

Commentary

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Oncolytic virus VG161 brings new hope for advanced HCC

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Abstract

The study titled “Oncolytic virus VG161 in refractory hepatocellular carcinoma” presents a promising advancement in third-line therapy for advanced hepatocellular carcinoma (HCC). VG161, derived from an oncolytic herpes simplex virus, is engineered to express interleukin (IL)-12, IL-15, IL-15R, and a fusion protein that blocks the programmed cell death protein-1 (PD-1)/programmed death-ligand-1 (PD-L1) pathway. In the multicenter phase 1 clinical trial, VG161 exhibited both strong efficacy and safety. This paper summarizes the study’s findings, discusses potential limitations, and proposes directions for future research.

Keywords: Advanced HCC, oncolytic virus, TME

INTRODUCTION

Hepatocellular carcinoma (HCC) remains one of the most deadly cancers worldwide^[1,2]. Although targeted therapy and immunotherapy have provided new hope for patients with advanced HCC, dose-dependent



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adverse effects often require dose reduction or treatment discontinuation, thereby affecting therapeutic efficacy^[3]. After the failure of second-line treatment, treatment options for HCC are limited, posing a serious threat to patient survival. Thus, new treatment methods are urgently needed for stage III HCC.

JX-594, an oncolytic virus engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF)^[4], showed safety in early clinical trials. However, subsequent studies revealed that its dual effect - activating both antitumor immune cells and myeloid-derived suppressor cells (MDSCs) - prevented sustained clinical efficacy. In contrast, VG161 reduces the risk of immunosuppression associated with GM-CSF by co-expressing interleukin (IL)-12, IL-15/IL-15R α , and a fusion protein that blocks the programmed cell death protein-1 (PD-1)/programmed death-ligand-1 (PD-L1) pathway^[5].

PHASE I CLINICAL TRIAL DESIGN AND PRELIMINARY RESULTS

This phase I clinical trial enrolled 44 patients with advanced HCC across three centers, with 11 assigned to the dose-escalation cohort and 33 to the dose-expansion cohort. In the dose-escalation phase, patients received intratumoral injections of VG161 at gradually increasing doses, ranging from 1.0×10^8 to 5.0×10^8 plaque-forming units (PFUs). Injections were administered for 1-3 consecutive days within a 28-day treatment cycle at different dose levels to evaluate safety and efficacy. Ultimately, a dose of 1.0×10^8 PFU for 3 consecutive days was chosen for the dose-expansion phase. In this phase, patients received intratumoral injections of 1.0×10^8 PFU per day for 3 consecutive days within each 28-day treatment cycle. No dose-limiting toxicities (DLTs) were observed during the dose-escalation phase. The neurotoxic gene ICP34.5 was deleted from VG161, thereby preventing neurotoxicity. The most common treatment-related adverse event (TRAE) was pyrexia (86.4%), while the most frequent grade 3 TRAE was lymphocyte count reduction (84.1%). No grade 4 TRAEs or treatment-related deaths were reported. Based on the duration of pyrexia and patterns of virus replication, the researchers hypothesized that pyrexia was induced by an antiviral immune response rather than systemic toxicity. Fever typically resolved by the second day after onset. Similarly, in studies of the HSV-1 derivative G47 Δ , pyrexia was also reported as a common but reversible adverse effect^[6]. According to the internationally recognized Modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria, VG161 treatment achieved an objective response rate (ORR) of 17.65% and a disease control rate (DCR) of 64.71%, highlighting VG161's potential as a third-line treatment option.

TME CHANGES UNDER VG161 TREATMENT

Single-cell RNA sequencing (scRNA-seq) and spatial transcriptome analyses of a surgical specimen from a HCC patient revealed that both injected and non-injected lesions underwent tumor regression, with non-injected lesions showing a greater degree of regression. In non-injected lesions, the proportions of T cells and natural killer (NK) cells were significantly higher than in injected lesions, and their interactions appeared more active. After intratumoral injection, VG161 enters HCC cells within the injected lesions and rapidly replicates using host metabolic resources, eventually leading to cell lysis. The resulting tumor cell death releases tumor-associated antigens, which trigger adaptive immune responses in both injected and non-injected lesions. Consequently, CD8⁺ T cell infiltration, along with the number and diversity of receptors across the tumor tissue, increased. The limited regression observed in injected lesions may be attributed to virus-induced antiviral responses and local immunosuppression. A similar mechanism of CD8⁺ T cell activation has also been proposed for hepatitis B virus antigen-specific T cell receptor (HBV-TCR) T cell therapy in HCC^[7]. Furthermore, VG161 treatment was associated with upregulation of PD-1 and PD-L1 expression. A comparable increase in PD-L1 expression has been reported following administration of oncolytic virus CF33-hNIS- Δ F14.5^[8]. Notably, combining CF33-hNIS- Δ F14.5 with an anti-PD-L1 antibody significantly enhanced therapeutic efficacy in a triple-negative breast cancer mouse model. These findings suggest that combination therapy with VG161 and checkpoint inhibitors (CPIs)

holds promise and warrants further investigation.

VIROPREDICT 1.0 MODEL

The researchers developed an efficacy prediction model (ViroPredict 1.0), designed to identify patients who are more likely to respond positively to VG161 treatment. The model incorporates five genes and their corresponding gene products: SEZ6 (seizure-related 6 homolog protein), AKR1C1 (aldo-keto reductase 1C1), LILRA5 (leukocyte immunoglobulin-like receptor A5), NCKAP5 (NCK-associated protein 5), and SETD9 (SET domain-containing protein 9). This model not only supports the development and improvement of VG161 technology but may also help patients and clinicians design more effective treatment strategies.

EXCLUDE THE INFLUENCE OF ANTI-HEPATITIS B AGENTS

Hepatitis B virus (HBV) infection ranks among the most widespread infectious diseases worldwide. More than 200 million people suffer from chronic HBV infection, which remains a major cause of HCC^[9]. Therefore, it is critical to evaluate whether anti-HBV drugs affect the efficacy of VG161. Entecavir, a nucleoside analog widely used in clinical practice, effectively inhibits HBV replication^[10]. Based on both animal and human studies, the researchers confirmed that Entecavir does not interfere with the replication or efficacy of the oncolytic virus, which is an important finding for the clinical development of VG161. This might be explained by the differences in viral replication mechanisms: HBV replication requires reverse transcription mediated by HBV polymerase, which has reverse transcriptase activity, whereas herpes simplex virus (HSV), a classical DNA virus, replicates independently of reverse transcriptase. Because Entecavir specifically targets HBV reverse transcription, it does not significantly affect HSV replication^[11-13].

LIMITATIONS

Although these preliminary results demonstrate therapeutic potential, the study has several limitations. First, the clinical analysis included only 44 patients, of whom 93% were Asian. This limits the generalizability of the findings to other populations and regions. Second, this study employed a historical control group rather than a concurrent randomized control design, and patient treatment regimens were inconsistent, which may have introduced bias in assessing therapeutic effects. Third, the ViroPredict model was developed from RNA sequencing (RNA-seq) data of just 21 samples, raising the risk of overfitting. Its predictive accuracy must therefore be validated in larger clinical cohorts. In light of these limitations, the findings should be interpreted with caution. Some of the observed results might be incidental effects arising from the small sample size.

DISCUSSION: THE COMBINED USE OF CPIS AND VG161

Sorafenib was the first targeted drug approved for the treatment of advanced HCC and has been widely used in clinical practice^[3]. However, many HCC patients eventually develop resistance to sorafenib, driven partially by diverse immunosuppressive mechanisms within the tumor microenvironment (TME)^[14]. CPIS can specifically bind to immune checkpoint proteins, block their interactions, and relieve the immunosuppressive state of antitumor T cells^[15]. Nevertheless, although CPIS can partially overcome sorafenib resistance in patients with advanced HCC, the TME continues to inhibit their efficacy through multiple mechanisms, such as a complex immune suppression network and tumor heterogeneity. Beyond PD-1/PD-L1, other immune checkpoint molecules exist in the TME, collectively forming a suppressive network that limits the ability of CPIS to fully reverse immune suppression^[16]. In addition, tumor heterogeneity plays a critical role. Different HCC tumors- and even distinct regions of the same tumor - exhibit diverse and complex molecular characteristics, making it difficult for CPIS to exert uniform effects across all tumor cells.

Biopsy samples from four patients treated with VG161 revealed increased expression levels of IL-12, IL-15, IL-15R α , PD-1, and PD-L1 in the TME following therapy. On the one hand, IL-12 initiates the interferon gamma (IFN- γ) signaling cascade and directly enhances both the number and infiltration of NK cells and CD8⁺T cells. The IL-15/IL-15R α complex supports the survival and function of effector T cells, preventing the rapid decline of immune responses and thereby transforming the TME from an immunologically “cold” state to a “hot” state. Relevant assays also showed significant T cell receptor (TCR) expansion and enrichment of the CD8⁺GZMH⁺ subset, suggesting that activated T cells possess specific cytotoxic potential against tumor antigens. On the other hand, levels of PD-L1 and PD-1 also increased. The upregulation of PD-L1 is a marker of adaptive immune resistance, indicating that T cells had infiltrated but were functionally suppressed. This upregulation, however, also provides additional targets for CPIs. Meanwhile, IL-12 and the IL-15/IL-15R α complex can further enhance T cell proliferation and cytotoxicity. Together, these effects may more effectively block tumor immune escape driven by the PD-1/PD-L1 axis. It is noteworthy that CPI-sensitive patients showed a more pronounced response to VG161 monotherapy, while CPI-insensitive patients experienced prolonged survival when treated with VG161 followed by subsequent systemic therapies (including CPIs). While the combination of VG161 and CPIs appears promising, potential risks must also be considered. With VG161 monotherapy, cytokine levels return to baseline within 15 to 28 days. In contrast, the continuous immunomodulatory activity of CPIs may drive immune cell activation beyond physiological limits, leading to excessive cytokine release. Combined therapy could prolong or intensify this process, potentially exacerbating fever, amplifying inflammatory responses, and even damaging normal organs. Moreover, excessive immune activation may accelerate clearance of VG161. Because VG161 is derived from herpesvirus, the host’s antiviral immune response can limit its replication^[17]. CPI-induced immune activation may further enhance this clearance, potentially weakening VG161’s oncolytic activity and diminishing the efficiency of the combined therapy. Although combining VG161 with CPIs shows clinical potential, further clinical trials are required to validate their synergistic effects.

CONCLUSION

VG161 appears to show promising potential for treating patients with advanced HCC, particularly those who have developed resistance to current targeted therapies and CPIs. Future studies should include larger cohorts and diverse ethnic populations to enable its translation into routine clinical practice as soon as possible.

DECLARATIONS

Authors’ contributions

Study concept and design, and supervision of the work: Zhou Y, Zhang H

Drafting of the manuscript: Hong Y, Cui X

Contribution to literature review and preparation of supporting materials: Chang R, Song S, Qian L, Zhu H, Tan L, Hong Z, Yi M

Critical revision of the manuscript and responsibility for the integrity and accuracy of the content: Hong Y, Zhang H

All authors read and approved the final version of the manuscript.

Availability of data and materials

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Conflicts of interest

Zhang H is a Junior Editorial Board member of the journal *Hepatoma Research*. He was not involved in any steps of the editorial process, notably including reviewer selection, manuscript handling, or decision making, while the other authors have declared that they have no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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