



Oncolytic virotherapy for hepatocellular carcinoma: A potent immunotherapeutic landscape

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Specialty type: Oncology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade C

Scientific Significance: Grade B

P-Reviewer: Abid S, Pakistan

Received: December 28, 2023

Revised: April 24, 2024

Accepted: May 13, 2024

Published online: July 15, 2024

Processing time: 197 Days and 3.6 Hours



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Abstract

Hepatocellular carcinoma (HCC) is a systemic disease with augmented malignant degree, high mortality and poor prognosis. Since the establishment of the immune mechanism of tumor therapy, people have realized that immunotherapy is an effective means for improvement of HCC patient prognosis. Oncolytic virus is a novel immunotherapy drug, which kills tumor cells and exempts normal cells by directly lysing tumor and inducing anti-tumor immune response, and it has been extensively examined as an HCC therapy. This editorial discusses oncolytic viruses for the treatment of HCC, emphasizing viral immunotherapy strategies and clinical applications related to HCC.

Key Words: Oncolytic virus; Immunotherapeutic; Hepatocellular carcinoma; Virotherapy; Editorial

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Core Tip: Since the discovery of oncolytic virus, various preclinical studies and clinical trials have been carried out on the application of virus therapy in hepatocellular carcinoma (HCC), and people have constantly tried to optimize the efficacy of this new drug. Based on this background, this editorial introduces oncolytic viruses for the treatment of HCC, including immunotherapy strategies, and looks forward to more good clinical results.

Citation: Xiao R, Jin H, Huang F, Huang B, Wang H, Wang YG. Oncolytic virotherapy for hepatocellular carcinoma: A potent immunotherapeutic landscape. *World J Gastrointest Oncol* 2024; 16(7): 2867-2876

URL: <https://www.wjgnet.com/1948-5204/full/v16/i7/2867.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v16.i7.2867>

INTRODUCTION

Hepatocellular carcinoma (HCC) is a frequently occurring malignancy and a major contributor to the global cancer-associated deaths. Environmental and genetic hazard agents strongly modulate HCC development. Among the most prominent and preventable hazard agents are oncogenic viral infection with hepatitis B virus or hepatitis C virus (HCV), alcohol abuse, obesity and diabetes[1]. With rising HCC incidences year by year, treatment options have also been improved, common therapies are surgical resection, liver transplantation, thermal ablation, intra-arterial therapy, radiotherapy, *etc.* Systemic therapies such as Sorafenib and Lenvatinib should be considered when the HCC is at an advanced stage and cannot be treated locally[2]. Despite the variety of treatment options for HCC, current treatments still do not extend overall survival for advanced HCC.

In recent ten years, with the deepening of cancer immunotherapy research, immunotherapy has become a hot spot for treating HCC. Immunotherapies are typically checkpoint inhibitors, adoptive cell therapy, and viral therapy[3]. Among them, viral therapy encompasses non-replicating viral delivery as delivery vectors and replicating oncolytic viruses. Oncolytic viruses belong to a large virus family that can directly kill tumor cells, and have been widely concerned owing to their strong oncolytic activity, good targeting and reduced drug resistance[4]. Nowadays, several oncolytic viruses are employed in cancer research, including adeno-, vaccinia-, reo-, vesicular stomatitis-, herpes simplex virus (HSV), and so on. The oncolytic mechanism of oncolytic virus mainly includes: (1) Direct oncolytic effect. The imbalance of specific proteins such as PTEN, TP53, RAS, and RB1 in tumor cells makes it preferentially infected by oncolytic virus[5]. The virus replicates itself with the help of host intracellular resources. When the amount of intracellular virus reaches a certain level, the virus lyses cells and releases excess progeny viruses to continue further infection of other tumor cells, therefore achieving oncolytic effect; (2) stimulate anti-tumor immune response, which is the most important part of anti-tumor effect[6]. Due to its own variability, tumor cells do not respond to the immune system, that is, forming cold tumors. However, restoring the tumor cells-induced immune response, and conversion of cold to hot tumors, is also a big challenge. As viral lysis of tumor cells (Figure 1), secretion of soluble tumor-related antigens, cell-derived damage associated molecular patterns, and viral pathogen associated molecular patterns are identified and sequestered by antigen-presenting cells, and both innate and adaptive immunity are activated, thus playing a proximal or distal anti-tumor role; (3) through genetic engineering, the virus can express some foreign genes, such as some tumor suppressor proteins or functional RNA. The insertion of foreign genes is accompanied by the deletion of some non-essential genes of the virus, which can give the virus higher safety and oncolytic effect. As the first oncolytic virus (OV), talimogene laherparepvec (T-Vec) received approval from the United States Food and Drug Administration, loss of *ICP47*, which encodes antigen-presenting inhibitors, facilitating entry of tumor-associated antigens and viral antigens into the major histocompatibility complex (MHC) Class I complex and promotes an immune response against tumor cells. Simultaneously, the granulocyte-macrophage colony-stimulating factor (GM-CSF) content accelerated dendritic cell maturation and enhanced their tumor cells-induced immune response[7]; and (4) OV can also generate neutrophil aggregations within blood vessels *via* its action on stromal cells in the tumor environment. These neutrophils promote fibrin accumulation and secrete clotting agents, thus ultimately impairing the tumor vasculature. Generally, the anti-tumor mechanisms of OV are diverse, and more and more preclinical studies have shown that oncolytic viruses have significant anti-tumor effects, and the clinical treatment results of OV are also satisfactory and encouraging.

ONCOLYTIC VIRUS THERAPY FOR HCC

Oncolytic viral treatment is highly efficacious in eradicating tumors. Oncolytic viruses used for treatment can be mainly divided into ssRNA and dsDNA viruses. dsDNA viruses are typically adenovirus, vaccinia virus (VV), herpes virus, and so on. ssRNA viruses are either just viruses (Coxsackie, Seneca Valley, or poliovirus) or negative viruses [measles, Newcastle disease, or vesicular stomatitis virus (VSV)][8]. DNA viruses possess extensive genome which facilitate genetic engineering operations, their life cycle and molecular biology are well understood, and most clinical studies use DNA viruses because they are relatively stable. RNA viruses also have the unique advantages of strong oncolytic effect and weak pathogenicity. Tumor selection mechanisms of oncolytic viruses vary, the oncolytic viral HCC treatment is also varied depending on the viral characteristics.

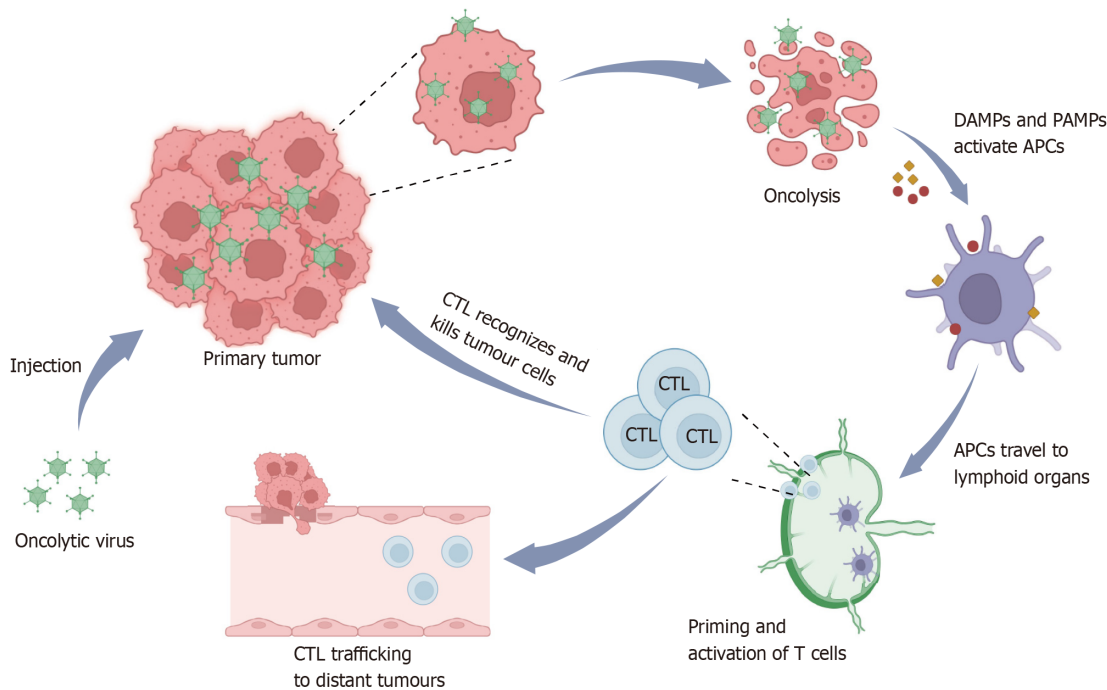


Figure 1 Oncolytic virus promotes both regional and systemic anti-tumor activity. Following viral infection of tumor cells, the virus replicates proficiently within the cell, and after lysis of tumor cells, the soluble tumor-associated antigens, viral pathogen-associated molecular models, and cell-derived damage-associated molecular models release recruits and activates antigen-presenting cells (APCs). APC then migrates to the lymph nodes and initiates adaptive T cell immunity to the tumor. These cytotoxic T cells identify and destroy proximal or distal tumor cells. CTL: Cytotoxic T cell; APC: Antigen-presenting cell; DAMP: Derived damage-associated molecular model; PAMP: Pathogen-associated molecular models.

Adenovirus is an icosahedral, unenveloped double-stranded DNA virus with about 34-36 KB genome size[9]. Adenovirus type 5 proliferation ability, within the host genome copy number is high, the virus particles have good stability, can produce high drop degree of virus particles in order to meet the experimental requirements, they can be used for gene therapy. The genome structure and life cycle of adenoviruses have long been well understood, and molecular modification of adenoviruses is relatively easy. Adenovirus replication-related genes are mainly *E1-E4* genes. Certain gene deletions can enhance safety and oncolytic performance of adenovirus. Such as delete defeat of *E1A-CR2* in tumor cell specificity for Ad replication[10]. In addition, replacing the *E1A* promoter of the virus with the liver cancer tissue-specific promoter alpha-fetoprotein may also enhance the safety of the virus. ZD55 is a novel oncolytic adenovirus vector with the *E1B-55K* deletion constructed by our group, which can express more foreign inserted genes than Ad. We constructed a recombinant ZD55-IL-24 adenovirus and successful IL-24 expression enhanced the oncolytic effect of the virus (about 100 times higher than that of ONYX-015), in addition, ZD55-IL-24 did not have significant cytotoxic and apoptotic effects on normal cells. Meanwhile, the ZD55-IL24 and cisplatin co-therapy increased tumor cell death[11]. We also employed this vector to deploy one fused gene (*ZD55-TRAIL-IETD-Smac*) into HCC cells. The *ZD55-TRAIL-IETD-Smac* combination therapy facilitated quick and effective apoptotic tumor cell activation and total elimination of tumor xenografts in all exposed animal models, its effect of completely eliminating xenograft liver cancer was matched with ZD55-TRAIL + ZD55-Smac which could be an effective treatment strategy for HCC[12]. Tumor suppressor lung cancer 1 (TSLC1) is frequently down-regulated in multiple cancer forms, such as, HCC, and we found that TSLC1 inhibits tumor growth by affecting the Wnt signaling pathway[13]. Further, we designed a dual-regulated oncolytic adenovirus Ad-wnt-*E1A*(Δ 24bp)-TSLC1, which modulates the Wnt and Rb axes and harbors the tumor suppressor gene TSLC1. The Ad-wnt-*E1A*(Δ 24bp)-TSLC1 can induce tumor cell autophagy death. *In vivo* investigations revealed that this recombinant adenovirus effectively induces hepatic cancer stem-like cell apoptosis, inhibits tumor metastasis and growth, and prolongs mice survivability. Hence, this new oncolytic adenovirus has a promising prospect in the treatment of liver cancer[14].

VV is a member of the poxviridae family and is a linear double-stranded DNA virus with 190kb genome size encoding over 200 genes[15]. VV has its own unique biological characteristics: The replication time is shorter, and the first generation of the virus is released 8 h after VV infects cells, and 48-72 h after the infected cells are lysed[16]. Genetically safe and stable, unlike other DNA viruses, VV always exists in the cytoplasm without entry into the nucleus from the beginning of its entry into the cell. Therefore, the viral DNA does not insert itself into the host genome and does not induce host genetic changes. The unique infection mode of VV determines that it can infect almost all cell lines, unlike adenovirus, and it does not need to enter the target cells through specific cell surface receptors, but infects the target cells through multiple membrane fusion pathways. In addition, compared with somatic cells in the non-dividing/resting phase, VV is more likely to infect cancer cells with active cell cycles. Even without the recognition of specific receptors on tumor cell surfaces, VV still has natural targeting to cancer cells. VV virus particles are stable, which is convenient for storage, transportation and clinical experiments[17]. However, the large genome of VV also brings risks to treatment, and

a large number of unclear genes bring certain risks to treatment[18]. At present, VV is mainly modified around targeting and efficacy. For example, by missing thymidine kinase (TK), VV is highly targeted to tumor cells. Because VV replication requires a high concentration of nucleotides, but normal cell proliferation requires TK, so the nucleotide concentration is usually low. However, tumor cells do not rely on TK for cell proliferation, so they have a higher concentration of nucleotide pools, which is conducive to VV replication. Therefore, oncolytic VV lacking TK tends to replicate in tumor cells[19,20]. The specificity of TK-deficient VV in tumor cells was reported in animal models of colon cancer, melanoma, sarcoma, and liver cancer[21]. Zhou *et al*[22] have evaluated the effectiveness of VV carrying Marine lectins. This study was to assess the cytotoxic effects of oncoVV harboring tachyplesus tridentatus lectin (oncoVV-TTL), aphrocallistes vastus lectin (oncoVV-AVL), white-spotted charr lectin (oncoVV-WCL), and asterina pectinifera lectin (oncoVV-APL) on HCC, the results show that oncoVV-AVL has the strongest anti-tumor effect, which may promote self-replication through various pathways including MAPK, Hippo, PI3K, lipid metabolism, and androgen pathway.

HSV is a coated double-stranded linear DNA virus carrying a sizable (152 kd) genome. HSV contains two serotypes, HSV-1 and HSV-2, among which type 1 is widely examined[23]. HSV as an oncolytic virus has the following advantages: The genome is large; it can introduce large fragments of genes or multiple foreign genes; the virus replication ability is strong; the host gene mutation is not easy to occur; and the host range is wide. However, the strong HSV-1 virulence and immunogenicity itself has a “double-edged sword” consequence, and its prompt immune-regulated viral clearance and possible cytotoxicity can cause delivery and safety issues, which increase the difficulty of administration, and the accumulation of muscular injection in the liver. Therefore, most therapeutic administration regimens are intratumoral injection[24]. Nakatake *et al*[25] used third-generation oncolytic HSV type 1 (HSV-1) T-01 to examine antitumor activities of HCCs. The results showed that T-01 was toxic to 13 of 14 cell lines (*in vitro*), the *in vivo* efficacy of T-01 was studied using human cells HuH-7, KYN-2, PLC/PRF/5, HepG2, and mouse cells Hepa1-6. T-01 inhibited human hepatoma- and hepatoblastoma cell line-mediated tumor growth. At present, several HSV mutants have been successfully created to adapt to different therapeutic strategies. For example, G207, reportedly the first HSV examined in clinical trials (CTs), replicates specifically in cancer, but not normal cells and neurons[26]. In preclinical studies, tumor model G207 induced systemic antitumor immune response[27] in a G207 treatment children with high grade glioma[28]. Herein, twelve high-grade glioma patients aged 7-18 years were treated. Median overall survival was 12.2 months (95% confidence interval: 8.0-16.4). As of June 5, 2020, 4 patients survived 18 months following G207 treatment. Evidence showed that during G207 treatment, “cold” to “hot” tumor transformation significantly increased the tumor-infiltrating lymphocyte quantity, (ClinicalTrials.gov number: NCT02457845) it is hoped that future research will be carried out in HCC therapy.

VSV is a coated negative strand RNA rhabdovirus[29]. Types of infection, almost can infect all types of cells, including normal, healthy cells, but owing to the form of interferon antiviral responses in healthy cells, the types of even after the infection of normal cells cannot copy within the cell[30]. However, interferon (IFN) signaling within tumor cells is often defective, so VSV is able to infect and selectively destroy tumor cells[31]. The G protein of VSV initiates the viral infection process by binding to cell surface receptors, and the M protein causes tumor cell apoptosis by inhibiting the host antiviral response[32]. Shinozaki *et al*[33] found that the recombinant VSV vector harboring B-galactosidase (VSV-b-gal) was injected through arteries into rats with orthotopic transplantation of multifocal HCC, resulting in extensive tumor lysis in hepatic multifocal HCC. This suggests that oncolytic VSV is a potential efficacious and safe therapy for multifocal HCC patients in the near future. Through hepatic artery drug types, within the scope of the maximum tolerated dose (MTD), selective replication can enter HCC lesions, leading to a large number of tumor necrosis, but to give the medicine more than MTD, experimental animals cause nerve toxicity and acute liver toxicity. When the MTD of the host to VSV is increased, the dosage of VSV can be increased to obtain better curative effect. Shinozaki *et al*[34] verified this hypothesis by using exogenous IFN in preventive treatment of rats, which improved the VSV MTD in rats, and the IFN presence had no effect on the replication ability of VSV. No damage to the curative effect of HCC, which in order to solve the limitations of clinical dosage provides a new train of thought.

Reovirus (REO) is a double-stranded RNA virus and benign human pathogen that discreetly replicates and lysis cells in cells with abnormal Ras pathways, which are associated with most cancers[35]. Wild type REO to tumor cells have natural targeting[36], and HCV is a critical contributor to viral liver cancer, and evidences revealed that REO-induced cytokine response effectively inhibits HCV replication *in vitro* and *in vivo* during HCV-HCC therapy, while showing good efficacy in HCC preclinical models by activating innate degranulated immune cells[37]. Therefore, REO is a potential alternative to complement and support the available HCV-HCC treatment.

Influenza virus (IV) is an enveloped negative strand RNA virus, which is known to cause influenza. It consists of four genera, A, B, C, and D, with type A being the most widely examined[38]. Because of its lack of reverse transcriptase and genome integration activity, it is an ideal carrier for oncolytic therapy[39]. However the health problems caused by the IV need to be special attention, therefore, which the IV is used as a soluble tumor agent needs to enhance its anti-cancer properties, and avoid the infectious pathogenic, and lack of nonstructural protein1 (delNS1) is a more attractive strategy. García-Sastre *et al*[40] demonstrated that influenza A virus delNS1 could not replicate in mice with normal IFN, nonetheless, it was lethal in mice with abnormal IFN signaling pathways. Due to many cancer IFN signaling pathway is not active, the lack of NS1 protein makes influenza A virus to malignant tissue targeting property[41]. A study successfully constructed an influenza A virus (delNS1-GM-CSF) expressing GM-CSF with partial deletion of NS1, and *in vitro* experiments found that the virus had selective cytotoxicity in multiple HCC cell lines, whereas no alteration was evident in normal liver cell line LO2. In a xenotransplantation model of human Hep-G2 liver cancer cell line, delNS1-GM-CSF significantly suppressed tumor development in a dose-reliant fashion after intratumoral injection, and the tumor inhibitory effect of delNS1-GM-CSF was observed in HCC clinical samples. These findings suggest that delNS1-GM-CSF is a highly efficacious oncolytic agent against HCC.

Newcastle disease virus (NDV) is a coated negative strand RNA virus that has a natural host in birds and they gain entry to cells *via* association with sialic acid residues that reside on human and rodent cancer cells[43]. The natural sensitivity of NDV to IFN, combined with defects in tumor cells' own IFN signaling pathway, makes NDV an ideal candidate for OV therapy[44]. However, compared to other Ovs, NDV virulence and pathogenicity were in the human body is lower, thus NDV in soluble tumor need to significantly improve performance. NDV enters cells by membrane fusion, a process in which fusion protein F is required[45]. Altomonte *et al*[46] demonstrated a new NDV vector that contains a mutation in the F gene leucine at amino acid 289 (L289A). Relative to the rNDV/F3aa control virus, recombinant vector rNDV/F3aa (L289A) enhances HCC fusion and cytotoxicity *in vitro*.

OVS COMBINED WITH IMMUNOTHERAPY

HCC is considered highly immune tolerance of the tumor, abnormal T cell activation, immune checkpoints to rise, immunosuppressive factors produced, immunosuppressive cells clustering cause of HCC was established highly immunosuppressive tumor microenvironment, the antitumor immune response paralysis[47]. Although researchers have made some advances in immunotherapy in recent years, such as the use of drugs such as the immune checkpoint inhibitor Immune checkpoint inhibitors, tumors have evolved immunoediting and thus have a greater ability to escape immune, so the treatment of HCC patients with these drugs remains limited. Emerging evidences suggest a strong role of the immune system in oncolytic virus therapy, and the use of oncolytic virus can reactivate the immune system and establish immune control against tumors.

A more attractive strategy is to add different immunomodulatory transgenes to the virus. For example, cytokines are proteins that regulate the immune response, and the VV performance is improved by carrying certain immune-stimulating molecules through VV. Arming VVS with cytokines namely GM-CSF, IL-2, IL-6, IL-12, IL-15, IL-23, and IL-24 exhibited superior anti-cancer activities and significant safety profiles in clinical and preclinical examinations[48,49]. For example, IL-24 suppresses tumor development, invasion, angiogenesis and metastasis, Promote cell apoptosis[50]. Deng *et al*[51] generated a VV Light 9 (VG9-IL24) containing IL-24 gene, and the results showed that VG9-IL24 had a strong ability to infect HCC cell lines *in vitro*, and could not infect normal cells. After VG9-IL24 infected cells, it significantly upregulated IL-24 content and promoted cell apoptosis. In animal models, tumor development was drastically inhibited with prolonged survival duration among mice treated with VG9-IL24. By combining oncolytic adenovirus with TIM-3 immune checkpoint molecular specific antibody (α -TIM-3), we also successfully constructed a novel adenovirus Ad-GD55- α -Tim-3, which can induce α -TIM-3 expression in hepatoma cells after infection, and augment anti-tumor efficiency and local immune response of oncolytic virus. Ad-GD55- α -TIM-3 is involved in a remarkably potent regional immune response in a simulated tumor immune microenvironment. Ad-GD55- α -TIM-3 oncolytic adenovirus is an HCC therapeutic candidate[52]. Zhang *et al*[53] successfully constructed an adenovirus Ad5-PC harboring bi-specific protein, one end of which expresses the PD-1 extracellular domain and the other end contains the CD137L extracellular domain (PD1/CD137L). Ad5-PC stimulates high level of interferon gamma production, continuously activates CD8+ T cells, and promotes immune cell infiltration. Induce anti-tumor immune response. Ad5PC significantly improved anti-tumor function in both ascites and subcutaneous HCC tumor models, with long-term cure rates of 70% and 60%, respectively. In addition, human *IFN- β* gene is specifically present within tumor cells and inhibit the growth of tumor cells, which is also a new tumor therapeutic target[54]. And, the double specificity and three specific antibodies in immune therapy also showed great prospect, a frontier study show that, the researchers used BITE forces soluble tumor adenovirus, This BITE interacts with the fibroblast activating protein on cancer-associated fibroblasts (CAF) and CD3e on T cells, effectively activating T cells while also inducing fibroblast death. Armed OV resulted in CAF-related immunosuppressive factor depletion, pro-inflammatory cytokine elevation, and upregulation of the antigen presentation, t cell function, and transport marker expressions, successfully killing tumor cells and fibroblasts. Clinical studies are expected[55]. The relatively new chimeric antigen receptor T (CAR-T) immunotherapy is reported to have excellent efficiency in hematological tumors, however, it does not efficaciously treat solid tumors[56]. Several investigations revealed that OV can be used as a complementary agent of CAR-T in solid tumors, helping CAR-T survival and accumulation, significantly improving the efficacy. This may be the future direction of the OV treatment for HCC[57].

Excitingly, immunomodulatory drugs could also act as perfect companions for oncolytic viruses. It is difficult for the immune system stimulated by oncolytic virus to obtain sustained anti-tumor response, and the existence of antiviral immune response is the main reason[58]. Once the OV in the host is cleared by the immune response, the tumor microenvironment with immunosuppressive response will be restored, and the tumor is easy to relapse. The up-regulated immune checkpoint in the tumor is an important reason for the generation of immunosuppressive tumor microenvironment. ICIs can inhibit the immunosuppressive signaling pathway, and the combination therapy with OV will be a promising anti-tumor strategy. OVH-aMPD-1, for example, is a kind of HSV targeting the PD-1/PD-L1 axis. Under interaction with anti-TIGIT antibodies, the percentage of immune-specific cells in tumor cells is significantly increased. Combined therapy blocks immune checkpoints and enhances tumor-specific immune response of subcutaneous implanted tumors, highlighting the benefits of collaborative therapy[59]. Pexastimogene devacirevec (Pexa-Vec, otherwise called JX-594) is a VV, and several CTs have examined its role in treating liver cancer. A phase I/II CT a JX-594 joint worth of sheet resistance as a first-line treatment for advanced HCC patients (ClinicalTrials.org: NCT03071094) was performed. Subjects received injections of JX-594 three times every two weeks and OPDIVO intravenously every two weeks (starting at week 2). The overall response rate for 12 cancer patients was 33.3% (9.9% to 65.1%). However, the severe adverse events risk in stage I and Stage II a was 85.71% and 80.00%, respectively, so the prospect of synergistic therapy should also consider how to overcome cytotoxicity problems.

CTS OF OVS FOR HCC

So far, we have searched for OV CTs on HCC at clinicaltrials.org (Table 1). Some experimental results have been encouraging. A Phase I CT (NCT00844623) evaluated the feasibility and safety of intratumoral first-generation HSV-TK gene-encoding adenovirus vector (Ad.TK) administration, with subsequent systemic ganciclovir therapy among advanced HCC patients. The results showed no hepatotoxicity, even in patients with cirrhosis. Fever, influenza-like syndrome, administration location pain, and pancytopenia were the most prevalent complications. There were no partial responses, and 60% participants exhibited stable tumors with injectable lesions. Importantly, the 2 patients given the highest dose exhibited some necrosis within the tumor on imaging. Among them, 1 attained sustained stability and was alive for 26 months[60]. CTs confirmed the good efficiency and safety profile of therapy.

JX-594 has good antitumor and immunotherapeutic effects, and is well tolerated, and is widely used in liver cancer. In a Phase I CT, 14 patients with refractory primary or metastatic HCC underwent JX-594 intratumoral shot in 3 cases of partial remission and 6 of stable disease[16]. Phase II CT to study the drug dose for the effects of the treatment of cancer of the liver (ClinicalTrials.org: NCT00554372) in 30 patients with advanced liver cancer, Survival (median survival 14.1 months) was substantially elevated among patients receiving the higher *vs* lower dose (6.7 months)[17]. It was primarily JX-594 that induced anti-tumor immunity in patients, and in addition, its anti-angiogenesis also resulted in improved survival.

OV from natural virus to recombinant virus, from single therapy to combination therapy, this is the clinical development trend, when patients tolerate drug therapy, the addition of OV can reverse this adverse situation, in the future, there could be more CTs of OV, which can enhance knowledge of OVT, far-reaching significance for subsequent treatment. A variety of treatment modalities will also benefit HCC patients.

CONCLUSION

Viruses are commonly used in cancer therapy for over a century, and with the understanding of the mechanism of virus action, coupled with the establishment of genetic engineering technology, OVTs have gradually become a mature means of cancer treatment from natural strains to recombinant viruses, the representative OVs discussed for the treatment of hepatocellular carcinoma are shown in Table 2. More and more studies have shown that OVs is also a powerful weapon of immunotherapy, OVs strongly dissolves tumor cells, and utilizes intricate modulatory networks namely immune system activation. However, the efficacy of single therapy may be limited, and the clinical research of OV therapy for HCC has gradually shifted from single therapy to OV combination therapy.

But there are still some problems to be solved. First of all, safety should be guaranteed first, in addition, the clinical drug OVs preparation is challenging and complex, and further research is needed to extract pure non-toxic single virus. Second, the system's OV management route still has shortcomings. In the systematic administration of OVs, intratumoral injection has limitations and cannot completely eradicate the tumor, and intravenous injection overcomes the obstacle of intratumoral administration, but OV suffers from the destruction of host immunity during systemic transport, and these fatal limitations remain to be solved[61]. In addition, the targeting specificity and oncolytic efficiency of OVs are important, and additional CTs are required to confirm the effectiveness of various strategies for arming and modifying viruses[62].

The application value of OV is extremely promising. In the future, more extensive and in-depth basic research and CTs will pave the way for the treatment of OV. The safety and anti-tumor activity of OVs will be the focus of future research, and combination therapy and the continuous optimization of drug administration strategy will be the future research direction.

Table 1 Clinical trials of oncolytic virus for hepatocellular carcinoma

Trial number	Virus	Disease	Status	Interventions	Trail phase	Study start
NCT00844623	TK99UN	HCC	Completed	Alone	I	2002
NCT00003147	Ad5CMV-p53 gene	Liver cancer	Completed	Alone	I	1998
NCT02509169	rAd-p53	HCC	Unknown status	Alone	II	2014
NCT00300521	ADV-TK	Advanced HCC	Completed	Alone	II	2000
NCT02418988	rAd-p53	Advanced HCC	Unknown status	TACE	II	2014
NCT01869088	H101	HCC	Unknown status	TACE	III	2013
NCT03790059	H101	HCC	Unknown status	RFA	Not applicable	2016
NCT03313596	ADV-Tk	Advanced HCC	Unknown status	LT	III	2013

NCT05113290	H101	HCC	Unknown status	Sorafenib	IV	2021
NCT00629759	JX-594	Primary hepatocellular carcinoma	Completed	Alone	I	2006
NCT00554372	JX-594	Primary hepatocellular carcinoma	Completed	Alone	II	2008
NCT02562755	JX-594	HCC	Completed	Sorafenib	III	2015
NCT01387555	JX-594	HCC failed sorafenib treatment	Completed	Alone	II	2008
NCT02509507	T-Vec	HCC <i>et al</i>	Active, not recruiting	Pembrolizumab	I/II	2016
NCT04313868	GEN2	Metastatic HCC	Recruiting	Alone	I	2014
NCT05223816	VG161	HCC <i>et al</i>	Recruiting	Nivolumab	II	2023
NCT01628640	VSV (IFN- β)	HCC	Active, not recruiting	Alone	I	2012
NCT04665362	M1 virus	Advanced/metastatic hepatocellular carcinoma	Unknown status	Anti PD-1 antibody and apatinib	I	2021

VSV: Vesicular stomatitis virus; IFN- β : Interferon-beta; HCC: Hepatocellular carcinoma.

Table 2 Representative oncolytic virus for hepatocellular carcinoma

Virus name	Mode of actions/target	Virus Modification	Potential implications	Ref.
ZD55-IL-24	Combine cisplatin <i>in vitro</i> /Bel-7404, SMMC-7721	IL-24 gene, E1B 55 kDa deletion	Enhance selective cytotoxicity	[11]
ZD55-TRAIL-IETD-Smac	Intratumoral injection/Bel-7404 nude mice model	TRAIL and Smac gene, E1B 55 kDa deletion	Enhance synergistic anti-tumor effect	[12]
Ad.wnt-E1A (Δ 24bp)-TSLC1	Intratumoral injection/MHCC-97H nude mice model	TSLC1 gene, 24 bp deletion of E1A CR2	Enhance tumor selectivity antitumor activity	[14]
OncoVV-AVL	<i>In vitro</i> /Hep-3B, PLC/PRF/5, Huh7	<i>Aphrocallistes vastus</i> lectin	Enhance the ability of replication	[22]
T-01	Left lobe of the liver injection/HuH-7, KYN-2, PLC/PRF/5, HepG2 athymic mice model	-	Enhance oncolytic safety	[25]
VSV- β -gal	Administered <i>via</i> the hepatic artery/Mca-RH7777 "multifocal" HCC in the rat liver	β -galactosidase	Enhance tumor-selective viral replication, and extensive oncolysis	[33]
Wild type REO	Oral gavage/Huh7 SCID mice model	-	Inhibit the replication of HCV in HCV-HCC	[37]
delNS1	Inoculation <i>in vivo</i> /STAT12/2 mice, STAT11/1 mice, C57BL/6 mice	Partial deletion of NS	Inhibit the host antiviral response	[40]
delNS1-GM-CSF	Intratumoral injection/HepG2 nude mice model	Partial deletion of NS, GM-CSF inserted	Enhance oncolytic efficacy and safety	[42]
rNDV/F3aa (L289A)	Administered <i>via</i> the hepatic artery/Mca-RH7777 "multifocal" HCC in the rat liver	A single amino acid substitution from alanine to L289A in the F protein	Enhance tumor specific syncytial formation and necrosis	[46]
VG9-IL-24	Intratumoral injection/SMMC-7721 nude mice model	IL-24	Induce apoptosis of tumor cells	[51]
Ad-GD55- α -TIM-3	Intratumoral injection/PBMC mixed Bel-7404 BALB/c nude mice model	GP73 promoter and α -TIM-3	Enhance the antitumor efficacy and the local immune response	[52]
OVH-aMPD-1	Combination with TIGIT blockade <i>In vivo</i> /hepa1-6 nude mice model	Express a scFv against PD-1 (aMPD-1 scFv)	Remodel immunosuppressive tumor microenvironment	[59]

NDV: Newcastle disease virus; scFv: Single-chain variable fragment; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; MHC: Major histocompatibility complex; TSLC1: Tumor suppressor lung cancer 1; VSV: Vesicular stomatitis virus; REO: Reovirus; delNS1: Nonstructural protein1; TIGIT: T cell immune receptor with Ig and ITIM domains; PBMC: Peripheral blood mononuclear cell; NS: Nonstructural protein; GM-CSF: Granulocyte-macrophage colony stimulating factor; oncoVV-AVL: *Aphrocallistes vastus* lectin; L289A: Leucine at amino acid 289.

FOOTNOTES

Author contributions: Xiao R, Jin H, and Huang F performed the literature, and drafted the manuscript; Huang B, Wang H, and Wang

YG revised the manuscript; and all the authors have read and approved the final version to be published.

Supported by the Public Welfare Technology Project of Zhejiang Province, No. LGF21H160033; Zhejiang Medical Technology Plan Project, No. 2021KY047; and Hangzhou Medical Health Science and Technology Project, No. B20220173.

Conflict-of-interest statement: The authors declare that there is no conflict of interest related to this study.

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S-Editor: Chen YL

L-Editor: A

P-Editor: Guo X

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