rras2 protein [35].

The use of OVs in CAR-T cell therapy represents a great field of research, but unexpected challenges are still encountered, relating to the potential immunosuppressive impact caused by the excessive synthesis and activity of cytokines. Proposed strategies, such as modified tumor-tagging methods, may offer an innovative approach, potentially counteracting treatment failures. These findings offer new perspectives in developing more effective CAR-T therapies but require further investigation into the precise mechanism of interaction. Current projections do not suggest that CAR-T and OVs therapies could constitute a standalone method for cancer treatment but rather complement traditional approaches. Although immunotherapy is more specific to mutating cells than chemotherapy and radiotherapy, there is no certainty that it can, on its own, lead to complete eradication of the tumor. The nature of cancer does not allow the preservation of even microscopic portions of the dividing tumor, risking the recurrence of the disease.

## Discussion

The existing research results indicate promising efficacy in both the single and combined use of CAR-T strategies. Nonetheless, to transfer this therapy into clinical practice, it is necessary to understand the mechanisms of action, identify the optimal conditions, and resolve associated challenges. Future studies should be directed towards developing more precise and personalized strategies of treatment to maximize effectiveness while minimizing the occurring side effects. The inherent nature of viruses is one of the potential obstacles. As pathogens, they can elicit diverse immunological responses that may be detrimental to the health and lives of patients undergoing innovative therapy.

In the process of creating virus-based drugs, scientists should continuously monitor and minimize potential risks, such as avoiding the silencing of genes responsible for the correct response to antiviral drugs, even at the expense of OVs efficacy. The other challenges related to OVs-CAR-T therapy should be considered, such as the immunosuppressive effects of cytokines, potential failures in tumor growth control, and limitations coming from tumor heterogeneity.

Identifying and addressing these issues will be crucial for further progress in designing combination therapies with traditional forms. Careless research on the interplay between modified viruses and T cells could have real consequences for the effectiveness of cancer treatment. In the case of tumor-tagging methods, it may be problematic to select the genetic material responsible for the expression of a specific receptor or membrane protein on the cancer cell. The more complex the design of a specific virus line against a tumor is, the higher the costs of individual therapy. Oncolytic virus-based cancer treatment may not be accessible to a larger patient population due to financial reasons.

The world's first oncolytic adenovirus-based drug was approved and utilized in therapy in China in 2005 (Oncorine) [36]. In 2015, in Europe and the United States, the first approved drug of this kind was talimogene laherparepvec (T-VEC), based on a modified *herpes simplex virus*, used in the treatment of melanoma [37]. This means OVs therapies are relatively new, and their long-term impact will only be observed after many years of use in oncology. In the case of innovative therapies, especially those based on gene modifications, obtaining voluntary consent of the participating patient in such treatment is crucial. Oncology patients often lack other effective treatment options, that is why it is essential to provide them with complete information about the experimental nature of the therapy and its potential benefits and risks. This allows the patient to make a decision in accordance with their own values and expectations. Research using such highly advanced methods to create drugs should be represented by the highest ethical standards and transparency about its research area. There should be no room for errors arising from cost-cutting, the bribery of employees, or patient. The importance of discussion in the context of the development of oncolytic virus--based cancer therapies is beyond dispute, and by addressing these issues appropriately, it can contribute to balanced and ethical progression in this area. The introduction of effective therapies of this type is not only a scientific issue, but also a social and moral one, thus it is important that research be conducted responsibly and with respect for patients' rights, in addition to ethical and legal standards.

## Conclusions

Viruses in anticancer therapy represent a fascinating and promising research area that is opening up new perspectives in cancer treatment. However, in order to realize the full potential of these therapies, there is a need for further research, the use of innovative technologies and collaboration between scientists and physicians. With progress in research into the use of viruses in anti-cancer therapy, it is expected that further breakthroughs will come in fighting cancer as well as improving patients' prognosis and quality of life.

**Author's contribution**

Study design – M. Grudnik
Data collection – K. Grudnik, M. Prokurat
Manuscript preparation – M. Grudnik, M. Słomian
Literature research – M. Grudnik, K. Grudnik, M. Słomian
Final approval of the version to be published – K. Lau, K. Kryszczyszyn-Musialik

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