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Oncolytic Viruses: A New Frontier in Cancer Therapy

Maged Naser [1], Mohamed M. Nasr [2], and Lamia H. Shehata [1]

[1] Mazahmiya Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of ob/gyn,

[2] Consultant of General and Endoscopic Surgery (MD, FRCS),

[3] Care National Hospital, Department of Radiology

Corresponding Author: Maged Naser

Abstract – Oncolytic viruses (OVs) have surfaced as a promising approach for combating tumors owing to their ability to selectively proliferate within cancer cells, trigger apoptosis, and activate immune responses. Nevertheless, the therapeutic potency of individual OVs is hindered by the intricate and immunosuppressive characteristics of the tumor microenvironment (TME). To tackle these obstacles, the engineering of OVs has become a pivotal area of research. This review spotlights engineering techniques and multimodal combination therapies for OVs aimed at overcoming delivery challenges, viral engulfment, and antiviral immune responses in cancer treatment. The engineering strategies examined involve amplifying in vivo immune responses, enhancing replication efficacy within tumor cells, boosting safety profiles, and refining targeting capabilities , while summarizing ongoing clinical trial data. By persistently refining engineering techniques , we can realize enhanced treatment outcomes and improved quality of life for cancer patients.

Keywords – Oncolytic Viruses, Cancer Treatment, Genetic Engineering, Clinical Trials .

1. Introduction

Oncolytic viruses (OVs) are a unique category of viruses that can specifically replicate within malignant cells, inducing apoptosis while also activating the immune response and safeguarding normal tissues from damage (1). Over the last twenty years, extensive exploration in genetic engineering, tumor immunology, and molecular biology has positioned oncolytic virus (OV) therapy as a hopeful avenue for cancer treatment (2,3). OVs can be classified into two primary types: naturally occurring viruses and genetically altered viruses (4). Naturally occurring OVs encompass reovirus, Newcastle disease virus (NDV), myxoma virus (MYXV; Poxvirus), and Seneca Valley virus (SVV), whereas the majority of OVs are genetically engineered or function as vectors, including measles virus (MV; Paramyxovirus), poliovirus (PV; Picornavirus), vaccinia virus (VV; Poxvirus), adenovirus (Ad), and herpes simplex virus (HSV). Genetic modifications seek to boost targeting specificity and safety of OVs towards cancer cells by enhancing selective replication and cleavage functions, as well as elevating host anti-tumor immune responses (1, 5, 6).

With the introduction of spatial transcriptomics (7), single-cell RNA sequencing (scRNA-seq), and proteomics technologies in cancer studies (8–10), the importance of the tumor microenvironment (TME) in cancer biology has been acknowledged. Cancer represents a complex evolutionary and ecological process characterized by interactions between tumor cells and TME (11). The complexity and diversity of TME are closely correlated with tumor growth, metastasis, and therapeutic responses, making it a vital target for cancer interventions (12). Although OVs have emerged as a potential therapeutic alternative for cancer owing to their precise targeting ability, high lethality, increment over time, and minimal adverse effects; deploying a single type of OV alone proves inadequate to surmount the hurdles presented by the immunosuppressive TME, resulting in restricted anti-tumor efficacy

(13). Hence, this review aims to encapsulate engineering enhancements of OVs and multimodal combination therapies that can address delivery obstacles, viral phagocytosis challenges, antiviral immune responses, alongside other complications encountered in OV-based cancer treatments (14–16). Moreover, we will present clinical data from leading studies related to OV.

1. Engineering enhancement of OVs

1.1. Amplification of OVs immune response in vivo

The immune response triggered by OVs is a fundamental mechanism in tumor therapy. Optimizing the in vivo immune response of OVs is a multifaceted endeavor that encompasses various aspects of enhancement and tactical strategies. Reports indicate that regulating the following factors can surmount the immune system barrier and bolster the in vivo immune response to OVs (1): augmenting T cell activation, polarization, and memory T cell creation (2); obstructing cancer immune evasion through cytokines and inhibiting immunosuppressive ligands (3); disrupting physical barriers and facilitating immune cell infiltration (4); inhibiting immunosuppressive cells (17). During this process, immune checkpoint proteins and various cytokines within the TME play crucial roles.

1.1.1. Modified OVs incorporating immune checkpoint molecules

The immune checkpoint molecules are pivotal in shaping immune system responses. They act as co-stimulatory receptors found on diverse immune cells, conveying inhibitory signals (18). Among the well-researched immune checkpoint molecules are CTLA-4, TIM-3, and PD-1, which proficiently manage the immune response to avert excessive immunological harm (19). Research by Ju et al. illustrated that OVs equipped with a single-stranded fragment variable (scFv) targeting PD-1 significantly boosted effector T cell activity in genetically modified mice. The findings disclosed that OVs expressing PD-1 inhibitors synergistically worked alongside anti-CTLA-4 or anti-TIM-3 agents to enhance the immune response in vivo and ultimately achieve tumor control (20).

Modifications in OVs engineering. (A) Amplifying in vivo immune response by equipping OVs with scFv aimed at PD-1 or by overexpressing particular cytokines through genetic engineering. (B) Improving replication efficiency of OVs in tumor cells through genetic modifications, such as the overexpression or downregulation of specific genes or proteins in tumor cells, or by selecting and designing more efficient viral vectors. (C) Engineering OVs to minimize off-target effects and damage to normal cells, creating a safer and more precise attenuated virus, thereby enhancing the safety profile of OV therapy. (D) Augmenting tumor targeting of OVs through five primary modification strategies: 1) Boosting virus affinity and binding efficacy to receptors that are overexpressed on tumor surfaces. 2) Leveraging tumor cell differentiation to enhance targeting precision. 3) Integrating differentially expressed microRNAs into OVs by means of transgenic technology. 4) Equipping OVs with bispecific or Tri specific T cell engagers.

1.1.2. Conceived OVs generating cytokines

Genetic modification of OVs to produce specific cytokines serves as an effective tactic to bolster the immune response of OV. A variety of antitumor responses may be modulated by cytokines (21), including (1): interferons (IFNs): IFNα, IFNβ, IFNγ; (2) Interleukin (ILs): IL-2, IL-12, IL-15, IL-17, IL-18; (3) chemokines: CXCL9, CXCL10, and CCL5; (4) Granulocyte-macrophage colony-stimulating factor (GM-CSF); (5) Tumor necrosis factor (TNF) .

1.1.2.1. IFNs

IFN is categorized into type I (IFNα and IFNβ) and type II (IFNγ), with type II primarily secreted by immune cells such as T-helper (Th) 1 cells and natural killer (NK) cells. Expression of IFN in OVs can effectively trigger tumor cell death by modulating various pathways (22). Research indicates that oncolytic adenovirus (OAd) expressing IFN (IFN-OAd) markedly inhibits tumor growth in hamster pancreatic cancer models, leading to an increase in tumor-infiltrating lymphocytes (TILs) (23). Furthermore, the integration of CD47 and the IFNγ genes into MYXV results in the production of MYXV_IFNγ and MYXV_CD47, respectively. This dual expression approach enhances anti-tumor immunity in a mouse melanoma model, showcasing the synergistic effects of CD47 and IFN (24). Hence, it is clear that the direct stimulation of immune cells by IFNs can amplify in vivo immune responses.

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1.1.2.2. ILs

ILs are a group of small protein molecules that can both promote tumor cell proliferation and inhibit tumors in cancer (25). Given their essential role in tumor progression, ILs can be incorporated into OVs for their antitumor properties. IL-2 acts as an anticancer cytokine by boosting the activity of NK cells and cytotoxic T cells. Prior studies have shown that IL-2 can be expressed in various OVs such as VV, Sendai virus, Ad, and other vectors. Alternatively, IL-2 can be co-expressed with additional anticancer transgenes in OVs to further bolster their immune characteristics (26). Recently, researchers engineered an OAd that co-encodes TNFα and IL-2, expressing them locally in hamster pancreatic cancer models. This strategy modifies the tumor microenvironment (TME) by enhancing AIM2 expression and inhibiting tumor growth (27). IL-12 activates NK cells and T cells while fostering a Th1 immune response. Previous research has demonstrated that engineering OAd (Ad5-ZD55-CCL5-IL12), which co-expresses CCL5 and IL-12, significantly increases the infiltration of chimeric antigen receptor (CAR)-T cells and TILs within tumors, resulting in potent anti-tumor effects with enhanced safety profiles (28). Additionally, treatment of colon cancer using oncolytic herpes simplex virus (oHSV) (O-HSV1211) modified to express both IL-12 and CXCL11 leads to greater infiltration of CD8+ T and CD4+ T cells into the tumor site (29). IL-15 serves as an upstream regulator of tumor-infiltrating CD8+ T cells, and the IL-15/IL-15Rα+ axis plays a pivotal role in anti-tumor immunity (30). Researchers engineered a fusion protein combining IL-15 and IL-15Rα (labeled OV-IL15C), which was expressed within gliomas and demonstrated the capacity to enhance cytotoxicity against glioblastoma (GBM) in both in vivo and in vitro settings, while also improving the survival of NK and CD8+ T cells (31). Moreover, expression of IL-15 within oncolytic VV (32) and a novel OV (SG400-E2F/IL-15) (33) also led to an improved immune response and antitumor efficacy in vivo. The synthesis of IL-18 is found in diverse cell types, including activated monocytes, macrophages, and dendritic cells (DCs). IL-18 serves a vital function as a cytokine in cancer (34). Recombinant Pseudorabies viruses (PRVs), specifically rPRV-PH20 and RPRV-IL-18-gamma-PH20, were developed utilizing pseudorabies virus (PRV) as the vehicle. The findings revealed a noteworthy surge in the penetration of CD4+ T and CD8+ T cells within tumor cells infected with the recombinant PRV strains. Furthermore, the oncolytic effect was notably stronger in the treatment cohorts that received rPRV-IL-18-gamma-PH20, rPRV-PH20 alone, or RPRV-IL-18-gamma-PH20 compared to the control group. Remarkably, among these groups, the most effective anti-tumor reaction was recorded with the rPRV-IL-18-γ-PH20 treatment. In summary, the co-expression of PH20 alongside IL-18 and IFNγ improved systemic anti-tumor immunity mediated by IL-18 (35).

1.1.2.3. Chemokines

Chemokines constitute a subgroup of cytokines, produced by varied cells in response to triggers such as pathogens, pharmaceuticals, or physical harm. These cells comprise white blood cells, endothelial cells, fibroblasts, and more. Chemokines are integral in facilitating cell migration throughout the body, especially for white blood cells. They also play a significant role in the regulation of immune function (36). The engineered expression of CCL5 shows potential as a strategy to amplify the immune response to OVs. For instance, an OV called OV-Cmab-CCL5 was engineered to express CCL5 specifically in the TME. In GBM infected with OV-Cmab-CCL5, there was an elevation in NK cell function, T cell activity, and macrophage activity accompanied by a reduction in tumor size (37). Additional research aimed at bolstering the immune response of OVs through engineering includes arming OAds with CXCL11 (38), overexpressing CXCR7 and CXCR4 in breast cancer cells using an armed OAd carrying CXCL12 (39), and employing CXCL10 as an enhancement for OAds (40).

1.1.2.4. GM-CSF

The integration of GM-CSF into OVs has shown considerable advantages for cancer patients. Examples of OVs used include, but are not limited to, oncolytic vesicular stomatitis virus (VSV) (41), oncolytic VV (42), oHSV type 1 (oHSV-1) (43), OAd (44), oncolytic Herpesvirus talimogene laherparepvec (T-VEC) (45), and oncolytic reovirus (46). Furthermore, the use of ONCOS-102 encoding GM-CSF and ONCOS-204 encoding ICOSL (the ligand for inducible T-cell co-stimulator) in modified adenoviruses further boosts the function of bi-specific antibodies (BsAbs)-activated T cells in melanoma cells. Notably, the combination of ONCOS-204 and EGFRxCD3 BsAb demonstrates a superior capability in enhancing T cell activation and cytotoxicity in comparison to ONCOS-102, with ONCOS-204 notably affecting CD4+ T cell subpopulations infected with tumor cells (44).

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1.2. Enhance the replication efficacy of OVs in tumor cells

The optimization of OV replication efficacy in tumor cells can be approached through two perspectives (1): Manipulation of gene or protein expression levels in tumor cells utilizing genetic engineering technologies (2). Selection and design of more efficient viral vectors. Through genetic engineering, specific genes and proteins can be manipulated to either amplify or diminish their expression levels in tumor cells. This modulation of gene expression can synergistically boost the replication efficacy and therapeutic effectiveness of OVs. For example, in an experiment, the death domain associated protein was downregulated, resulting in enhanced viral replication efficiency. Additionally, the overexpression of the precursor terminal protein helped ameliorate poor viral replication, leading to a higher quantity of total viral particles (47). To tackle the replication defect caused by insufficient arginine succinate synthetase 1 (ASS1) expression in tumors, a series of recombinant oncolytic MYXV constructs expressing exogenous ASS1 were developed (48). Moreover, the upregulation of MHC class I chain-related polypeptide A (MICA), which activates the NKG2D receptor on NK cell and T cell subpopulations as an OV gene engineered transgene, was observed in tumor cells. The application of MICA-expressing oncogenic adenovirus named ICOVIR15KK-MICAMut showed improved control over tumor growth compared to other viruses devoid of MICA expression. This enhanced control is ascribed to the virus's heightened replication rate within tumor cells, resulting in increased oncolytic activity and a more vigorous immune-mediated tumor cell destruction (49).

Through the screening and optimization of virus strains, more efficient and tumor-selective OVs can be identified. In a clinical trial for cancer treatment using reovirus serotype 3 Dearing (T3D), the Patrick Lee laboratory strain (T3DPL type) manifested enhanced replication efficiency and greater oncolytic performance (50). To bolster the anti-tumor immune activity of chimeric poxvirus deVV5, a chimeric virus with thymidine kinase deletion and a suicide gene, FCU1, was generated. The deVV5-fcu1 group exhibited superior replication efficiency compared to the control group, with findings indicating that it achieved the highest rate of virus production from Hep G2 liver cancer cells (51). In a research project centered around engineered adenoviruses, a chimeric vector of serotype Ad5/3, referred to as OV, was constructed by leveraging adenovirus type 3 (Ad3) receptors. Results indicated that the Ad5-ΔE3-Luc grouping exhibited superior in vivo replication capabilities compared to the Ad5/3-ΔE3-Luc counterpart. These investigations demonstrate that altering OAd type 3 can enhance the replication efficiency of serotype chimeric Ad5/3 vectors, warranting consideration in forthcoming research initiatives (52). A recent exploration focused on the expression of a novel generation OAd named Ad5 KT-E1A-IL-15 (TS-2021), alongside Ki67 and TGF-β2 proteins, aimed at enabling selective replication in GBM cells and boosting effectiveness in the destruction of GBM tumors (53).

1.3. Enhanced safety

The acknowledgment of viruses as agents of pathogenicity has been prevalent for a long time, leading to ongoing prudent discussions about the safety of OVs. It has been shown that OVs eliminate tumor cells while also unintentionally affecting normal cells, resembling the adverse effects seen with chemotherapy (54). In light of these concerns, a variety of studies have illustrated that OVs can be engineered into attenuated viruses with improved targeted specificity. For example, the deletion of the γ34.5 gene inhibits oHSV-1, an OV, from infecting normal neurons (55–57). The OV VG161, developed by Virogin Biotech Canada Ltd., helps maintain the target's susceptibility to drugs such as acyclovir, effectively controlling its virulence and safety in clinical uses an essential advantage concerning safety (58–60). Additionally, Yiye Zhong et al. have crafted an OV that contains targets for neuron-specific microRNA-124 and granulocyte-macrophage colony-stimulating factor, significantly enhancing its safety concerning neurons while minimally affecting its replication potential (61).

Despite the tumor cell-specific engineering, there remains a risk of off-target effects and unforeseen toxicities arising from genetic modifications. Moreover, complications like viral mutation, evolution, recombination, cytotoxic gene products, and the transmissibility of the virus may occur (62). Based on these observations, several studies have pinpointed certain substances that can alleviate these risks when paired with OVs. For instance, Alba et al. found that combining Ad5-hexon with coagulation factor X (FX) facilitates liver transduction. They also created a genetically FX-bound ablative Ad5-hexon vector for alleviating symptoms (63).

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1.4. Improve targeting

The capability of OVs to selectively infect tumor cells while sparing normal cells is regarded as a promising strategy for the safe and efficient treatment of cancer (64). Despite numerous clinical trials validating the excellent targeting prowess of OV therapy, certain limitations persist that necessitate resolution. There are four main modification strategies available to boost the tumor-targeting potential of OV. The first strategy involves enhancing the affinity and binding capability of the virus towards the overexpressed receptor on the surface of tumors. By engineering OVs to specifically recognize receptors that are heightened in tumors, their targeting can be refined. For example, Yang et al. indicated that a chimeric adenovirus, consisting of Ad35 knobs and axles binding to Ad5, improves targeting and oncolytic effects across a range of cancers by utilizing CD46 as a differential receptor (65). Conversely, understanding membrane-associated tumor-associated antigens (TAAs) has allowed researchers to fully engineer a virulent OV with selective tropism for tumor cells by substituting viral glycoproteins involved in cell entry with antibody fragments targeting specific TAAs like HER2, PSMA, and MSLN (66, 67). Tomer Granot et al. leveraged Sindbis virus (SV) vectors to deliver TAAs and enhance viral targeting. They revealed that the efficacy of SV/TAA therapy resulted not from direct tumor cell targeting but from the transient expression of TAAs in lymph nodes draining the injection site. This process triggered early T-cell activation, followed by a substantial influx of NKG2D-expressing, antigen-specific cytotoxic CD8 T cells into the tumor. Ultimately, this resulted in the generation of long-lasting memory T cells, which provided protection against rechallenge with tumor cells (68). Furthermore, certain CD molecules that are overexpressed in malignant tumors are valuable targets for constructing targeted viral vectors to facilitate OV homing. For instance, CD20-positive non-Hodgkin lymphoma (NHL) has been used to develop CD20-targeted MV vectors for lymphoma targeting with encouraging outcomes (69). The escalating identification of tumor-specific receptors or antigens will yield more precise strategies for enhancing OV targeting.

The second approach involves boosting targeting precision by utilizing the unique characteristics of tumor cells. For instance, OV can enhance its targeting selectivity by modulating genes or signaling pathways within tumor cells. Chen et al. accomplished this by inhibiting the antiviral response of cells through blocking the alpha subunit of the IFN receptor using B18R (70). Additionally, overexpressing certain genes or proteins in tumor cells can also bolster OV's targeting precision. By substituting the endogenous E1A promoter with GOLPH2 (also known as GP73), E1B 55kD Ad deletion leads to significant cytotoxic effects in prostate cancer stem cell (CSC)-like cells through GP73 overexpression and exhibits more potent oncolytic effects (71). Moreover, equipped with a full-length antibody targeting CD47, oHSV is adept at specifically homing in on GBM and ovarian carcinoma (72,73). Additionally, the IL-12-loaded oHSV considerably boosts IL-12 concentrations within the tumor microenvironment (TME) and prompts the infiltration of effector T cells, NK cells, and antigen-presenting cells (APC) into tumors to amplify anti-tumor efficacy (74).

Furthermore, the incorporation of differentially expressed microRNAs into oncolytic viruses (OVs) through transgenic methods represents an alternative approach to improve targeting specificity. In essence, OVs can function as carriers for the selective delivery of microRNAs aimed at regulating cancer development (75). MicroRNAs, which are short non-coding RNA sequences, are pivotal in modulating gene expression by interfering with the translation of target mRNAs. The dysregulation of these microRNAs has been linked to tumor progression, invasion, angiogenesis, and metastasis in multiple cancer types (76,77). The OV vector effectively delivers pre-tumor suppressive miRNA into cancer cells. Specifically, the precursor interference microRNAs dissociate in the cytoplasm and undergo cleavage to produce mature microRNAs that subsequently lead to the inactivation of target mRNAs. Oncolytic adenovirus (OAd) carrying the tumor suppressor gene miR-143 promotes apoptosis and curtails tumor growth by downregulating KRAS expression in HCT116 xenografts (78). In a similar vein, the oncolytic vesicular stomatitis virus, when serving as a delivery vehicle, shows comparable anti-tumor effects in osteosarcoma cells with miR-143 (79). To further refine oncolytic specificity while reducing toxicity, Yang et al. have incorporated miR-34a targets into both the 5' untranslated region (UTR) and 3' UTR of the virus genome, creating a dual-targeting engineered variant of oncolytic Coxsackievirus B3 that maintains nearly full oncolytic activity but exhibits lower toxicity (80).

Lastly, employing bispecific or Tri specific T cell adaptors (BiTE or TriTE) molecules is another strategic avenue for modifying oncolytic viruses (OVs). BiTE is a recombinant protein that comprises two single-chain variable fragments (scFvs) that bind to a T cell surface molecule and a cancer cell antigen, respectively. Arming OVs with a BiTE effectively addresses their extremely short

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serum half-life, while the next-generation TriTE contains three domains, such as CD3 × dual tumor antigens or tumor antigen × CD3/CD28. This technique involves fusing two distinct ScFv antibodies, allowing each fragment to attach to both T cell and malignant cell surfaces. Consequently, this strategy lessens the potential for immune evasion stemming from antigen loss and minimizes adverse effects associated with targeted detumescence, ultimately enhancing tumor targeting (81). Chen et al. showcased that CS1-NKG2D bispecific antibodies augment immune synapses between CS1+ multiple myeloma (MM) cells and NKG2D+ cytolytic innate as well as antigen-specific effector cells. This activation leads to more effective clearance of multiple myeloma (82). Numerous other OVs bearing bispecific antibodies have demonstrated distant effects through T-cell-mediated activation and tumolysis. Furthermore, FAP and EGFR have been shown to bolster T cell activation and accumulation in the tumor milieu, thereby enhancing anti-tumor efficacy (83–85). Additionally, OV-encoded bispecific antibodies promote T cell infiltration into the TME, showcasing anti-tumor activity by amplifying T cell activation and cytokine production. Immune cold tumors, characterized by a deficit in immune cell infiltration and activity, are typically resistant to immunotherapies. By fostering T cell infiltration and activation, OV-encoded bispecific antibodies assist in transforming these immune cold tumors into immune hot tumors, which have a higher abundance of active immune cells and exhibit greater responsiveness to immunotherapeutic interventions (86, 87).

2. Combination therapy

2.1. OV combined with chemotherapy

Chemotherapy, recognized as a fundamental approach for cancer management, induces DNA damage by inhibiting essential processes such as DNA synthesis, mitosis, and cell division. Recent clinical trials have showcased the potential synergistic interaction of combining chemotherapy with OVs, offering a promising alternative in cancer therapy. Cyclophosphamide (CTX), an alkylating chemotherapeutic compound, was the first drug combined with OVs. CTX undergoes metabolic activation into cytotoxic agents within tumor cells, triggering tumor cell death. Moreover, it also acts as an immunosuppressive agent, exerting effects on both innate and adaptive immunity. Studies have indicated that early-stage low-dose CTX combined with Oad therapy can stimulate TH-1 immunity by lowering regulatory T cells (Treg cells), converting the TME from a ‘cold’ state to a ‘hot’ state, thereby improving anti-tumor efficacy (88).Talimogene laherparepvec (T-VEC) is an oncolytic virus proposed to enhance the response of triple-negative breast cancer (TNBC) to neoadjuvant chemotherapy (NAC). The rationale behind combining T-VEC with chemotherapy stems from the observation that TNBC tumors with significant pre-existing lymphocytic infiltration respond more positively to neoadjuvant therapy. Preclinical investigations have evidenced a synergistic effect between oncolytic viruses and chemotherapy, further validating this combination strategy. In a Phase II clinical trial of T-VEC mixed with NAC in TNBC, this combination treatment improved the response rates of TNBC tumors injected with T-VEC during NAC. This provides a theoretical basis for continued exploration of T-VEC alongside NAC for TNBC therapy (89).Temozolomide (TMZ), an alkylating agent and immunomodulator, is widely utilized in tackling various solid tumors including glioma and melanoma. TMZ has been demonstrated to improve the replication and tumor lysis effects of OAds in lung cancer cell lines, but not in non-cancerous cells; this enhanced anti-tumor activity may partially stem from the induction of autophagy in these lung cancer cells (90).

Furthermore, gemcitabine (GCB), a nucleoside analogue antimetabolite chemotherapy drug, is extensively employed either independently or in tandem with other anticancer agents across various cancers (91). In one investigation, scientists used replicative adenovirus-mediated double suicide gene therapy (Ad 5-DS) alongside the standard intravenous GCB at prescribed dosage levels; this dual approach was found to be safe and well-tolerated among patients (92). These findings highlight the critical significance of understanding the interaction between oncolytic viruses (OVs) and anti-cancer chemotherapeutics in enhancing the formulation of combination therapies for cancer treatment.OV combination therapy transforms the tumor microenvironment (TME). Administering tumors with OVs alone or in conjunction with radiotherapy, chemotherapy, cellular therapy, and immune checkpoint inhibitors (ICIs) modifies the immune environment of the tumor, shifting it from a "cold tumor" to a "hot tumor," with the reshaping effect being more pronounced in combined therapies. Additionally, OV combination therapy diminishes the tumor infiltration of immunosuppressive cells (such as Treg cells and M2-polarized macrophages), while promoting the expansion of activated immune cells (like CAR-T cells, CAR-NK cells, TILs, NK cells, M1-polarized macrophages, and dendritic cells), thereby exerting a more powerful anti-tumor response. Nevertheless, subsequent research has disclosed that chemotherapy might negatively affect the efficacy of oncolytic herpes simplex virus (oHSV) immunoviral therapy. TMZ chemotherapy currently stands as the standard

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treatment for glioblastoma multiforme (GBM); however, when TMZ is used in conjunction with G47Δ-IL 12 for treating tumor-bearing mice, it counteracts the positive effects of G47Δ-IL 12 and negatively influences intratumor T cells, macrophages, and spleen cells (93). Meanwhile, there remains sparse clinical evidence backing the combination of OVs and chemotherapy; thereby further experiments and clinical studies are necessary to verify its safety and effectiveness.

2.2. OV combined with radiotherapy

Radiotherapy is the most effective cytotoxic approach for localized solid tumors (94). Its underlying principle involves irradiating the DNA of tumor cells, inducing DNA damage and halting their endless proliferation until death ensues. It primarily includes alpha, beta, gamma rays, as well as various types of X-rays. Radiotherapy is commonly applied in combination with chemotherapy to improve patient survival (95). Nevertheless, the substantial adverse effects of chemoradiotherapy and the variability of therapeutic outcomes are prompting researchers to investigate novel combination therapies.The joint application of OV and radiotherapy not only displays a synergistic effect but also has shown enhanced therapeutic outcomes in several studies. GBM, the most prevalent primary malignant brain tumor (96), is identified as a "cold tumor" in immunology due to limited lymphocyte infiltration and unresponsiveness to current immunotherapeutic approaches. Consequently, researchers are actively seeking innovative methods to convert “cold” tumors into “hot” tumors, thereby creating new opportunities for cancer therapy (97) (Figure 2). One research demonstrated that GBM mice treated solely with OVs achieved a 13.3 percent curative rate, while those receiving radiation alone had a curative rate of 21.4 percent. However, with the integration of both therapies, mice with brain cancer displayed an impressive curative rate of up to 66.7 percent. The success of combination therapy is further emphasized through the extended survival time seen in these mice. The median survival span for the control group (PBS group) was merely 29 days, which rose to 39.5 days in the radiotherapy group and 41 days in the viral therapy group. Notably, when radiotherapy was paired with viral therapy, the median survival time reached beyond 76 days. Further exploration revealed that this extraordinary impact of combination therapy stemmed from a significant increase in CD3+ cell counts and proportions of CD3+ T/CD8+ T and CD8+ T/Treg cells in mice (98).

Additionally, merging OVs with radiotherapy may amplify the "distant site effect" of radiotherapy (the regression of untreated metastases away from the irradiated area) (99), possibly due to radiotherapy's capacity to facilitate OV replication and enhance cancer cell sensitivity (100). Moreover, OVs can bolster the effectiveness of immune checkpoint inhibitors when synergized with radiotherapy. A study featuring Newcastle disease virus (NDV) revealed that combining NDV with radiotherapy and PD-1 antibody extended mouse survival and significantly reduced tumor growth compared to groups receiving solely PD-1 antibody or combinations of PD-1 antibody/NDV or NDV/radiotherapy (101).Research into the combination of OVs and radiotherapy remains limited. However, existing investigations have uncovered considerable potential in this combined therapy, which is anticipated to improve efficacy and safety in tumor management, bringing hope to an increased number of patients.

2.3. OV integrated with cell therapy

2.3.1. OV integrated with CAR-T

In recent times, the implementation of CAR-T cell therapy has showcased remarkable success in scenarios where traditional cancer therapies fall short, especially for challenging hematological cancers like leukemia, myeloma, and non-Hodgkin B-cell lymphoma (102). This method distinctly focuses on targeting and obliterating tumor cells, yielding substantial advancements. Furthermore, there has been a surge in clinical trials employing CAR-T cells for solid tumor treatments, with notable achievements in certain solid tumor types. For example, GBM displays high levels of IL-13Rα2, while normal brain cells exhibit lower levels. This trait renders IL-13Rα2 an appealing target for CAR-T cell therapy against GBM. Brown et al. (NCT02208362) infused IL-13Rα2-CAR-T cells directly into the excised tumor cavity via intracranial delivery, witnessing regression of all intracranial and spinal tumors that lasted for 7.5 months (103). Additionally, a Phase I clinical trial (NCT03182816) showed the safety and viability of treating patients with advanced relapsed/refractory non-small cell lung cancer (NSCLC) utilizing epidermal growth factor receptor (EGFR) CAR-T cells produced through the piggyBac transposon system instead of viral methods (104). However, in spite of these progressions in CAR-T cell therapy for solid tumors, numerous challenges and complications persist, including tumor heterogeneity, antigen escape by tumor cells, transportation barriers encountered by CAR-T cells at the tumor site, and difficulties in invasion and expansion within the TME itself (105).

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Significantly, the combination of OVs with CAR-T cell therapy presents great potential for enhancing the efficacy of CAR-T cells in solid tumors and addressing associated obstacles. Presently, there are four OVs approved globally for cancer therapy, with T-VEC being the only OV sanctioned by the Food and Drug Administration (FDA) that has exhibited favorable safety and efficacy in clinical trials (100). Moreover, successful CAR-T cell products are already available in the market, providing a solid foundation for merging OV and CAR-T therapy. Additionally, OVs possess the capability to convert a "cold" tumor into a "hot" one. In a "cold" tumor, immunosuppressive cells like Treg cells and M2-polarized macrophages infiltrate surrounding tissues extensively, while immune cell infiltration remains insufficient and their function suppressed, allowing tumor cells to elude immune system assaults. Conversely, a "hot" tumor characterized by ample infiltration of active immune cells is associated with high response rates to immunotherapy (81); OVs can effectively remodel such an environment .

Furthermore, multiple preclinical studies have illustrated various enhancements achieved by combining CAR-T cells with OVs. For instance (1): Enhanced transportation and persistence of CAR-T cells: Researchers infected DS CAR-T cells with VSV and reovirus as delivery agents to target tumors; these OVs replicated within tumor cells, resulting in the expansion of the DS CAR-T cell population while rupturing tumor cells. Moreover, systemic activation by reovirus reactivated virus-specific CAR-T cells, yielding long-term remission exceeding 60 days in six out of seven tested mice; this approach also significantly increased the in vivo persistence of CAR-T cells (106) (2). As mentioned earlier, OVs engineered with multiple cytokines or chemokines have been developed to amplify the therapeutic impact of CAR-T cell therapy. These include TNFα (107), IL-21 (108), IL-7 (109), CXCL11 (110), among others. Genetically modified OVs can generate a wider spectrum of chemokines that facilitate the infiltration of cytotoxic T cells, DCs, macrophages, and other immune cells into the TME for enhanced anti-tumor effects (111). Wang et al. assessed the utilization of CXCL11-armed OAds to improve CAR-T cell infiltration in GL261 GBM models and reprogram the immunosuppressive TME. This technique resulted in increased infiltration of CD8+ T lymphocytes, NK cells, and M1-polarized macrophages, while diminishing myeloid suppressor cells (MDSCs), Tregs, and M2-polarized macrophages. The study illustrated that combining CXCL11 with oAd within the tumor environment led to a sustained anti-tumor response (38) (3). OV-mediated targeted delivery of surface antigens in tumor cells (112). Anthony K Park and colleagues created an oncolytic VV that expresses a non-signal-intercepting CD19 protein (CD19t), enabling precise delivery of CD19t to the surface of solid tumor cells. This viral infection triggers antigen-specific CD19-CAR-T cell-mediated antitumor activity, resulting in both viral release from dying tumor cells and the expansion of CD19t expression in the tumor (113). Furthermore, an oHSV (oHSV T3011) was engineered to deliver truncated CD19 and BCMA double antigens in combination with either CD19-specific CAR-T (CAR-TCD19) or BCMA-specific CAR-T (CAR-TBCMA) cell therapy, culminating in a synergistic antitumor response. oHSV T3011 is a recombinant herpes OV that expresses IL-12 and anti-PD-1 antibodies, contributing to improved TME inhibition and enhanced overall anti-tumor activity (114).It is important to recognize the conflicting mechanisms present in the combined therapy of OV and CAR-T. The VSV-IFNβ triggers the release of type I interferon, which in turn elevates the levels of inhibitory receptors LAG3, PD-1, and TIM3. This phenomenon is especially noticeable in transduced cells and correlates with the CAR expression level. Thus, when used alongside CAR-T therapy, IFNβ may hinder the antitumor efficacy of CAR-T cells by activating the CAR signaling pathway to boost CAR expression and altering inhibitory receptor expression to limit the active state of CAR-T cells (115).

2.3.2. OV united with CAR-NK

NK cells, key components of the innate immune system, exhibit a unique cytotoxic mechanism distinct from adaptive T lymphocytes and can directly destroy target cells without previous antigen sensitization (116). NK cells showcase a wide variety of activating and inhibitory receptors that govern their function. Activating receptors include NCR, CD16, NKG2D, DNAM1, and signaling lymphocyte activation molecule (SLAM), whereas inhibitory receptors encompass immunoglobulin-like receptors (KIRs), NKG2A, and leukocyte immunoglobulin-like receptors (LILRs) (117,118). These receptor families are crucial for mediating the immune response of NK cells towards tumors. The advent of CAR technology has revealed significant promise in cancer immunotherapy by augmenting the recognition and destruction abilities of immune cells (102,119). At present, five CAR-T cell therapies have received FDA approval for treating B-cell-derived lymphoma, leukemia, and hematological malignancies like multiple myeloma (120). Nonetheless, due to the limitations of CAR-T cells in addressing solid tumors—such as difficulties infiltrating tumor tissue, absence of suitable targets, and associated toxicity (102) . it is essential to develop new strategies and technical methods to overcome

these hurdles and improve the efficacy and practicality of CAR-T cell therapy for solid tumors. CAR-NK cell therapy may offer a compelling alternative. Unlike CAR-T cell therapy, NK cells can be sourced from various origins including peripheral blood, umbilical cord blood, induced pluripotent stem cells, and NK cell lines (121). This enables the large-scale production of CAR-NK cells with considerably shorter treatment time. Moreover, CAR-NK cells do not face restrictions from histocompatibility complex (MHC) on target cell surfaces and demonstrate a wider range of anti-tumor effectiveness. A Phase 1/2 clinical trial (NCT03056339) involving the injection of CD19 CAR-NK cells into 11 patients with relapsed or refractory CD19-positive cancers indicated that this approach was effective in most patients without any notable release of inflammatory cytokines such as IL-1 or IL-6. Additionally, there was no correlation observed between this treatment and the onset of cytokine release syndrome, neurotoxicity, or graft-versus-host disease (122).

Given the remarkable success of combination therapy utilizing CAR-T cells and OVs, researchers have suggested integrating OVs with CAR-NK cells. As tumor cells infected with OVs disintegrate and burst, they express ligands associated with cellular stress like MICA/B proteins and ULBP family proteins, thereby broadening the recognition targets for CAR-NK cells. This results in more effective elimination of remaining tumor cells and a more thorough clearance effect (119). Xilin Chen et al. identified that EGFR was abundantly expressed on breast cancer cell surfaces, and employing EGFR-CAR-NK-92 cells alone or in coordination with oHSV-1 led to significant destruction of cancer cells. This combination yielded a more effective killing impact compared to monotherapy and considerably prolonged survival in tumor-bearing mice, establishing it as a viable treatment for breast cancer brain metastases (123). Recently, several GBM cell lines infected with the herpes simplex type I virus (OV-IL15C), expressing a human IL-15/IL-15Rα sushi domain fusion protein, secreted soluble IL-15/IL-15Ra complex to enhance NK and CD8+ T cell survival rates. When paired with EGFR-CAR-NK cells, this synergy increased the longevity of CAR-NK cell activity, effectively suppressing tumor expansion and significantly boosting survival rates (31).

2.3.3. OV paired with TILs

TILs generally consist of clusters of T cells and B cells (124, 125), with the type and persistence of these immune cells in tumors linked to cancer patient prognosis (124). Research findings have shown that OV treatment of tumors positively influences TIL infiltration and activity, thereby affecting tumor progression. The combination of OV with TIL may produce lasting antitumor effects by amplifying TIL activity. For example, modified OVs based on OX40L and IL-12 present a promising therapeutic strategy for solid tumors. By infecting tumor cells, this specific OV can provide essential signals to activate T cells while transforming tumor cells into artificial antigen-presenting cells (126). Consequently, it not only stimulates T cell activation but also enhances their cytotoxic potential. Notably, significant tumor reduction and long-term immune memory effects were documented when combined with TILs in tumor models (126).This indicates that this method possesses promise for sustained and efficient management of solid tumor proliferation and metastasis. With a more thorough grasp of the pertinent experiments, we can obtain a deeper insight into how OX40L and IL-12 based modified OVs mechanistically impede solid tumor proliferation while refining curative rates. Ultimately, this forward-looking tactic provides fresh optimism in the domain of cancer treatment as it could emerge as a fundamental element in upcoming personalized cancer management approaches (126). Another investigation showcased that the amalgamation of OAd carrying human IL-2 (hIL2) and TNFα, along with TILs, displayed prolonged effectiveness, raised the incidence of both CD4 and CD8 TILs in vivo, and boosted splenocyte proliferation ex vivo, implying that the cytokines were crucial for T cell endurance and growth, markedly enhancing the efficacy of TIL therapy (127). TNFα and IL-2 are integrated into OAds to selectively target cancer cells via tumor-specific promoters and knob protein swapping, thereby improving cancer cell entry (128). Furthermore, employing TILs as vehicles to transport the virus to tumors can amplify both the concentration and effectiveness of the virus at the tumor site (128). Meanwhile, OV can exert a more potent anti-tumor effect by boosting TIL infiltration and augmenting TIL functionality.

2.3.3.1. Amplified TIL infiltration

Engineered OVs have the capability to bolster TIL infiltration during disease treatment. Genetically altered herpetic virus type 1 (HSV-1) G207 has been utilized in pediatric patients with high-grade glioma for therapeutic outcomes. By triggering an immune response and drawing cells through G207 infection, it is feasible to transform “cold” tumors into “hot” tumors, thereby increasing

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the number of TILs and enhancing treatment effectiveness (129) (Figure 2). In the context of GBM treatment using G47Δ, a third-generation oncolytic HSV-1 with triple mutations, a notable increase in CD4+ and CD8+ lymphocyte populations was observed as they swiftly infiltrated tumor tissue. The sustained rise in these lymphocytes not only persisted over time but also showed a strong correlation with improved treatment results (130). By genetically modifying the bovine pox virus to express IL-7 and IL-12, it is possible to heighten the sensitivity of anti-PD-1 and CTLA4 antibody therapy. This alteration also leads to an uptick in the expression of major histocompatibility complex II (MHC II) in antigen-presenting cells, thereby modifying the immune landscape and systemic immune response within the TME. Consequently, there is an increase in the influx of CD8+ T cells, CD4+ T cells, NKT cells, and NK cells into the tumor site (131). The introduction of adenovirus-mediated n-terminal gasdermin domain expression instigates pyroptosis in tumor cells while attracting TILs into the brain. This mechanism heightens their infiltration and subsequently enhances anti-tumor efficacy (132). Delta-24-RGD OAd directly lyses tumor cells and activates anti-tumor immune responses, fostering invasion by T cells (133). OBP-502 is a telomerase-specific OAd that releases immunogenic cell death markers like adenosine triphosphate (ATP) and high mobility group box 1 protein (HMGB1) upon treatment. This release draws CD8+ lymphocytes while inhibiting Foxp3 positive lymphocyte infiltration into tumors, resulting in anti-tumor effects (134). OVs modified with glycosylation-PEGX can enhance selective infection and destructive capability against tumor cells. Additionally, they boost infiltration of T cells and NK cells, thus amplifying anti-tumor immune reactions (135). Treatment with oncolytic HSV-1 leads to the regression of lymphoma-guided tumors associated with substantial invasion of antigen-specific CD8+ T cells (136). Furthermore, MSC-mediated delivery of OAds to osteosarcoma encourages greater infiltration of TILs (137).

2.3.3.2. Enhancement of TIL function

The application of OV or modified OV treatment for relevant afflictions may facilitate the enhancement of TIL activation, metabolic capacity, and durable anti-tumor responses. Researchers have genetically fine-tuned the OV to incorporate humanized PD-1 single-chain antibodies (hPD-1scFv) to bolster its effect on TILs (20). Modified OV therapy has demonstrated an intensified anti-tumor effect on CD8+ T cells, leading to increased infiltration of effector CD8+ T cells into tumors and establishment of memory CD8+ T cells, while concurrently diminishing associated depletion of CD8+ T cells (20). The expression of leptin by engineered OVs within tumor cells can facilitate metabolic reprogramming of TILs, thereby boosting their metabolic activity and aiding disease treatment (138). Recently, it has been revealed that oHSV can transform the immune microenvironment in pancreatic ductal adenocarcinoma (PDAC) by enhancing immune activity. Through scRNA-seq and multicolor fluorescence activated cell sorting analysis, researchers noted a significant decline in tumor-associated macrophages (TAMs), particularly anti-inflammatory macrophages, following oHSV treatment. Moreover, there was a rise in the proportion of TILs, including activated cytotoxic CD8+ T cells and Th1 cells (139).Tumor cells infected with CCL5-modified oncolytic viruses (OVs) demonstrated the ability to generate CCL5 without impairing their infectivity, facilitating the accumulation of NK cells and enhancing the therapeutic effect (140). Vv-scfv-tigitt, a engineered OV harboring immune checkpoint inhibitors (ICIs), has been shown to stimulate T cell infiltration and boost CD8+ T cell activation in tumor models, leading to the establishment of enduring immunity (141). The CD40L-armed oncolytic HSV amplifies T cell cytotoxicity and encourages the activation of dendritic cells (DCs) and T cells within the tumor microenvironment (TME) by promoting the expression of tumor-associated antigens (TAAs) and increasing the tumor cells' immunogenicity. This strategy presents promising potential as a treatment method for pancreatic ductal adenocarcinoma (PDAC) (142). The OX40L-armed OV (OV-mOX40L) reduces the population of Foxp3+ regulatory T cells (Tregs) while activating CD4+ and CD8+ T cells through engagement with OX40L. Furthermore, it diminishes exhausted cytotoxic T lymphocytes (CTLs) and fosters T cell activation, leading to enhanced release of pro-inflammatory cytokines such as IFNγ. As a result, this adjusts the immunosuppressive TME into a more immunologically vibrant state (143). The combined use of an OV and anti-PD-1 substantially increases the levels of CD8+ and CD4+ T cells, activates the central immune system, and improves therapeutic outcomes (144). Adenoviruses possess the capability to serve as tools for immunotherapy through the stimulation of tumor-infiltrating lymphocytes (TILs) by delivering TNFα and IL-2. Findings suggest that adenoviruses can reshape cytokine responses and activate TILs within the TME, thereby enhancing their anti-tumor response (145).

2.3.4. MSCs as Vectors for OVs

The application of OVs for therapeutic purposes may trigger an immune response, which could hinder viral dissemination and

infection, ultimately reducing treatment effectiveness. Additionally, the lack of specific targeting in viral delivery may expose non-target tissues to infection, resulting in undesirable effects and toxicity. At the same time, existing immune tolerance can obstruct the inter-tumoral movement of the virus, representing a challenge in the treatment of metastatic diseases, as it is necessary to address both injected and distant tumors (146). To address these challenges in OV delivery, researchers are actively pursuing a variety of exploratory studies.MSCs exhibit low immunogenicity, inherent affinity for tumors, multi-lineage differentiation capabilities, excellent migration abilities (147), homing potential, and various therapeutic attributes. These fundamental characteristics render them ideal candidates for drug delivery and OV vectors (148, 149). Utilizing MSCs as carriers for OVs in tumor therapeutics can improve the virus delivery efficiency, boost the oncolytic effect on cancer cells, enable precise drug targeting, and reduce systemic side effects (150).

Researchers have enhanced the targeting capabilities of MSCs and modulated the drug release timing to increase the effectiveness of oncolytic adenoviruses (OAds), allowing them to act as both a source and vector for OAds. They further assessed the bioavailability of the virus post-MSC injection. This method significantly augmented viral output, tumor targeting, timely viral release at tumor sites, and the oncolytic effect of the adenovirus. Such findings indicate that engineered MSCs can significantly improve the anti-tumor effects of oncolytic viruses without compromising safety, potentially broadening the clinical use of oncolytic adenoviruses (151). In a mouse model of pulmonary melanoma, MSCs delivered an IL-15-carrying tumor-lytic MYXV construct, leading to sustained viral presence and increased accrual of NK cells and CD8+ T cells. This approach converted the tumor into a “hot tumor” and led to notable regression (152) (Figure 2). Another study utilized neural stem cells (NSCs) to encapsulate CF33 for enhanced delivery in a cisplatin-resistant model of peritoneal ovarian metastasis, proving to be a more effective alternative than traditional methods (153). The MYXV, which carried the LIGHT (TNFSF14) gene, was pre-loaded into adipose-derived mesenchymal stem cells (ADSCs) and applied in pancreatic cancer treatment in mice. Results indicated that the virus, when combined with carrier cells, could be effectively deployed to pancreatic cancer sites, allowing cell survival while efficiently eliminating pancreatic cancer cells, leading to tumor reduction and extended survival time in treated mice (154). Moreover, in comparison to standard OV treatment for colorectal cancer, combination therapies utilizing MSCs as carriers and prodrug activation showed improved therapeutic efficacy and safety, along with tumor specificity and innovative benefits through prodrug activation (155). Thus, employing MSCs as carriers for transporting OVs represents a novel strategy in tumor virotherapy, possessing promising prospects for application.

2.4. OV Plus ICIs

Immune checkpoint inhibitors (ICIs) are a form of immunotherapy that has gained extensive interest in recent years for their potential in tumor treatment by targeting and inhibiting immune checkpoints, such as CTLA-4 and PD-1, to spur the immune response (156).Nonetheless, research has shown that ICIs might not be appropriate for every patient, as some endure significant negative effects during their treatment (157). A mere fraction of patients secure effective disease management after ICI therapy. Additionally, ICIs have proven ineffective against immunologically "cold" tumors, which are marked by scarce levels of TILs (158). As a result, many researchers are diligently looking into agents that can stimulate the transformation of "cold" tumors into "hot" tumors when paired with ICI treatment to address the illness. OVs have been demonstrated in various studies to provoke anti-tumor immune responses, enhance the effectiveness of current cancer treatments, and modify unresponsive TME, thus converting "cold" tumors into "hot" tumors and increasing their responsiveness to checkpoint blockade immunotherapy (159).

Therefore, OVs represent an ideal complement to ICIs. Sachin R Jhawar et al. explored the effectiveness of this combination therapy utilizing in vitro mouse models, human cancer cell lines, and murine skin cancer models. After an initial treatment of OV and radiotherapy, ICIs were introduced later to create a triple therapy consisting of OV, radiotherapy, and ICI. The findings indicated that this triple therapy effectively hindered tumor growth and extended survival. Furthermore, the researchers noted that a PD-1 refractory patient suffering from squamous cell carcinoma of the skin enjoyed an extended duration of disease control and survival following triple therapy with OV, radiotherapy, and ICI, with the tumor showing no substantial progression for 44 months. The reasoning behind these results is that OV in conjunction with radiotherapy and ICI can not only convert immunologically "cold" tumors into "hot" tumors but also enhance the infiltration of CD8+ T cells (160). ONCOS-102 is a meticulously engineered Ad vector that has undergone thorough preclinical evaluations in the past few years (161) and has progressed to Phase I clinical trial

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stage (NCT03003676) in combination with the ICI pembrolizumab. The Phase I trial, which involved 12 patients with advanced or unresectable solid tumors, confirmed that ONCOS-102 showed no dose-limiting toxicity and reached the maximum tolerated dosage compared to the pre-treatment level. Examination of tumor biopsies post-combination therapy revealed a notable increase in CD3+ T cells infiltration (5.9-fold) and CD8+ T cells (4.0-fold). Among the 10 patients assessed via PET/CT scans after 3 months, disease control was recorded in 4 patients (40%), with a median overall survival of 9.3 months (162).

Beyond demonstrating effectiveness, numerous investigations have validated the safety of pairing OVs with ICIs. In a study conducted by Targovax ASA et al., where ONCOS-102 was coupled with pembrolizumab in treating PD-1-resistant advanced melanoma patients, treatment tolerance was thoroughly established. Among the 20 patients in the study, an objective response was achieved in seven cases, along with lesion regression at non-injection sites - indicating a systemic anti-tumor effect arising from local ONCOS-102 administration. Sequential biopsies conducted on injected tumors displayed significant CD8+ T cell and CD4+ T cell infiltration following ONCOS-102 administration. Hence, these results imply that further inquiry into the combination therapy involving ONCOS-102 and PD-1 inhibitors shows promise for treating PD-1-resistant melanoma (163). Professor Gelareh Zadeh's research team at the University of Toronto, Canada, published their Phase I/II clinical study outcomes in Nature Medicine, demonstrating that the combination of OV therapy DNX-2401 with pembrolizumab for recurrent GBM treatment resulted in a 52.7% one-year survival rate, with some patients even surviving beyond 60 months of therapy. Two patients achieved a complete response (CR), while three patients attained a partial response (PR). With an overall response rate (ORR) of 10.4% (90% CI: 4.2-20.7%) in the intention-to-treat cohort and 11.9% in patients receiving the maximal trial dose (declared dose), this combination treatment strategy is anticipated to emerge as a novel therapeutic option for recurrent GBM (164). Additionally, Hemminki's team recently reported on two OVs expressing TNFα and IL-2 respectively. In melanoma studies performed on mice, they discovered that when paired with anti-PD-1 antibodies, the virus importantly amplified the numbers of CD8+ T cells in comparison to using the virus alone; moreover, the combination of OV with ICIs considerably curtailed tumor progression and extended survival relative to utilizing either the virus or ICIs independently. Intriguingly, merging NDV with anti-CTLA-4 antibodies also displayed synergistic effects in mouse tumor models by boosting CD8+ T cell infiltration while hindering tumor growth and prolonging survival (165). T-VEC is a genetically modified oHSV-1 (166). In a single-center, single-arm, Phase II study, 24 resectable patients with stage IIIB-IVM1a melanoma who underwent intrafocal T-VEC injection alongside systemic nebuliuzumab exhibited a major pathological complete response rate of up to 45%. The primary mechanism behind this is that the combination of T-VEC and ICI alters the immune cell infiltration, transforming "cold" tumors into "hot" tumors, thus enhancing the immune response (167).In a preliminary report on another clinical trial that has initiated investigations into C-REV combined with the PD-1 inhibitor nivolumab (NCT03259425) for patients with resectable stage IIIB, IIIC, or IVM1a melanoma, individuals treated with the duo of C-REV and nivolumab exhibited greater T cell infiltration compared to those receiving treatment alone in earlier clinical evaluations (168).To summarize, the synergistic use of OVs and ICIs has yielded outstanding outcomes by fostering lymphocyte infiltration and significantly extending survival durations. These results firmly bolster the idea that OVs represent optimal adjunctive treatments for ICIs.

2.5. OV Combined with ultrasound-targeted therapy

Ultrasound-targeted therapy is a technique that utilizes the inherent properties of ultrasound to accurately identify and treat tumors. Its core principle revolves around the cavitation and thermal effects of ultrasound to disrupt tumor tissues while employing acoustic radiation force to augment microbubble-mediated ultrasound-targeted drug delivery systems. This amplifies drug concentration at the tumor site and improves therapeutic effectiveness. Furthermore, ultrasound can temporarily boost the permeability of tumor blood vessels, facilitating the infiltration of drugs or gene carriers, subsequently enhancing treatment efficiency (169). Given its non-invasive characteristics, precise targetability, and minimal side effects, ultrasound-targeted therapy has shown immense potential in the management of various solid tumors (170–172).The fusion of ultrasound-targeted therapy with OVs opens new pathways for cancer therapy. OVs can selectively infect and eliminate tumor cells, while ultrasound-targeted techniques can enhance the effectiveness of infection and the precision of OV distribution (173). For example, Bazan-Peregrino et al. examined how ultrasound-induced cavitation facilitates the extravasation and dissemination of a potent breast cancer-selective oncolytic adenovirus, AdEHE2F-Luc, to tumor regions distant from vascular structures. Inertial cavitation proved to be more efficient than

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stable cavitation in augmenting the delivery, distribution, and efficacy of the oncolytic virus (174). Moreover, utilizing microbubble carriers to encapsulate OVs and employing ultrasound-guided targeted administration guarantees effective release and infection of OVs at the tumor site. Greco et al. illustrated that ultrasound-targeted microbubbles/Ad.mda-7 (a replication-incompetent adenovirus expressing melanoma differentiation–associated gene-7/interleukin-24) significantly diminished tumor load in xenografted nude mice.

The microbubbles ruptured under ultrasound, discharging OVs directly into tumor cells and enhancing the oncolytic impact (175). Additionally, the mechanical effects of ultrasound can elevate the permeability of tumor cell membranes, promoting OV entry and broader dissemination within the tumor. For instance, Okunaga et al. discovered that ultrasound heightened the efficiency of HSV-1 infection in human squamous cell carcinoma cells and tumors in nude mice, potentially amplifying the antitumor effect of oncolytic HSV-1 in head and neck cancer therapy (176).This combination therapeutic strategy not only enhances the targeting and therapeutic performance of OVs but also mitigates their dissemination in normal tissues, thereby minimizing adverse effects. Various targeting ligands integrated into acoustically active materials, such as nanoparticles (170, 177), polymeric micelles, and liposomes (178), contribute to this outcome. Thus, the future utilization of ultrasound-targeted technology combined with OVs promises to evolve into an efficient, precise, and comprehensive cancer treatment paradigm, providing new hope for cancer patients.

3. Clinical trials

In recent years, OV genetic engineering therapy has shown significant promise in the realm of tumor treatment. Research teams are harnessing genetically modified viruses, like MV and HSV, to develop targeted methodologies for selectively eradicating tumor cells while safeguarding normal cells. We present an exhaustive overview of key clinical trials involving engineered OVs to investigate their potential applications in oncology therapy. For instance, an embryonic MV (MV-CEA) expressing recombinant carcinoembryonic antigen (CEA) and an oncolytic MV (MV-NIS) encoding a thyroid sodium-iodine cotransporter were utilized in a clinical trial for ovarian and peritoneal carcinoma (NCT00408590). These investigations aimed to ascertain the safety and optimal dosage of engineered viral therapy for progressive, recurrent, or refractory tumors. Another clinical investigation concentrated on recurrent brain cancer (NCT00028158), where the engineered herpesvirus G207 was directly injected into the brain and administered bedside after surgical excision to evaluate its safety, therapeutic efficacy, and new treatment avenues for patients with brain cancer. Furthermore, recent clinical studies have largely focused on assessing the safety and efficacy of the engineered oncolytic virus injection R130 (a modified HSV-1 containing the gene coding for anti-CD3 scFv/CD86/PD1/HSV2-US11) in patients with recurrent/refractory cervical and endometrial cancers (NCT05812677).In conclusion, these clinical trials emphasize the promise of engineered OVs as an exciting approach in cancer treatment, showcasing their safety, effectiveness, and groundbreaking therapeutic uses.

Simultaneously, clinical investigations regarding the synergy of OVs with various pharmaceuticals for tumor therapy have revealed a significant trend. These studies have evaluated the viability and safety of pairing OVs with immunotherapeutic agents, ICIs, and other compounds, aiming to boost tumor treatment effectiveness and potentially beat resistance against standard and immune therapies (Table 2). For example, one trial (NCT02977156) sought to evaluate the practicality and security of combining anti-CTLA-4 therapy with intertumoral injections of Pexa-Vec, an OV. This combination intended to enhance antitumor effects by provoking virus-induced tumor cell destruction and releasing tumor antigens, while also recruiting, maturing, and activating antigen-presenting cells through GM-CSF induction, alongside blocking or depleting Tregs using anti-CTLA-4. Furthermore, new clinical trials have begun to investigate the potential of OV combination therapies. The NCT06196671 trial seeks to assess the effectiveness of an oncolytic virus combined with a PD-1 inhibitor in patients suffering from advanced pancreatic cancer. Additionally, the NCT06346808 trial is configured to assess the safety and efficiency of merging an oncolytic virus with a PD-1 inhibitor and chemotherapy as a preoperative strategy for individuals facing borderline resectable and locally advanced pancreatic cancer. In summary, these trials highlight the encouraging potential of OV combination therapies in amplifying tumor treatment efficacy and surmounting therapeutic resistance, particularly through the integration of ICI or chemotherapy approaches.

Taken as a whole, these clinical inquiries unveil the promise of OV genetic engineering therapy in combatting tumors. By accurately targeting cancer cells and minimizing effects on healthy tissue, these studies open new pathways for future cancer treatments and

provide hope to patients. Nevertheless, additional validation through further research is essential to improve the safety and effectiveness of these therapies in clinical settings, thereby benefiting a broader range of cancer patients. Concurrently, these investigations provide important insights into the combination of OVs with other therapeutic agents for tumor management, underlining the potential of this treatment approach to enhance therapeutic effectiveness and address drug resistance. However, continued research and clinical trials are necessary to confirm these preliminary results and establish the most effective treatment regimen.

4. Clinical hurdles

4.1 Delivery challenge

Intertumoral delivery of oncolytic viruses continues to be the principal method of administration to date. In both preclinical and clinical studies, after the intertumoral delivery of oncolytic viruses, a reduction in both treated and untreated tumor sites suggests that intertumoral viral delivery possesses distant effects. The dichotomy between the clinical necessity for intravenous delivery and the requirement for intertumoral injection poses a significant challenge for the clinical deployment of OVs. Intravenous delivery facilitates extensive OV infection across all lesions and circumvents the necessity for localization specialists, especially when tumors are inaccessible. Although intravenous delivery provides myriad advantages, several drawbacks warrant consideration. Firstly, viral particles could be swiftly eliminated by neutralizing antibodies, further hindering their efficacy. Moreover, the ideal dosage remains undefined once the virus is diluted in systemic circulation, rendering the bioavailable titers at the tumor site unpredictable. Consequently, innovative tactics to evade neutralization must be developed. Various strategies, including retargeting (179,180), utilizing cell carriers (181,182), polymer coatings (183, 184), and encapsulation in liposomes (185), have been investigated to protect oncolytic viruses from neutralizing antibodies.

Several early-stage clinical trials are exploring the intravenous administration technique for OVs. One investigation involving enadenotucirev, a chimeric oncolytic adenovirus, confirmed that viral particles were consistently identified in resected tumors after the virus was administered intravenously prior to surgery (186). Another trial involving the oncolytic vaccinia virus Pexa-Vec, administrated intravenously to melanoma and colorectal cancer patients before surgery, demonstrated a tolerable safety profile and verified the presence of OVs in resected tumor specimens (187). Recent advancements in nanotechnology and its applications for delivering nucleic acids are setting the stage for innovative carrier systems to tackle the challenges associated with intravenous (IV) delivery of oncolytic viruses. Kennedy et al. initiated the development of a nanoparticle-based delivery platform capable of enabling repeated IV administration of viral immunotherapies (188).

4.2 Concerns regarding safety

Oncolytic viruses (OVs) are actively replicating viruses that warrant attention due to risks of inadvertent transmission from patients to surrounding individuals and the environment when applied in clinical settings. There is a necessity for guidelines and protocols concerning storage, handling, administration, measures for managing accidental spills and overdoses, as well as proper sterilization procedures for contact areas; numerous guidance protocols are currently accessible (189–191). So far, there have been no documented transmissions to contacts or reported exposures. One study indicated that 8.4% of household contacts with T-VEC reported cold sores, who were not confirmed to have infections and exhibited mainly mild symptoms (186). There are also apprehensions about viral shedding, particularly in immunocompromised individuals, alongside the risk that OVs containing recombinant DNA components could recombine with naturally occurring wild-type viruses. In a review of 97 clinical trials (192), there were no confirmed cases of OV transmission to contacts or exposures. The investigation into the presence of viruses within tissue aimed to grasp virus delivery mechanisms to tumor sites and identify potential tissue or fluid reservoirs for viral shedding. Blood or serum was found to be the most commonly examined site for OV shedding, followed by urinary excretions and tumor biopsy records. Additional fluids or tissues such as saliva, oral swabs, as well as cerebrospinal fluid, peritoneal washing, and injection sites have also shown viral shedding.

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5. Enhancing oncolytic virotherapy

5.1 Strategies for arming

A remarkable characteristic of OVs is their capability to express transgenes through genetic alterations, thereby augmenting their functionality. When considering gene modifications, aspects such as backbone virus properties (intrinsic lytic and immune-modulatory characteristics), the action site of the virus, therapy duration, and material costs should be taken into account (193).

5.2 OVs equipped with antigens

OVs have the ability to evoke vaccine-like responses by expressing tumor-associated antigens (TAAs) in cold tumors, like oncolytic vaccinia virus expressing ERBB2 (194) or Maraba MG1 rhabdo virus encoding melanoma-associated antigen 3 (MAGEA3) (195). Additionally, the replication and dissemination of OVs can stimulate T cell activation (196,197), a trait that can be enhanced by transgenes associated with T cell homing (for example, the expression of chemokines like CCL19) (198). Armed OVs could express distinct antigens on infected tumor cells making them recognizable by CAR-T cells, thus positioning OVs favorably for combination with chimeric antigen receptor (CAR)-T therapies (199–202).

OVs equipped with bispecific (CD3 and TAA) T-cell engager (BiTE) molecules could address the limitations of BiTE, which has a brief serum half-life, yet OV replication could extend BiTE expression. This approach was initially reported in VV, which encodes a secretory bispecific T-cell engager consisting of two single-chain variable fragments targeting CD3 and the tumor surface antigen EphA2 (EphA2-T-cell engager-armed VV (EphA2-TEA-VV)). It demonstrated strong antitumor efficacy when compared to control VV plus T cells within a lung cancer xenograft model (203). OHSV2 armed with bispecific antibodies targeting PD-L1/CD3 has been shown to improve T-cell-mediated tumor lysis in vitro, regardless of the PD-L1 expression levels on tumor cells (204). OVs armed with BiTEs have also shown effective engagement of cytotoxic T cells and oncolysis, leading to immune-mediated tumor destruction in both primary ex vivo patient samples and in vivo xenograft models (205, 206).

5.3 OVs armed with Th1-stimulating cytokines

Armed OVs that express Th1 cytokines can activate T-cell migration, proliferation, and homing toward the tumor microenvironment (TME), thereby enhancing the antitumor immune response (207) and successfully partnering with CAR-T cell therapies in xenograft tumor models (208). Cytokines such as GM-CSF, IL-2, IL-12, and IFN-α are vital in cancer treatment; however, they typically have short half-lives, function over limited distances, and necessitate frequent administration to maintain effective bioavailability, hence restricting their widespread clinical application. Researchers are striving to secure that cytokines are expressed locally within tumors to boost OV antitumor activity and mitigate side effects. Utilizing OVV as a case study, Liu et al. developed several membrane-bound vaccinia virus-armed cytokines, like IL-2 , IL-12 (209), or IL-23 (210), aiming to prevent potential systemic toxicity, and demonstrated substantial antitumor effects, especially in conjunction with anti-PD-1/PD-L1 antibodies, curing the majority of late-stage tumors in murine models. Other Th1-cytokine-armed OVVs, including IL-7, IL-12 (211), IL-10 (212), IL-15 (213), IL-21 (214), IL-24 (215), and IL-36γ (216), have been created and proven effective and safe across various tumor models.

5.4 OVs armed with immune checkpoint blockers (ICBs) to mitigate immune suppression

OVs armed with ICBs engineered to express checkpoint inhibitor antibodies targeting PD-L1 or CTLA-4 show enhanced antitumor effectiveness compared to OVs paired with ICB therapies. Several studies have highlighted the advantages of these armed OVs expressing ICB molecules (217–220).These strategies come with drawbacks. Initially, armed oncolytic viruses (OVs) induce tumor-specific immune checkpoint blockade (ICB), yet the optimal efficacy of ICB necessitates immune cells in peripheral regions, not solely within the tumor itself. Furthermore, the immune response might necessitate ICB and OV administered on distinct timelines. A research investigation into measles viruses modified to express anti-CTLA-4 demonstrated an enhanced capacity for controlling tumor growth, albeit survival outcomes were akin between viruses expressing anti-CTLA-4 or anti-PD-L1 antibodies compared to the control cohort (221). Variability could arise from differing antitumoral immune cycles for CTLA-4 during the initial T-cell response generation phase, contrasted with PD-L1 in the effector phase.

Strategies for arming to bolster the impacts of ICBs include agents that shape the early phases of immune responses. One study

indicated that a Newcastle disease virus engineered to express inducible T-cell co-stimulator (ICOS) ligand, essential for T-cell survival and function (221), not only triggered T-cell infiltration within tumors but also amplified antitumor effectiveness when combined with a CTLA-4 blocking antibody (222). Another entity, OX40 or its ligand (OX40L), a costimulatory molecule that activates T-cells (223), has been explored alongside OVs (224,225); however, an increased T-cell response was not translated into corresponding tumor inhibition when paired with an OX40 agonist combined with VSV-IFNβ (225). These findings suggest that research on armed OVs must identify the appropriate phase and schedule, rather than solely focus on combination strategies.

6. Addressing in vivo response barriers

Significant obstacles, including both physical and immunological elements, restrict the clinical advantages of OVs. Strategies besides arming and combination factors need to be utilized to surmount in vivo challenges and enhance treatment outcomes.The tumor microenvironment (TME), akin to cancer-associated fibroblasts, may lead to the accumulation of extracellular matrix, impeding the diffusion of OVs, resulting in limited replication locales, and constraining immune cell migration into tumors (150). Armed OVs equipped with transgenes to modify extracellular matrix components, such as hyaluronidase, decorin, or relaxin, through ECM degradation may facilitate viral spread, normalize vascular structures, and promote immune cell infiltration (151–153).Insufficient penetrance due to mislocalization can adversely affect OV delivery. Inhalation devices for aerosol dispersal present a non-invasive approach for lung delivery (154). OV delivery via ultrasound cavitation, a method employing ultrasound with microbubble formulation, can enhance replication and dissemination (155), as well as boost intertumoral uptake of systemically administered vaccinia virus (156). The use of cationic lipids (157) or pupylation (PEG) (158) may reduce liver sequestration and mitigate OV toxicity.

In most instances, antiviral immune responses pose a significant obstacle for systemically administered OVs, and ongoing studies are aimed at diminishing vector neutralization while promoting T-cell responses to overcome these immunological challenges. Strategies to evade this include utilizing cell carrier tropism to target tumor tissues, such as peripheral blood mononuclear cells, which serve as carriers for oncolytic reoviruses (159), potentially enabling OVs to be shielded within cells. Additionally, antibody-blinded viruses, which have had neutralizing antibody epitopes on the viruses preidentified and mutated, might transcend OV delivery issues even in the presence of preexisting immunity (160). Conversely, the effects of antiviral immunity can serve as a double-edged sword. Zamarin's team demonstrated that preexisting immunity to NDV might bolster its therapeutic efficacy through the amplification of systemic antitumor immunity (51). Furthermore, another study revealed that the anticancer effectiveness of an HSV-1 OV could be augmented through preimmunization and multi-cycle administration (161). The Cerullo group also indicated that preexisting antiviral immunity might enhance OV-driven antitumor immunity in oncolytic adenoviruses (162).

Insufficient T-cell priming can result in inadequate viral recognition and insufficient lysis. Homologous (repeated doses of the same virus) and heterologous (multiple doses of different viruses) prime-boost regimens can enrich T-cell responses and encourage priming via OVs. A study reported in 2017 showed that the combination of three distinct treatments (priming with systemic Reovirus, followed by double boosting with systemic VSV-ASMEL and anti-PD-1) significantly improved survival rates, yielding long-term cures in comparison to any single or double combination therapies, which correlated with strong Th1 and Th17 responses to tumor antigens, indicating the potential to create fully systemic, highly effective antitumor immune-virotherapy by integrating oncolytic virus therapy (163).

7. Approved and promising novel OVs across various cancers

Numerous OVs are presently advancing in clinical evaluation. Various tumors, comprising melanoma, liver carcinoma, head and neck carcinoma, glioma, bladder carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, and lung carcinoma are being treated using OVs that are registered for clinical trials. One review (118) encompassed 97 studies presenting data from 119 publications spanning from 2000 to 2020 about OVs, revealing adenovirus as the most prevalent OV in clinical trials, with melanoma being the most commonly studied tumor. Herein, we outline several OVs that have already received approval along with those in later stages of clinical progress that offer optimistic clinical indications-VEC, talimogene laherparepvec; HSV1, herpes simplex virus type 1; BCG, bacillus Calmette–Guerin; DRR, durable response rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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7.1 Melanoma

Melanoma stands out as an ideal candidate for the utilization of oncolytic virotherapy (OV). Talimogene laherparepvec (T-VEC), a modified oncolytic herpes simplex virus type 1 (HSV1), underwent evaluation in a prospective randomized study among patients with operable and unresectable melanomas. The durable response rate (DRR) was 16.3% for those treated with T-VEC against 2.1% for participants receiving GM-CSF, alongside enhancements in overall survival (OS) (23.3 months vs. 18.9 months), culminating in full FDA endorsement in 2015 (226). T-VEC has also garnered approval for deployment in Europe, Australia, and Israel.ECHO-7, a genetically unmodified, oncotropic and oncolytic echovirus, received initial approval in 2004 in Latvia, followed by authorizations in Georgia and Armenia for its diminished risk of disease advancement compared to other experimental immunotherapies, HR 6.67 ($P < 0.001$) (227).Several clinical trials for melanoma therapy using OVs remain in progress. HF10, an HSV1-derived OV, is currently under scrutiny with metastatic or unresectable melanomas, either combined with ipilimumab (228) or as a standalone treatment for advanced-stage cutaneous solid tumors (229). Initial reports indicate an ORR of 41% at 24 weeks, with 68% of patients maintaining stable disease, median PFS at 19 months, and median OS reaching 21.8 months, exhibiting good tolerance (228).

7.2 Nasopharyngeal carcinoma

The oncolytic adenovirus H101, featuring E1B-55KD and a partial E3 deletion, was the first approved OV in China for treating head and neck cancers in 2005 (230). In a phase III randomized clinical study, H101 was administered via intertumoral injection alongside chemotherapy for managing squamous cell carcinoma of the head and neck or esophagus, with the ORR measuring at 72.7% in the combination group as opposed to 40.3% with chemotherapy alone. Injection site reactions were noted in 28.3% of patients, while 9.8% experienced flu-like symptoms (231, 232).

7.3 Malignant glioma

Malignant glioma is notably aggressive, presenting a median OS of around 15 months (233). Glioma remains confined to the CNS, and local therapeutic strategies, including OVs, are viable options, employing HSV1, adenoviruses, and polioviruses. A single-arm phase II trial revealed that the third-generation HSV1-based OV, Telepicture (G47Δ), exhibited a 1-year OS of 84.2% in recurrent and/or residual glioblastoma patients, with manageable adverse events such as fever, vomiting, nausea, and leukopenia, leading to its approval in Japan for malignant glioma sufferers (234). Concurrently, G207, another oncolytic HSV1 strain, was evaluated in pediatric glioma patients afflicted with high-grade glioma, yielding benefits in nearly all participants (11/12) with a median OS of 12.2 months (235, 236) and resulted solely in grade 1 adverse effects.

Tasadenoturev, an OV derived from adenovirus type 5, was explored in 12 pediatric glioma patients diagnosed with diffuse intrinsic pontine glioma, resulting in measurable tumor shrinkage in 75% of cases, and a median OS of 17.8 months; however, three incidents of muscle weakness and headaches classified as grade 3 were reported (174). Subsequently, the tolerability and efficacy of tasadenoturev were examined in 37 adult patients with recurrent glioma (237), where 20% survived three years post-therapy, which included three individuals with nearly complete responses (approximately 95% tumor mass loss) (238), with only two patients experiencing treatment-related adverse effects.Beyond DNA viruses, RNA viruses, including poliovirus, are being investigated in clinical trials. PVS-RIPO, a recombinant attenuated poliovirus, was evaluated in a phase II study involving recurrent glioblastoma patients who received intratumoral PVS-RIPO, resulting in a 1-year OS of 21% albeit with grade 3–5 adverse events in 19% of the subjects (which included one treatment-related fatality) (239, 240).

7.4 Bladder cancer

Nonmuscle invasive bladder cancer (NMIBC) also represents a target for OV therapy, with the majority of tumors originating in the urothelium of the bladder, suitable for direct administration via intravesical infusions.An adenovirus serotype 5-based OV, CG0070, which encodes GM-CSF, was assessed in a phase I/II trial revealing a complete response rate of 48.6% in a dose-dependent manner among 35 patients, with a median response duration of 10.4 months (241).

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II- Conclusion

OV therapy stands as a cutting-edge method for cancer management, leveraging viruses that specifically target tumor cells to trigger their demise and curb tumor proliferation. Gene-engineered OVs have attracted considerable interest and investigation as a viable option for tumor treatment. This paper delivers a thorough review and assessment of the engineering enhancements, combination strategies, and clinical investigations associated with OVs, seeking to examine its future possibilities and obstacles in tumor care. In addition to the previously mentioned four strategies, it is noted that engineered OVs encompass diverse techniques to improve their therapeutic effectiveness against tumors. For example, the incorporation of particular functional proteins or enzymes can potentially amplify the antitumor response. This discovery brings promising implications for the prospective use of engineered OVs in cancer immunotherapy. Nevertheless, it is essential to emphasize that substantial theoretical research backing, along with meticulous animal studies and clinical trials, remains necessary to advance and substantiate this approach.

Meanwhile, in combination therapy, the integration of OVs with chemotherapy does not consistently produce favourable outcomes and could negatively affect tumor immunoviral therapy. Moreover, research on OV in conjunction with chemoradiotherapy is limited; however, existing investigations reveal its considerable promise. This indicates that we might alleviate the adverse effects of chemoradiotherapy through engineered modifications of OVs and achieve improved synergistic results. Furthermore, concerns arise regarding possible antagonistic interactions between OVs and CAR-T therapy based on preclinical evidence. Hence, further exploration into their interplay is crucial to refine this combination therapy approach. Additionally, Tumor-Infiltrating Lymphocytes (TILs) are also vital in this framework. OV therapy not only directly targets and eradicates tumor cells when paired with TILs but also stimulates TILs, boosting their immune reaction against tumors. This enhanced immune response leads to improvements in the Tumor Microenvironment (TME) by augmenting T cell infiltration and activity, ultimately fortifying the immune system's capacity to confront tumors. In the domain of ultrasound-targeted therapy, while microbubble inertial cavitation can greatly improve the delivery efficacy of drugs or gene carriers, it also entails unavoidable collateral damage, including microvascular leakage, capillary harm, and blood cell extravasation, resulting in localized swelling and inflammation. Consequently, before progressing ultrasound-mediated OV delivery to clinical trials, additional research is imperative to refine this technology and mitigate its adverse effects. Despite being in the nascent phase with sparse studies, ultrasound-mediated microbubble delivery combined with OVs exhibits substantial potential, not only for OVs but also for alternative viral therapies, significantly enhancing therapeutic outcomes and overcoming established barriers.

To conclude, OV therapy signifies a encouraging and inventive strategy for tumor treatment. Through persistent enhancement of engineering methods, investigation of combination therapies, and clinical inquiries, we can further bolster the safety, effectiveness, and precision of OVs to advance treatment outcomes and patient quality of life. The future clinical applications of OV combination therapies present considerable promise. The possibility of synergistic outcomes, particularly with chemoradiotherapy, opens new pathways for overcoming resistance and achieving more sustained responses. Nonetheless, challenges, such as comprehending the intricate interactions between OVs and immune cells, along with managing potential antagonistic impacts with CAR-T cells, necessitate careful investigation. Future studies should concentrate on optimizing dosage schedules, sequencing therapies, and establishing criteria for patient selection to maximize benefits while mitigating risks. Furthermore, the incorporation of advanced genetic engineering methods could enhance OV specificity and diminish off-target effects, paving the way for personalized cancer treatments. Despite these strides, potential challenges in the clinical landscape include regulatory impediments, elevated development expenses, and the requirement for large-scale manufacturing capabilities. Addressing these hurdles will be pivotal for the successful transition of OV therapies from laboratory to patient care. The formulation of standardized procedures and robust clinical trials will be essential in validating the therapeutic effectiveness and safety profile of these innovative treatments. Through sustained interdisciplinary collaboration and technological advancements, the future of OV combination therapies seems bright, with the potential to markedly enhance cancer treatment.

Abbreviations

TME : tumor microenvironment

CTLA-4 : Cytotoxic T-lymphocyte-associated antigen 4

TIM-3 : T cell immunoglobulin and mucin-containing molecule 3

AIM2 : Absent in melanoma 2 (AIM2) is a novel member of interferon (IFN)- inducible PYHIN proteins

TILs : Tumour-infiltrating lymphocytes

CD4 + T cells : are crucial in achieving a regulated effective immune response to pathogens

CD8+ T cells : known as cytotoxic T lymphocytes (CTLs), are important for immune defence against intracellular pathogens, including viruses and bacteria, and for tumour surveillance

CD47: is recognized as an important innate immune checkpoint

NAC : N-acetylcysteine

TNBC : triple-negative breast cancer

TVEC : Talimogene laherparepvec

GBM : Glioblastoma multiforme

Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution

Authors have equally participated and shared every item of the work.

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