Oncolytic Viruses and Cancer, Do You Know the Main Mechanism?

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The global rate of cancer has increased in recent years, and cancer is still a threat to human health. Recent developments in cancer treatment have yielded the understanding that viruses have a high potential in cancer treatment. Using oncolytic viruses (OVs) is a promising approach in the treatment of malignant tumors. OVs can achieve their targeted treatment effects through selective cell death and induction of specific antitumor immunity. Targeting tumors and the mechanism for killing cancer cells are among the critical roles of OVs. Therefore, evaluating OVs and understanding their precise mechanisms of action can be beneficial in cancer therapy. This review study aimed to evaluate OVs and the mechanisms of their effects on cancer cells.

Keywords: oncolytic virus, cancer immunotherapy, cancer vaccine, targeted treatment, immune checkpoint

BACKGROUND

Millions of individuals are affected by cancer annually. Cancer is considered the leading cause of death and the most important barrier to the increase in life expectancy in the twenty-first century. In 2018, 18.1 million new cancer cases (17.0 million cancer cases excluding non-melanoma skin cancers) were reported. The mortality due to cancer in 2018 was 9.6 million (9.5 million, excluding non-melanoma skin cancers) (1). Significant developments in cancer treatment started in 1900. The achievements of this progress include the development of diagnostic, surgery, chemotherapy, hormone therapy, gene therapy, and cell therapy methods. Regardless of these advancements, human is still incapable of combating cancer, as none of the identified treatment methods could be used in all stages of cancer (2). Many of cancer patients experience a relapse of disease progression regardless of the primary response to treatment.

Furthermore, complete resection of the tumor is difficult or impossible in many cases (3). Immunotherapy has evolved as a practical treatment choice against malignant diseases during the past decades. Studies in oncolytic virotherapy (OVT) developed in the early twentieth century as an observational science for the cases of spontaneous regression of tumors were reported due to infection with specific viruses (4).

Oncolytic viruses (OVs) include a group of viruses that selectively affect and kill malignant cells, leaving the surrounding healthy cells unaffected. OVs have direct cytotoxic effects on cancer cells and augment host immune reactions and result in the destruction of the remaining tumoral tissue and establish a sustained immunity (5). Indeed, OVs function in four ways against tumor cells, including oncolysis, antitumor immunity, transgene expression, and vascular collapse (6). Regarding the fact
that cancer cells are developed to avoid detection and destruction by the host immune system and also to resist apoptosis, which are the critical responses of normal cells in limiting viral infections, OVs can kill cancer cells through a spectrum of actions ranging from direct cytotoxicity to induction of immune-mediated cytotoxicity. OVs can also indirectly destroy cancer cells by destroying tumor vasculature and mediating antitumor responses (7). Furthermore, in order to augment the therapeutic characteristics, modifications in OVs by genetic engineering such as insertions and deletions in the genome have been employed in many investigations; thus, additional antitumor molecules can be delivered to cancer cells and effectively bypass the widespread resistance of single-target anticancer drugs (8).

It should be noted that the use of OVs in cancer therapy was limited due to the pathogenicity and toxicity of these viruses in human cases. Recent advancements in genetic engineering have optimized the function of OVs through genetic modifications and therefore have become the issue of interest in OVT (9). Each virus tends to a specific tissue, and this tendency determines which host cells are affected by the virus and what type of disease will be generated. For instance, rabies, hepatitis B, human immunodeficiency virus (HIV), and influenza viruses affect neurons, hepatocytes, T lymphocytes, and respiratory tract epithelium, respectively. Several naturally occurring viruses have a preferential but not exclusive tendency towards cancer cells. This issue is more attributed to tumor cell biology compared to the biology of the virus.

OVs are generally categorized into two groups. One group is preferentially replicated in cancer cells and is not pathogenic for normal cells due to the increased sensitivity to the innate immune system’s antiviral signaling or dependence on the oncogenic signaling pathways. Autonomous parvovirus, myxoma virus (MYXV; poxvirus), Newcastle disease virus (NDV; paramyxovirus), reovirus, and Seneca valley virus (SVV; picornavirus) are categorized in this group. The second group of OVs includes viruses that are either genetically modified for purposes including vaccine vectors such as mumps virus (MV; paramyxovirus), poliovirus (PV; picornavirus), and vaccinia virus (VV; poxvirus), or genetically engineered through mutation/deletion of genes required for replication in normal cells, including adenovirus (Ad), Herpes simplex virus (HSV), VV, and vesicular stomatitis virus (VSV; rhabdovirus) (10).

Furthermore, the mutation in cancer cells, drug adaptation, resistance, and cell immortality were effective in the initiation and speed of viral dissemination. Today, researchers are trying to discover and identify a new generation of OVs to save more patients’ lives from cancer. Evaluation of OVs and identification of the exact mechanism of action of these viruses can be helpful in this way (11). This review study aimed to evaluate OVs and their mechanism of action against cancer cells.

**METHODOLOGY**

The key terms in the literature search included oncolytic virus, cancer, immunotherapy, innate immunity, adaptive immunity, virotherapy, viral therapy, oncolytic, and virus were searched in international databases, namely, Web of Science, PubMed, and Scopus from 2004 to 2021. The inclusion criterion was the evaluation of viruses using standard in vivo and in vitro laboratory methods. Exclusion criteria were lack of access to full text articles and incomplete description or assessment of diseases other than cancers.

**RESULTS**

The primary search yielded 1,450 articles. Finally, 47 articles were included in the review after eliminating irrelevant and duplicate studies. The characteristics of the 47 included articles are presented in Table 1, performed from 2004 to 2021. The OV families assessed in the studies included Ad, MV, PV, NDV, SFV, HSV, VV, Reovirus, and bovine herpesvirus (BHV). The most commonly assessed virus was adenovirus (Ad) (n = 15), followed by the herpesvirus (HSV) (n = 12) and measles virus (MV) (n = 7). The least assessed viruses were BHV, SFV, and Reovirus (n = 1).

According to Table 1, OVs may employ multifunction against tumor cells; however, the most antitumor actions of OVs were related to cytolysis activity and inducing antitumor immunity (n = 26) in which adenovirus (n = 11) and HSV (n = 9) were the most responsible OVs in their categories, respectively. However, the last action was associated with vascular collapse. The collective data in Table 2 exhibited a summary of clinical trials of OVs implicated in malignancies highlighting the most considerable focus on engineered VV by TK<sup>del</sup> GMCSF<sup>exp</sup> (JX-594) on solid tumors supported by Jennerex Biotherapeutics Company. The majority of studies under clinical trials involve a transgene virus encoding an immune-stimulatory or proapoptotic gene to boost the oncolytic features of the virus. As Table 2 reveals, granulocyte–macrophage colony-stimulating factor (GM-CSF) and pro-drug-converting enzymes are the most popular transgenes, although many OVs encoding novel therapeutic cargos are in clinical development. Strey et al., in phase I clinical trial, examined the effects of HSV1716 on relapsed/refractory solid tumors. Despite the fact that none of the patients exhibited objective responses, virus replication and inflammatory reactions were seen in patients (58). In another clinical trial, Desjardins et al. reported a higher survival rate in grade IV malignant glioma patients who received recombinant nonpathogenic polio–rhinovirus chimera (59). In a phase I clinical trial, Rocio Garcia-Carbonero et al. discovered that endenotucirev IV infusion was associated with high local CD8+ cell infiltration in 80% of tumor samples evaluated, indicating a possible endenotucirev-driven immune response (60). TG4023, a modified vaccinia Ankara viral vector carrying the FCU1 suicide gene, was used in a phase I trial to convert the non-cytotoxic prodrug flucytosine (5-FC) into 5-fluorouracil (5-FU) in the intratumor. Finally, 16 patients with liver tumors were successfully injected; the MTD was not achieved, and a high therapeutic index was demonstrated (61). Dispensieri et al. examined MV-NIS effects in patients with relapsed, refractory myeloma and reported satisfactory primary results (62).
| Virus                  | Cancer                  | Model                                | Effects                                                                                                                                                                                                 | Mechanism                                                                                                                                                                                                 | References |
|-----------------------|-------------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Adenovirus            | Head and neck squamous cell carcinoma | Murine Ad-derived IL-12p70 prevents the destruction of HER2.CAR-expressing T cells at the tumor site. | Enhanced antitumor effects of HER2 CAR T cells by CAd12_PDL1                                                                                                                              | Controlling of primary tumor growth and metastasis.                                                                                                                                                      | Shaw et al., 2017 (12) |
| Renal cell carcinoma  | Murine HRE-K67-Decorin suppressed tumor growth and induced decorin expression in the extracellular matrix (ECM) assembly. | Treatment of lung cancer is possible by targeting LCSCs with armed oncolytic adenovirus genes.                                                                                                           | Zhang et al., 2020 (13)                                                                                                                                  | Yang et al., 2015 (14)                                                                                                                                  |
| Lung cancer stem cell (LCSC) | Murine Tumor necrosis factor (ZD55-TRAIL) increased cytotoxicity and induced A549 sphere cells apoptosis through a mitochondrial pathway | Enhance cell killing in primary leukemic blasts                                                                                                                                            | Significant autophagic cell death                                                                                                                  | Tong et al., 2013 (15)                                                                                                                                   |
| Leukemia              | Murine Induction of autophagic cell death | A positive effect against advanced orthotopic was that CD44+CD24−/low-derived tumors were observed.                                                                                              | Eriksson et al., 2007 (18)                                                                                                                               | Guo et al., 2006 (17)                                                                                                                                   |
| Breast cancer         | Murine Tumor killing due to 5ox2 and oct4 expression and Hoechst 33342 exclusion CD44+CD24−/low cells | Delta24 can replicate and help the E1-deleted adenovector replicate in cancer cells                                                                                                          | GD55 had a higher effect in suppressing tumor growth than oncolytic adenovirus ZD55.                                                                      | Zhang et al., 2016 (18)                                                                                                                                   |
| Liver cancer stem-like cells | Murine Significant apoptosis inhibition angiogenesis in xenograft tumor tissues inhibition of the propagation of cells occurred due to GD55 | CD8 cytotoxicity viruses efficiently lysed tumors                                                                                                                                               | Activation the immune system                                                                                                                            | Wei et al., 2020 (19)                                                                                                                                   |
| B16F10                | Murine Infiltration of effector CD4+ and CD8+ T cells increasing secretion of TNF-α and IFN-γ | These viruses completely eradicated CD44+low CD24−/cells in vitro                                                                                                                           | Creating a proinflammatory environment                                                                                                               | Davies et al., 2021 (20)                                                                                                                                   |
| exvβ6-positive tumor cell lines of pancreatic and breast cancer | Murine Cells expressing high levels of exvβ6 (EvBc, PANC0403, Suit2) were killed more efficiently by oncolytic AdSdnull−A20 than by oncolytic Ad5 | Significant antitumor activity in CD44+CD24−/low-derived tumors in vivo                                                                                                                     | Significant antitumor activity in CD44+CD24−/low-derived tumors in vivo                                                                           | Bauerleursct et al., 2008 (24)                                                                                                                                  |
| Advanced metastatic tumors | Murine Increase in CD8+ T cells Reduction of IFN-γ secretion | A valuable immunotherapeutic agent for melanoma is ORCA-010                                                                                                                                 | González et al., 2020 (25)                                                                                                                               | Yano et al., 2013 (26)                                                                                                                                   |
| Breast cancer         | Murine Inflammation and neutrophil infiltration due to oncolytic adenovirus-GM-CSF. | Anti-cancer immune response                                                                                                                                                                    | Killing cancer cells                                                                                                                                   |                                                                    |
| Solid tumors          | Murine CD8 cytotoxicity viruses efficiently lysed tumors | Significantly prolonged survival                                                                                                                                                              | Gürlevik et al., 2010 (23)                                                                                                                               |                                                                    |
| Metastatic ductal breast cancer | Murine Each virus featured 5/3 chimerism of a promoter controlling the expression of E1A and fiber, which was also deleted in the Rb binding domain for additional tumor selectivity | These viruses completely eradicated CD44+low CD24−/cells in vitro                                                                                                                           | Significant antitumor activity in CD44+CD24−/low-derived tumors in vivo                                                                           | Bauerleursct et al., 2008 (24)                                                                                                                                  |
| Metastatic melanoma   | In vitro Activation and an increased costimulatory capacity of monocyte-derived antigen-presenting cells | A valuable immunotherapeutic agent for melanoma is ORCA-010                                                                                                                                 | González et al., 2020 (25)                                                                                                                               | Yano et al., 2013 (26)                                                                                                                                   |
| Gastric cancer        | Murine Cell death in stem cells such as CD133 resident cancer by stimulating cell-cycle-related proteins | Anti-cancer immune response                                                                                                                                                                    | Ghouse et al., 2020 (28)                                                                                                                               |                                                                    |
| Herpesvirus           | Bearing M3-9-M tumors | Increasing the incidence of CD4+ and CD8+ T cells and no correlation with the CD4+CD25+Foxp3+ regulatory T-cell populations in the tumor | An efficient therapy strategy for soft tissue sarcoma in childhood                                                                                                                         | Chen et al., 2017 (27)                                                                                                                                     |
| Breast cancer         | Murine Regulation of CD8+ T cell activation markers in the tumor microenvironment Inhibition of tumor angiogenesis | Tumor regression Anti-cancer immune response                                                                                                                                               | Ghouse et al., 2020 (28)                                                                                                                               |                                                                    |
| Colon carcinoma       | Murine Decreased inhibitory immune cells Increased positive immune cells in the spleen. | Generate tumor-specific immunity Elimination of primary tumors Developing immune memory to inhibit tumor recurrence and metastasis. | Zhang et al., 2020 (29)                                                                                                                               |                                                                    |
| Ovarian carcinoma     | Murine DC maturation and tumor infiltration of INF-γ+ CTL | The antitumor immune responses are facilitated                                                                                                                                               | Benencia et al, 2008 (30)                                                                                                                               |                                                                    |
| Tumor                 | Murine T-cell responses against primary or metastatic tumors | Antitumor immune response Prevention of tumor growth Induction of immunogenic cell death (ICD) Recruitment of viral and tumor-antigen-specific CD8+ T cells | Li et al., 2007 (31)                                                                                                                                   | Bommarlceddy et al., 2019 (32)                                                                                                                                  |
| STING low-metastatic melanoma | Murine Release of DAMP factors Release of IL-1β and inflammatory cytokines Induction of host antitumor immunity | (Continued)                                                                                                                                                                                                                                               | (Continued)                                                                                                                                             | (Continued)                                                                                                                                             |
| Virus                     | Cancer                          | Model     | Effects                                           | Mechanism                                                                 | References |
|--------------------------|---------------------------------|-----------|--------------------------------------------------|---------------------------------------------------------------------------|------------|
| Osteosarcoma cells       | Murine                          | Antitumor efficacy in vivo | Inducing antitumor immunity                        | STING expression as a predictive biomarker of T-Vec Response              | Sceboll et al., 2011 (33) |
| HCT8 human colon cancer  | Murine                          | Cytotoxicity, viral replication, and Akt1 expression | Therapy of TIC-induced tumors with NV1066 slowed tumor growth and yielded tumor regression | Sceboll et al., 2011 (33) |
| Glioblastoma-derived     | Murine                          | Infection with HSV G47Delta killed GBM-SCs and inhibited their self-renewal and the inability of viable cells to form secondary tumor spheres | Significant anti-tumor effect against xenografts in mice and effective killing of CSCs | Wakimoto et al., 2009 (35) |
| cancer stem-like cells   | Human                           | The induction of adaptive antitumor immune responses | All patients were seropositive. No local recurrence was observed in patients and disease-specific survival was 82.4% | Harrington et al., 2010 (38) |
| (GBM-SC)                 |                                  |           |                                                  |                                                                            |            |
| Solid tumors             | Murine                          | Induction of adaptive anti-tumor immune responses | Biopsies contained residual tumor was observed in 19 patients after treatment that 14 of them showed tumor necrosis (extensive, or apoptosis) | Hu et al., 2006 (37) |
| Breast, head and neck,   | Human                           | ICP47 deletion increases US11 expression and enhances virus growth and replication in tumor cells | Overall survival at 12 and 24 months were 58% and 52%, respectively. | Senzer et al., 2009 (38) |
| and gastrointestinal     |                                  |           |                                                  |                                                                            |            |
| cancers, and malignant   |                                  |           |                                                  |                                                                            |            |
| melanoma                 |                                  |           |                                                  |                                                                            |            |
| Metastatic melanoma      | Human                           | GOS/MV-Edm significantly increases viral replication in tumor mass | Increased survival in passive antiserum immunized tumor-bearing mice | Xa et al., 2019 (39) |
| Measles virus            | Murine                          | Overexpression of the CD133 target receptor or increased kinetics of proliferation through tumor cells | CD133-targeted measles viruses selectively removed CD133þ cells from tumor tissue | Bach et al., 2013 (40) |
| Solid tumor              | Human                           | Infiltration of CD68þ cells innate immune cells. | Oncolytic MVs is versatile and potent agents for the treatment of human mesothelioma. | Li et al., 2010 (41) |
| Multiple myeloma         | Murine                          | Induction of adaptive anti-tumor immune responses | Virus-infected T cells may induce systemic measles virus therapy in the presence of ABS antiviral. | Ong et al., 2007 (42) |
| Breast cancer            | In vitro                        | Inducing apoptosis | Induction of cell death leads to infection of breast cancer cells with rMV-BNiP | Lal and Rajala et al., 2019 (44) |
| Breast cancer            | In vitro                        | Increased percentage of apoptotic cells in infected MCF-7 cells | Significant apoptosis in breast cancer cell lines. | Abdullah et al., 2020 (44) |
| T-cell lymphomas         | Human                           | An increase in the IFN-γ/CD4 and IFN-γ/CD8 mRNA ratio and a reduced CD4/CD8 ratio | MV can affect CTCL treatment. | Heinzlering et al., 2005 (45) |
| (CTCLs)                  |                                  |           |                                                  |                                                                            |            |
| Newcastle disease virus  | Murine                          | Caspase-dependent apoptosis associated with increased caspase-3 processing and ADP-ribose polymerase cleavage. | A potential strategy for targeting lung CSCs | Hu et al., 2015 (46) |
| Lung cancer              | Murine                          | Treatment with systemic CTLA-4 blockade was due to long-term survival and tumor rejection | Distant tumors are prone to systemic therapy with immunomodulatory antibodies using localized therapy with oncolytic NDV | Zamarin et al., 2014 (47) |
| B16 melanoma             | Murine                          | DAMP release Autophagy induction | Inhibited tumor growth | Ye et al., 2018 (48) |
| Lung cancer              | Murine                          | GBM susceptibility to NDV is dependent on the loss of the type I IFN | Trigger ICD | Garcia-Romero et al., 2020 (49) |
| GBM                      | Murine                          | Treatment with systemic CTLA-4 blockade was due to long-term survival and tumor rejection | Distant tumors are prone to systemic therapy with immunomodulatory antibodies using localized therapy with oncolytic NDV | Zamarin et al., 2014 (47) |
| Vaccinia virus           | Murine                          | PD-L1 inhibition | NEOantigen presentation | Wang et al., 2020 (50) |
| Melanoma                 | Murine                          | Activated the inflammatory immune status | Complete tumor regression long-term tumor-specific immune memory | Nakao et al., 2020 (51) |
| Solid tumors             | Murine                          | Replication was activated by EGFR/Ras pathway signaling, cellular TK levels, and cancer cell resistance to IFNs | Selectively cell lysis and stimulation of antitumoral immunity | Parato et al., 2012 (52) |

(Continued)
TABLE 1 | Continued

| Virus            | Cancer                        | Model   | Effects                                | Mechanism                                           | References                          |
|------------------|-------------------------------|---------|----------------------------------------|-----------------------------------------------------|-------------------------------------|
| M1 virus         | Melanoma                      | Murine  | CD8+ T-cell-dependent therapeutic effects | Immuneogenic tumor cell death                       | Yang Liu et al., 2020               |
|                  |                               |         | long-term antitumor immune memory      | Restores the ability of dendritic cells to prime T cells | Liu et al., 2021 (11)               |
|                  |                               |         | Upregulating the expression of PD-L1   | CDDO6 inhibition resulted in better antitumor activity |                     |
| Bladder tumor    |                               | Murine  | Inhibition of CDDO6 improve viral replication and then induced endoplasmic reticulum stress to facilitate M1 virus oncolytic effects. | Tumor regression and improved survival              | Mathilde et al., 2020 (53)         |
| Poxyvirus        | MC-38 colon adenocarcinoma tumors | Murine  | Excited TILs with lower quantities of exhausted PD-1+Tim-3+ CD8+ T cells and regulatory T cells | Oncolytic PV recombinants may affect tumor cells by viral receptor CD155 | Ochiai et al., 2004 (54)           |
| Poliovirus       | Breast cancer                 | Murine  | Primary oncolytic viral receptors are highly expressed in tumor cells and transmitted among cells. | Initiating apoptotic signaling events required for virus release and spread. | Garant et al., 2016 (56)           |
| Reovirus         | Solid tumor                   | Murine  | Induction of Golgi fragmentation and accumulation of oncogenic Ras in the Golgi body | Induction of T cell-mediated antitumor immune responses. | Jing Ma et al., 2020 (57)          |
| Adenovirus (Ad)  | Osteosarcoma                  | Murine  | Activates immunogenic apoptosis        | Increased cell death processes                      |                                    |
| Semliki Forest virus (SFV) and Vaccinia virus (VV) |         |         | Triggering phagocytosis and maturation of DCs Th1-cytokine release by DCs and antigen-specific T-cell activation. |                                    |                                    |

PD-L1, programmed death-ligand 1; Ad, adenovirus; MV, measles virus; GBM, glioblastoma; NDV, Newcastle disease virus; VV, Vaccinia virus; Th, T helper; ICD, immunogenic cell death; EGFR, epidermal growth factor receptor; TK, thymidine kinase; IFN-I, type-I interferon; HSV, herpes simplex viruses; TIL, tumor infiltration lymphocytes; DC, dendritic cells; BVH, bovine herpesvirus; DAMP, damage-associated molecular pattern; TRAIL, TNF-related apoptosis-inducing ligand; GD-S9, GOLPH2-regulated oncolytic adenovirus; GOS, graphene oxide arms PV, polo virus; LAPV, Israeli acute paralysis virus; CP, cisplatin; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Cohn et al., in phase II clinical trial, evaluated the effects of oncolytic reovirus (Reolysin®) plus weekly paclitaxel in women with recurrent or persistent ovarian, tubal, or primary peritoneal cancer. The results did not show any improvement in the patient status (63), although Mahalingam et al. showed that REOLYSIN®, plus carboplatin and paclitaxel, is an effective treatment in advanced malignant melanoma (64). Packiam et al. showed that CG0070 (GM-CSF expressing adenovirus) has a 47% CR rate at 6 months for all patients and 50% for patients with carcinoma-in situ (65).

Geletney et al. evaluated H-1 parvovirus (H-1PV) effects in recurrent glioblastoma patients and reported microglia/macrophage activation and cytotoxic T-cell infiltration in the infected tumors, proposing initiation of the immunogenic response (66).

Andtbacka et al., in a phase III study, evaluated Talimogene laherparepvec (T-VEC) in stage IIIc and stage IV malignant melanoma. T-VEC was the first approved OVs against melanoma in a phase III clinical trial. This virus compared with GM-CSF showed a higher durable response rate and overall survival (67). In another newest phase III study, Talimogene laherparepvec was approved by the Food and Drug Administration (FDA) in the USA, European Union, and Australia (68).

**DISCUSSION**

As a challenge in cancer therapy approaches (1), the exclusive features of oncolytic viruses have attracted plenty of researchers in recent years. OVs have the dramatic capability to selectively infect tumor cells leading to direct or indirect cancer cell death without harming normal cells (7). This study focused on some mechanisms employed by OVs against tumor cells, which are exactly various from virus to virus (Figure 1).

According to most studies, OVs can target cancer cells and benefit from tumor conditions in favor of replication in infected cells, eventually leading to oncolysis. Indeed, tumor cells tend to resist apoptosis and translational suppression, which are both compatible with the growth of several viruses (7). One of the main actions of OVs is to take advantage of immune-evading properties of cancer cells to escape from recognition and destruction by the immune system. Antiviral processes in normal cells are associated with the interferon pathway in which the secretion of type I interferon (IFN) cytokine can trigger an antiviral response and induce ISGs to block viral replication (69). This subsequently leads to cell apoptosis, as it is known that the IFN-I signaling regulates the expression of proapoptotic genes such as tumor necrosis factor alpha (TNF-α), FAS ligand, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (70).

Regarding the IFN-I signaling is defective in most tumor cells, it makes tumor cells susceptible to being infected by some OVs including NDV, VSV, MXXY, and raccoon pox virus (71–73). Garcia-Romero et al. showed that NDV was able to replicate in glioblastoma (GBM) cancer stem cells (CSCs) due to type I IFN gene loss occurring in more than 50% of patients. Infection of GBM with NDV represents oncolytic and immunostimulatory properties through the production of type I IFN in non-tumor cells such as tumor infiltrated macrophages and DC or other cells present at the tumor microenvironment (49). NDV therapy also declines CSCs self-renewing capacity to improve their differentiation ability and facilitate cancer therapy (49, 74).

OVs can also benefit from the abnormal expression of the proto-oncogene RAS which generally occurs in normal cells but actives in tumor cells (75). OV infection outcomes can be
affected by up-regulation of RAS in tumoral cells and further down-regulation of interferon-inducible genes due to activation of RAS/MEK signaling pathway that reduces viral response in tumoral cells (76). On the contrary with this attempt, Garant et al. demonstrated that reovirus could translocate and accumulate RAS into Golgi apparatus to increase apoptotic signaling events required for virus release (56). This highlighted that the outcomes of OVT are exclusively associated with the characteristics and type of OVs.

High expression of some viral receptors by cancer cells permits higher viral uptake in cancer cells than in normal ones. Some receptors such as CAR (77), laminin (78), CD155 (79), and CD46 (80) are overexpressed in various cancer cells which result in increased uptake of Ad (81), Sindbis virus (82),

### TABLE 2 | The summary of clinical trials for oncolytic viruses.

| Phase | Virus | Tumor | Interventions | Trial code  | Country | Company |
|-------|-------|-------|---------------|-------------|---------|---------|
| Phase I | JX-594 | Refractory solid tumors | Intratumoral injection | NCT01169584 | USA | Jennerex Biotherapeutics |
|       | JX-594 | Refractory solid tumors | Intravenous infusion | NCT00625456 | Canada | Jennerex Biotherapeutics |
|       | HSV-1, TBI-1401 (HF10) | Solid tumor with superficial lesions | Intratumoral administration | NCT02428036 | Japan | Takara Bio Inc. |
|       | Recombinant measles virus | Ovarian cancer Primary peritoneal cavity cancer | Intraperitoneal administration | NCT00408590 | USA | Mayo Clinic |
|       | GM-CSF-Adenovirus CGTG-102 | Malignant solid tumor | In combination with low dose cyclophosphamide | NCT01598129 | Finland | Targovax Oy |
|       | Adenovirus VCN-01 | Solid tumor | Intravenous administration with or without gemcitabine | NCT02045602 | Spain | VCN Biosciences, S.L. |
|       | REOLYSIN® | KRAS mutant metastatic colorectal Cancer | Intravenous administration with trinotecan/Fluorouracil/Leucovorin and Bevacizumab | NCT01274624 | USA | Oncolytics Biotech |
|       | Adenovirus VCN-01 | Pancreatic cancer | Intratumoral injections with intravenous Gemcitabine and Abraxane® | NCT02045589 | Spain | VCN Biosciences, S.L. |
|       | JX-594 | Hepatic carcinoma | Transdermal injection | NCT00629759 | Korea | Jennerex Biotherapeutics |
|       | Attenuated Vaccinia Virus, GL-ONC1 | Solid organ cancers | Intravenous administration | NCT00794131 | United Kingdom | Genelux Corporation |
|       | Coxackievirus Type A21 | Melanoma | Intratumoral injection | NCT00438009 | Australia | Oncolytics Biotech |
|       | REOLYSIN® | Pancreatic adenocarcinoma | Intravenous administration with Pembrolizumab (KEYTRUDA®) | NCT02620423 | USA | Genelux Corporation |
|       | Vaccinia Virus (GL-ONC1) | Head and neck carcinoma | With concurrent Cisplatin and radiotherapy | NCT01584284 | USA | Genelux Corporation |
| Phase II | TBI-1401(HF10) | Melanoma | In combination with Ipilimumab | NCT03153085 | Japan | Takara Bio Inc. |
|       | OncoVEX®GM-CSF | Malignant melanoma | With Ipilimumab | NCT02272855 | Japan | Takara Bio Inc. |
|       | Edmonston strain of Measles Virus Expressing NS | Refractory multiple myeloma | Systemic Administration with cyclophosphamide | NCT02192775 | USA | University of Arkansas |
|       | Reovirus Serotype 3 | Non-small cell lung cancer | Intravenous administration with paclitaxel and carboplatin | NCT00861627 | USA | Oncolytics Biotech |
|       | JX-594 | Hepatocellular carcinoma | Intratumoral injection | NCT00564372 | USA | Jennerex Biotherapeutics |
|       | CG0070 | Non-muscle invasive bladder carcinoma | – | NCT02365818 | USA | CG Oncology, Inc. |
|       | Wild-type Reovirus | Bone and soft tissue sarcomas | Intravenous injection | NCT00603295 | USA | Oncolytics Biotech |
| Phase I/II | Vaccinia Virus JX-594 | Melanoma | Intratumoral injection | NCT00429312 | USA | Jennerex Biotherapeutics |
|       | Parvovirus H-1 | Glioblastoma multiforme | Intratumoral/Intracerebral injection | NCT01301430 | Germany | Onyx GmbH & Co. KG |
|       | HSV1716 | Malignant pleural mesothelioma | Intraperitoneal injection | NCT01721018 | United Kingdom | Vittu Biologics Limited |
|       | Ad-MAGEA3 | Metastatic non-small cell lung cancer | With pembrolizumab | NCT02879760 | Canada | Turnstone Biosciences, Corp. |
|       | REOLYSIN® | Recurrent malignant gliomas | Intraleisional administration | NCT00528684 | USA | Oncolytics Biotech |
|       | JX 594 | Colorectal carcinoma | Multiple intravenous with irinotecan | NCT01394939 | USA | Jennerex Biotech |
|       | Vaccinia Virus GL-ONC1 | Peritoneal Carcinomatosis | Intraperitoneal administration | NCT01443260 | Germany | Genelux GmbH |
PV (83), and MV (84) respectively. Interestingly, some viral proteins are poisonous for neoplastic cells and can directly kill cells before viral replication. This was evidenced by the E3 death protein and E4orf4 proteins encoded by Ads and are toxic for cells that end in cytolysis at the time of virus exposure (3). However, deletion in specific viral genes can be another mechanism for the action of the OVs. These genes are necessary for the longevity of viruses in normal cells but not essential for viral activity in cancer cells. Thymidine kinase (TK) is an indispensable enzyme for nucleic acid metabolism encoded in infection with wild type vaccinia virus and enables the replicating of the virus in normal cells. Lister strain virus with TK gene deletion as a type of VV has shown a beneficial antitumor potency and cancer-selective replication in vivo since tumoral cells have a high TK content, which enables the virus to replicate in cancer cells regardless of the deletion in viral TK gene (85). In parallel with this study, Parato et al. analyzed the mechanism of cancer-selectivity by an engineered vaccinia virus with TK deletion and epidermal growth factor (EGFR) and lac-Z transgenes observing the replication in tumor cells was related to activation of EGFR/RAS signaling, high cellular TK level and tumor cell resistance to IFN-I (52). These results displayed noticeably the beneficial implication of OVs with inherent and engineered mechanistic properties in cancer therapy approaches.

Oncolytic viruses may interfere with normal physiological process of tumor cells to induce the secretion of pro-inflammatory mediators or even lead to the exposure of tumor-associated antigens (TAA), pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) following apoptosis or oncolysis. These responses can also result in a change in tumor status from immune desert to inflamed status and further recruit a collection of immune cells such as cytotoxic T lymphocytes, dendritic cells, natural killer cells and phagocytic cells to induce immune cell death along with antiviral responses (86, 87).

Remarkably, most viruses continue their infection by expressing genes responsible for escaping the immune system and disseminating in host cells (88). Mutation in these genes can probably improve immune induction and thus increase the antitumoral responses regardless these mutations may reduce virus replication further (10). Thus, oncolytic viruses are often engineered to express various genes aided in the overall antitumoral efficacy of the virus. Transgenes mostly include ranging from immune-stimulatory (IL-2, IL-4, IL-12 and GM-CSF) to pro-apoptotic (tumor necrosis factor alpha, p53 and TRAIL genes inserted into oncolytic viruses (87, 89–94). Interestingly, bystander effects of OVs through local release of cytokines can potentially cause immune response against nearby tumor cells even without direct antigen expression (95).
Furthermore, OVs can destroy tumor vasculature and impede sufficient intratumoral blood reserve, which is essential for tumor progression and metastasis (96). Breitbach et al. demonstrated that intravenous injection of JX-594, an engineered vaccine virus with TK deletion and overexpression of human granulocyte-monocyte colony-stimulating factor (hGM-CSF), led to replication of the virus in endothelial cells of the nearby tumor and disrupted tumor blood flow, which ultimately ended in intensive tumor necrosis within 5 days. Consistently, patients with advanced hepatocellular carcinoma, hypervascular and VEGFhigh tumor type, treated by JX-594 in phase II clinical trials confirmed the efficiency of the JX-594 OV in tumor vasculature disruption without toxicity to normal blood vessels in which inhibition of angiogenesis can passively result in tumor regression (97). This evidence may open promising technologies toward cancer therapy in a way tumor cells are targeted selectively and bypass the side effects of conventional approaches.

Recently, conditionally replication-competent adenoviruses (CRCA) have been introduced as a successful method for cancer therapy. Sarkar et al. showed that Ad.PEG-E1A-mda-7, a cancer terminator virus (CTV), selectively replicated in cancer cells, inhibits their growth and induces apoptosis (98).

Qian et al. showed that ZD55 expressing melanoma differentiation-associated gene-7/interleukin-24 (ZD55-IL-24) affects B-lymphoblastic leukemia/lymphoma through upregulation of RNA-dependent protein kinase R, enhance phosphorylation of p38 mitogen-activated protein kinase, and induce of endoplasmic reticulum (ER) stress (99).

Azab et al. showed that Ad.5/3-CTV potently suppressed in vivo tumor growth in mouse (100).

Bhoopathi showed that Ad.5/3-CTV induces apoptosis through apoptosis-inducing factor (AIF) translocation into the nucleus, independent of the caspase-3/caspase-9 pathway (101).

In an interesting study, Bhoopathi et al. introduced a novel tripartite CTV “theranostic” adenovirus (TCTV) that targets virus replication, cytokine production, and imaging capabilities uniquely in cancer cells. This TCTV permits targeted treatment of tumors while monitoring tumor regression, with the potential to simultaneously detect metastasis due to the cancer-selective activity of reporter gene expression (102).

Greco et al. showed that ultrasound (US) contrast agents guided MB/Ad.mda-7 complexes to DU-145 cells successfully and eradicated not only targeted DU-145/Bcl-xL-therapy-resistant tumors but also nontargeted distant tumors (103).

T-VEC, adenovirus, and vaccinia virus are the most popular OVs in clinical trials. Approving T-VEC by FDA for the first time could pave the way for other OVs in the clinic. Oncolytic viruses have a broad therapeutic method; hence, their clinical development requires a multidisciplinary view. It is necessary to understand viral generation and viability in infected cells. To improve clinical trials, important factors such as viral entrance, replication, dissemination, oncolysis, and immune activation should be controlled. These factors can vary between tumor types and OVs. It is also critical to understand the immune composition of diverse cancers and the immunological repercussions of viro-immunotherapy.

CONCLUSION AND FUTURE DIRECTION
Cancer is among the most important causes of mortality worldwide, and many chemotherapies and radiotherapy approaches do not have a specific effect on cancer cells and are sometimes accompanied by side effects. Today, a biological war has evolved against cancer by genetically modifying natural pathogens to activate them against neoplastic cells. OVT is a promising therapeutic option in cancer therapy. The mechanisms of action of OVs differ entirely from the mechanism of action of chemotherapy, radiotherapy, surgery, and embolization. They can result in success in the treatment of cancers that are resistant to other therapeutic modalities. Better understanding and acquiring comprehensive information regarding OV therapy and the biology of cancer is an essential step in assessing and controlling cancer programs.

AUTHOR CONTRIBUTIONS
Conceptualization, WK and HE. Methodology, MF and RD. Validation, BI. Data curation, MB. Writing—original draft preparation, HE and WK. Writing—review and editing, all. All authors have read and agreed to the published version of the manuscript.

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