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Hot Topic Commentary

Therapeutic Use of Viruses: Newcastle Disease Virus HK84 Oncolytic Treatment for Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the most frequent primary liver tumor worldwide and, despite regional therapeutic and diagnostic differences, it stands among the three most lethal cancers found in humans. Resection or ablative treatments, together with liver transplant, are the most successful clinical approaches, frequently ensuring complete HCC healing and the best survival rates. However, curative techniques are applicable only in patients at early stages of the disease (limits: one nodule ≤5 cm in diameter or not more than three nodules all less than 3 cm in diameter).[1] A significant percentage of HCC patients (≥50%) have a more advanced stage at diagnosis and must rely on less effective treatment or palliative care, thus signifying the need for alternative systemic therapies. Sorafenib, a tyrosine kinase inhibitor (TKI) was the first effective HCC drug treatment discovered after negative results were obtained with canonical cytotoxic chemotherapy. In 2018 lenvatinib, another TKI, was approved in the USA as a first line treatment for HCC. Recently immunotherapy combining the checkpoint inhibitor, atezolizumab with the VEGF-antibody bevacizumab, has improved survival rates compared with previous TKI-based monotherapies.[2] Despite treatment improvements, 1-year survival is attained by only two-thirds of patients, thus prompting investigation of more effective therapies for advanced stage HCC.

Interest in oncolytic virus (OV) therapy (i.e., an anticancer treatment based on the use of virus) has increased in the past century. The possibility of genetic manipulation of wild-type viruses, transforming them into more specific therapeutic tools is a further boost in OV research,[3] General mechanisms supporting OV use in cancer are (1) direct cytotoxicity and (2) a subsequent increased release of tumor antigens enhancing host immune response. In the interaction between neoplastic cells and OVs, the role of interferons (IFNs) is particularly intriguing.[4] In fact, if various cancers repress the IFN cellular pathway to elude immune-mediated elimination that results in susceptibility to viral infection, then genetically modified OVs may reactivate intracellular IFN cascades thereby restoring immune responses against the same cancer tissues.

Chen *et al*.[5] recently reassessed the issue of OV therapy in an experimental HCC model. As the main targets in the application of OV therapy are (1) effective oncolysis; and (2) safety from the possible onset of side effects induced by the virus by itself or associated with genetic manipulation, the study focused on the effectiveness of a new H84 strain of Newcastle disease virus (NDV), a widely studied OV. NDV is a paramyxovirus with an avian host and a low capability to infect healthy human cells.[6] Human cancer cells are more easily infected by NDV than benign cells because of the impairment of antiviral defenses such as the IFN cascade, which supports the potential of this viral class for oncolytic therapy. Chen *et al*.[5] compared nine different NDV strains *in vitro*, finding that HK84 was the only virus to provide a consistent >80% growth inhibition of the SK-HEP-1 HCC cells despite multiple changes in infection rate ranging from 20–0.2%. Further *in vitro* evidence demonstrated increased apoptosis when NDV-HK84 was exposed to either SK-HEP-1 or HEP3B cell while suppressing SK-HEP-1 wound healing, an evaluation of cell spreading capability, by the same strain. Translation of this research into an *in vivo* model of subcutaneous xenotransplantation of SK-HEP-1 cells in nude mice demonstrated decreased tumor growth in all NDV-HK84-treated animals. Tumor growth was evaluated at baseline and on days 7, 10, 13, 16, and 19. They observed complete absence of tumor tissue in 60% of mice within 2 weeks. Finally, gene expression analysis during NDV-HK84/SK-HEP-1 interaction revealed activation of several genes (*DDX58*, *OASL*, *IFITM1*, *MX1*, *XAF*, *IFI44*, *ISG15*) involved in the immune response, which also influenced the type-I IFN (I-IFN) cascade.

Taken together, the preclinical findings suggest a possible new strategy for HCC immune therapy in humans. Studies of OVs in HCC have been performed in the past,[7] but they were mainly preclinical and based on viruses including adenovirus, herpes simplex virus, and others that raise concerns for possible negative effects on healthy cells during cancer therapy in humans. A phase I clinical trial of NDV (strain PV701) was undertaken in patients with different solid cancers.[8] Patients with HCC were not included; however, PV701 had a valid safety profile, with modest flu-like symptoms as the most frequently recorded side effect.

Abbreviations: HCC, hepatocellular carcinoma; IFN, interferon; NDV, Newcastle disease virus; OVs, oncolytic viruses; TKI, tyrosine-kinase inhibitor.

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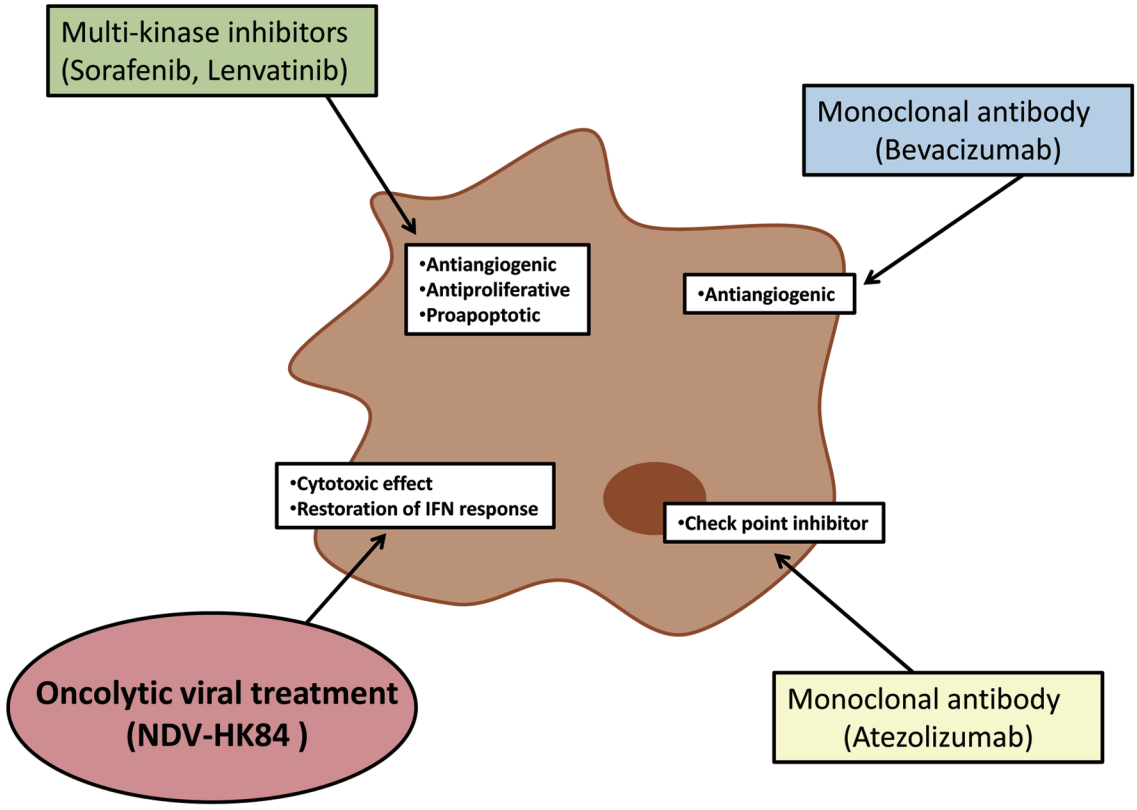

Fig. 1. Effects of drugs used in hepatocellular carcinoma and those possibly associated with oncolytic viral therapy.

Moreover, this manifestation faded after repeated virus injections.

Considering NDV safety, Chen *et al*.[5] aimed to systematically evaluate the possible effects of this infection on HCC. Their preclinical data appear encouraging for the possible use of NDV in the treatment of HCC. However, despite the validity of the research, several areas remain to be addressed for the translation of this strategy into clinical practice. For example, the experimental models used by Chen *et al*.[5] pose some unavoidable limitations that unfortunately are characteristic of preclinical studies. The use of nude mice (BALB/c nu female mice) did not allow investigation of the anticancer immune response, which is considered of great importance in OV therapy, because of the immunologic permissiveness of the strain. Further, the possibility of developing an antibody response to NDV-HK84, would limit its usefulness in clinical settings and should also be considered. The SK-HEP-1 HCC cell line that was mainly used for *in vitro* experiments and exclusively used for *in vivo* experiments, raises some concerns of recapitulating HCC, as SK-HEP1 has a gene expression pattern and cellular markers that more resemble an endothelial cell phenotype than a hepatocyte phenotype.[9] Finally, the observation that I-IFN signaling is possibly activated by NDV-HK84 in HCC cells is clearly interesting, but needs to be further characterized in future research on HCC. Specifically, (1) IFN treatment has already been evaluated in HCC clinical therapy. The utility of this moiety, even if it was demonstrated to reduce HCC recurrence, remains controversial.[10] (2) enhanced I-IFN response elicited by OV may not endure and/or HCC cells may develop resistance to I-IFN; and (3) I-IFN response restoration may promote OV elimination on its own.

Despite the above possible pitfalls that may contribute to creating a translational gap for the application of NDV-HK84 in human therapy, the data of Chen *et al*.[5] are of interest, and their study supports the use of OV therapy as a possible further approach for immune therapy in human HCC. The possibility of combining standard treatment of HCC by either immune-based or targeted drugs with OVs represents an intriguing opportunity. Figure 1 depicts the mechanism of action of different drugs mentioned here in comparison with OV therapy. In conclusion, preclinical results of OV treatment, alone or possibly in combination with other agents, support its application in the field of HCC, a cancer with a dismal prognosis in a large population of patients.

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Conflict of interest

GA and HF have been editorial board members of *Journal of Clinical and Translational Hepatology* since 2013. LB has no conflict of interests related to this publication.

Author contributions

Manuscript writing and revision (LB, HF); manuscript conceptualization and revision (GA). All authors have made a significant contribution to this study and have approved the final manuscript.

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