Original Article

The efficacy and safety of oncolytic viruses in the treatment of intermediate to advanced solid tumors: a systematic review and meta-analysis

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Background: Cancer treatment remains one of the most formidable challenges worldwide. Some novel treatment strategies, including molecularly targeted therapy, gene therapy, and cellular immunotherapy, have also been investigated to improve therapeutic effects for cancer patients and have demonstrated unexpected positive effects. This systematic review and meta-analysis evaluated the efficacy and safety of oncolytic virus (OV) monotherapy or combination therapy for intermediate to advanced solid tumors.

Methods: We retrieved articles from PubMed, Embase, Web of Science, CNKI, Wanfang and VIP. The quality of the included studies was assessed by Review Manager Software version 5.3. STATA software was used to perform meta-analyses of efficacy, overall survival (OS) and adverse reactions.

Results: A total of 22 studies involving 3,996 patients were included in this analysis, including 13 H101 studies, 5 T-VEC studies, 2 Pexa-Vec studies, 1 HF10 study and 1 Reolysin study. Regarding oncolytic adenovirus H101, meta-analysis showed that patients treated with H101 monotherapy or H101 combined with chemotherapy had a significantly higher objective response rate (ORR) than those treated with chemotherapy. Patients in the H101 and T-VEC groups had significantly longer effect size (ES) than the control group patients. The odds ratio (OR) and ES of patients with hepatocellular carcinoma, lung cancer and melanoma treated with OV were analyzed. For the safety profile, the total incidence of adverse reactions was similar in both groups. In terms of the other OVs, according to a systematic review, we found that after Reolysin treatment, the ORR was 26.9% in patients with head and neck cancer. The phase I study of HF10 exhibited some therapeutic potential. The adverse events (AEs) associated with the other OVs mainly included fever, nausea and vomiting, leukopenia, and hypotension.

Discussion: OVs are effective and well tolerated for the treatment of intermediate to advanced solid cancer and represent a promising therapeutic approach for solid cancers.

Keywords: Oncolytic virus (OV); intermediate to advanced solid tumor; efficacy; safety; systematic review; meta-analysis

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Introduction

Cancer is the second leading cause of death following heart disease (1). Cancer treatment remains one of the most formidable challenges worldwide. Some novel treatment strategies with multiple mechanisms of action (MOAs), including molecularly targeted therapy, gene therapy, and cellular immunotherapy, have also been investigated to improve therapeutic effects for cancer patients and have demonstrated some unexpected positive effects (2). Oncolytic virus (OV) therapy is a novel and promising approach for tumor immunotherapy (3) that appears to have a wide spectrum of anticancer activity with minimal human toxicity.

OVs are used in their natural state or genetically modified to enhance the selectivity of the viruses for cancer cells and reduce virulence to normal cells without integrating into host cellular chromosomes. Hence, OVs can selectively replicate in cancer cells and lyse them, and then the viral infection spreads to and kills surrounding tumor cells, eventually leading to a reduction in the tumor volume (3). Different types of OVs have certain limitations in the treatment of tumors. First, the replication ability of such viruses is limited. OVs can also induce systemic antitumor immunity (cancer vaccine properties) (4) by enhancing antigen release/recognition and subsequent immune activation. OVs are generated from two distinct mechanisms: selective replication in tumor cells, resulting in a direct lytic effect on tumor cells, and induction of systemic antitumor immunity. OVs kill tumor cells and release tumor-associated antigens, viral pathogen-associated molecular pattern signals, cellular danger-associated molecular pattern signals, and cytokines. These molecules promote the maturation of antigen-presenting cells and active effector T cells, which mediate antitumor immunity upon antigen recognition (5).

Currently, OVs include adenovirus (Ad), herpes simplex virus (HSV), Newcastle disease virus (NDV), measles virus, reovirus, parvovirus, etc., which have been investigated in numerous preclinical or clinical settings (3). Despite the numerous viruses investigated, some OVs have not been approved for clinical use worldwide. For example, reovirus oncolysis has been linked to activation of RAS mutations with inactivation of double-strand RNA-activated protein kinase, thereby promoting reovirus replication (6). Pexa-Vec (pexastimogene devacirepvec; JX-594) is a thymidine kinase gene-inactivated oncolytic vaccinia virus that was well tolerated in liver cancers via intratumoral injection in phase 1/2 trials (7).

Presently, only three kinds of OVs have been approved for clinical use worldwide, including H101 (Oncorine®), talimogene laherparepvec (Imlygic, T-VEC) and Rigvir H101. In 2005, the State Food and Drug Administration of China approved H101 for the treatment of advanced nasopharyngeal carcinoma (8). T-VEC is a recombinant HSV expressing human granulocyte-macrophage colony stimulating factor (GM-CSF) (9). T-VEC has been approved by the US Food and Drug Administration for the treatment of melanoma, and although a phase I clinical trial in liver cancer has been carried, research on other solid tumors has not yet been conducted. Rigvir is an OV belonging to the Picornaviridae family, *Enterovirus* genus, ECHO group, type 7, that has not been genetically modified but has been selected and adapted for melanoma (10). In a study involving gastric cancer patients, an increase of up to 20% in T lymphocytes in the tumor and mucous was observed after Rigvir administration before surgery in early-stage gastric cancer patients.

Although OVs have demonstrated a number of positive therapeutic features in solid tumors over the past 15 years, the efficacy and safety of OVs in intermediate to advanced solid tumors remain controversial (11). This systematic review combined related randomized controlled trials (RCTs) and retrospective studies to evaluate the efficacy and safety of OVs in patients with solid tumors. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-905).

Methods

Literature search strategy

The two authors (Peng Gao and Guanxiong Ding) independently performed study selection to identify articles from PubMed, Embase, Web of Science, CNKI, Wanfang and VIP. We systematically searched these databases to identify all relevant studies published in English or Chinese up to June 19, 2020. RCTs or retrospective articles of OVs in intermediate and advanced tumors were collected. The following search terms were used: 'oncolytic virus H101', 'oncolytic virus', 'oncolytic poxvirus', 'solid tumor', 'herpes simplex virus', 'reovirus, vaccine virus', 'newcastle disease virus' 'Oncorine', 'recombinant human adenovirus type 5' 'oncolytic adenovirus H101', 'HF10', 'Pexa-Vec', 'Reolysin', 'Talimogene Laherparepvec' and 'T-VEC'. Obviously irrelevant articles were excluded by reading the titles and abstracts to conduct preliminary screening. The authors

evaluated the secondary selection of literature for inclusion by carefully reading the whole texts. Any disagreement was resolved by a third reviewer. Sensitivity analyses were performed to examine robustness by removing individual studies one at a time.

Study selection

The studies met the following criteria: (I) patients were diagnosed with intermediate to advanced solid tumors, regardless of nationality, sex or race; (II) the study design was an RCT, retrospective study or clinical study; (III) OVs were administered as monotherapy or combined with chemotherapy; and (IV) the outcome measures contained at least one of the following criteria: the objective response rate (ORR), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), overall survival (OS), progression-free survival (PFS), disease control rate (DCR), time to progression (TTP) and safety. Studies were excluded if they met the following criteria: (I) unpublished literature; (II) studies without OV administration; (III) the study design was not rigorous (e.g., the criteria for outcome measures were not standardized, the sample data were not explained clearly or completely); (IV) the studies were not in Chinese or English; and (V) duplicate data.

Data extraction

Data were extracted from the included articles by the authors independently. The following information was obtained from each study: the author, publication year, participants' details (the number of patients enrolled, participant demographics, cancer types), intervention measures, outcomes, and adverse events (AEs).

Quality assessment

The quality of the included articles was evaluated with the Cochrane Risk of Bias tool (version 5.1.0, updated in March 2011), which consists of seven evaluation domains, including 'random sequence generation', 'allocation concealment', 'blinding of participants', 'blinding of key personnel', 'incomplete outcome data', 'selective outcome reporting' and 'other sources of bias'. Each assessment was divided into three levels: low risk, unclear risk and high risk.

Statistical analysis

The meta-analysis was conducted with STATA 15.0 software. For continuous variables, we extracted the mean and standard deviation to calculate the weighted mean deviation and 95% CI. For binary variables, we extracted the OR or HR with the corresponding 95% CI. Heterogeneity was assessed with the chi-square (χ^2) test and the index of heterogeneity (I^2) statistic at an alpha level of 0.10. Moderate to substantial heterogeneity was identified if $P \leq 0.1$ or $I^2 \geq 50\%$, which warranted a random effects model. If no interstudy heterogeneity was found with $P > 0.1$ or $I^2 < 50\%$, we used a fixed effects model. Subgroup analysis was performed according to the possible heterogeneous factors, and sensitivity analysis was also performed to analyze the stability of the meta-analysis.

Results

Identification and selection study

First, a total of 31,867 articles were obtained by using the retrieval strategy. Then, 31,828 studies were excluded after title and abstract evaluations. After reading the full texts, 23 articles were eliminated due to incomplete or duplicate data, and 22 articles were finally included. The study selection procedures were performed in accordance with the PRISMA flowchart (*Figure 1*).

Characteristics of the included studies and quality assessment

A total of 3,996 patients were included in the 22 articles (7,12-32), including 7 articles (7,12-17) on hepatocellular carcinoma (HCC), 5 articles (18-22) on lung cancer, 5 articles on melanoma (23-27), 2 studies (28,29) on pancreatic cancer, 1 article (30) on head and neck cancer, 1 study (31) on esophageal cancer, and 1 study (32) was on cancer. Five types of OVs (H101, HF10, Pexa-Vec, Reolysin and T-VEC) were used among the included studies. The characteristics of the included studies are shown in *Table 1*. The included articles contained 15 RCTs and 7 retrospective studies. Most RCTs reported randomized methods, and a few studies used blinded methods and allocation concealment. The assessment of the risk of bias in the included studies is shown in *Figure 2*.

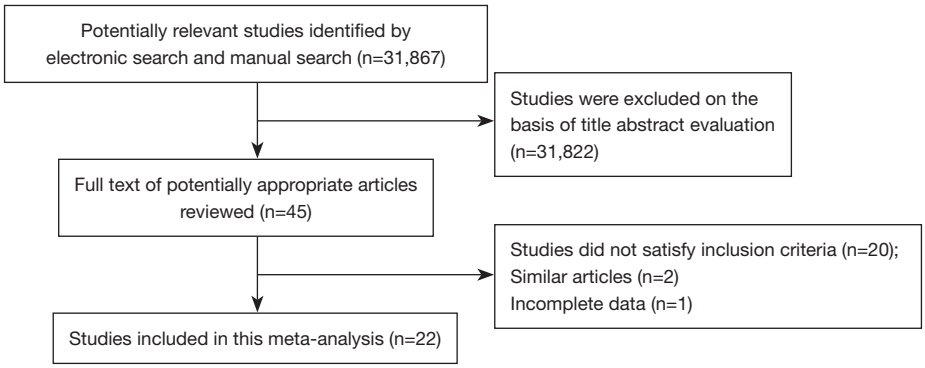

Figure 1 Flow diagram of the literature search and study selection.

Efficacy

A total of 12 articles (12,14-16,18-22,28,31,32) reported the ORR of H101 in the treatment of solid tumors, such as HCC and lung cancer, 5 of which (19-22,28) compared H101 monotherapy versus chemotherapy, while 7 articles (12,14-16,18,31,32) compared H101 combined with chemotherapy versus chemotherapy alone. The fixed effects model showed that the ORR in patients treated with H101 was significantly higher than that in patients treated with chemotherapy [OR =1.94, 95% CI: (1.61, 2.33), P<0.001], without heterogeneity among articles (P=0.536, I^2=0) (*Figure 3A*). Subgroup analysis showed that treatment with H101 monotherapy or H101 combined with chemotherapy was more effective [OR =2.99, 95% CI: (1.79, 4.97), P<0.001] [OR =1.81, 95% CI: (1.49, 2.21), P<0.001] than chemotherapy alone. In addition, this study also showed that T-VEC had a significant therapeutic effect on melanoma [OR =6.73, 95% CI: (3.52, 12.84), P<0.001] (*Figure 3B*).

Combined with funnel plots and Egger's test, publication bias was identified among the included studies as a whole, whereas no publication bias was found among the combined treatment studies (P>0.05) or among the monotherapy studies (P<0.05) (*Figure 4*). Pooled analysis of 4 articles (13,14,18,31) showed the OS rates between the H101 group and chemotherapy group. The results of the fixed effects model indicated that compared with that for the chemotherapy group, the median survival ratio of the experimental group to the control group was estimated to be 1.16 (0.83, 1.61) (*Figure 5A*). The median survival ratio point estimate and 95% CI for OS obtained from both effect models were 1.23 (1.15, 1.31), indicating that the median survival in the intervention group was 1.23 times that in the control group (*Figure 5B*). Furthermore, we analyzed the therapeutic effects of H101 on different types of tumors and found that the OR of H101 for liver cancer was the lowest; that is, the therapeutic effect was the least obvious (*Figure 6*). At the same time, the results showed that T-VEC had the most obvious therapeutic effect on melanoma.

Safety

A total of 7 articles reported the adverse reactions in patients treated with H101 in detail (15,16,18,19,22,28,31). Pooled analysis of the random effects model identified that the overall incidence rate of treatment-related adverse effects was similar between the H101 group and the control group [OR =1.20, 95% CI: (0.91, 1.59), P>0.05], and heterogeneity existed among these studies (I^2=71.8%, P=0.001). Subgroup analysis showed that compared with that in the chemotherapy group, only the incidence rate of fever was higher in the H101 group [OR =3.84, 95% CI: (1.44, 10.24), P<0.05], and the incidence rates of other adverse reactions, such as gastrointestinal reaction [OR =1.11, 95% CI: (0.76, 1.61), P>0.05], leucopenia [OR =0.85, 95% CI: (0.55, 1.32), P>0.05] and myelosuppression [OR =0.64, 95% CI: (0.26, 1.61), P>0.05], were similar (*Figure 7*).

In terms of the other OVs, after treatment with Pexa-Vec in liver cancer, the most frequent minor complications were fever (8%) and hypotension (8%) (17). Using Reolysin for head and neck cancer, the most frequent adverse reactions were influenza-like symptoms (such as chills, fatigue, myodynia and fever), and others were neutropenia (16.1%), asymptomatic lymphopenia (6.5%) and anemia (3.2%) (30) (*Table 2*). The most common AEs with T-VEC were fatigue,

Table 1 The basic characteristics of the included studies

Studies	Interventions (treatment *vs.* control)	Articles types	Cancer types	Numbers (treatment *vs.* control)	Outcome measures
Xiao-Jun Lin *et al.* (12)	H101 + TACE *vs.* TACE	Retrospective	HCC	87/88	ORR
Chao-Bin He *et al.* (13)	H101 + TACE *vs.* TACE	Retrospective	HCC	238/238	OS
Jun Dong *et al.* (14)	H101 + TACE *vs.* TACE	Retrospective	HCC	149/150	ORR; OS; safety
Qing-Chun Sun. (15)	H101 + TACE *vs.* TACE	Retrospective	HCC	42/42	ORR; safety
Jian-An Liu *et al.* (16)	H101 + TACE *vs.* TACE	RCT	HCC	480/480	ORR; safety
Wei Lu *et al.* (32)	H101 + chemotherapy *vs.* chemotherapy	Retrospective	Cancer	46/46	ORR; safety
Cai-Cun Zhou *et al.* (18)	H101 + chemotherapy *vs.* chemotherapy	RCT	Lung cancer	19/17	ORR; OS; safety
Ran Zhang *et al.* (31)	H101 + chemoradiotherapy *vs.* chemoradiotherapy	Retrospective	Esophagus cancer	30/31	ORR; OS; safety
Fan Yang *et al.* (19)	H101 *vs.* chemotherapy	RCT	Lung cancer	26/26	ORR; safety
Xian-Jun Liu *et al.* (20)	H101 *vs.* chemotherapy	RCT	Lung cancer	23/22	ORR; safety
Wei Wang *et al.* (21)	H101 *vs.* chemotherapy	RCT	Lung cancer	30/30	ORR
Xiao Tang *et al.* (22)	H101 *vs.* chemotherapy	RCT	Lung cancer	52/52	ORR; safety
Ying-Wei Zhu *et al.* (28)	H101 *vs.* chemotherapy	RCT	Pancreatic cancer	16/10	ORR; safety
M. Moehler *et al.* (17)	Pexa-Vec + BSC *vs.* BSC	RCT	HCC	86/43	OS; safety
Jeong Heo *et al.* (7)	Pexa-Vec high-dose *vs.* Pexa-Vec low-dose	RCT	HCC	16/14	OS
A Nakao *et al.* (29)	A single arm study of HF10	RCT	Pancreatic cancer	6	ORR
Allison J. Black *et al.* (30)	A single arm study of Reolysin®	Retrospective	Head and neck cancer	26	ORR; OS
Robert H. I. Andtbacka *et al.* (23)	T-VEC *vs.* GM-CSF	RCT	Unresectable stage III–IV melanoma	295/141	ORR; OS; safety
Robert H. I. Andtbacka *et al.* (27)	T-VEC *vs.* GM-CSF	RCT	Unresected stage IIIB/C/IV melanoma	61/26	ORR; OS
Robert H. I. Andtbacka *et al.* (24)	T-VEC *vs.* GM-CSF	RCT	Advanced melanoma	295/144	ORR; OS; safety
Jason Chesney *et al.* (25)	T-VEC + ipilimumab *vs.* ipilimumab	RCT	Advanced, unresectable melanoma	98/100	ORR
Kevin J. Harrington *et al.* (26)	T-VEC *vs.* GM-CSF	RCT	Stage IIIB/c and IV1a melanoma	163/86	ORR; OS; safety

TACE, transhepatic arterial chemoembolization; HCC, hepatocellular carcinoma; OS, overall survival; RCT, randomized controlled trial; T-VEC, Talimogene laherparepvec; GM-CSF granulocyte-macrophage colony-stimulating factor; ORR, overall response rate.

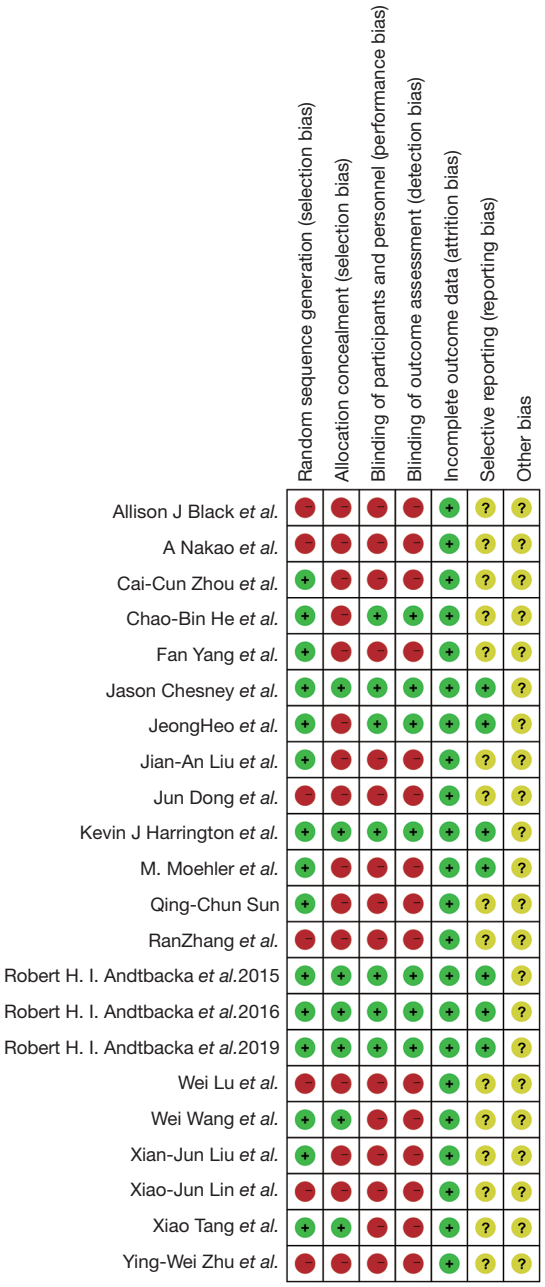

Figure 2 Authors' judgments about the risk of bias in the included studies.

chills, and pyrexia. The only grade 3 or 4 AE occurring in 2% of T-VEC-treated patients was cellulitis (2.1%) (23). The AEs of OVs in the treatment of intermediate to advanced solid tumors mainly included fever, nausea and vomiting, leukopenia, hypotension, etc. No serious complications were observed. The side effects of OVs were similar to those of traditional therapies. Therefore, OV has acceptable clinical safety in solid cancers.

Sensitivity analysis

Sensitivity analysis was also performed by sequentially removing individual studies to determine whether their exclusion resulted in a substantial change in the pooled estimates and heterogeneity. The pooled analysis of efficacy in the treatment of intermediate to advanced solid tumors was reliable and stable between both groups (*Figure 8*).

Discussion

In China, the incidence and mortality of liver cancer, lung cancer and esophageal cancer are relatively high. At present, traditional treatments of cancer, radiotherapy and chemotherapy usually cause severe side effects and cannot completely kill cancer cells. In recent years, OVs, a new type of antitumor drug, have gradually attracted people's attention due to their unique advantage of killing tumor cells specifically without damaging normal cells. H101 plays an important role in the antitumor field as the first approved OV drug. With numerous clinical trials, H101 has been demonstrated to have excellent efficacy and good safety in the treatment of solid tumors, especially in liver cancer and lung cancer. To date, T-VEC intrahepatic injection in combination with intravenous pembrolizumab at standard doses in patients with HCC or liver metastases has been demonstrated to be feasible and tolerable (33). Most clinical trials of OVs are still under research and development.

In this study, 22 studies were included to explore the efficacy and safety of OVs in the treatment of intermediate to advanced solid tumors. The results showed that OVs could improve the efficacy and prolong the survival time of patients. The common adverse reactions among patients in the OV group were fever, vomiting, leukopenia, etc., without serious AEs. Compared with that of chemotherapy alone, the efficacy of H101 monotherapy or H101 in combination with chemotherapy for solid tumors was significantly better. Zhang *et al.* (31) studied 87 patients and found that the efficacy, OS rate (1-, 2- and 3-year), median OS and median PFS were significantly higher in the H101 combined with chemotherapy group and were superior to chemotherapy monotherapy in the treatment of tumors. Moreover, the incidence of adverse reactions was similar. The ORR of patients in the H101 treatment group was significantly higher than that in the chemotherapy alone

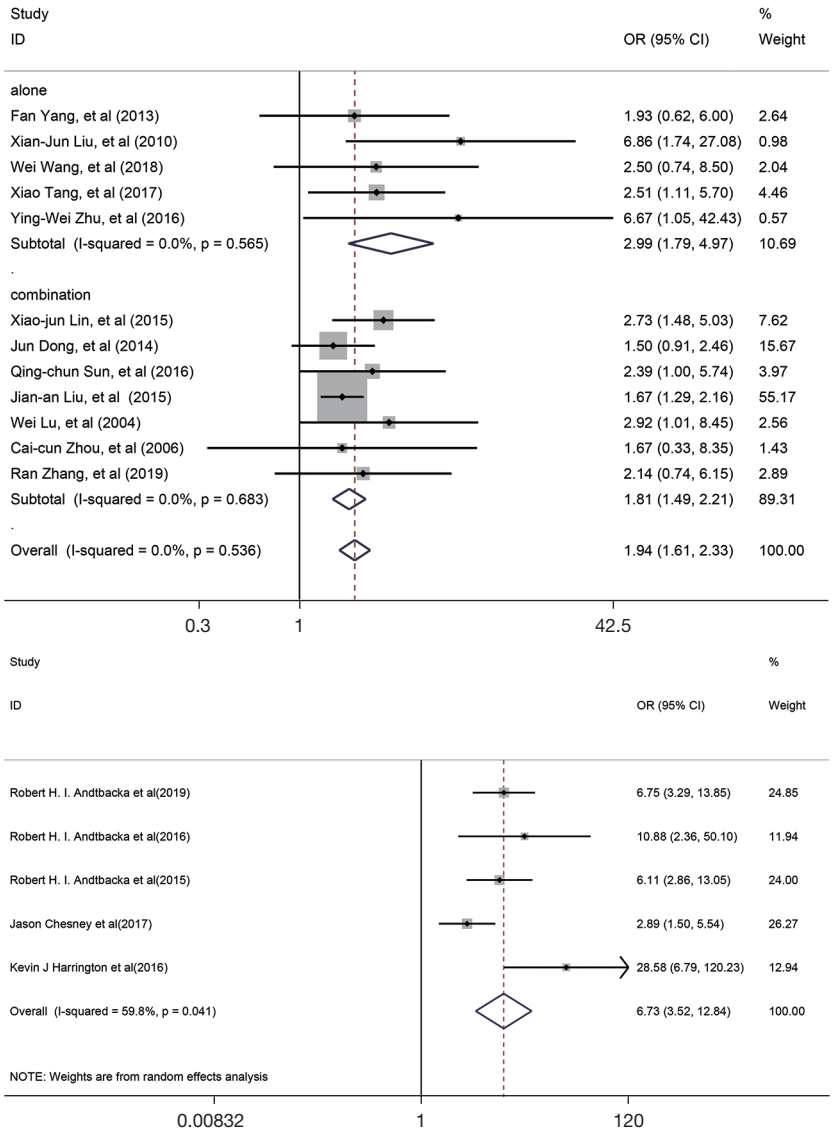

Figure 3 Forest map of the ORRs between the H101 and T-VEC groups. ORR, objective response rate; OR, odds ratio; CI, confidence interval.

group, and H101 prolonged patient OS. H101 has a good therapeutic effect and yields a good prognosis for patients. In this systematic review, the subgroup analysis showed that the incidence of fever in the H101 group was significantly higher than that in the chemotherapy group. Other adverse reactions, such as nausea, vomiting, leukopenia, bone marrow suppression, etc. were similar between H101 and chemotherapy alone, which indicated that OVs have good tolerance. Moreover, fever can promote the body's own resistance to disease, induce autoimmune ability, accelerate antitumor immunity and enhance antitumor effects. T-VEC was well tolerated and resulted in a higher DRR (P<0.001) and longer median OS (P=0.051), particularly in untreated patients or those with stage IIIB, IIIC, or IVM1a disease (23). Administration of talimogene laherparepvec was associated with an improved ORR, DRR, and OS (24).

Additionally, the OS rates, median OS time, disease control rate (DCR) and mortality were analyzed by various types of studies. Four studies (12-14,31) proved that the 1-, 2-, and 3-year OS rates in the H101 group were higher than those in the chemotherapy group. As displayed in *Table 2*, the 1-, 2-, and 3-year OS rates in the H101 group

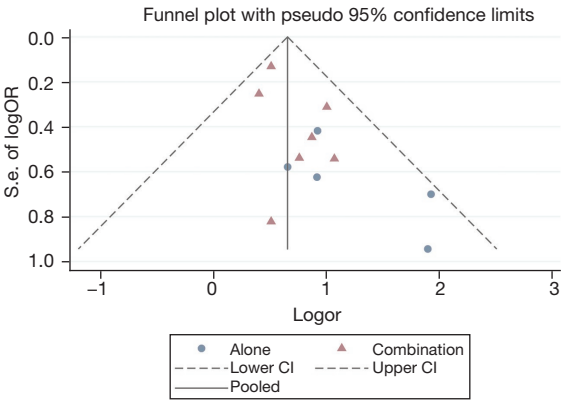

Figure 4 Forest map of OS between the H101 and T-VEC groups. OS, overall survival; CI, confidence interval.

ranged from 61.3% to 87.5%, 35.6% to 60% and 29.5% to 40.5%, respectively. Five studies assessed the effect of H101 on the median OS time (12,13,18,21,22). All these studies reported improved effects on the median OS time after H101 intervention. Dong *et al.* (14) investigated the effect of H101 on the DCR but found no significant results. Zhu *et al.* (28) suggested that treatment with H101 significantly reduced mortality compared with chemotherapy.

In terms of other OVs, only one study by treatment with Reolysin reported that the ORR was 26.9% for head and neck cancer (30). A randomized multicenter Phase IIb trial (TRAVERSE) of Pexa-Vec revealed that Pexa-Vec plus Best Supportive Care (BSC) did not improve OS compared with BSC alone. The median OS was 4.2 months

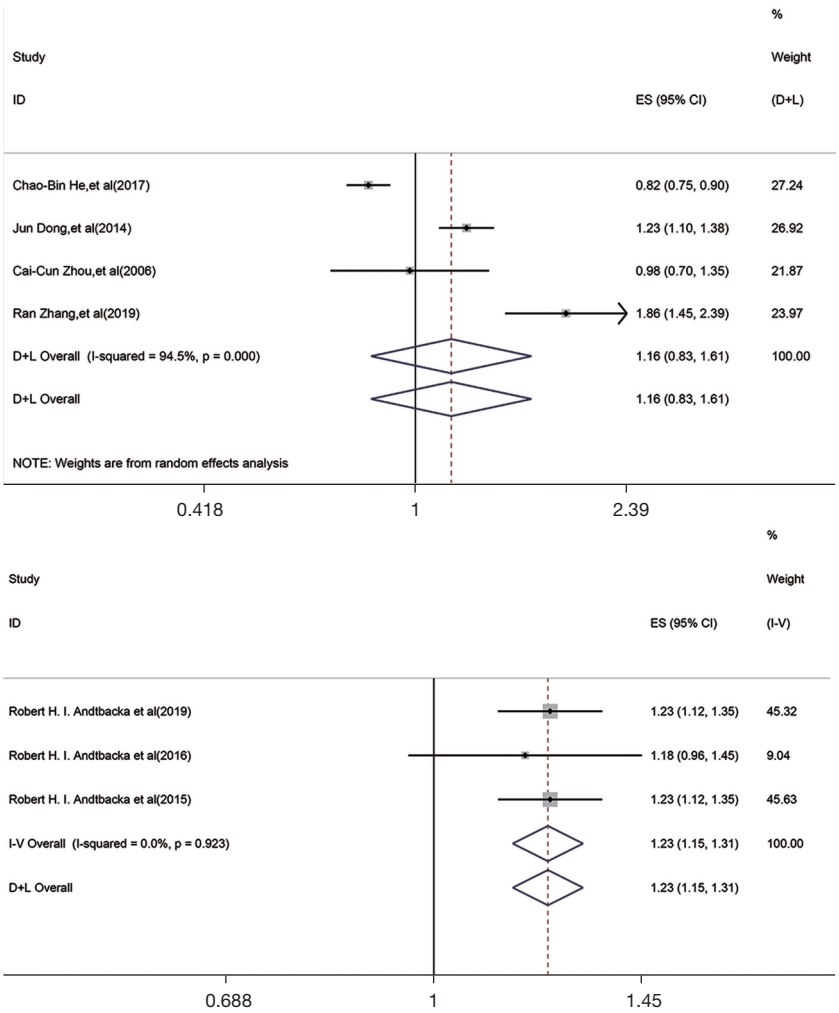

Figure 5 Forest map of OS between the H101 and T-VEC groups. OS, overall survival; ES, effect size; CI, confidence interval.

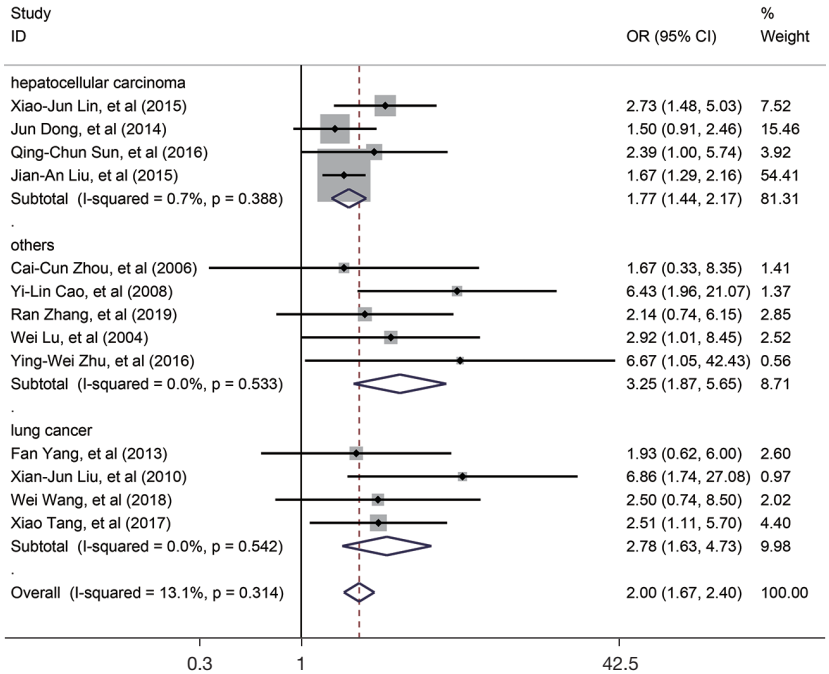

Figure 6 The OR of different H101-treated cancer types. OR, odds ratio; CI, confidence interval.

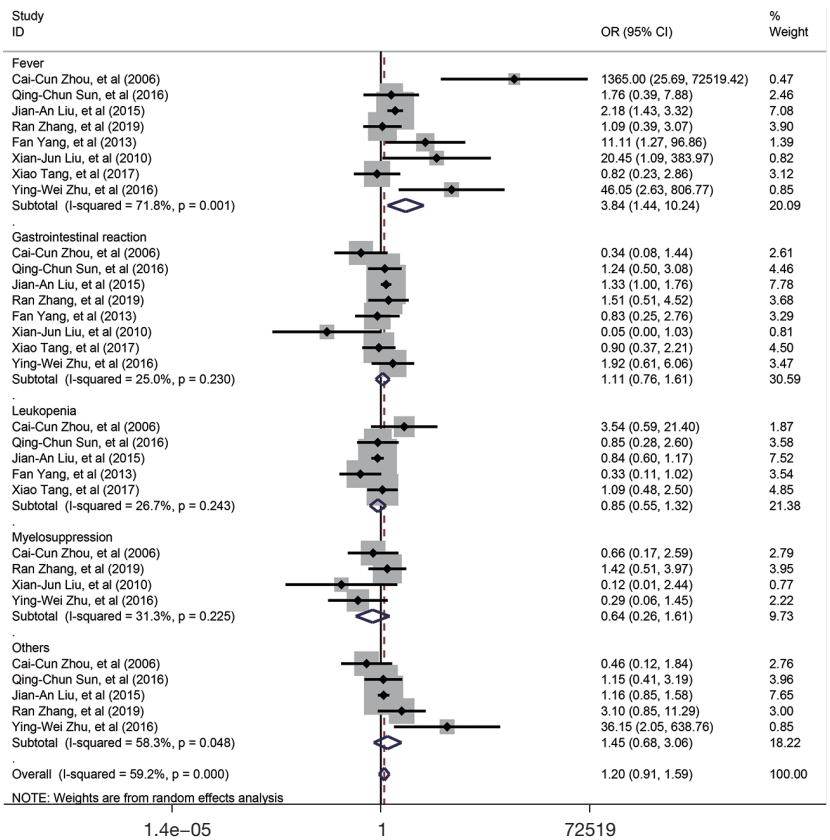

Figure 7 Forest map of adverse reaction rates between the H101 and chemotherapy groups. OR, odds ratio; CI, confidence interval.

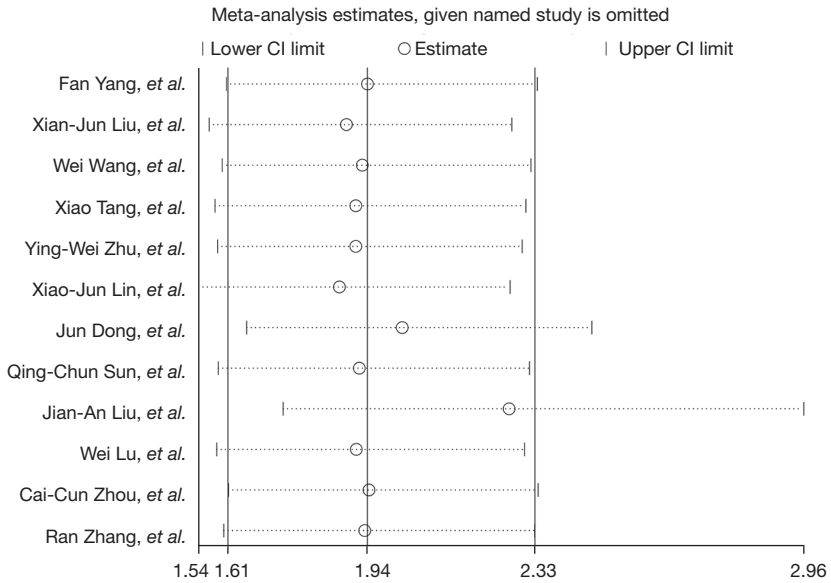

Figure 8 Sensitivity analysis of efficacy between the H101 and chemotherapy groups. CI, confidence interval.

for Pexa-Vec combined with BSC and 4.4 months for BSC alone. However, a randomized Phase 2 dose-finding trial of Pexa-Vec indicated that subject survival was significantly associated with the dose of Pexa-Vec (median survival of 14.1 months on the high dose compared to 6.7 months on the low dose). There was no significant difference in TTP between Pexa-Vec combined with BSC and BSC alone (17). A phase I study in six patients concluded that after treatment with HF10 OV, two patients were classified as progressive disease, three patients as stable disease and one patient as partial response according to modified RECIST criteria. The serological tumor marker CA19-9 was decreased in three patients. Thus, HF10 had some therapeutic potential. Early reports from a phase Ib clinical trial of T-VEC and ipilimumab suggest a response rate of 56% and a CR rate of 33%; a randomized phase II study is ongoing (34). The meta-analysis had the following limitations. First, the study did not focus on one tumor due to insufficient articles to analyze the efficacy and safety of OVs, which may increase heterogeneity. Second, the sample size was small, and most of the studies did not describe the random methods, allocation concealment or blinding methods. Therefore, the methodology was not of high quality. Third, except for H101, studies of other OVs are few. Heterogeneity may be affected by disease type or virus type. Therefore, the above conclusions indicated that there is a high probability of publication bias. However, this systematic evaluation showed that OVs have significant effects and good safety for cancers. However, to obtain a more reliable conclusion, large-sample and multicenter RCTs are still needed.

On the basis of the meta-analysis, OVs have a significant antitumor effect on cancers and are superior to traditional treatment. Many of the adverse reactions are fever and vomiting, with good safety and no serious side effects. However, more high-quality studies are needed to verify this hypothesis. By equipping OVs with functional transgenes, a complete set of OVs will have multiple antitumor functions in the future, and appropriate virus combinations can be selected according to the type and stage of cancer.

Conclusions

- The ORR in patients treated with H101 or T-VEC was significantly higher than that in the control group.
- Compared with the control group, the H101 or T-VEC group had notably prolonged OS.
- Patients treated with H101 or T-VEC had significantly reduced mortality compared with those treated with chemotherapy.
- The overall incidence of treatment-related adverse effects was similar between the H101 group and chemotherapy group.
- The AEs associated with OVs in the treatment of intermediate to advanced solid tumors mainly included fever, nausea and vomiting, leukopenia, hypotension, etc.

Table 2 The therapeutic effects of OVs based on included studies

Studies	Survival benefits		P value
	Treatment group	Control group	
Xiao-Jun Lin *et al.* (12)	median OS time =12.8 months (12.95 ±8.36 months); the OS rates at 1 and 2 years were 69% and 60%; PFS =10.49 months; ORR =60.9%	median OS time =11.6 months (12.87 ±8.28 months); The OS rates at 1 and 2 years were 60 and 44%; PFS =9.72 months; ORR =36.4%	All P<0.05
Chao-Bin He *et al.* (13)	Median OS was 17 months (range, 2 –71 months); 1-, 2- and 3-year OS rates were 61.3%, 44.2%, and 40.5%	Median OS was 14 months (range, 0–65 months);1-, 2- and 3-year OS rates were 53.8%, 33.4%, and 22.4%	All P<0.05
Jun Dong *et al.* (14)	Mean OS =1,526 d (95% CI: 1,365.7–1,685.9 d); 1-, 2- and 3-year OS rates were 61.7%, 35.6%, 29.5%; ORR =73.8%; DCR =75.8%	Mean OS =1,236 d (95% CI: 939.6–1,531.8 d); 1-, 2- and 3-year OS rates were 54.0%, 30.0%, 21.3 %; ORR =65.3%; DCR =66.7%	OS P<0.05; ORR, DCR P>0.05
Qing-Chun Sun (15)	ORR =59.5%; AFP positive rate =28.6%	ORR =38.1%; AFP positive rate =50.0%	All P<0.05
Jian-An Liu *et al.* (16)	ORR =50.0%; AFP positive rate =20.67%	ORR =37.5%; AFP positive rate =40.83%	All P<0.05
Wei Lu *et al.* (32)	ORR =30.4%	ORR =13.0%	P<0.05
Cai-Cun Zhou *et al.* (18)	ORR =26.3%	ORR =17.6%	–
Ran Zhang *et al.* (31)	Median OS =34.6 months; 1- and 2-year OS rates were 87.5%, 58.3%; median PFS =23.8 months; ORR =46.7%	Median OS =18.6 months; 1- and 2-year OS rates were 61.5%, 26.9%; median PFS =14.8 months; ORR =29%	All P<0.05
Fan Yang *et al.* (19)	ORR =69.23%	ORR =53.84%	P<0.05
Xian-Jun Liu *et al.* (20)	ORR =82.61%, CR =47.83%	ORR =40.91%; CR =18.18%	All P<0.05
Wei Wang *et al.* (21)	ORR =83.3%; the average quality of life was improved by 15 points	ORR =66.7%; the average quality of life was improved by 5 points	All P<0.05
Xiao Tang *et al.* (22)	ORR =73.08%	ORR =51.92%	P<0.05
Ying-Wei Zhu *et al.* (28)	ORR =62.5%; mortality rate =60%; median OS =8.8±0.5 months	ORR =20.0%; mortality rate =80.8%; median OS =(7.4±0.4) months	P<0.05
M. Moehler *et al.* (17)	Mean OS =4.2 months; TTP =1.8 months	Mean OS =4.4 months; TTP =2.8 months	P>0.05
Jeong Heo *et al.* (7)	Mean OS =14.1 months; mean OS rate =13.6%	Mean OS =6.7 months; mean OS rate =4.3%	All P<0.05
A Nakao *et al.* (29)	PR =1; SD=3; PD =2		–
Allison J. Black *et al.* (30)	ORR =26.9%; median OS =7.1 months		–
Robert H. I. Andtbacka *et al.* (23)	ORR =31.5%; median OS =23.3; DRR =19.0%	ORR =6.4%; median OS =18.9; DRR =1.4%	P<0.05
Robert H. I. Andtbacka *et al.* (27)	ORR =47.5%; median OS =29.7; DRR =36.1%	ORR =7.7%; median OS =25.2; DRR =3.8%	P<0.05
Robert H. I. Andtbacka *et al.* (24)	ORR =26.4%; median OS =23.3; DRR =16.3%	ORR =5.7%; median OS =18.9; DRR =2.1%	P<0.05
Jason Chesney *et al.* (26)	ORR =39%;	ORR =18%;	P<0.05
Kevin J. Harrington *et al.* (25)	ORR =40.5%; median OS =40.1; DRR =25.2%	ORR =2.3%; median OS =21.5; DRR =1.2%	P<0.05

PR, partial response; PD, progressive disease; OS, overall survival; PFS, progression free survival; DRR, durable response rate; ORR, overall response rate; AFP, serum a-fetoprotein; DCR, disease control rate; CI, confidence interval.

❖ OVs have acceptable clinical safety in solid cancers and are superior to traditional treatment.

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Footnote

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