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CANCER IMMUNOTHERAPY PERSPECTIVES: CAN VIRUSES BE CONSIDERED ALLIES?

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Abstract: Cancer, a non-infectious disease and one of the leading causes of death worldwide, is characterized by its ability to evade natural control mechanisms. The immune system plays a crucial role in the recognition and elimination of tumor cells; thus, immunotherapy emerges as a promising strategy. In particular, oncolytic viruses have stood out in this field for their ability to selectively replicate in tumor cells, leading to direct lysis and activation of an antitumor immune response. It is important to review their efficacy and safety to validate their therapeutic potential. In addition, it is important to understand the mechanisms by which they can induce the immune system to promote immunogenic cell death and thus exploit their advantage. This article reviews advances in cancer immunotherapy, focusing on oncolytic viruses as selective agents that act either directly or as inducers of an immune response.
Keywords: Oncolytic viruses, immunotherapies, cancer, immunogenic cell death

INTRODUCTION

Worldwide, cancer is considered one of the leading causes of death and an obstacle to increasing life expectancy. According to estimates by the World Health Organization (2019), cancer is a leading cause of death among people under 70 years of age. In about 112 of 183 countries, cancer is responsible for 3 to 10 deaths from any non-transmissible disease[1]. In the Globocan 2022 database (version 1.1) - 08.02.2024 it is estimated that by 2050 there will be 18.3 million deaths (men and women) worldwide due to some type of cancer. The importance of this disease has led the scientific community to develop strategies to reduce its impact. This need has led to the emergence of therapies such as immunotherapy, which aims to boost or reactivate the immune response against tumor cells. In this context, the use of oncolytic viruses[2–4] emerges as an innovative strategy and has gained relevance due to their ability to selectively replicate in tumor cells, providing not only the advantage of direct destruction of these cells, but also the apparent promotion of an antitumor immune response.

This article explores relevant advances in cancer immunotherapy, with a focus on oncolytic viruses and their ability to induce immune responses. It also looks at the mechanisms underlying their activity, including an opinion on the possible landscape in the field of oncology in the future.

IMMUNOSUPPRESSION IN CANCER

It is estimated that each tumor cell usually has more than 11,000 different genomic mutations compared to the healthy cells surrounding the tumor, allowing it to differentiate from "normal" cells of the same organism[5,6]. A tumor develops due to a combination of genetic and epigenetic changes that favor its uncontrolled proliferation, which triggers the appearance of "neoantigens". Those that would expect to contribute to malignant cell being recognized and destroyed by the immune system[7–9]. In this sense, how do cancer cells manage to evade the immune system and proliferate out of control? In fact, a tumor creates a niche of suppression of the immune response, both innate and adaptive, which limits the deployment of neoantigens and hides the evolving set of mutant regulatory proteins ("mutanome") within itself, together allowing tumor cells to escape from homeostatic regulatory systems[10].

CANCER IMMUNOSURVEILLANCE AND IMMUNOEDITING

At the end of the 20th century, two hypotheses were put forward to explain the role of the immune system as a protector or promoter of tumor progression[9]. These hypotheses were termed cancer immune surveillance and immunoediting[11]. Basically, they are complementary and sequential processes that describe how a competent immune system is related to tumor development. Immunosurveillance refers to the continuous recognition and attack of malignant cells due to immune activity, with relying on the activity of lymphocytes, which are expected to act as sentinels by identifying and eliminating somatic cells transformed by mutations[12]. On the other hand, the immunoediting process involves three phases: first, elimination, in which cancer cells are destroyed by immunosurveillance mechanisms; second, equilibrium, when cells that survive the initial immune attack and undergo successive rounds of epigenetic and genetic and functional changes that favor their adaptation, i.e., increased plasticity of malignant cells within the tumor microenvironment (TME) co-populated by immune cells; finally, escape, in which the growth of resistant clones induces and supports the development of immunosuppressive microenvironment that favors uncontrolled proliferation, tumor formation and, ultimately, progression to metastasis[13–15].

The complexity of these interactions between tumor cells and the immune system has been increasingly elucidated, so that manipulation of host immunity as a therapeutic concept has become more valid and relevant in the fight against cancer.

CANCER IMMUNOTHERAPIES

Immunotherapy has become a useful tool in cancer treatment since immune checkpoint inhibitors (ICBs) were first approved by the FDA in 2011 for the treatment of advanced melanoma[16,17].

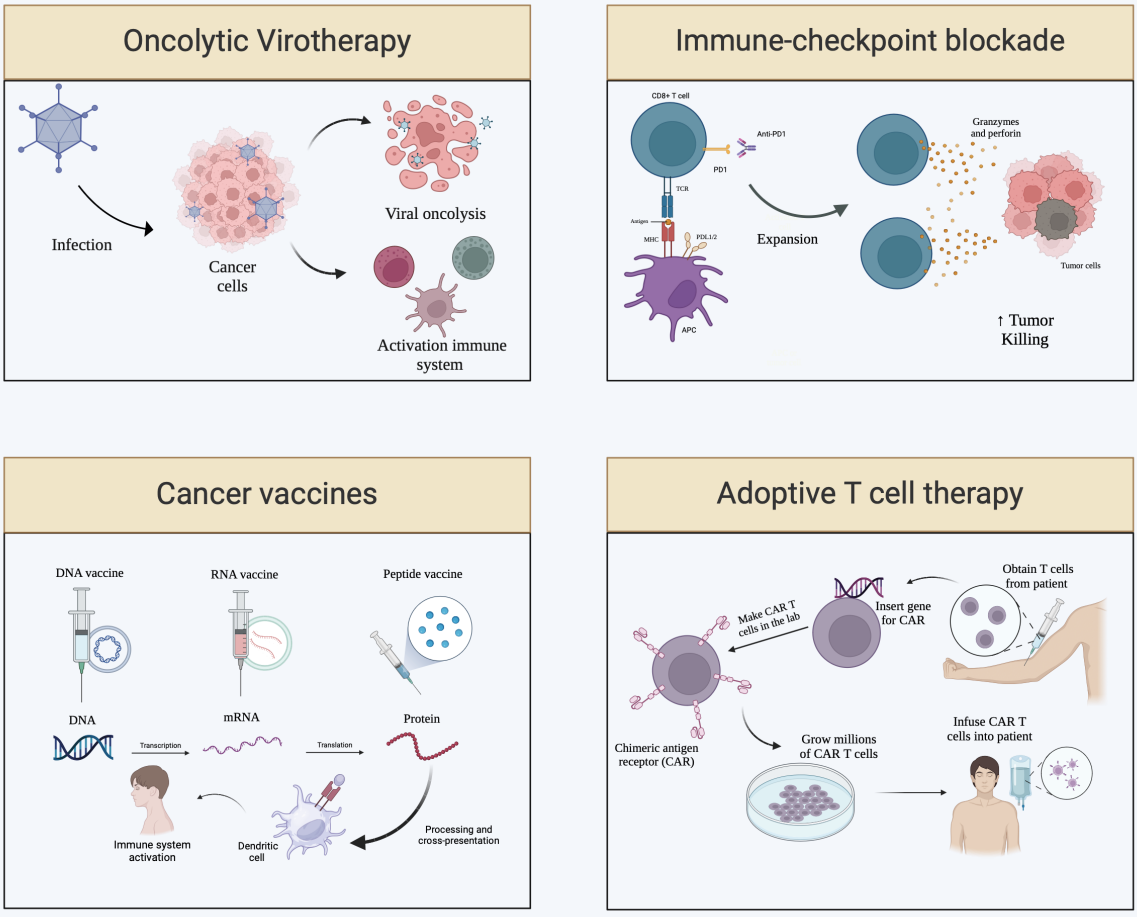
The main goal of immunotherapy is to reverse the suppression of immune effector functions and recruit tumor-infiltrating lymphocytes (TILs) to lymphocyte-deficient sites[18]. It is important to note that effective cancer immunotherapy depends on many factors, such as the state of the immune response within the tumor microenvironment, where a large number of TILs is necessary. In addition, for tumor eradication, immune recognition of tumor-associated antigens is essential for effective and selective cytotoxic function[19].

In light of these considerations, it is necessary to develop new therapeutic strategies aimed at promoting immune function through various mechanisms, classified according to the way they interact with host immunity (Fig. 1) [20]. Thus, conducting clinical trials has increased over the years, and there are now many studies addressing immunotherapy-based therapeutic approaches. Table 1 shows some of them, describing what they consist of, and the date they were approved by the FDA. Thus, in 1991 the first in immunotherapy was used, based on the use of cytokines, which lead to the development of other therapies in the same field, such as cancer vaccines, immune checkpoint inhibitory antibodies and adoptive cell therapy.

Although these therapies have shown therapeutic efficacy when used as monotherapy, it may be promising to combine their immunotherapeutic activity with the antitumor potential of oncolytic viruses to enhance the immune response.

As mentioned above, one of the main goals of immunotherapy is to promote T-lymphocytes infiltration into the tumor, so this feature is also described in the table.

Cancer immunotherapy



Immunotherapy is a type of cancer treatment. It helps the immune system to fight cancer. When immune system works efficiently, it detects and destroys abnormal cells and, most likely, prevents or slows the growth of many cancers. Several types of immunotherapies had been used to treat cancer. In the case of oncolytic viruses, whose therapeutic purpose is to destroy tumor cells without damaging healthy tissue, while activating the immune system. Immune checkpoint inhibitors, which are drugs that block immune checkpoints. By blocking them, these drugs allow immune cells to respond more strongly to cancer. Treatment vaccines, which work against cancer by boosting the immune system's response to cancer cells. The adoptive T-cell therapy, which is a treatment that enhances the natural ability of T cells to fight cancer. Created in BioRender.

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Therapy	Description	FDA approved (first year approved)	Advantages of combination therapy with OVs	Priming and activation of T cells	T cell migration to tumors	T cell infiltration of the tumor	Ref
Immunostimulatory cytokine	Cytokines are small proteins naturally produced and secreted by several immune system cells. They are crucial in signaling between immune cells, as well as between immune cells and several other cell types in the body. It proved to be effective if administered in large quantities to patients with metastatic cancers through enhancing the production of lymphocytes T.	In 1991, the US FDA approved the use of interleukin 2 as an immunotherapeutic treatment for the treatment of metastatic kidney cancer.	Promotes T cell priming, activation and recruitment	High	High	High	[5,21]
cancer vaccines	Cancer vaccines prompt the immune system to protect the body from cancer and fall into two categories, prophylactic and therapeutic. Prophylactic vaccines against hepatitis B and human papillomavirus have been instrumental in reducing the incidence of hepatocellular carcinoma and cervical cancer, respectively. These are classic vaccines used to prevent infection by oncogenic viruses. By contrast, therapeutic vaccines aim to harness the immune system to eliminate disease-causing cells that are already neoplastic.	2010: the FDA approved the first autologous cancer vaccine, known as sipuleucel-T, for treatment of castration resistant prostate cancer	Being highly immunogenic, they can activate CD4+ and CD8+ immune response.	High	High	-	[22,23]
Immune-checkpoint blockade (ICB)	Antibody-based immune checkpoint inhibition (ICI) therapy aims to fight cancer by essentially interrupting tumor immunosuppressive signals and restoring the anti-tumor immune response by targeting checkpoint proteins such as programmed cell death protein 1 (PD-1) and its ligand PD-L1, or alternatively cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The benefits of ICI increase in tumors that are considered immunologically 'hot', as they often have high levels of tumor-infiltrating lymphocytes (TILs), a high mutational burden and higher PD-L1 expression. Conversely, in immunologically "cold" tumors, this benefit is diminished due to lack of tumor-associated antigen (TAA) expression and/or presentation, low TIL density, infiltration of suppressive immune cells (such as regulatory T cells), and expression of immunosuppressive substances (IL-10, PD-L1, CD73, among others).	2011: The first checkpoint inhibitor approved by the FDA was ipilimumab for the therapy of advanced melanoma.	Maintains activated T cells in tumor microenvironment	High	High	High	[24–27]
Adoptive T cell therapy	Adoptive Cell Therapy (ACT) involves the isolation of patient's T cells (recently also termed NK cells), which are tumor-specific, modification and multiplication of those cells in the laboratory and then re-injection back to the patient.	2017: Relapsed B-cell acute lymphoblastic leukemia in children was the first disease to be FDA approved for CAR T cells therapy.	The OVs precondition tumors to enable enhanced activated T-cell function	-	Moderate	High	[28, 29]

Table 1. Immunotherapy approaches

ONCOLYTIC VIRUSES (OVS)

Viruses are characterized by their genome, which can be either single-stranded or double-stranded RNA or DNA, and the capsid, a protein envelope containing the genetic material (Table 2). However, there are many factors that influence the selection of an oncolytic virus for used in immunotherapy, including tumor tropism, ability to be genetically modified and to encode therapeutic transgenes, achievable viral titers, viral stability, immunogenicity and potential pathogenicity. These characteristics also vary depending on the viral species, dose, route of administration, and the pre-existing host immunity[30].

Oncolytic viruses (OVs) have been selected as a highly versatile potential tool for cancer treatment[31]. Used as replicative biotherapeutics, they can be administered systemically or locally and can therefore have the potential to act on both primary and metastatic tumors[32]. A common principle for their selection is to attenuate or eliminate virulence factors so that OVs cannot replicate in normal tissues, but retain the ability to replicate and kill cancer cells[33]. Table 2 illustrates some of the viruses, their characteristics and their potential for use as possible biotherapeutics, describing the type of cellular receptor they recognize to initiate their infection process.

Table 2. Properties of select oncolytic viruses

	Adenovirus	Vaccinia Virus	Herpes Virus	Measles Virus	Newcastle disease virus	Poliovirus
						
Family	*Adenoviridae*	*Poxviridae*	*Herpesviridae*	*Paramyxoviridae*	*Paramyxoviridae*	*Picornaviridae*
Baltimore classification	Group I: dsDNA	Group I: dsDNA	Group I: dsDNA	Group V: ss(−) RNA	Group V: ss(−) RNA	Group IV: ss(+) RNA
Genome size	Moderate (32 kb)	Large (130–375 kb)	Large (152 kb)	Small (~16 kb)	Small (~15 Kb)	Small (7.5 kb)
Genetic modifications	Yes	Yes	Yes	Yes	Yes	Yes
Cell entry receptors	Adenovirus enters the cell using the coxsackie-adenovirus receptor (CAR), VCAM1; CD46	GAGs; EFC	HSV-1 can infect many types of cells through viral surface glycoproteins, HVEM, and nectin 1 and nectin 2.	Measles virus uses the signalling lymphocytic activation molecule (SLAM) receptor, and/or CD46	Neuraminidase receptor; sialoglyco-conjugates	Poliovirus enters cells by binding to CD155
Clinical trials	Yes	Yes	Yes	Yes	Yes	Yes

Glycosaminoglycans (GAGs); EntryFusion Complex (EFC).Created in BioRender. Villanueva, B. (2024) BioRender.com/a84o309

MECHANISM OF ACTION OF OVS

OVs have the ability to induce two main effects. First, they can infect, replicate and selectively lyse cancer cells, a mechanism known as "oncolysis"[37]. Oncolysis induced by OVs involves several processes, ranging from mechanical rupture of the cell plasma membrane (called lysis) to the initiation of cell death processes such as apoptosis, necroptosis, ferroptosis or pyroptosis[38].

Second, they can indirectly target cancer cells by promoting antitumor immunity[39]. In particular, the antitumor activity of oncolytic viruses involves multiple mechanisms encompassing natural interactions between viruses, tumor cells and the immune system[40].

SELECTIVITY OF OVS: GENES AND SIGNALING PATHWAYS

An important characteristic that an oncolytic virus must fulfill in order to be used in cancer immunotherapy is tumor tropism, which consists of selective viral replication in tumor cells to the exclusion of healthy tissue. This tropism may occur naturally in some viruses; however, their specificity can also be improved by genetic modification to enhance selective infection in tumor cells[30,41]. In general, the ability of oncolytic viruses to selectively replicate in tumor cells depends on both, the properties of the virus and the type of cancer cells to be targeted. This selectivity is regulated by specific factors, including viral replication, the entry into the cell, and the viral binding to cancer cell receptors. In addition, the susceptibility of each type of cancer cell to undergo different forms of cell death (apoptosis, necrosis, pyroptosis and autophagy)[42]. As described in Table 2.

Such tumor selectivity is mainly attributed to alterations in the signaling pathways that normally detect and block viral replication. These aberrations are found in some genes, such as RAS, TP53, RB1, PTEN, which encode proteins involved in the WNT signaling pathway, and sensitize cancer cells to viral infection by creating a permissive environment for it[43,44].

There are viruses such as Newcastle Disease Virus (NDV), vaccinia virus (VV), vesicular stomatitis virus (VSV) and measles virus (MV) that use the interferon (IFN)/ protein kinase R (PKR) signaling pathway for their natural oncotropism. IFN production in normal virus-infected cells, activates the Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathway, which leads to positive regulation of PKR, an intracellular protein kinase that recognizes double-stranded RNA and other viral elements[45]. Autophosphorylation of PKR, together with the phosphorylation of the alpha subunit of eIF-2, inhibits protein synthesis and viral replication. By contrast, in a tumor cell, the IFN pathway is deregulated, and PKR activity is abnormal as it remains unphosphorylated, so that viral clearance is truncated.[46,47]

In addition, the RAS signaling pathway is hyperactivated in tumor cells, favoring the inhibition of PKR signaling and allowing the replication of OVs such as reoviruses, herpes simplex virus (HSV), and VV[48]. In combination with the defective tumor cell signaling, host tissue selectivity is also determined by the expression of specific receptors on the surface of tumor cells, which increase the susceptibility to viral entry. For example, poliovirus binds to PVR/CD155, overexpressed in melanoma, glioma, and other cancers. A useful *in silico* tool to predict this information are databases such as The Human Protein Atlas, EMBL-EBI and GENT2, which can provide information about specific surface proteins on malignant cells[49,50].

INDUCTION OF INNATE AND ADAPTIVE IMMUNITY MEDIATED BY OVS.

The balance between viral immunogenicity, i.e. when the immune system tries to eliminate the viral infection, and antitumor immunity; when the immune system attacks and eradicates tumor cells, is crucial for the therapeutic efficacy of using OVs. This balance must allow the viruses enough time to replicate, and use their ability to kill tumor cells, and finally initiate antitumor immunity. A premature elimination of the virus is unfavorable because it would truncate its oncolytic activity[40,51,52].

Induction of innate and adaptive immune responses generally occurs after oncolytic cell death (Fig. 2). Thus, tumor cells release tumor-associated antigens (TAAs), viral pathogen-associated molecular patterns (PAMPs), Damage-Associated Molecular Patterns (DAMPs) and the local cytokine release, all of which to-

gether promote the maturation of antigen-presenting cells (APCs) that activate CD4+ and CD8+ T-cell responses. Once CD8+ T cells are activated, they expand and execute their cytotoxic effector mechanism[30,40,53].

In addition, cytokines such as type 1 IFNs and DAMPs can also activate natural killer (NK) cells as part of an innate immune response. NK cells can attack tumor cells due to their low expression of major histocompatibility complex class 1 (MHC-1). However, NK cells can interfere with the efficacy of OV by also killing OV-infected cells[54]. It is not yet well understood wow to manipulate the factors that may influence the promotion of any of these mechanisms. On the other hand, the role of type I interferons is also not fully elucidated because, although they are crucial regulatory cytokines for promoting an adaptive immune response, it has been observed that excessive interferons production increases the expression of immune checkpoint molecules, such as PD1 and PDL1, which can suppress the immune system[55].

Dendritic cells (DCs) play an important role in innate immunity. Immature DCs that are commonly recruited to the tumor can be CD8α+ and CD103+, which depend on the transcription factors IRF8 and BATF3 for their differentiation. They are collectively referred to as BATF3+ DCs. Their importance is based on evidence from preclinical data confirming that BATF3+CD103+ DCs are required to promote host antitumor immunity in a B16-F10 melanoma model, in which modified vaccinia virus Ankara (MVA) was administered intratumorally[56–58].

Innate immunity may also be favored by increased expression of MHC class I and class II, as well as co-stimulatory molecules: CD40, CD80, CD83 and CD86 on DCs. Recognition of viral elements by pattern recognition receptors (PRRs) is essential to overcome the immunosuppressive state within the TME. Due to, PRRs promote the release of pro-inflammatory cytokines, tumor necrosis factor (TNF), and chemokines, which together recruit and activate innate lymphoid cells[59].

INDUCTION OF IMMUNOGENIC CELL DEATH

As mentioned above, OVs have the ability to induce several forms of cell death[60]. OVs induce endoplasmic reticulum (ER) stress and "immunogenic cell death" (ICD) of infected cells. This type of death is characterized by different molecular signals. Characteristically, dying tumor cells begin to release damage-associated molecular patterns (DAMPs) such as uric acid or extracellular ATP; these signals often act as chemoattractant for immune cells. In addition, translocation of calreticulin (CALR) to the cell surface acts as an "eat me" signal for APCs, as CALR neutralizes the CD47 receptors present on tumor cells, preventing them from being phagocytosed by macrophages and DCs. Another feature is the release of high-mobility box 1 protein (HMGB1), which acts as an activation signal for immune cells [61–64]. Together, these signals characteristic of ICD induction favor the activation of immune responses against the tumor.

OVERVIEW OF THE IMPLEMENTATION OF OVS AS A THERAPY

Talimogene Laherparepvec (T-VEC), was the first OV approved by the FDA in 2015 for treatment in metastatic melanoma, initiating the development of new clinical trials for future implementation of OVs as oncotherapy. T-VEC is derived from Herpes simplex virus type 1 (HSV-1) and is characterized by two key modifications. First, it has a deletion in the ICP34.5 gene, which antagonizes the activity of protein kinase-dependent RNA (PKR, also known as EIF2AK2), an interferon-induced gene product that inhibits the translation of cellular proteins. Also contains a gene dele-

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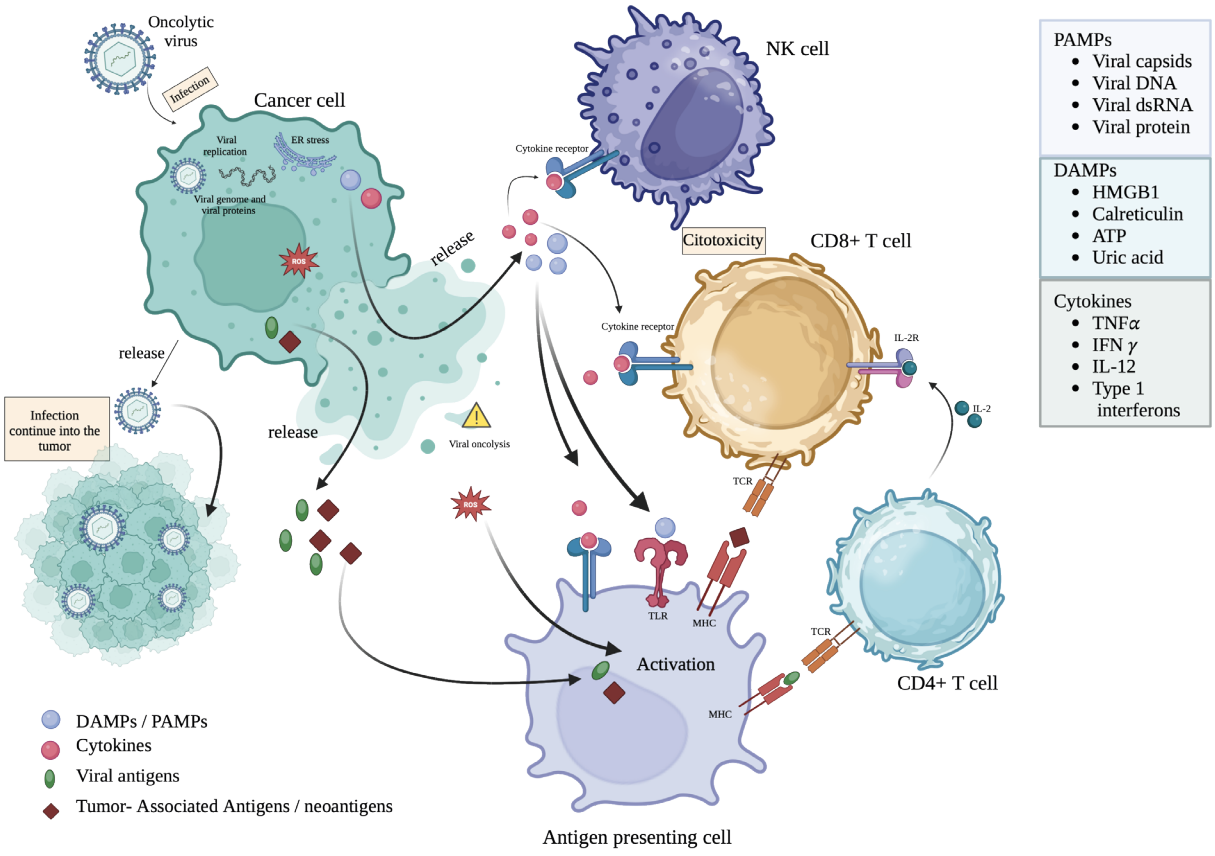

Fig. 2. The therapeutic power of oncolytic viruses lies in the combination of direct lysis of cancer cells and indirect activation of antitumor immune responses. When an oncolytic virus infects a cell, several responses are initiated, including endoplasmic reticulum (ER) stress, which leads to the overproduction of reactive oxygen species (ROS) and antiviral cytokines, in particular type I interferons (IFNs). These molecules are released from the infected tumor cell and trigger a response in natural killer (NK) cells, antigen presenting cells (APCs) and CD8+ T cells. Oncolysis then occurs, releasing virions, PAMPs, DAMPs and TAAs, including neoantigens. The released viral progeny propagate infection in neighboring tumor cells, while PAMPs and DAMPs stimulate the immune system by activating Toll-like receptors (TLRs). In addition, the released TAAs and neoantigens are captured by APCs, leading the generation of effective immune responses against tumor cells. Created in BioRender. Villanueva, B. (2024) BioRender.com/a84o309

TYPE OF VIRUS	Type of cancer	Description	Phase	Study start date	Clinical Trial ID
ADENO-VIRUS	Cervical Malignancies	The recombinant oncolytic adenovirus injection (KD01) primarily consists of a recombinant human type 5 adenovirus with a deletion in the E3 region, where the ADP gene is replaced by the tBID apoptosis protein gene.	Phase I	01/04/24	NCT06552598
	Advance Solid Tumors	The purpose of this study is to assess the safety and tolerability of Recombinant L-IFN adenovirus injection and to determine the recommended phase 1 dose for further study.	Early phase I	30/11/24	NCT05180851
	Recurrent glioblastoma	Evaluate the safety and tolerability of recombinant L-IFN adenovirus injection in the treatment of patients with recurrent glioblastoma.	Early phase I	27/06/23	NCT05914935
	Advanced Solid Tumors	TILT-123 is an oncolytic adenovirus encoding for tumor necrosis factor alpha and interleukin 2.	Phase I	11/01/21	NCT04695327

Malignant pleural mesothelioma	Evaluate the efficacy and safety of Oncolytic Adenovirus(H101) combined with PD-1 inhibitor in patients	No reported	20/07/23	NCT06031636
Cervical cancer	Evaluate whether the regimen could improve the objective response rate by intratumoral injection of oncolytic virus (recombinant human adenovirus type 5 injection, H101) combined with anti-PD-1 antibody (camrelizumab).	Phase II	01/03/23	NCT05234905
Malignant solid tumors	Safety, Tolerability, and Pharmacokinetics of Recombinant Human nsIL12 Oncolytic Adenovirus Injection (BioTTT001) in patients	Phase I	22/01/24	NCT06215846
Non-muscle-invasive bladder	The objective of this phase II clinical trial is to investigate the safety and efficacy of H101 combined with PD-1 inhibitor Camrelizumab in patients	Phase II	26/08/22	NCT05564897
Malignant melanoma	Efficacy of PD1 monoclonal antibody combined with recombinant human adenovirus type 5 injection in patients	Phase I	27/10/22	NCT05928962
Non-Small Cell Lung cancer	The safety of oncolytic adenovirus TILT-123 in combination with Pembrolizumab	Phase I	20/03/24	NCT06125197
Advance hepatocellular carcinoma	Verify the effect and safety of recombinant human adenovirus type 5 combined with sorafenib	Phase IV	28/12/21	NCT05113290
Melanoma and SCCHN	Safety of oncolytic adenovirus TILT-123 in combination with avelumab	Phase I	08/03/23	NCT05222932
Non-Muscle Invasive Bladder Cancer	Evaluate the RFS of TURBT followed by cretostimogene grenadenorepvec	Phase III	14/12/23	NCT06111235
Liver metastasis	Test an experimental oncolytic oncolytic adenovirus called DNX-2440 in patients	Phase I	15/02/21	NCT04714983
Cholangiocarcinoma	Verify the effect and safety of recombinant human adenovirus type 5 combined with Hepatic Artery Infusion Chemotherapy	Phase IV	01/08/22	NCT05124002
Biliary tract cancer	Evaluate the efficacy and safety of oncolytic virotherapy combined with Tislelizumab plus lenvatinib	Phase II	30/12/23	NCT05823987
Non-Muscle Invasive Bladder Cancer	Evaluate the safety of CG0070, a GM-CSF expressing oncolytic adenovirus,	Phase I	01/03/24	NCT06253845
Solid tumors	AdAPT-001 is an oncolytic virus that is injected directly into the tumor or via intraarterial administration.	Phase II	29/03/21	NCT04673942
Non-Small Cell Lung cancer	The oncolytic effect of MEM-288 combined with the presence of CD40L and type 1 interferon (IFN) in injected tumors	Phase I	23/02/22	NCT05076760
Gastric cancer	Evaluate the Safety and Efficacy of Recombinant Human nsIL12 Oncolytic Adenovirus Injection (BioTTT001) in Combination With SOX and Toripalimab	Phase II	02/04/24	NCT06283121
Ovarian cancer	Safety of oncolytic adenovirus TILT-123 in combination with Pembrolizumab, or Pembrolizumab and Pegylated Liposomal Doxorubicin in patients with platinum resistant	Phase I	27/05/22	NCT05271318
Colorectal cancer	BioTTT001 in combination with Toraplizumab and Regorafenib in patients	Phase I	02/04/24	NCT06283134
Hepatocellular carcinoma	Efficacy of oncolytic virotherapy combined with Tislelizumab plus lenvatinib	Phase I	01/03/23	NCT05675462
Solid tumors	Characterize safety and tolerability, evaluate biodistribution, biological effects and immunogenicity, and evaluate the preliminary clinical efficacy of SynOV1.1	Phase I	23/06/22	NCT04612504
Head and neck carcinoma	Study of OBP-301 in combination with pembrolizumab and SBRT	Phase II	03/05/21	NCT04685499

HSV	Pediatric High--grade glioma	safety of intratumoral inoculation of G207 (an experimental virus therapy) combined with a single 5 Gy dose of radiation	Phase II	03/06/24	NCT04482933
	Solid tumors	determine the safety and tolerability of VG2025 a Recombinant Human IL12/15 Dual-Regulated Oncolytic HSV-1 Injection.	Phase I	23/08/22	NCT05477849
	Solid tumors	evaluate the safety and efficacy of the recombinant herpes simplex virus I, R130	Early phase I	02/03/23	NCT05860374
	Head and neck carcer	evaluate the safety and efficacy of the recombinant herpes simplex virus I, R130	Early phase I	27/03/23	NCT05830240
	Bone and soft tissue tumors	evaluate the safety and efficacy of the recombinant herpes simplex virus I, R130	Early phase I	12/07/23	NCT06171282
	Ovarian cancer	evaluate the safety, tolerability, and efficacy of the recombinant herpes simplex virus I, R130	Phase I	02/12/22	NCT05801783
	Brain cancer	determine how safe and how well-tolerated the experimental study drug, C134, a genetically engineered herpes simplex virus, is when re-administered	Phase I	Estimated: 01/08/25	NCT06193174
	Cervical cancer metastasis	This is a two-stage phase I clinical trial with oncolytic viruses BS-006	Phase I	16/09/22	NCT05393440
	Central Nervous System tumors	Clinical Study of Oncolytic Virus (OH2) Injection in the Treatment of Patients Undergoing Surgery	Phase II	16/11/21	NCT05235074
	Pancreatic cancer	evaluates the safety and efficacy of OH2 in patients	Phase II	02/02/21	NCT04637698
	Colorectal cancer	therapy with an oncolytic immunotherapy (RP2 or RP3) in combination with atezolizumab and bevacizumab in patients with advanced Microsatellite Stable	Phase II	29/06/23	NCT05733611
	High-grade glioma	the safety and tolerability of the oncolytic herpes simplex virus 1 (oHSV1) study drug, MVR-C5252, administered intratumorally	Phase I	11/06/24	NCT06126744
	Colorectal cancer	evaluate the efficacy and safety of intratumoral injection of OH2 combined with capecitabine	Phase II	17/10/23	NCT05648006
	Advanced Solid Tumors	Safety, Tolerability, Biodistribution and Pharmacodynamic of T3011 Herpes Virus Administered Via Intravenously	Phase I,II	01/03/22	NCT05598268
	Hepatocellular carcinoma	clinical study evaluating RP3 in combination with atezolizumab plus bevacizumab as First- or Second-line Systemic Therapy in patients	Phase II	01/04/24	NCT05733598
	Uveal melanoma	measure the clinical benefits of the combination of RP2 and nivolumab as compared with the combination of nivolumab and ipilimumab in patients	Phase II, III	Estimted: 27/01/25	NCT06581406
	Colorectal cancer	clinical study of T3011 in combination with Toraplizumab and Regorafenib in patients with liver metastases from colorectal cancer	Phase I	02/04/24	NCT06283303
	Squamous cell carcinomas of the head and neck	study evaluating RP3 in combination with concurrent chemoradiation therapy (CCRT) followed by nivolumab or combined with chemotherapy and nivolumab	Phase II	30/01/24	NCT05743270
VACCINIA VIRUS	Advanced Solid Tumors	The goal of this clinical trial is to evaluate the safety, tolerance, pharmacokinetics, and biological properties of recombinant human IL-21 oncolytic vaccinia virus injection (hV01) in patients	Phase I	05/07/23	NCT05914376
	Advanced Solid Tumors	Safety, tolerability, viral distribution and shedding patterns, pharmacodynamics, immunogenicity, and antitumor efficacy of GC001 oncolytic virus injection	Phase I	26/04/23	NCT06508307
	Solid tumors	find a safe and effective dose of VET3-TGI when administered by direct injection into tumor(s) alone and in combination with pembrolizumab in patients	Phase I	01/08/24	NCT06444815
	Solid tumors	evaluate the safety, viral load kinetics and shedding, pharmacodynamic, and anti-tumor activity of PF-07263689, either alone or in combination with sasanlimab	Phase I	20/10/21	NCT05061537

	Ovarian cancer	to determine if KM1 is well tolerated with anti-tumor activity in patients	Phase I	01/02/23	NCT05684731
	B-cell lymphoma	evaluate the maximum tolerated dose (MTD) and dose-dependent toxicity (DLT) of a novel oncolytic vaccinia virus expressing bispecific antibody RGV004	Phase I	08/02/22	NCT04887025
	Ovarian cancer	safety and efficacy of Olvi-Vec followed by platinum-doublet chemotherapy and bevacizumab	Phase III	31/08/22	NCT05281471
	Non-Small Cell Lung cancer	This is a phase I, open-label, dose-escalation trial of TG6050 administered by single or repeated IV infusion(s).	Phase I	05/04/23	NCT05788926
	Non-Small Cell Lung cancer	evaluate the efficacy and safety of an intravenously delivered oncolytic vaccinia virus, Olvi-Vec, followed by platinum-doublet chemotherapy + Physician's Choice of Immune Checkpoint Inhibitor (ICI)	Phase II	01/07/24	NCT06463665
	Metastatic/ Advanced solid tumors	BT-001 with repeated IT administrations alone and in combination with IV infusions of pembrolizumab.	Phase I, II	25/02/21	NCT04725331
MEASLES VIRUS	Medulloblastoma	determine the safety and recommended phase 2 dose of the modified measles virus (MV-NIS) in children and young adults	Phase I	22/02/17	NCT02962167
	Breast cancer	the side effects and best dose of using a modified measles virus, MV-s-NAP, in treating patients	Phase I	23/09/20	NCT04521764
	Relapsed myeloma	determine the clinical efficacy of MV-NIS (measles virus-sodium iodide symporter) therapy	Phase II	01/03/15	NCT02192775
	Urothelial carcinoma	test the tolerability and feasibility of intravesical therapy with an attenuated Measles virus (MV-NIS) in patients who are undergoing radical cystectomy but are ineligible or do not desire neoadjuvant chemotherapy.	Phase I	20/07/18	NCT03171493
	Non-Small Cell Lung cancer	determine the maximum tolerated dose (MTD) and toxicity of attenuated Measles virus (MV-NIS) combined with Atezolizumab	Phase I	03/08/17	NCT02919449
	gastrointestinal tumors	determine the safety and tolerability of TMV-018 when given alone or in combination with the prodrug 5-Fluorocytosine (5-FC) or an anti-PD-1 checkpoint inhibitor in patients	Phase I	23/11/20	NCT04195373
	Malignant peripheral nerve sheath tumor	determine the maximum tolerated dose (MTD) of intratumoral administration of an Edmonston strain measles virus genetically engineered to express neurofibromatosis type 1 (NIS) (oncolytic measles virus encoding thyroidal sodium iodide symporter [MV-NIS])	Phase I	22/03/17	NCT02700230
	Ovarian, fallopian or peritoneal cancer	studies how well oncolytic measles virus encoding thyroidal sodium iodide symporter (MV-NIS) compared to investigator's choice chemotherapy works in treating patients	Phase II	13/03/15	NCT02364713
NDV	Glioblastoma Multiforme, sarcoma and neuroblastoma	The study will measure progression-free disease and posits that it will be extended.	Phase I, II	01/07/11	NCT01174537
	Solid tumors	The reason for the study is to find out if MEDI5395 and durvalumab will work and be safe.	Phase I	24/10/19	NCT03889275
POLIOVIRUS	Breast cancer	examine PVSRIPO bioactivity in tumor tissue after intratumoral administration of PVSRIPO	Phase I	30/06/19	NCT03564782
	Malignant glioma tumors	To determine the maximally tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) of PVSRIPO when delivered intracerebrally by convection-enhanced delivery (CED).	Phase I	25/04/12	NCT01491893
	Malignant glioma tumors	confirm the safety of the selected dose and potential toxicity of oncolytic poliovirus (PV) immunotherapy with PVSRIPO for pediatric patients	Phase I	07/11/17	NCT03043391

Table 3. Oncolytic viruses tested in current clinical trials

tion of ICP47, which blocks antigen presentation by inhibiting transporter proteins involved in antigen processing (TAPs)[34–36].

This has paved the way for oncolytic virus-based therapeutic platforms to be development at the clinical level in the last decade, either as monotherapies or in combination with immune system modulators or other current cancer treatments. A complete list of clinical trials using OVs can be found at *ClinicalTrials.gov,* however, some recent trials for the virus types previously described in Table 2 are listed in Table 3. The information in the tables emphasizes in works that want to guarantee the safety of administration and the maximum dose that can be tolerated. In addition, it is interesting to note that the effect of the OVs is supported by their used in conjunction with other immunotherapies, mainly immunotherapy of immune checkpoints. It is important to highlight that some clinical trials have shown that genetically modify viruses, have improved their potential as OVs. The main viruses used in clinical trials are adenovirus and herpes simplex.

CONCLUSION

OV therapy was initially developed with the aim of creating a tool capable of overcoming the defense mechanisms of tumor cells by inducing a massive collapse through "viral oncolysis". It is now known that several conditions must be met for viral oncolysis to be effective, such as tumors lacking viral defense systems and the selected therapeutic agent not being affected by the patient's adaptive antiviral immune response. Thus, a more effective treatment will be one that combines viral oncolysis with an effective and long-lasting antitumor immune response. Although it has been observed that some OVs alone can achieve this effect, the conditions that favor this outcome are not clearly known. There are numerous OV platforms and mechanisms of selectivity that have been studied in detail. Certainly, there is a need to develop effective and selective agents. However, the true value of that distinguishes OVs lies, firstly, in conjugating a highly selective infection with tumor cells, disrupting the immune tolerance established in the tumor microenvironment (TME), and secondly, reactivating immune surveillance mechanisms to eliminate these neoplasms. Therefore, improvement of oncolytic viral systems is capable of maximizing replication and selective lytic capacity, so that enhancing immunogenic properties should be the goal to be achieved[65–68].

PERSPECTIVES

After briefly reviewed the history of immunotherapy and the current state of art. It is worth taking advantage of this gap to consider what new directions can be taken. Thus, the lack of clinical trials using NDV as an oncolytic agent represents an opportunity to explore the antitumor effects that OVs can provide. NDV, a naturally oncolytic virus [69,70] of the *Paramyxoviridae* family, is a serious infectious disease of poultry, NDV could be used as a therapeutic agent due to its non-pathogenicity in mammals[71]. There are reports evaluating in vitro NDV oncolytic potential in cervical cancer models and its ability to induce tumor cell apoptosis[72] . In addition, it has been shown to enhance both innate and adaptive immune responses[73]. Finally, there are reports that NDV induce signaling pathways activation such as TNFα and NF-kB in canine mammary cancer cells[74]. However, there are still not many studies that show what role NDV plays in prostate cancer, so it is worth making a guess.

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