JCOMS eISSN:2783-3127 https://journalofcoms.com

Journal of

Current Oncology and Medical Sciences

Vol. 4, No.2

Review Free Access

Mechanisms, challenges, and future prospects of the oncolytic virotherapy: a comprehensive review

Fizza Maryam [1]*, Sana Gul [2]

[1] Department of Biological Sciences, National University of Medical Sciences, Islamabad, Pakistan

[2] Department of Medicine, Institution affiliation, New Mexico University, USA

Abstract

Oncolytic viruses (OVs) are a promising cancer-fighting agent that has gained widespread attention due to recent advances in virology and molecular biology. These viruses selectively infect and multiply inside tumor cells, causing them to rupture and release newly synthesized viruses that stimulate the body's immune system to target the tumor cells. Clinical investigations have shown that OVs can effectively eliminate cancer cells that are resistant to traditional treatments, which is why over 100 clinical trials are currently exploring the possibility of combining them with other therapies for better efficacy. Although OVs have demonstrated enormous potential, their effectiveness in treating solid tumors is still limited. Therefore, researchers are continuously developing new viral families that can exclusively replicate in tumor cells. Currently, T-VEC is the only FDA-approved oncolytic virus, but with ongoing phase I-III clinical studies, more promising treatments are on the horizon. Furthermore, this review article provides a comprehensive overview of OVs, including their mechanism of action delivery routes, challenges in oncolytic virotherapy, current developments, the efficacy of OVs when combined with other cancer treatments, and prospects for future research.

Keywords: Cancer, Cancer therapy, Clinical trials, Oncolytic viruses, Virotherapy

Corresponding Authors: Fizza Maryam

✉ Email: fizza.maryam272000@gmail.com

Receive: 2024.3.17, Accepted: 2024.6.5

Introduction

Genetic and epigenetic changes transform normal cells into abnormal ones, which results in cancer. Increasing numbers of cancer cases and deaths make cancer the second leading cause of death worldwide. A WHO study estimates that there will be a 60% increase in cancer cases worldwide in the next 20 years (1). Cancer has been recognized as a serious threat to human health and welfare. Chemotherapy, radiotherapy, and surgical procedures could improve the survival rate in cancer patients, but many patients with advanced cancer do not have access to these treatments due to their high costs, especially in low- and middle-income countries (LMICs). Studies have shown that significant disparities can occur in treatment and outcomes due to the financial burden associated with cancer treatment (2). Additionally, advanced tumors often create an immunosuppressive environment that reduces the effectiveness of traditional therapies (3). In this context, oncolytic virotherapy offers a novel and potentially more affordable treatment modality by leveraging viruses that can specifically target and destroy cancer cells while activating the immune system. The particular oncolytic viruses modulate immunological processes. These are viruses that target specific types of cancer cells. They may be naturally occurring or genetically modified. By incorporating a tumor-specific promoter element within their genomes or by deleting essential portions of their genomes, so they selectively replicate within cancer cells (4). In the 19th century, researchers observed that viruses could selectively lyse cancer cells rather than healthy cells, which led to the development of oncolytic virology, the study of viruses that kill cancer cells. Various viral families have been examined to use them as an oncolytic agent; several viruses have been in preclinical studies during the past decade, and some have already been tested in clinical trials (5). It's truly remarkable how much progress has been made in the field of oncolytic virotherapy. The advances in viral retargeting, viral delivery systems, gene editing, tracking strategies, OV-based gene therapy, and combination approaches have all contributed to expanding the potential applications of this therapy in oncology. The possibilities for using these cutting-edge technologies to treat and even cure cancer are truly exciting to consider. However, due to the challenges associated with genetic engineering and safety concerns, oncolytic virology has made little progress over the previous 20 years (4). The review likely incorporates recent breakthroughs in virology and molecular biology that have contributed to the understanding and development of oncolytic viruses. This could include advancements in viral retargeting, and viral delivery systems. Given the dynamic nature of research in this field, there may have been discoveries of new viral families or innovative therapeutic approaches for oncolytic virotherapy. The review likely discusses any new viruses that have shown promise as oncolytic agents or novel strategies for enhancing the efficacy of existing viruses. Overall, the review aims to highlight the evolving landscape of oncolytic virotherapy and its potential in addressing the challenges posed by cancer, showcasing the progress made in the field over the past years and outlining avenues for future research.

History

Long before the first official clinical trial using an OV was published in 1949, several cases reported from the mid-1800s revealed that spontaneous microbial infections could sometimes occasionally regress tumour burden in cancer patients (6). A leukemic patient in the late 1890s developed a "flu-like" illness that was accompanied by generalized inflammation and a reduction in tumour cells, providing additional proof of the therapeutic potential of viruses. In 1949, the results of these studies led to the launch of several clinical trials at Memorial Sloan-Kettering, treating more than 150 patients with wild-type RNA viruses Bunyamwera (bunyaviridae), Ilheus (flaviviridae), Semliki Forest (togaviridae), Newcastle disease (paramyxoviridae) West Nile (flaviviridae), and Dengue (flaviviridae) (7, 8). In addition, RIGVIR and Oncorine have received approval for use as OVs in various nations as cancer treatments. In 2004, the Latvian government legalized the use of the non-genetically virus strain RIGVIR, also known as enteric cytopathic human orphan type 7, to cure melanoma (9, 10). In November 2005, the Chinese Food and Drug Administration approved the use of genetically altered oncolytic adenovirus, known as H101 (Oncorine), in combination with chemotherapy to treat nasopharyngeal cancer (11, 12). The oncolytic virus T-VEC (Imlygic) also known as OncoVEX^{GM-CSF}, a

modified version of the HSV-1, had been approved by the FDA in 2015 to treat melanoma (13, 14). The deletion of particular genes in the virus increases antigen presentation and promotes selective replication within cancer cells (15). The approval of T-VEC in 2015 gained the attention of researchers to work further on oncolytic virotherapy to make them a powerful weapon against cancer in the future.

Candidates for the oncolytic virus

Currently, extensive research suggests that DNA and RNA viruses, HSV, measles virus, and many other viruses mentioned in (Table 1), are major candidates for cancer therapy (16, 17). In particular, adenoviruses and herpesviruses have been developed to precisely detect and target cells expressing fetoprotein or prostate-specific antigen, which is the cancer marker. Also, the surface proteins of the measles and polioviruses were modified to alter their specificity to target only the cancerous cells, not the healthy cells (18, 19).

Table 1. key oncolytic virotherapy candidates during the past 20 years are listed below.

Genome	Family	Strain	Genus	References
DNA	Herpesviridae	HSV 1	Simplexvirus	(20, 21)
		HSV 2		(22, 23)
		Bovine herpesvirus 1	Varicellovirus	(24)
		Suid herpesvirus 1		
	Adenoviridae	Human adenovirus C serotype 5	Mastadenovirus	(25)
		Human adenovirus B serotype3		
	Parvoviridae	H-1PV	Parvovirus	(26)
		Minute virus of mice		
RNA	Picornaviridae	Encephalomyocarditis virus	Cardiovirus	(27, 28)
		Echovirus 1	Enterovirus	(29, 30)
		Coxsackievirus A13, A15, A18		(31)
		Poliovirus		(32)
	Orthomyxoviridae	Influenza A	Influenzavirus	(33)
	Paramyxoviridae	Newcastle disease virus	Avulavirus	

	Measles virus	Morbillivirus	(34)
	Rubululavirus	Mumps virus	(35)
Reoviridae	Bluetongue virus-10	Orbivirus	(36)
	Reovirus serotype 3	Orthoreovirus	(20, 37)

Mechanisms of oncolytic virotherapy

The immune system is suppressed in tumours, which are referred to as immunosuppressive environments. Various mechanisms are employed by tumors to evade detection and destruction by the immune system in this immunosuppressive environment. There is evidence that tumors can produce immunosuppressive cytokines such as TGF-ß and interleukin-10 (IL-10), which can inhibit the activity of immune cells. In addition, tumors can produce immune checkpoint proteins like PD-L1, which bind to PD-1 receptors on T cells, effectively deactivating these cells and preventing them from attacking cancer. A tumor microenvironment may also recruit regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), both of which suppress immune activity. This immunosuppressive mechanism prevents the immune system from recognizing or fighting cancer cells effectively (38). In this context, the immunotherapeutic technique of oncolytic viruses (OVs) holds promise for promoting antitumour immunity. Consequently, both innate and adaptive immune responses facilitate this process (39, 40). OVs, either naturally or after genetic alterations selectively replicate inside cancer cells. Normal cells are left unaffected. It is believed that cancer cells are thought to differ from normal cells due to a number of changes in their physiology, such as the inability of cancer cells to undergo apoptosis, sustained angiogenesis, tissue invasion, the ability to replicate indefinitely, and metastasis. Consequently, these characteristics make cancer cells a generous host for viruses, which can promote selective replication of OVs in cancer cells. These viral cancer-targeting strategies can be broadly accomplished by removing viral genes that are involved in replication in normal cells but not in tumour cells and utilizing tumor-specific promoters for viral genes essential for replication (7). It is possible to target specific tumours by targeting molecular steps/regulators during the cell cycle (41). Here, it is crucial to understand how the immune system functions during oncolytic viral therapy. Basically, OVs destroy cancer by two main mechanisms: direct cell lysis and induction of antitumor immunity. The lysis of tumour cells is the initial reaction that follows a viral infection. Lysing tumour cells cause the release of cytokines, viral pathogen-associated molecules, PAMPs and DAMPs which support immune system responses (4, 42-44). Accumulating evidence suggests that T cell-attracting chemokines are released due to viral infection and replication, which causes an inflammatory reaction. These chemokines attract tumour-and virus-specific T cells, which migrate towards the tumour to perform their function. New virions are released during the lysis of an infected cell and will infect nearby cancer cells. Viruses can release tumour antigens that can act as immunomodulators or tumour vaccines by inducing an immune response (45). An antigen-presenting cell (APC), specifically a dendritic cell (DC), can display foreign antigens on the major histocompatibility complex (MHC) during the immune response (46). Infection with the oncolytic reovirus increased the expression of transporter associated with antigen processing (TAP-1, TAP-2) and MHC class I, in a mouse model but not in control cells (47). Additionally, these immune responses will begin to form tumour antigen-specific memories that will also act on distant metastases. Moreover,

engineered OVs have further enhanced the immune response (48). This strategy changes the immunosuppressive tumour microenvironment by incorporating immune-stimulating molecules into OV genomes. There is a new immune stimulatory factor known as GM-CSF added into OV to mature and attract APCs, particularly DCs, and to induce tumour-specific T cells.(49) OVs, including adenovirus and vaccinia virus, can be altered to encode transgenes (armed oncolytic viruses), such as cytokines or antibodies (50, 51). This ensures targeted delivery to the tumour microenvironment and further stimulates an anticancer immune response. To improve intracellular antigen delivery and presentation, the oncolytic adenovirus genome was altered to overexpress the HSP70 protein (52). More CD4+, NK cells and CD8+ T cells were produced when the modified oncolytic adenovirus was administered (Figure 1) (44, 53).

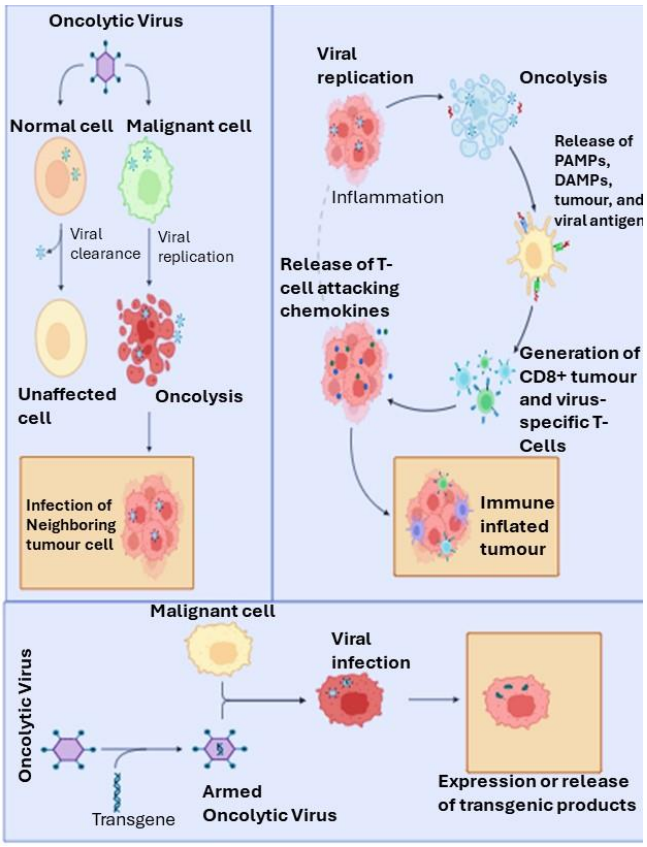

Figure 1. The figure shows oncolytic viruses selectively replicating in cancer cells, not healthy cells. It also depicts immune responses against tumors induced by viral infection and transgene expression in Ovs.

PAMPS: Pathogen associated molecular pattern; Damp's: Damage associated molecular pattern; DCs: Dendritic cells.

Clinical trials

Researchers have investigated a wide range of viral families, including the poxviridae, herpesviridae, rhabdoviridae, reoviridae, adenoviridae, paramyxoviridae, and parvoviridae, for their potential as oncolytic agents over the past 20 years (5, 54). Despite being in the preclinical stages of testing, some have already completed clinical trials at different stages. Several clinical studies are being conducted currently for DNA (153 trials) and RNA viruses (70 trials) (55). All clinical studies using oncolytic viruses that are indexed in PubMed were analyzed. The type of oncolytic virus utilized, the delivery route, the research design, the type of disease, the primary outcome, and the side effects were all evaluated in the trials (56). We found 226 trials; Phase I trials accounted for 124, phase I/II combined trials for 47, phase II trials for 48, and phase III trials for five till 2021 (Figure 2a) (55). In these trials almost 30 are completed, 30 are active and 85 are recruiting (Figure 2b). Some key findings from these trials include: Many trials have demonstrated that oncolytic viruses reduce tumor size and improve survival rates, especially when combined with other treatments. There is evidence that combination therapies can improve the immune response against tumors. In trials, oncolytic viruses have generally been well tolerated by patients, with manageable side effects. Injection site reactions and mild flu-like symptoms are common side effects, which are related to the viral nature of the treatment (57). Typically, intratumoral injections provide direct access to tumors while minimizing adverse effects on the system. A few studies have investigated intravenous administration as a more effective way of treating metastatic cancers (58). The three oncolytic viral therapies RIGVIR, Oncorine, and T-VEC, are currently licensed for use in some clinical cancer treatments (11). Until now, the FDA and several countries including Europe, Australia, Switzerland, and Israel have only approved one oncolytic virus therapy, T-VEC (59). Recently, in June 2021 a modified HSV-1 for malignant gliomas called teserpaturev (DELYTACTR) has acquired a conditional and temporary approval in Japan (60, 61). Recent approvals and ongoing clinical trials indicate that oncolytic viruses are becoming increasingly accepted as a viable cancer treatment option. Our understanding of immunomodulation and developments in bioengineering techniques suggest that more therapies may be developed in the near future as a result of new viral vectors, combination therapies, and improved delivery methods (48).

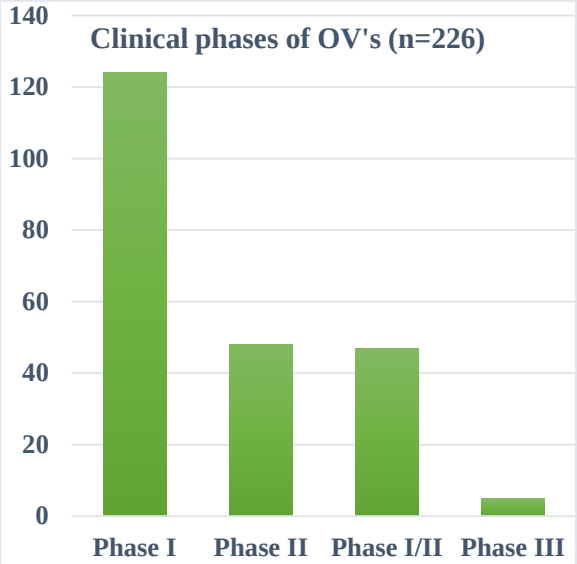

Figure 2a. In Clinical trials, Phase I trials accounted for 124, phase I/II combined trials for 47, phase II trials for 48, and phase III trials for five . Data were analyzed from clinical trial.

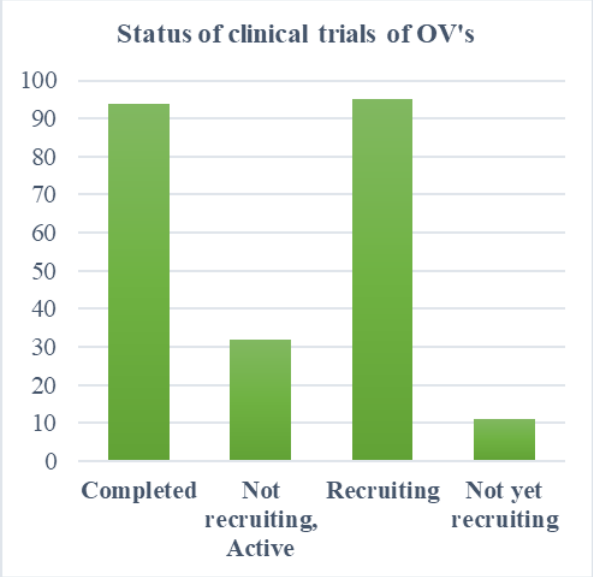

Figure 2b. The status of these clinical phases. Data were analyzed from clinical trials.gov.

Below are the examples of some of the studies in clinical trials. It mentions the viral vector, modification/changes to OVs that promote direct infection and killing activities, route of administration, and its status. These are summarized in Table 2 (4, 5, 37, 44, 55, 62, 63).

Table 2. A summary of the clinical trials of key oncolytic viruses that have been published. Not all oncolytic viruses are present. Data were analyzed from clinicaltrials.gov.

Virus (Type)	Developer	Modification	Clinical phase	Tumor Type	Route of Administration	Combination/ Therapeutic Approach	Status	Clinical Trials. gov Identifier	Ref
Adenovirus (dsDNA)									
DNX-2401	DNAtrix	Δ24RGD insertion	I	Brain and ovarian cancer	Intratumoural	Both combination or oncolytic virus only	Active completed	NCT03178032 NCT01956734	(7)

Colo-Ad1	PsiOxus Therapeutics	Chimeric Ad11/3 group B	I	Colon cancer, NSCLC, renal cell carcinoma, and bladder cancer	Intratumoural	Oncolytic virus only	Completed	NCT02053220	(8)
VCN-01	VCN Biosciences	PH20 hyaluronidase	I	Neoplasms, pancreatic, neck, Retinoblastoma, and head cancer	Intratumoural	Both combination or oncolytic virus only	Recruiting	NCT03284268 NCT03799744	(9)
ICOVIR5	-	Modified DNX 2401-E2F promoter optimized	I,II	Solid tumour, and melanoma	Intravenous	Only oncolytic virus	Completed Completed	NCT01864759 NCT01844661	(40)
H101	Shanghai Sunwaybio	Partial E3 deletion, E1B deletion,	I, III	Head, squamous cell carcinoma, and neck cancer	Intratumoural	Only combination	Recruiting Recruiting	NCT03790059 NCT03780049	(67)
ProstAtak	Advantagene	TK insertion	II, III	Breast, mesothelioma, prostate, and pancreatic cancer	Intratumoural	Both combination or oncolytic virus only	Recruiting Active	NCT01436968 NCT02768363	(61)
HSV-1 (dsDNA)									
T-VEC	Amgen	US11 deletion, ICP34.5 deletion, GM-CSF insertion	I,III	Head, Melanoma, pancreatic, and neck cancer	Intratumoural	Combination or oncolytic virus only	Recruiting Recruiting Completed	NCT03086642 NCT03069378 NCT01368276	
G207	Medigene	UL39 disruption ICP34.5 deletion	I,II	Brain cancer	Intratumoural	Oncolytic virus only	Recruiting	NCT03911388	
HF10	Takara Bio	UL56 deletion	I,II	Breast, melanoma, pancreatic cancer	Intratumoural	Combination or oncolytic virus only	Completed Terminated	NCT03153085 NCT03259425	
Reovirus (dsRNA)									

Reolysin	Oncolytics Biotech	None	I,III	A variety of cancers, including head pancreatic gliomas, sarcomas, colorectal cancers, NSCLCs, ovarian, multiple myeloma, and neck cancers	Intravenous, Intratumoral	Combination or oncolytic virus only	Completed Completed Completed	NCT01166542 NCT02620423 NCT01656538	(66)
Vaccinia (dsDNA)									
GL-ONC1	Genelux	Thymidine kinase disruption, F14.5L disruption	I,II	Head, lung, neck cancer and mesothelioma	Intraperitoneal, Intratumoural, and Intravenous	Both combination or oncolytic virus only	Completed Active	NCT01443260 NCT02759588	
Newcastle Disease Virus (ssRNA)									
Wellstat Biologics	None	I	Larynx, salivary gland cancer	Intravenous	Oncolytic virus only	Terminated Completed		NCT00081211 NCT00055705	

dsDNA: double-stranded DNA, dsRNA: double-stranded RNA, ssRNA: single-strand RNA, NSCLC: Non-small cell lung cancer, RGD: arginine-glycine-aspartic acid, US11: unique short 11 glycoprotein.

Combination of cancer treatment strategies with OV's

In general, monotherapies alone are ineffective for treating cancer, especially in metastatic or advanced stages. Certain types of cancer have already seen significant improvements with the combination of numerous therapies. OVs are using in combination with other anticancer treatments, such as immunotherapy, drugs, and radiation. These can improve therapeutic outcomes, increase therapeutic effectiveness, and focus on a larger variety of tumour types (64). Scientists are just beginning to understand how oncolytic viruses work in conjunction with chemotherapy and radiotherapy. A further benefit that makes OVs a desirably combined platform is their engineering feasibility and confirmed safety profiles (65). These OV-drug combinations are clearly effective if they are chosen correctly, along with properly chosen medications and the type of cancer attacked. Several combination strategies have been tested for natural or synthetic OVs in recent decades, both in the lab and in clinical trials. The majority of cancer patients are still treated with chemotherapy. Combining chemotherapy with oncolytic virotherapy causes a significant apoptotic induction in a number of preclinical tumour models. For example, patients with advanced melanoma who received T-VEC plus the immune checkpoint inhibitor ipilimumab showed improved response rates compared to ipilimumab alone (66). Another study demonstrated that patients with solid tumors who received an oncolytic adenovirus along with pembrolizumab, another immune checkpoint inhibitor, had durable responses (67). Likewise, Ad-H101was approved for the treatment of cancer by China, particularly for the neck and head cancer in 2005 following phase III clinical trials that revealed that, when Ad-H101 combined with chemotherapy with 5-FU which shows its effectiveness upto 79-72 percent vs. 40 percent with chemotherapy alone (64, 68). Moreover, one of the most prevalent cancer treatments is radiotherapy, which kills the cancer cells, shrinks the tumour, and damages normal tissues and cells in the surrounding area. When the human body is exposed to radiation, radionuclides enter it. By promoting the accumulation of radionuclides in tumor cells, the selective replicative capacity of OV can be enhanced to improve the precision and safety of radiation therapies. The OVs can increase the susceptibility of tumor cells to radiation, causing them to be more vulnerable to radiation-induced damage (69). By disrupting cellular repair mechanisms, viral infections enhance radiation treatment effectiveness at lower doses, resulting in improved safety since healthy tissues are not exposed to radiation (70). Additionally, OVs can deliver radionuclides directly to tumor cells. It is possible to deliver radiation to tumors specifically by engineering OVs to express or carry radionuclide-conjugated proteins. In this way, radionuclide therapy is more targeted, targeting cancer cells while limiting exposure to normal tissues. Furthermore, combining OVs with radionuclide therapy could further broaden the therapeutic window because of the dosage range within which the treatment is effective and safe. The selective targeting and synergistic effects of OVs can allow for lower doses of radiation to achieve the desired therapeutic effect, improving overall safety and reducing side effects (66). Likewise, there have been many studies conducted on the interaction between radionuclide therapy and among those viruses that have been genetically modified to express membrane protein, which is sodium iodide symporter (NIS) that facilitates the cellular uptake of radionuclides such as ^{131}I (71-73). When vaccinia viruses that express NIS are administrated prior to ^{131}I treatment, intramural production of NIS proteins raises the cellular content of radioiodine, and the combined therapy is more effective in case of prostate cancer cells as compare to use either OVs or ^{131}I alone (74, 75). The results of these studies suggest that OV-drug combinations can improve clinical outcomes and enhance the immune response against tumors.

Delivery of oncolytic viruses

When conducting research, selecting the appropriate delivery method is crucial. Researchers consider their research goals and the resources available to determine the most effective approach. Oncolytic viruses are delivered to the host via three routes: intravenous, intratumoral, and intraperitoneally. Intrathecal and subcutaneous methods are utilized by researchers as supplementary delivery routes, in addition to the three primary ones mentioned above. There are some

advantages and disadvantages of all these three routes. In intravenous delivery, oncolytic viruses move throughout the circulatory system when injected into a peripheral vein, reaching tumour lesions in nonspecific organs and systems. It's an effective option when it is difficult to directly introduce the oncolytic virus into tumour (76). In preclinical and clinical settings, intravenous (IV) delivery are commonly used. IV delivery allows the virus to circulate systemically and potentially reach metastatic or deep-seated tumors. However, this method can face hurdles such as the immune system neutralizing the virus before it reaches the tumor, and limited virus penetration into the tumor microenvironment (77). The second technique involves delivering oncolytic viruses directly to tumors for treatment. This approach, known as intratumoral delivery, has a direct therapeutic effect on the malignancy. This method delivers a concentrated dose of oncolytic virus in vitro directly to the targeted tissue, allowing for a clear and significant impact to be observed (78, 79).However, its application in vivo, particularly in deep or inaccessible lesions, is challenging. Additionally, intraperitoneal injection of the oncolytic virus into the peritoneum is the third delivery route. Once absorbed, it either diffuses directly into tumour lesions within the peritoneal cavity or into the peritoneum veins, where it reaches tumour lesions via the circulatory system. The main benefit of this approach it's simple to administer and requires few specialization skills. Compared to subcutaneous injections, intraperitoneal injections are quickly absorbed (80). The intraperitoneal is the best choice for treating abdominal organs, but it is slowly absorbed compared to intravenous injection (Figure 3) (81, 82).

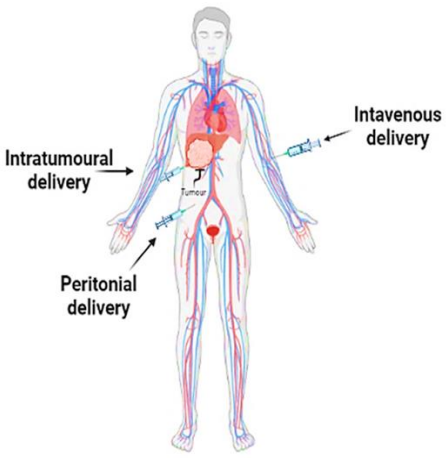

Figure 3. Main delivery route of oncolytic viruses.

Challenges and their solutions in oncolytic virotherapy

Even though oncolytic virotherapy has great potential, it still faces many challenges that need to be addressed for it to be more effective and safe. There are several types of challenges that can be categorized as follows:

Immune-related challenges

There are many challenges and drawbacks of cancer-specific oncolytic virotherapy, which include antiviral immune responses, antibodies frequently inactivating circulating viruses, off-target infection, adverse conditions in the tumor microenvironment, insufficient immunogenicity, and a number of barriers inhibiting systemic delivery of oncolytic viruses (44, 83, 84). Host defense system prevent the majority of oncolytic viruses from infecting tumours following systemic delivery. When delivering oncolytic viruses to the body, there are several obstacles that must be overcome. These include blood cells, neutralizing antibodies, antiviral cytokines, nonspecific uptake by other tissues, tissue-resident macrophages, and difficulty in virus escape from the vascular compartment (85-87). This technique needs a virus that preferentially infects tumour cells while remain in the circulation without depleting or degrading.

Safety concerns

Oncolytic viruses have the potential to cause extensive organ damage and inflammation when a significant volume of them are circulated throughout the body. For replication-competent viruses, it may even be risky to assume that a few mutations will modify these profiles entirely for scientific and clinical purposes, but still it could be dangerous. For this reason, to assure safety, preclinical assessments are necessary. Due to these restrictions, there may be some discrepancies in the efficacy and safety margins between research on animals and humans (88). The effects of animal-derived oncolytic viruses can be studied in a variety of methods, but it cannot be expected that the results gained in animal models would be reproducible in people (84). The use of oncolytic virotherapy may worsen comorbid conditions such as coagulopathies, heart disease, liver disease, and lung disease (18). Antiviral medication may already being administered to some individuals with chronic viral infections, which

could prevent viral oncolysis. Early clinical trials revealed a phenomenon known as pseudoprogression, in which the treated tumours grew larger and displayed more heterogeneity, likely as a result of infections that caused inflammation or edema (89). Careful consideration will also be given to the choice of patients. There is a possibility that immunocompromised patients will not be suitable candidates due to their weakened oncolytic virus-mediated antitumor immunity.

Research and development challenges

Numerous problems have arisen and will continue to arise in the field of virotherapy and oncolytic research. Despite this, some efforts have been made to avoid or at least mitigate the worst effects of viral infections and to improve the effectiveness, safety, and usefulness of virotherapy (90). Making an accurate diagnosis may require the development of novel molecular markers. For example, human telomerase reverse transcriptase exhibits elevated expression level in tumour cells but not in normal cells, which increases the effectiveness of telomerase in targeting tumours and modifies the tropism of viruses, allowing them to bind only to specific receptors on tumour cells, such as the adenovirus Delta-24RGD (39, 91).

Delivery challenges

The main difficulty with this therapy is properly delivering the virus to the tumour. Systemic administration rarely works because of preexisting immunity. An off-target infection may occur where oncolytic viruses infect healthy cells instead of tumor cells, causing unwanted side effects. As an example, a virus that targets cancer cells in the liver might also infect healthy liver cells or other tissues if it lacks sufficient specificity. A patient may experience adverse effects due to this off-target infection causing damage to healthy organs and tissues. A key to minimizing these risks is ensuring that the virus only infects tumor cells and not healthy tissues. Since intratumoral injection is costly and challenging, especially in cases of malignant gliomas, it is necessary to optimize virus delivery in order to improve systemic delivery. The use of complex viral particle ligands, nanoparticles, and immunomodulatory drugs are a few of the novel strategies being studied (92). The technically challenging image-guided delivery approach is used to introduce viruses into tumours using nanoparticles.

Conclusion and future prospect

OVs have become promising immunotherapeutic treatments for advanced malignancies over the past 20 years. Interest in oncolytic virotherapy increased after the US-FDA approved T-VEC in 2015. Several viruses have been evaluated as prospective candidates for oncolytic virotherapy, including vaccinia, reovirus, parvovirus, and picornavirus. Oncolytic virotherapy has not become a common practice in medicine due to a number of biological and technical obstacles. However, there are numerous OVs being tested in clinical trials right now, and several aspects, such as the optimum way to administer and their optimal combinations, are still being taken into consideration. Several natural and genetically modified oncolytic viruses are now being evaluated for monotherapy or combination therapy, and the majority of them seem safe and have few dose-limiting toxicities. Some of these viruses have progressed to various phases of clinical trials despite being in preclinical stages. A total of 153 trials are currently underway for DNA viruses and 70 trials for RNA viruses. As of 2021, 124 clinical studies indexed in PubMed were Phase I trials, 47 Phase I/II trials, 48 Phase II trials, and five Phase III trials. There have been numerous clinical trials demonstrating the effectiveness of OVs in reducing tumor size and improving patient survival rates, particularly when combined with other treatment options. Oncolytic virotherapy could have a profound impact on cancer treatment. In the future, new genetically altered OVs, new delivery techniques, and new combination therapies will be developed. OVs will be the most effective therapeutic approach for treating cancer once they have overcome the existing obstacles to oncolytic virotherapy, such as physical obstacles, immunosuppressive TME, and host clearing of OVs. If the issues mentioned above are properly resolved, oncolytic viruses could one day be a perfect and painless therapeutic choice for cancer patients. To effectively utilize OVs for novel approaches and overcome existing challenges, a collaboration between the fields of immunology, molecular biology, structural biology, genomics, and bioinformatics is necessary. In

the near future, oncolytic viral therapies should be developed further due to their continued clinical need.

Author contribution

Both authors participated in the study design. The data collection was done by **FM** and **SG**. The manuscript was written, reviewed, and edited by **FM** and **SG**. Both authors read and verified the final manuscript.

Conflict of interest

The authors have no conflict of interest.

Funding

The authors express that no funds or other support were received during the preparation of this manuscript.

References

1. Bray F, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63.

2. Mariotto AB, et al. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst. 2011;103(2):117-28.

3. Bates JP, et al. Mechanisms of immune evasion in breast cancer. BMC Cancer. 2018;18(1):1-14.

4. Kaufman HL, Kohlhapp FJ. Oncolytic viruses: a new class of immunotherapy drugs. Nature reviews Drug discovery. 2015;14(9):642-62.

5. Chaurasiya S, et al. Oncolytic virotherapy for cancer: clinical experience. 2021;9(4):419.

6. Rahman MM, McFadden G. Oncolytic Viruses: Newest Frontier for Cancer Immunotherapy. Cancers (Basel). 2021;13(21).

7. Zhang S, Rabkin SD. The discovery and development of oncolytic viruses: are they the future of cancer immunotherapy? Expert Opin Drug Discov. 2021;16(4):391-410.

8. Southam CM. Present status of oncolytic virus studies. Trans N Y Acad Sci. 1960;22:657-73.

9. Alberts P, et al. Long-term treatment with the oncolytic ECHO-7 virus Rigvir of a melanoma stage IV M1c patient, a small cell lung cancer stage IIIA patient, and a histiocytic sarcoma stage IV patient-three case reports. APMIS. 2016;124(10):896-904.

10. Doniņa S, et al. Adapted ECHO-7 virus Rigvir immunotherapy (oncolytic virotherapy) prolongs survival in melanoma patients after surgical excision of the tumour in a retrospective study. Melanoma Res. 2015;25(5):421-6.

11. Cao G-d, et al. The oncolytic virus in cancer diagnosis and treatment. 2020;10:1786.

12. Zhang QN, et al. Recombinant human adenovirus type 5 (Oncorine) reverses resistance to immune checkpoint inhibitor in a patient with recurrent non-small cell lung cancer: A case report. Thorac Cancer. 2021;12(10):1617-9.

13. Ferrucci PF, et al. Talimogene Laherparepvec (T-VEC): An Intralesional Cancer Immunotherapy for Advanced Melanoma. Cancers (Basel). 2021;13(6).

14. Pol J, et al. First oncolytic virus approved for melanoma immunotherapy. Oncoimmunology. 2016;5(1):e1115641.

15. Howells A, et al. Oncolytic Viruses-Interaction of Virus and Tumor Cells in the Battle to Eliminate Cancer. Front Oncol. 2017;7:195.

16. Johnson PA, et al. Advances in DNA- and RNA-Based Oncolytic Viral Therapeutics and Immunotherapies. 2022;2(2):319-29.

17. Watanabe D, Goshima F. c. Adv Exp Med Biol. 2018;1045:63-84.

18. Sze DY, et al. Oncolytic virotherapy. J Vasc Interv Radiol. 2013;24(8):1115-22.

19. Dorer DE, Nettelbeck DM. Targeting cancer by transcriptional control in cancer gene therapy and viral oncolysis. Advanced Drug Delivery Reviews. 2009;61(7):554-71.

20. Rowan K. Oncolytic Viruses Move Forward in Clinical Trials. JNCI: Journal of the National Cancer Institute. 2010;102(9):590-5.

21. Kaufman HL, Bines SD. OPTIM trial: a Phase III trial of an oncolytic herpes virus encoding GM-CSF for unresectable stage III or IV melanoma. Future Oncol. 2010;6(6):941-9.

22. Li H, et al. Coadministration of a herpes simplex virus-2 based oncolytic virus and cyclophosphamide produces a synergistic antitumor effect and enhances tumor-specific immune responses. Cancer Res. 2007;67(16):7850-5.

23. Li H, et al. Virotherapy with a type 2 herpes simplex virus-derived oncolytic virus induces potent antitumor immunity against neuroblastoma. Clin Cancer Res. 2007;13(1):316-22.

24. Rodrigues R, et al. Bovine herpesvirus type 1 as a novel oncolytic virus. Cancer Gene Ther. 2010;17(5):344-55.

25. Hemminki O, et al. Oncolytic adenovirus based on serotype 3. Cancer Gene Ther. 2011;18(4):288-96.

26. Wollmann G, et al. Targeting human glioblastoma cells: comparison of nine viruses with oncolytic potential. J Virol. 2005;79(10):6005-22.

27. Roos FC, et al. Oncolytic targeting of renal cell carcinoma via encephalomyocarditis virus. EMBO Mol Med. 2010;2(7):275-88.

28. Adachi M, et al. Destruction of human retinoblastoma after treatment by the E variantof encephalomyocarditis virus. J Neurooncol. 2006;77(3):233-40.

29. Berry LJ, et al. Potent oncolytic activity of human enteroviruses against human prostate cancer. Prostate. 2008;68(6):577-87.

30. Shafren DR, et al. Oncolysis of human ovarian cancers by echovirus type 1. Int J Cancer. 2005;115(2):320-8.

31. Au GG, et al. Oncolysis of malignant human melanoma tumors by Coxsackieviruses A13, A15 and A18. Virol J. 2011;8:22.

32. Toyoda H, et al. Oncolytic poliovirus therapy and immunization with poliovirus-infected cell lysate induces potent antitumor immunity against neuroblastoma in vivo. Int J Oncol. 2011;38(1):81-7.

33. Sturlan S, et al. Endogenous expression of proteases in colon cancer cells facilitate influenza A viruses mediated oncolysis. Cancer Biol Ther. 2010;10(6):592-9.

34. Galanis E, et al. Phase I trial of intraperitoneal administration of an oncolytic measles virus strain engineered to express carcinoembryonic antigen for recurrent ovarian cancer. Cancer Res. 2010;70(3):875-82.

35. Myers R, et al. Oncolytic activities of approved mumps and measles vaccines for therapy of ovarian cancer. Cancer Gene Ther. 2005;12(7):593-9.

36. Hu J, et al. Selective in vitro cytotoxic effect of human cancer cells by bluetongue virus-10. Acta Oncol. 2008;47(1):124-34.

37. Pol J, et al. Oncolytic viruses: A step into cancer immunotherapy. Virus Adaptation and Treatment. 2011;2012:4:1-21.

38. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.

39. Bai Y, et al. Updates to the antitumor mechanism of oncolytic virus. Thorac Cancer. 2019;10(5):1031-5.

40. Filley AC, Dey M. Immune System, Friend or Foe of Oncolytic Virotherapy? Front Oncol. 2017;7:106.

41. Otto T, Sicinski P. Cell cycle proteins as promising targets in cancer therapy. Nat Rev Cancer. 2017;17(2):93-115.

42. Wang L, et al. Remodeling the tumor microenvironment by oncolytic viruses: beyond oncolysis of tumor cells for cancer treatment. Journal for immunotherapy of cancer. 2022;10(5):e004167.

43. Liu Y, Zeng G. Cancer and innate immune system interactions: translational potentials for cancer immunotherapy. J Immunother. 2012;35(4):299-308.

44. Goradel NH, et al. Oncolytic virotherapy: Challenges and solutions. 2021;45(1):100639.

45. Tornesello AL, et al. Virus-like Particles as Preventive and Therapeutic Cancer Vaccines. 2022;10(2):227.

46. Garmaroudi GA, et al. Therapeutic Efficacy of Oncolytic Viruses in Fighting Cancer: Recent Advances and Perspective. Oxid Med Cell Longev. 2022;2022:3142306.

47. Boagni DA, et al. Current strategies in engaging oncolytic viruses with antitumor immunity. Molecular Therapy - Oncolytics. 2021;22:98-113.

48. Tian Y, et al. Engineering strategies to enhance oncolytic viruses in cancer immunotherapy. Signal Transduction and Targeted Therapy. 2022;7(1):117.

49. Mashima H, et al. Generation of GM-CSF-producing antigen-presenting cells that induce a cytotoxic T cell-mediated antitumor response. Oncoimmunology. 2020;9(1):1814620.

50. de Graaf JF, et al. Armed oncolytic viruses: A kick-start for anti-tumor immunity. Cytokine Growth Factor Rev. 2018;41:28-39.

51. Zhao Y, et al. Oncolytic Adenovirus: Prospects for Cancer Immunotherapy. Front Microbiol. 2021;12:707290.

52. Jhawar SR, et al. Oncolytic Viruses-Natural and Genetically Engineered Cancer Immunotherapies. Front Oncol. 2017;7:202.

53. Groeneveldt C, et al. Immunotherapeutic Potential of TGF-β Inhibition and Oncolytic Viruses. Trends Immunol. 2020;41.

54. de la Nava D, et al. Immunovirotherapy for Pediatric Solid Tumors: A Promising Treatment That is Becoming a Reality. Front Immunol. 2022;13:866892.

55. ClinicalTrials.gov. U.S. National Library of Medicine [Available from: https://clinicaltrials.gov.

56. Lauer UM, Beil J. Oncolytic viruses: challenges and considerations in an evolving clinical landscape. 2022;18(24):2713-32.

57. Macedo N, et al. Clinical landscape of oncolytic virus research in 2020. Journal for immunotherapy of cancer. 2020;8(2).

58. Hemminki O, et al. Oncolytic viruses for cancer immunotherapy. J Hematol Oncol. 2020;13(1):84.

59. Raman SS, et al. Talimogene laherparepvec: review of its mechanism of action and clinical efficacy and safety. Immunotherapy. 2019;11(8):705-23.

60. Sugawara K, et al. Oncolytic herpes virus G47Δ works synergistically with CTLA-4 inhibition via dynamic intratumoral immune modulation. Mol Ther Oncolytics. 2021;22:129-42.

61. Zeng J, et al. Oncolytic Viro-Immunotherapy: An Emerging Option in the Treatment of Gliomas. Front Immunol. 2021;12:721830.

62. Mondal M, et al. Recent advances of oncolytic virus in cancer therapy. Hum Vaccin Immunother. 2020;16(10):2389-402.

63. Yang L, et al. Oncolytic Virotherapy: From Bench to Bedside. Front Cell Dev Biol. 2021;9:790150.

64. Wennier S, et al. Bugs and Drugs: Oncolytic Virotherapy in Combination with Chemotherapy. Curr Pharm Biotechnol. 2011;13:1817-33.

65. Engeland CE, et al. Improving immunovirotherapies: the intersection of mathematical modelling and experiments. ImmunoInformatics. 2022;6:100011.

66. Chesney J, et al. Randomized, Open-Label Phase II Study Evaluating the Efficacy and Safety of Talimogene Laherparepvec in Combination With Ipilimumab Versus Ipilimumab Alone in Patients With Advanced, Unresectable Melanoma. J Clin Oncol. 2018;36(17):1658-67.

67. Andtbacka RH, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. J Clin Oncol. 2015;33(25):2780-8.

68. Garber K. China Approves World's First Oncolytic Virus Therapy For Cancer Treatment. JNCI: Journal of the National Cancer Institute. 2006;98(5):298-300.

69. Peter M, Kühnel F. Oncolytic Adenovirus in Cancer Immunotherapy. Cancers (Basel). 2020;12(11).

70. Gujar SA, et al. Oncolytic virus-initiated protective immunity against prostate cancer. Mol Ther. 2011;19(4):797-804.

71. Goel A, et al. Radioiodide imaging and radiovirotherapy of multiple myeloma using VSV(Delta51)-NIS, an attenuated vesicular stomatitis virus encoding the sodium iodide symporter gene. Blood. 2007;110(7):2342-50.

72. Opyrchal M, et al. Effective radiovirotherapy for malignant gliomas by using oncolytic measles virus

strains encoding the sodium iodide symporter (MV-NIS). Hum Gene Ther. 2012;23(4):419-27.

73. Galanis E, et al. Oncolytic measles virus expressing the sodium iodide symporter to treat drug-resistant ovarian cancer. Cancer Res. 2015;75(1):22-30.

74. Zhang B, Cheng P. Improving antitumor efficacy via combinatorial regimens of oncolytic virotherapy. Mol Cancer. 2020;19(1):158.

75. Mansfield DC, et al. Oncolytic vaccinia virus as a vector for therapeutic sodium iodide symporter gene therapy in prostate cancer. Gene Ther. 2016;23(4):357-68.

76. Hu C, et al. Intravenous injections of the oncolytic virus M1 as a novel therapy for muscle-invasive bladder cancer. Cell Death Dis. 2018;9(3):274.

77. Bauzon M, Hermiston TW. Oncolytic viruses: the power of directed evolution. Adv Virol. 2012;2012:586389.

78. Fend L, et al. Immune Checkpoint Blockade, Immunogenic Chemotherapy or IFN-α Blockade Boost the Local and Abscopal Effects of Oncolytic Virotherapy. Cancer Res. 2017;77(15):4146-57.

79. Selman M, et al. Dimethyl fumarate potentiates oncolytic virotherapy through NF-κB inhibition. Sci Transl Med. 2018;10(425).

80. Chen CY, et al. Cooperation of Oncolytic Herpes Virotherapy and PD-1 Blockade in Murine Rhabdomyosarcoma Models. Sci Rep. 2017;7(1):2396.

81. Li L, et al. Delivery and Biosafety of Oncolytic Virotherapy. Front Oncol. 2020;10:475.

82. O'Leary MP, et al. Novel oncolytic chimeric orthopoxvirus causes regression of pancreatic cancer xenografts and exhibits abscopal effect at a single low dose. J Transl Med. 2018;16(1):110.

83. Yang M, et al. Cancer Immunotherapy and Delivery System: An Update. 2022;14(8):1630.

84. Davis JJ, Fang B. Oncolytic virotherapy for cancer treatment: challenges and solutions. J Gene Med. 2005;7(11):1380-9.

85. Ferguson MS, et al. Systemic delivery of oncolytic viruses: hopes and hurdles. Adv Virol. 2012;2012:805629.

86. Wong HH, et al. Oncolytic Viruses for Cancer Therapy: Overcoming the Obstacles. Viruses. 2010;2(1):78-106.

87. Shashkova EV, et al. Macrophage depletion combined with anticoagulant therapy increases therapeutic window of systemic treatment with oncolytic adenovirus. Cancer Res. 2008;68(14):5896-904.

88. Hamidi-Sofiani V, et al. Oncolytic viruses and pancreatic cancer. Cancer Treatment and Research Communications. 2022;31:100563.

89. Sze DY, et al. Dr. Gary J. Becker Young Investigator Award: Intraarterial Adenovirus for Metastatic Gastrointestinal Cancer: Activity, Radiographic Response, and Survival. J Vasc Interv Radiol. 2003;14(3):279-90.

90. Chaurasiya S, Fong Y. Viroimmunotherapy for breast cancer: promises, problems and future directions. Cancer Gene Ther. 2021;28(7):757-68.

91. Fujiwara T. Multidisciplinary oncolytic virotherapy for gastrointestinal cancer. 2019;3(4):396-404.

92. Yokoda R, et al. Oncolytic virus delivery: from nano-pharmacodynamics to enhanced oncolytic effect. Oncolytic Virother. 2017;6:39-49.