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Review Article

Advances in the clinical development of oncolytic viruses

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Abstract: Objectives: Oncolytic viruses (OVs) are natural or recombinant viruses that selectively infect and kill cancer cells without harming normal cells. This review aimed to explore some ongoing and completed clinical studies on OVs, in China and worldwide, to depict a comprehensive landscape of OV clinical trials, and summarize the existing evidence on safety and effectiveness of oncolytic therapy against tumors. Methods: Used the Center for Drug Evaluation of China National Medical Products Administration (NMPA), Chinese Clinical Trial Registry (ChiCTR), International Clinical Trials Registry Platform, ClinicalTrials.gov website, China National Knowledge Infrastructure (CNKI), and PubMed. Results: As of October 1, 2021, 408 clinical trials on 31 OV products have been conducted, with oncolytic DNA viruses being the most investigated ones; phase I and phase II clinical studies accounted for approximately 80% of all studies. Published clinical studies have shown that OVs, such as H101, T-VEC, G47Δ, OH2, T3011, and Pelareorep, have significant anti-tumor effects on various tumors, with only mild adverse events. When OVs are used together with antiviral drugs in the clinic, drug interactions should be considered based on the sensitivity of OVs to antiviral drugs. Conclusions: OVs exhibit accurate oncolysis and favorable safety, and have positive effects on a variety of tumor treatments. It is worth noting that most of the OVs under development are still in their early stages, which is both a challenge and a promising prospect.

Keywords: Oncolytic viruses, virotherapy, tumor, immunotherapy, antiviral drugs

Introduction

Tumor immunotherapy has attracted much attention owing to its safety and significant efficacy [1]. Oncolytic viruses (OVs) have been increasingly recognized as a new class of immunotherapeutic agents against tumors. OVs form a class of natural or recombinant viruses that selectively infect and kill tumor cells without damaging normal cells [2]. In 1891, William B. Coley was the first one to inject “Colitoxin” into a patient with cancer, following which, the tumor disappeared, making it the first successful use of OVs to cure tumors [3]. With the continuous progress in science and technology, OVs have been used to treat various tumors, and have now progressed to the third generation. Recently, in the UK, a 61-year-old patient with Hodgkin’s lymphoma reported the disappearance of a tumor nearly 4 months after contracting coronavirus disease (COVID-19), which suggested a powerful oncolytic effect of an OV [4].

Compared to other tumor immunotherapies, OVs have multiple mechanisms of antitumor activity, such as (1) specific replication in tumor cells, (2) induction of chemokines to turn “cold” tumors into “hot” tumors and stimulate local and systemic antitumor immune response; for example, OVs can kill the tumor cell to release tumor antigens, activate dendritic cells, increase T cell infiltration and recruitment of other immune-related molecules, and finally clear the distant and uninfected tumor cells [5], (3) infection and destruction of tumor vascular system to induce neutrophil influx, vascular collapse, and tumor cell death, and (4) genetic modification of OVs to delete gene fragments that recognize normal cells and insert gene fragments that help kill tumors, thereby enhancing specific anti-tumor effects [5-10].

To date, dozens of OV drugs [11] have been developed for tumor treatment and relevant clinical studies have been carried out. According to data from clinical trials registered

Table 1. Antitumor activity of oncolytic viruses

	Type	Name	Antitumor activity
Natural OVs	Reovirus	Reolysin	Patients with advanced solid tumors DCR: 45%; PR: 5.6%; SD: 38.9%; No dose-limiting toxicity [55].
	Coxsackie virus	CAVATAK	Advanced melanoma patients: total response rate: 28.1%; One-year survival rate: 75.4% [12].
	Adenovirus	H101	Patients with malignant pleural effusion: ORR=40%; DCR=75%; PR=27.5; CR=12.5%; SD=35% [56].
Recombinant OVs	Herpes simplex virus	T-VEC	Melanoma patients DRR: 16.3%; ORR: 26.4%; CR: 10.8%; Mean overall survival: 23.3 months (95% CI, 19.5-29.6 months) [25].
	Herpes simplex virus	OrienX010	Patients with liver metastases from melanoma ORR: 8.3% (1 PR); DCR: 41.7% (1 PR, 4 SD); mPFS: 13.3 weeks (95% CI 8.3-18.4); OS treatment endpoint was not reached [57].
	Vaccinia virus	JX-594	Colorectal cancer patients SD: 67% [58]; Patients with advanced refractory renal cell carcinoma 6 weeks DCR: 76% [59].
	Newcastle disease virus	PV701	Patients with advanced solid tumors PFS: 4-31 months [60].

Note: DCR, disease control rate; PR, partial response; SD, stable disease; ORR, objective response rate; CR, complete response; PFS, progression free survival; DRR, durable response rate; OS, overall survival.

Table 2. Basic information about 31 OV products at present

Clinical stage	OV	Indications	Administration route
Listed drugs	H101, T-VEC, G47Δ	Nasopharyngeal cancer; Melanoma; Glioma	Intratumoral injection
Phase III clinical	Pexa-Vec (Phase III clinical suspension, unable to be listed as planned); ADV-TK, Reolysin (Canada); ProstAtak; CG0070; E10A; Toca511; PV-10, EDS01	Bladder cancer; Head and neck cancer; Ovarian cancer; Liver cancer and pancreatic cancer	Intravenous injection Intratumoral injection Intrathoracic injection
Phase I-II clinical	T3011; EDS01; OrienX010; KH901; OH2; E10A; CAVATAK; MG1-MAGEA3 etc.	Melanoma; Prostate cancer; Lung cancer; Bladder cancer; NSCLC; Head and neck cancer	Intravenous injection Intratumoral injection

NSCLC, Non-small cell lung cancer; OV, oncolytic virus.

between 2000 and 2021, the five most common types of OVs are adenovirus, HSV-1, reovirus, vaccinia virus, and Newcastle disease virus. Natural OVs only include reovirus reolysin and coxsackievirus CAVATAK as shown in **Table 1**. Both natural and recombinant OVs have significant antitumor activity [12]. Currently, three OVs, namely recombinant human adenovirus type 5 (Oncorine®, H101), talimogene laherparepvec (imlygic®, T-VEC), and teserpaturev (Delytact®, G47Δ), have been approved for commercial use. Research on OVs has been constantly refined with progress in science and technology, and several other OVs, such as OH2, T3011, and Pelareorep, are currently undergoing clinical trials; an increasing number of anti-tumor studies using OVs are underway.

This review aims to explore ongoing and completed clinical studies on OVs in China, and worldwide, using the Center for Drug Evaluation of China National Medical Products Administration (NMPA), Chinese Clinical Trial Registry (ChiCTR), International Clinical Trials Registry Platform, ClinicalTrials.gov websites, China National Knowledge Infrastructure (CNKI), and PubMed. We collected the details of these clinical trials (such as OV type, clinical stage, tumor type, treatment method, and administration method), conducted data analysis, summarized the progress in clinical development of OVs, and reviewed the safety and effectiveness of oncolytic therapy against tumors.

Clinical stage of OVs

As of October 1, 2021, 408 clinical trials of OVs have been conducted. The clinical trials, either ongoing or completed, are as follows:

The clinical stages of approximately 31 OV products are displayed in **Table 2**. Among all the anti-tumor studies on OVs, phase I, and phase II studies accounted for approximately 80% of the total studies. Phase III studies accounted for approximately 6% of the total studies, and many phase III studies are still in their infancy. Even if the drug enters phase III clinical trials, there is still a risk of failure. On 2 August 2019, Labiotech.cn reported that in the phase III clinical study of vaccinia virus Pex-

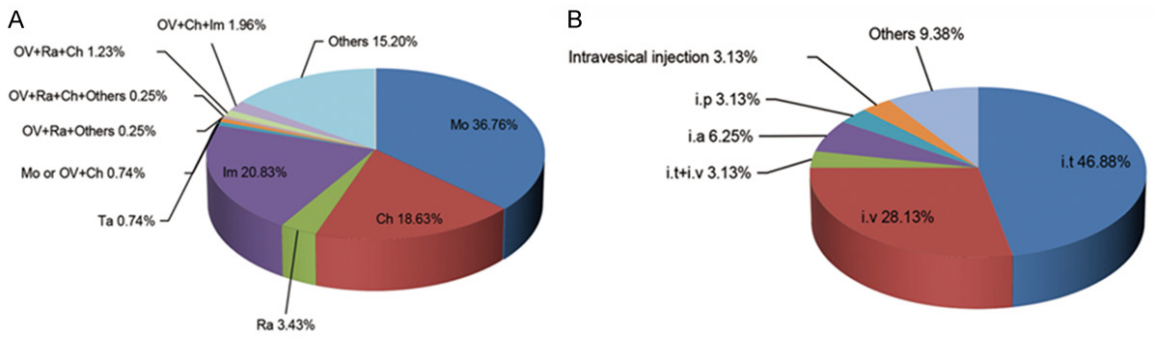

Figure 1. Classification of OVs. A. Proportion of DNA/RNA viruses in clinical studies. B. Proportion of OV types in clinical studies. OV, oncolytic virus.

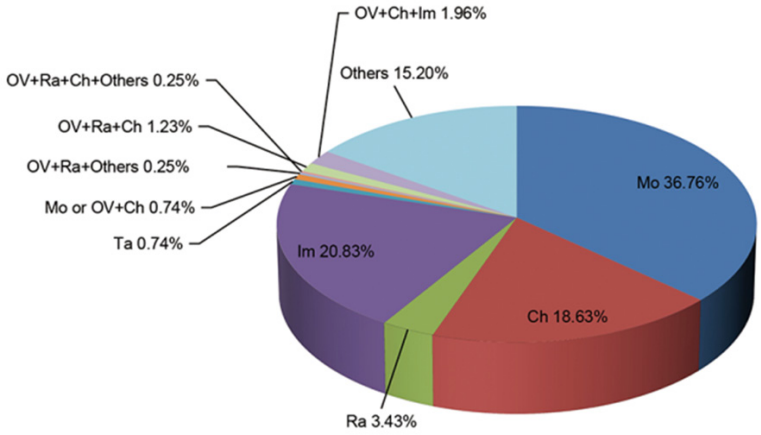

Figure 2. OVs combined with other therapies to treat tumors. OV, oncolytic virus; Ra, radiotherapy; Ch, chemotherapy; Im, immunotherapy; Ta, targeted therapy; Mo, monotherapy.

Vec (JX-594) in the treatment of liver cancer, which was expected to be completed in 2020, the interim analysis showed that although the efficacy of Pex-Vec combined with sorafenib was better than that of sorafenib alone, the possibility of prolonging patient survival was low. Pex-Vec in combination with sorafenib may not reach its primary endpoint; therefore, the study was declared a failure and terminated in advance.

Among the OVs investigated to date, DNA viruses accounted for 81.4% (**Figure 1A**) of the total, including adenovirus (41.86%), herpes simplex virus (25.58%), and vaccinia virus (13.95%). RNA viruses accounted for 9.3%, including reovirus (2.33%), coxsackie virus (4.65%), poliovirus (2.33%), and others (9.30%). Among all the viruses currently under development, the most popular types being studied are adenovirus and herpes simplex virus, accounting for 41.9% and 25.6%, respectively (**Figure 1B**). Thus, oncolytic DNA viruses are the most studied viruses, and adenoviruses and herpes simplex viruses are the most common among them.

Tumor types

Data regarding the types of tumors treated with OVs were collected from the registered clinical trials. More than 30 types of tumors were found to be treated by OVs. Among them, melanoma, glioma, liver cancer, and head and neck cancers were the most common.

Drug combination

The treatment strategies of OVs in the registered clinical trials were either as OV monotherapy (36.77%), combination of oncolytic virotherapy with chemotherapy (18.63%), immunotherapy (20.83%), radiotherapy (3.43%), or targeted therapy (0.74%) (**Figure 2**). As shown in **Figure 2**, OV monotherapy is the most commonly used therapeutic strategy, followed by the combination of oncolytic virotherapy with common administration route for OV products is an intratumoral injection.

With an understanding of the majority of solid tumors and the heterogeneity between tumors, it may be that OVs in combination with other therapies will maximize the efficacy of OVs. It is important to consider whether the drug will counteract the efficacy of OVs when designing a combination therapy and take into account sequential combination to minimize the coun-

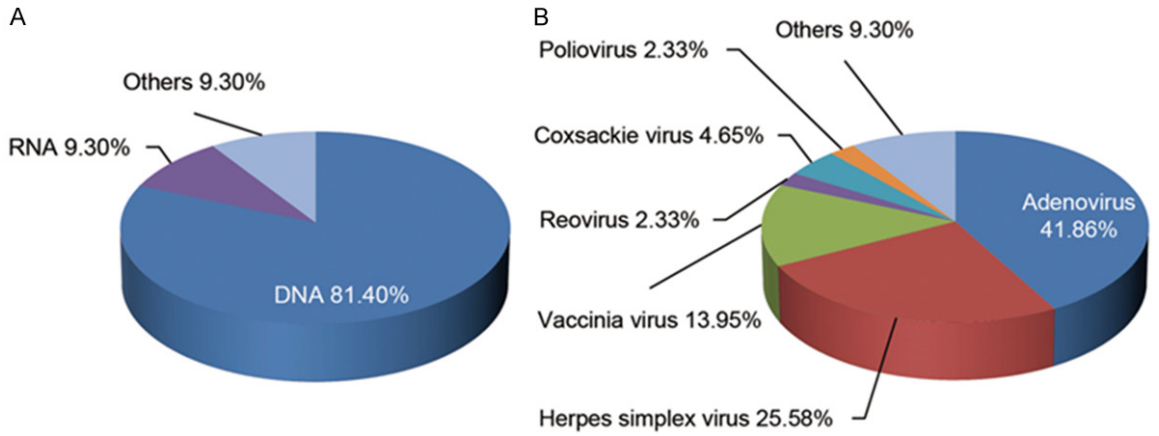

Figure 3. Proportion of drug administration routes in global clinical studies of OV products. A. Proportion of drug administration routes in clinical studies of OV products. B. Proportion of administration routes in phase III clinical studies of OV products worldwide. OV, oncolytic virus; Ra, radiotherapy; Ch, chemotherapy; Im, immunotherapy; Ta, targeted therapy; Mo, monotherapy.

teraction [13, 14]. Chemotherapy can inhibit DNA synthesis, and mitosis and cell division, and induce DNA damage. OVs replicate in tumor cells and participate in the induction of DNA damage. Therefore OVs combined with chemotherapy can synergistically enhance the anti-tumor effect [14]. OVs infect tumor cells, replicate, and survive to kill tumor cells. Targeted therapy blocks cancer growth by interfering with specific molecules needed for tumor growth, which makes it possible to combine OVs with targeted therapy to fight cancer [14]. OVs regulate the tumor microenvironment, turning "cold" tumors that do not respond to immune checkpoint blockade into "hot" tumors, and enhancing antitumor activity in combination with immune checkpoint inhibitors [14-16]. Radiotherapy can inhibit tumor proliferation by inhibiting tumor-related signaling pathways, and OVs can increase the sensitivity of tumor sites to radiation therapy, so the combination of radiotherapy and OVs has a synergistic effect on tumor treatment [11].

Routes of OVs administration

Among the various administration routes in global OV studies, intratumoral injection accounted for 58.6%, followed by intravenous (23.03%) and arterial injections (1.47%) (**Figure 3A**).

According to the statistics of the distribution of drug administration routes in phase III clinical trials worldwide, intratumoral injections accounted for 46.88% of all phase III studies, intravenous injections accounted for 28.13%, intratumoral injections combined with intravenous injection accounted for 3.13%, and other modes of administration accounted for 9.38% (**Figure 3B**). This reveals that for OV products with the fastest marketing potential, an intratumoral injection might be the major administration method while an intravenous injection was only approximately 1/3 as common. A possible reason could be that an intratumoral injection of OV products is safer and can reach the target directly compared to an intravenous injection.

Antitumor efficacy of OVs

As of October 1, 2021, 132 clinical studies on OVs have been completed. Based on their findings along with those of other published studies, OVs, such as H101, T-VEC, G47Δ, OH2, T3011, and Pelareorep were found to exert significant anti-tumor effects on various tumors (**Table 3**).

H101

H101 is one of the earliest OV products successfully listed in China for tumor treatment. In 2005, H101 was approved by the National Medical Products Administration, for the treatment of nasopharyngeal carcinoma (NPC) in combination with chemotherapy. H101 includes an E1B-55KD deletion, based on human adenovirus type 5. The virus could selectively

Table 3. List of OV products on the market

Product	Oncorine (Recombinant human adenovirus type 5)	Imlygic (T-VEC)	Delytact (G47Δ)
Virus type	Human adenovirus type 5	Herpes simplex virus type I	Herpes simplex virus type I
Gene construction	Deleted E1b-55kd, E3 gene fragment (78.3-85.8 mu)	Deleted the ICP34.5 and ICP47 regions of herpes simplex virus type I, inserted GM-CSF gene	Deleted the γ34.5 gene and the 312 bp base of α47 gene; Insert ECOL-I LacZ gene into ICP6 (UL39) region
Goal of gene construction	Deletion of E1B-55KD: the virus could selectively infect and multiply tumor cells with dysfunction of RB/P53 pathway Deletion of part of E3 gene: enhanced immune induction ability of virus, induced lymphocyte infiltration of lesions, and virus entering vascular system could be more easily cleared by immune recognition, enhancing safety	Deleted the γ34.5 gene of HSV-1: increased tumor cell infection specificity Insertion of GM-CSF gene: enhanced antigen delivery capacity	Knockout of the γ34.5 gene and the 312 bp base of α47 gene to eliminate the neurotoxicity of the virus, improve the replication and reproduction capacity of the virus Insertion of ECOL-I LacZ gene into ICP6 (UL39) region leads to inactivation of nucleotide reductase (RR), allowing the virus to reproduce only in tumor cells, improve the oncolytic effect
Clinical application	Approved indications: advanced head and neck cancer, nasopharyngeal carcinoma Related research: liver cancer, MPE, pancreatic cancer, cervical cancer, gastric cancer, etc.	Approved indications: advanced melanoma Related research: liver cancer, MPE	Approved indication: glioma Related research: breast cancer
Examination and approval	NMPA	FDA	MHLW
Approval time	2005.11.04	2015.10.27	2021.06.11

MPE, malignant pleural effusion; HSV-1, herpes simplex virus type 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; NMPA, National Medical Products Administration; FDA, U.S. Food and Drug Administration; MHLW, Ministry of Health, Labor, and Welfare.

infect tumor cells with dysfunction of the RB/P53 pathway, replicate, and multiply. Meanwhile, part of the E3 gene fragment was deleted to enhance the immune induction ability of the virus and induce lymphocyte infiltration into the lesion. Viruses entering the vascular system are more likely to be cleared by immune recognition, thereby enhancing safety [17, 18].

Intratumoral injections of H101 significantly inhibited tumor growth, resulting in viral replication, cell degeneration, and necrosis [19]. The anti-tumor efficacy of H101 combined with chemotherapy was evaluated by comparing to standard chemotherapy. In the phase III clinical trial of H101, 160 patients were randomly assigned to either of the H101 combined chemotherapy and chemotherapy alone groups (mainly cisplatin and fluorouracil (5-FU)), intratumoral injection of H101 combined with chemotherapy or chemotherapy alone, 21 days as a treatment cycle, for two treatment cycles. The results showed that the overall response rate of H101 combined with chemotherapy (78%) was significantly better than that of chemotherapy alone (39.6%). Chemotherapeutic drugs such as cisplatin and 5-FU have no inhibitory effect on viral replication, but H101 combined with chemotherapy can synergistically inhibit tumor, so H101 combined with chemotherapy is completely feasible in clinical anti-tumor treatment. Patients with advanced hepatocellular carcinoma (HCC) are most often treated with transarterial chemoembolization (TACE). Previous studies have shown that TACE may provide clinical survival benefits in combination with recombinant human adenovirus type 5 (H101) [20]. In a retrospective study, patients with advanced liver cancer received H101 in combination with TACE or conventional TACE alone. Results analysis found the therapeutic effect of H101 combined with transcatheter arterial chemoembolization (TACE) to be significantly better than that of TACE alone in patients with liver cancer. The overall survival (OS) rates of H101 plus TACE vs. TACE alone at 1-year, 2-years, and 3-years were 61.3% vs. 53.8%, 44.2% vs. 33.4%, and 40.5% vs. 22.4%, respectively ($P<0.05$) [21]. H101 activation of the host immune system and enhancement of the immune response may contribute to tumor regression, thereby enhancing the anti-tumor effect of TACE therapy. Several other studies have reported H101 to be effective in treating a variety of solid tumors, such as lung cancer and malignant pleural effusion [22, 23].

T-VEC

T-VEC, manufactured by Amgen, was the first OV product approved for marketing by the United States Food and Drug Administration

(US-FDA) in October 2015 to treat skin and lymph node lesions and melanoma that could not be completely removed by surgery. T-VEC is a genetically modified herpes simplex virus-1 (HSV-1) with deletions of ICP34.5 and ICP47 genes and insertions of granulocyte-macrophage colony-stimulating factor (GM-CSF) gene. The deletion of ICP34.5 and ICP47 genes caused the inhibition of neurovirulence of the pathogen and promotion of antigen presentation, respectively. The addition of GM-CSF gene led to the local production of GM-CSF, enhancement of antigen presentation ability, recruitment of APCs into the tumor microenvironment, and improvement in anti-tumor effect [24].

In a multicenter randomized controlled study evaluating the antitumor effect of T-VEC compared with GM-CSF, the results found that among 436 randomly assigned patients with melanoma, the durable response rate was significantly higher with T-VEC (16.3%) than with GM-CSF (2.1%), T-VEC can regulate the tumor microenvironment to benefit patients clinically, and they concluded that T-VEC is a novel potential therapy for patients with advanced melanoma [25]. In a randomized open-label phase II study, patients with unresectable stage IIIB to IV melanoma were randomly assigned 1:1 to receive talimogene laherparepvec plus ipilimumab or ipilimumab alone. The objective response rate was 39% in the combined treatment group and 18% in the single treatment group, suggesting that the combination has higher antitumor activity [26]. Currently, evidence of T-VEC improving the OS rate of patients with melanoma is insufficient. This study is the first to demonstrate that T-VEC combined with immunotherapy synergistically improves the survival benefit of patients, which may be related to the synergistic regulation of T-VEC and ipilimumab in tumor microenvironment. There is no evidence in support of T-VEC being effective in preventing melanoma metastasis to the brain, bone, liver, lung, or other internal organs.

G47Δ

In 2021, G47Δ was approved by the Ministry of Health, Labor, and Welfare (WHLW) for the treatment of glioma. G47Δ is a third-generation oncolytic herpes simplex virus vector, in which the γ34.5 gene was deleted to eliminate the neurotoxicity of the virus and 312 bp of the α47 gene was deleted to improve the replication and reproduction capacity of the virus while improving its anti-tumor activity [27, 28]. Insertion of ECOL-I LacZ gene into the ICP6 (UL39) region led to the inactivation of nucleotide reductase (RR), allowing the virus to reproduce only in tumor cells, thus improving its oncolytic effect [27]. G47Δ has shown strong replication ability in a variety of cancers, effectively induced specific antitumor immunity, and demonstrated high safety profiles [29]. It could also kill cancer stem cells very effectively. A Phase II clinical trial involving patients with recurrent glioma, each patient received stereotactic injections with G47Δ into the tumor, every 4 weeks, for the maximum 6 times, interim analysis of clinical trial data showed that the 1-year survival rate of the included 13 patients was 92.3%. Serious adverse events related to G47Δ occurred in only 2 patients, both of whom had grade 2 fever. The repeated stereotactic injections were well-tolerated [29]. G47Δ was designated by the Japanese government as “Sakigake Breakthrough Therapy drug” and as “Malignant glioma orphan drug”. It is the second oncolytic herpes simplex virus drug approved, after T-VEC, and is the world’s first OV drug approved for the treatment of malignant glioma [28].

Fifty-four patients with metastatic cancers were treated with a single dose of OH2 or OH2 plus HX008. The duration of response was 11.25+ and 14.03+ months for two partial-response patients treated with a single dose of OH2, and 1.38+ and 2.56+ months for two responders in the combined cohort [30]. The intratumoral OH2 injection was proven to have persistent antitumor activity in patients with metastatic esophageal and rectal cancers [30, 31].

Others

In June 2021, a phase I study on T3011 for the treatment of malignant tumors was presented at the American Society of Clinical Oncology (ASCO). It was reported that in 8 out of 11 assessable patients with advanced cutaneous or subcutaneous malignancy, tumor shrinkage was observed. One patient discontinued treatment due to progressive disease and 9 of the 11 subjects remained in the study. T3011 was well tolerated with no grade 3 treatment-relat-

ed adverse event (AE). T3011 is the product of herpes simplex virus modification and insertion of IL-12 and GM-CSF genes. It is this structural modification that enables T3011 to have significant anti-tumor activity and good safety, and bring clinical benefit to patients. A phase II trial on Pelareorep in combination with pembrolizumab for pancreatic cancer, presented at ASCO, showed that among the 12 evaluable patients, disease control rate was 42% with one patient achieving a partial response and four being in stable condition.

Antitumor safety of OVs

Adverse events

OVs have better safety than traditional antitumor treatments. Generally, AEs are mild and get resolved without treatment. The common AEs of OVs include pain at the injection site, nausea, vomiting, diarrhea, fever, influenza-like symptoms, liver function damage, and leukopenia [9, 20, 25, 32-35]. The most common AEs in the OPTiM study of T-VEC were fatigue (50.9%), chills (49.7%), fever (39.9%), influenza-like illness (33.7%) and nausea (33.7%). AEs occur frequently in the first cycle of OV treatment and decrease over time [36]. Pelareorep treatment for pancreatic cancer has few side effects. The most common grade 1 or 2 AEs included fever, chills, fatigue, headache, anemia, vomiting, and flu-like symptoms. A small number of patients experienced grade-3 or 4 adverse events [37].

However, there were certain safety problems with different administration methods and certain risks in intra-arterial injection of OV products. OVs might lead to a strong immune response, and an excessive inflammatory response can lead to damage to some organs, resulting in death in some cases. In a phase I trial conducted in 1999, an 18-year-old patient died after an injection of adenovirus into a branch of the hepatic artery. Professor James Wilson had proposed that adenovirus vectors and transgenes are found in all organs (including the testis) of patients during autopsy [38]. Based on the first death report of gene therapy, the latter was considered to have inherent risks and serious side effects. Therefore, when developing an OV product for intra-arterial injection, its safety must be considered while increasing the dose to ensure efficacy. At present, intravenous injection-related OV products are basically used at phase I and II clinical stages, and have not yet reached phase III.

Virus shedding

Virus shedding from a treated patient may pose risks to the environment and human health. FDA guidelines have described virus shedding studies in detail. The guidelines cover the design of clinical trials for shedding studies, and collection and analysis of shedding data. Moreover, they have pointed out that virus shedding might be dose-dependent; thus, a shedding study should be conducted after the phase I dose-escalating trial.

In the shedding study of H101, blood, urine, injection site, and throat swab samples were collected from patients for PCR detection. No H101 virus was detected within the detection sensitivity range, indicating that H101 did not replicate in blood or spread in vivo after an intratumoral injection. There was no evidence of any environmental harm [39].

A study of the biological distribution and viral shedding of T-VEC found that approximately one-third of blood samples contained detectable T-VEC DNA during treatment, with a higher incidence of HSV-1 seronegative patients than seropositive patients. The overall incidence of T-VEC DNA in urine, oral mucosa, and anal swab was low (1.2%-3.0% of samples) and did not appear to be significantly affected by baseline HSV-1 serum status. The amount of DNA in these samples increased again during the second cycle. However, T-VEC DNA was cleared from the blood and urine at the end of the treatment [40].

In a shedding study on reolysin by Morris et al., urine, feces, and cerebrospinal fluid samples of all patients (before and after reolysin treatment) were collected for RT-PCR detection, and results were found to be negative for virus shedding [41]. In a phase I clinical study of HSV1716, regarding the treatment of tumors, blood, oral swab, rectal swab and urine samples were collected, and no virus shedding was observed [42]. A shedding study of Ad5/3-ΔOVs showed the level of adenovirus genomic DNA to have increased significantly in many patients treated with a low dose of Ad5/3-ΔOVs, whereas shedding was more fre-

quent in patients in the middle and highest dose cohorts [43]. NV1020 OVs were not detected in any serum, saliva, or genital swab sample in the first month of treatment in the shedding study. However, wild-type HSV-1 DNA was detected in single-day serum samples from each of the four patients at random times and within multiple days in one patient [44].

As can be seen from the previous studies, the virus shedding situation of OVs is uncertain, which calls for the further evaluation of the safety of OVs in phase I clinical studies in order to address the additional risks of environmental release in future treatments.

Effect of antiviral drugs on the efficacy of OVs

OVs have significant anti-tumor efficacy; however, in some patients with cancer, this is accompanied by viral infection, requiring long-term antiviral therapy. Therefore, whether antiviral drugs have an impact on the efficacy of OVs needs to be evaluated.

A study evaluated the effects of three categories of antiviral drugs, namely first-line drugs for the treatment of hepatitis B virus (HBV) infection, new therapies recommended for hepatitis C virus (HCV) infection, and broad-spectrum antiviral drugs with the oncolytic effect of M1 virus (M1 is a natural virus that selectively infects and kills a variety of cancer cells, and has no side effects on normal cells). Results indicated that HBV nucleotide/nucleoside analogs, HCV, and ribavirin (RBV) in combination with direct-acting antivirals (DAAs) do not inhibit M1-induced oncolytic effect, although IFN-α-induced antiviral immunity inhibited viral replication and weakened the oncolytic effect of the M1 virus. Hence, when M1 oncolytic therapy was considered for hepatocellular carcinoma (HCC) patients, simultaneous use of IFN-α should be avoided to improve its efficacy [45].

A similar conclusion was reached in another study, which showed that H101 combined with TACE resulted in a higher survival rate and antitumor activity than conventional TACE alone. Stratified analysis by anti-HBV therapy indicated that antiviral therapy had no significant effect on the antitumor efficacy of H101. Overall, there was no evidence to prove that the commonly used antiviral drugs had any potential influence on adenovirus infection [46].

A previous study by Haines et al. showed that OV G207 might be sensitive to interferon and ONCR-177 might be sensitive to acyclovir. OV G207, a herpes simplex virus with ICP34.5 deletion, was inhibited to a greater extent (135 times) in the presence of IFN-α than in its absence. The replication capacity of ONCR-177 was moderately inhibited (4.5-6 times) by IFN-α. Retention of neurotoxic factors (ICP34.5) makes it possible for ONCR-177 to replicate in tumor cells in the presence of IFN-α. Meanwhile, mutation of the tegument protein UL37 of ONCR-177 contained in the structure retained its sensitivity to acyclovir (broad-spectrum antiviral drug, nucleoside antiviral drug), ensuring the safety of ONCR-177 in treatment. The latter was shown to be sensitive to acyclovir *in vitro* [47].

In summary, IFN-α, in the third class of broad-spectrum antiviral drugs, showed a strong inhibitory effect on the natural M1 of OVs. IFN-α antagonizes the oncolytic effect of M1 virus by stimulating the expression of antiviral genes in human hepatoma cells. Interferons effectively inhibit the activity of G207 in tumors. Therefore, co-administration of IFN-α and OVs is not recommended for patients with HCC having abundant expression of interferon-stimulating genes (ISGs) in tumors. Herpes simplex virus ONCR-177 was found to be highly sensitive to acyclovir; however, other common antiviral drugs, such as HBV nucleotide/nucleoside analogs, HCV, and RBV, had no effect on adenovirus H101 or natural virus M1.

Advances in preclinical studies of OVs

After OVs infection lyses tumor cells, DC cells are activated by tumor-associated antigens released by dead tumor cells. As a result, immune cells such as T cells and NK cells are recruited into the tumor microenvironment, increasing tumor-specific immune responses to remove distant or uninfected tumor cells. If treating cancer is a “just war”, OVs are the dogrobber and the spearhead in the war. OVs are the first to recognize tumor cells, and then signal the immune system by releasing tumor antigens from lysed tumor cells. OVs tell the immune system where the tumor is and summon immune cells from all directions to help

Table 4. Research on OVs in China

Name	Oncolytic virus type	Administration routes	Indications	Clinical phase
Pexa-Vec	Pox virus	Intratumor injection	Hepatocellular Carcinoma	III (fail)
TG6002	Pox virus	Intravenous injection	Glioma	II
OBP-301	Adenovirus	Intratumor injection	Melanoma	II
Toca511	Retrovirus	Intratumor injection	Glioma	III
Reolysin (AN1004, pelareorep)	Reovirus	Intravenous injection	Breast cancer	III
ADV-TK	Adenovirus	Intratumor injection	Malignant tumor	III
E10A	Adenovirus	Intratumor injection	Head and neck squamous cell carcinomas	III
EDS01	Adenovirus	Intratumor injection	Head and neck cancer	II
KH901	Adenovirus	Intratumor injection	Head and neck cancer	II
OrienX010	HSV	Intratumor injection	Melanoma	II
OH2	Herpes virus	Intratumor injection	Colorectal cancer	II
T3011	HSV	Intratumor injection	Solid tumor	I
SynOV1.1	Adenovirus	Intratumor injection	Solid tumor	I

HSV, Herpes simplex virus.

kill the tumor [15, 48]. Due to defects in the interferon (IFN), tumor cells cannot regulate the virus defense system [49]; therefore, OVs can replicate in tumor cells. In addition, overactive RAS signaling in tumor cells can also promote selective replication of reovirus HSV and VV in tumor cells [5, 12, 48]. An animal study evaluating the efficacy of recombinant vaccinia virus JX-594 in combination with a PD-1 inhibitor and a CTLA-4 inhibitor found that the combination promoted the regression of renal cancer mass and the development of long-term specific immune memory against renal cancer in mice, improving survival [50]. An evaluation of oncolytic adenovirus CAdTrio (CD44v6) BiTE insertion into CAdDuo increased the antitumor activity of HER2-targeting CAR T cells. Results showed that CAdTrio and HER2.CAR T cells can bind to different classes of receptors (CAR and natural T cell receptor [TCR]), thus achieving dual targeting of both tumor antigens and producing a wide range of tumors Effective and long-lasting antitumor activity prolonged the survival of mice [51].

Development status of OVs in China

In 2018, Opdivo (nivolumab) and Keytruda (pembrolizumab) were approved for commercial use, driving the development of immunotherapy in China. As a type of immunotherapy, OV has a significant therapeutic effect on solid tumors, and its indications continue to expand in clinical trials. With the rapid development of medical field in China and improvement of the government's regulatory system for the OV industry, more than 10 types of OVs are being investigated currently in China (**Table 4**), with broad application prospects in consideration. The development of OVs in China has already made remarkable achievements. Toca511, Reolysin, ADV-TK, and E10A OVs have already entered phase III clinical stages.

At present, H101 is the only OV product in the Chinese market and is constantly being explored for its new indications. Despite the evidence accumulated over a decade regarding the treatment of patients with advanced nasopharyngeal carcinoma using H101 in combination with chemotherapy, as well as that of other solid tumors, there are still many mechanisms and clinical indications that have remained unexplored. The antitumor effect of H101 along with the underlying mechanisms and new clinical indications including malignant pleural effusion, melanoma, liver cancer, and lung cancer, need exploring. Since 2019, studies on H101 have achieved remarkable progress in basic and clinical settings. A survey of the recently registered clinical studies and related articles has revealed nine registered clinical studies of H101 in tumor treatment (**Table 5**) and 19 articles published since 2019 (**Table 6**).

Challenges and prospects

OVs have attracted increasing attention owing to their remarkable efficacy in antitumor treat-

Table 5. Clinical trials of H101 in recent years

Clinical Registration Number	Title	Investigator	Combined therapies	Indication	Time	Clinical stages
ChiCTR2100051250	Observation of the Clinical Efficacy of Recombinant Human Adenovirus Type 5 Intraperitoneal Injection Compared with Cisplatin in the Treatment of Malignant Ascites	First Teaching Hospital of Tianjin University of Traditional Chinese Medicine	Single drug	Malignant pleural/ peritoneal effusion	2021/10-2023/12	Others
NCT05051696	Intra-Tumor Injection of Oncolytic Viruses H101 Combined with or Without Radiotherapy in Refractory/Recurrent Gynecological Malignancies	First Affiliated Hospital of Xi'an Jiaotong University	Radiotherapy	Gynecological cancer	2021/09-2023/12	Others
ChiCTR2100045010	Recombinant Human Adenovirus Type 5 Compared with Intraperitoneal Injection of Cisplatin in the Treatment of Malignant Ascites	First Teaching Hospital of Tianjin University of Traditional Chinese Medicine	Single drug	Malignant pleural/ peritoneal effusion	2021/04-2023/12	Others
NCT04771676	Intraperitoneal Injection of Oncolytic Viruses H101 for Patients with Refractory Malignant Ascites	Fudan University Shanghai Cancer Center	Single drug	Malignant pleural/ peritoneal effusion	2021/03-2022/12	II
ChiCTR2000036827	Clinical Study on the Efficacy and Safety of Oncorine (Recombinant Human Adenovirus Type 5 Injection) Combined With PD-1 Monoclonal Antibody and Anti-Vascular Drugs in the Treatment of Advanced Malignant Melanoma with Liver Metastasis	Shanghai Skin Disease Hospital	Immunotheray	Melanoma	2020/10-2022/09	0
ChicTR2000037525	The Efficacy and Safety of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Combined with Recombinant Human Adenovirus Type 5 and Chemotherapy in the Treatment of Metastatic Osteosarcoma: A Prospective, Single-Arm, Exploratory Trial	Shanghai Sixth People's Hospital	Immunotheray + Chemotheray	Osteosarcoma	2020/10-2022/09	II
ChiCTR2000033959	Clinical Study on the Efficacy and Safety of Oncorine (Recombinant Human Adenovirus Type 5 Injection) Combined With PD-1 Monoclonal Antibody in the Treatment of Advanced Malignant Melanoma	Shanghai Tenth People's Hospital	Immunotheray	Melanoma	2019/12-2022/04	IV
ChiCTR1900027922	Clinical Study for Efficacy and Safety of Oncorine (Recombinant Human Adenovirus Type 5 Injection) Combined with Mfolfox6+ Bevacizumab in the Treatment of Unresectable Colorectal Adenocarcinoma with Liver Metastases	Shanghai Tenth People's Hospital	Chemotherapy + Radiotherapy	Liver metastases of colorectal cancer	2019/10-2021/10	IV
ChiCTR1900025112	Therapeutic Effect of Oncorine Intratumor Injection Combined with Sintilimab and Tegafur, Gimeracil and Oteracil Porassium Capsules in Advanced Pancreatic Cancer	Affiliated Hospital of Nantong university	Chemotherapy	Pancreatic cancer	2019/09-2021/08	IV
NCT03780049	HAIC Plus H101 Vs HAIC Alone for Unresectable HCC At BCLC A-B	Sun Yat-sen University	Chemotherapy	Liver cancer	2018/10-2023/10	III
ChiCTR1800017971	Clinical Study of Recombinant Human Adenovirus Type 5 (H101) Combined with PD-1 Antibody in The Treatment of Advanced Solid Tumors	The Second Hospital of medical University	Immunotheray	Others	2018/09-2022/09	IV
NCT03790059	Radiofrequency Ablation Combined with Recombinant Human Adenovirus Type 5 in the Treatment of Hepatocellular Carcinoma	Institute of hepatobiliary surgery, Southwest Hospital	Radiotherapy	Liver cancer	2016/10-2020/09	Others
NCT02579564	Systemic Chemotherapy Combined with Recombinant Human Adenovirus Type 5 and Endostatin Injections for Treatment Malignant Hydrothorax in NSCLC Patients	Xinqiao Hospital of Chongqing	Chemotherapy	Malignant pleural/ peritoneal effusion/ lung cancer	2016/10-2018/12	III
ChiCTR-OPN-15006746	TAI Versus TAI Plus H101 on NSCLC	West China Hospital Sichuan University	Chemotherapy	Lung cancer	2015/06-2017/06	IV
ChiCTR-OPC-15006142	The Treatment of Locally Advanced Cervical Cancer by Recombinant Human Adenovirus Type 5 Injection (H101) Combined with Radiotherapy and Chemotherapy	Cancer Hospital of The University of Chinese Academy of Sciences	Chemotherapy + Radiotherapy	Cervical cancer	2015/03-2017/12	II
NCT01869088	TACE Plus Recombinant Human Adenovirus for Hepatocellular Carcinoma	Cancer Center, Sun Yat-sen University	Chemotherapy	Liver cancer	2013/01-2018/01	III
ChiCTR2000037761	Clinical Study on the Efficacy and Safety of Oncolytic Adenovirus Combined With PD-1 Monoclonal Antibody in Advanced Unresectable Malignant Melanoma	Shanghai Skin Disease Hospital	Immunotheray	Melanoma	-----	0

Table 6. Documents published on H101 from 2020 to 2021

Title	Published year	Name of published journals/conferences	IF/Core Journals
A Tumor-Targeted Replicating Oncolytic Adenovirus Ad-TD-nsIL12 as a Promising Therapeutic Agent for Human Esophageal Squamous Cell Carcinoma	2020	Cells	SCI (IF=6.602)
A recombinant human adenovirus type 5 (H101) combined with chemotherapy for advanced gastric carcinoma: A retrospective cohort study	2021	Frontiers in Oncology	SCI (IF=6.244)
A Review on the Advances and Challenges of Immunotherapy for Head and Neck Cancer	2021	Cancer Cell Int.	SCI (IF=5.721)
Clinical Efficacy and Safety of Recombinant Human Adenovirus Type 5 Injection Combined with Chemotherapy for Advanced Gastric Carcinoma	2021	Scientific Reports	SCI (IF=4.371)
Clinical Efficacy and Safety of Recombinant Human Adenovirus Type 5 Injection Combined with Chemotherapy for Advanced Cervical Cancer	2021	Scientific Reports	SCI (IF=4.371)
Successful treatment of a 19-year-old patient with locally advanced clear cell adenocarcinoma of the uterine cervix using recombinant human adenovirus type 5 (Oncorine) combined with chemoradiotherapy: a case report	2021	Annals of Translational Medicine	SCI (IF=3.932)
Recombinant Human Adenovirus Type 5 (Oncorine) Reverses Resistance to Immune Checkpoint Inhibitor in a Patient with Recurrent Non-Small Cell Lung Cancer: A Case Report	2021	Thoracic Cancer	SCI (IF=3.504)
Advanced Hepatocellular Carcinoma Treated by Radiofrequency Ablation Combined with Oncolytic Virus and Anti-PD-1 Antibody Therapy: A Case Report and Literature Review	2021	Journal of International Medical Research	SCI (IF=1.673)
The Efficacy and Safety of Recombinant Human Type-5 Adenovirus H101 in the Treatment of Intermediate to Advanced Solid Tumors: A Systematic Review and Meta-Analysis	2021	Translational Cancer Research	SCI (IF=1.24)
Shanghai Expert Consensus on the Clinical Application of Oncolytic Viruses in the Treatment of Malignant Tumors (2021 Edition)	2021	China Oncology	CSTPCD, PKU
Progress in Treatment of Breast Cancer with Oncolytic Viruses	2020	Chinese Journal of Clinical Oncology	CSTPCD, PKU
Progress in Clinical Application of Oncolytic Virus Anti-Tumor Therapy	2021	Chinese Journal of Clinical Oncology	CSTPCD, PKU
Progress in Application of Recombinant Human Adenovirus Type 5 Injection in Different Solid Tumors	2021	Chongqing Medical Journal	CSTPCD, PKU
Recombinant Human Adenovirus Type 5 Injection Combined with Haploidentical Natural Killer Cell Immunotherapy for Ovarian Cancer Malignant Peritoneal Effusion: A Case Report	2020	China Journal of Modern Medicine	CSTPCD, PKU
Aspergillus A (TSA) Enhances the Antitumor Activity of H101 Virus in Thymic Carcinoma by Up-Regulating Coxsackievirus and Adenoviral Receptor (CAR) Expression Through Inhibition of MAPK/ERK Pathway	2020	Chinese Journal of Microbiology and Immunology	CSTPCD, PKU
Clinical Study of Local Intratumoral Injection of Recombinant Human Adenovirus Type 5 in the Treatment of Advanced Liver Cancer	2021	China Modern Doctor	No Core Journal
ASCO Poster of Oncorine Science and Technology Commission Study Protocol-Summary of Colorectal Cancer Liver Metastasis Cases	2021	ASCO	
Clinical Efficacy and Local Immune Response Evaluation of Intraperitoneal Injection of Oncolytic Virus in Malignant Ascites	2021	CSCO	
CSCO Conference Live Broadcast of Oncorine Science and Technology Commission Study Protocol - Summary of Colorectal Cancer Liver Metastases	2020	CSCO	
Study Protocol CSCO Poster of Oncorine Science and Technology Commission - Summary of Lung Cancer Metastasis Cases	2020	CSCO	
CSCO Poster of Oncorine Science and Technology Commission Study Protocol - Summary of Melanotic Cancer Metastasis Cases	2020	CSCO	

IF, Impact Factor; SCI, Science Citation Index; ASCO, American Society of Clinical Oncology; CSCO, Chinese Society of Clinical Oncology; CSTPCD, Chinese Scientific Papers and Citation Database; PKU, Chinese Core Journal Criterion of Peking University.

ment. However, considering the status of more than 40 drugs currently under development, that of OV drugs is still in the initial stage, and there are many problems yet to be solved, such as (1) targeting (the key problem in the treatment of tumors is to improve the targeting of tumors), (2) selection of vector cells (improvement in the efficiency of virus infection in vector cells and the time and place of virus release by cells), (3) antibody neutralization (the virus enters the human body to trigger an immune response that produces antibodies to neutralize the virus and reduce its efficacy), and (4) viral diffusion (large primary tumors limit effective viral diffusion, thus reducing the efficacy of oncolytic drugs) [5, 11, 52, 53].

Other areas of concern include whether OV drugs enter the ecological environment with excreta, and whether the virus infects nurses, family members, or other surrounding people during the treatment of patients. Therefore, a systematic evaluation of the possibility of impact of oncolytic drugs on the environment, the degree of impact, and mitigation measures would be necessary in future.

At present, the administration routes of OVs are mostly intratumoral and intravenous injections. Intratumoral injections could make the OVs directly reach the lesion with high safety; however, the OVs might not be evenly distributed in the tumor, thus reducing the efficacy. Intravenous injections of OV products avoid the operational difficulties of localization to each tumor; however, there is a risk that the virus cannot be transported to the tumor site, limiting the biological distribution of the virus, along with other issues, such as dilution of the virus, antibody neutralization, and untargeted infection [54]. How to improve the effect of oncolytic drugs and reduce the risk, how to choose the administration routes according to the characteristics of OVs and characteristics of patients' tumors, and whether special devices would be required for drug delivery remains to be explored in future studies.

The effect of antiviral drugs on the efficacy of OVs is a concern in clinical treatment. OVs with different structural modifications have different sensitivities to antiviral drugs. The latter cannot be avoided in the treatment of some tumors. Therefore, when OVs are combined with antiviral drugs, drug interactions should be avoided, according to the sensitivity of OVs to antiviral drugs, and a drug administration plan should be formulated only after specific analysis.

Conclusion

OVs show accurate oncolysis and activate immune responses against various types of tumors, which have a positive effect on the treatment of patients with cancers and could be used in the treatment of a variety of tumors. The AEs are mild and may be resolved after intervention or drug discontinuation. How to further improve the effectiveness and safety of OVs, optimize the route of administration in clinics, and promote the development of biomarkers are the main tasks for the future. Oncolytic virotherapy is expected to realize personalized and precise immunotherapy in the near future. However, most of the OVs under development are still in an early stage, and need refinement before being brought to market.

Disclosure of conflict of interest

None.

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