

Viral Oncolytic Therapy

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Abstract

Viral oncolysis broadly refers to the use of modified viruses to infect and subsequently lyse tumor cells. This concept arises from the observation that viral replication is itself effective in destroying tumor cells. This effect is then amplified by reinfection of adjacent tumor cells by the progeny virion released from lysed tumor cells. Herpes simplex virus 1 (HSV-1) has been the primary focus of current efforts in viral oncolysis. It is a double-stranded DNA virus that is a ubiquitous pathogen transmitted by direct mucosal contact. HSV-1 possesses several features well suited to viral oncolytic therapy. It does not integrate into the cellular genome, has a large transgene capacity of up to 50 kb, and is already highly prevalent in the general population. In addition, effective antiherpetic agents are available to stop unwanted viral replication. HSV-1 mutants that preferentially replicate in neoplastic cells rather than normal cells have been characterized, and several variants of replication deficient HSV-1 mutants have been created and studied. They follow a common theme in that their replication is significantly attenuated in normal cells, while activated in cancer cells. Studies have been performed in various strains including those known as G207, NV1020, talimogene laherparepvec, and rRp450, and are reviewed here. Viral oncolysis is an exciting area of research with applications to tumors throughout the body. It holds promise as a new treatment for primary and metastatic liver cancer and may soon become a relevant therapy in interventional oncology.

Keywords

- ▶ viral oncolysis
- ▶ interventional oncology
- ▶ viral oncolytic therapy

Introduction

The liver is a common site for primary or metastatic disease. In addition to primary liver tumors, such as hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma, several cancers are known to present with isolated hepatic metastasis, including colorectal carcinoma, ocular melanoma, and neuroendocrine cancers. Moreover, in patients with additional sites of extrahepatic disease, it is the hepatic disease burden that is often the cause of morbidity and mortality.

Liver resection, liver transplantation, and ablation remain the treatments of choice for prospects of cure; however, many patients are not ideal candidates due to number or size of lesions or other comorbidities. The response rate of primary liver tumors to chemotherapy is low.

Interventional oncology approaches including chemotherapy and radioembolization make use intra-arterial

access to the liver for delivering therapy. Recent advances in oncolytic viruses, however, offer a new and promising intra-arterial therapy.

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Herpes simplex virus 1 (HSV-1) has been the primary focus of current efforts in viral oncolysis.^{1–4} It is a double-stranded DNA virus that is a ubiquitous pathogen transmitted by direct mucosal contact. Infection with HSV-1 is common, reported to be 66 to 84% in the United States. Skin or mucosal infection with HSV-1 is typically followed by transmission via sensory nerves to the trigeminal ganglia where lifelong latent infection occurs. Reactivation from ganglionic neurons may occur resulting in an epithelial ulcer

(e.g., “cold sore”) with viral shedding into the oral cavity or epithelia in the trigeminal distribution.

HSV-1 possesses several features well suited to viral oncolytic therapy. It does not integrate into the cellular genome, has a large transgene capacity of up to 50 kb, and is already highly prevalent in the general population. The presence of antibodies against HSV-1 does not attenuate its oncolytic efficacy. Despite the very high prevalence of exposure to HSV-1, it rarely causes severe illness, and effective antiherpetic agents are available to terminate unwanted viral replication.

HSV-1 mutants that preferentially replicate in neoplastic cells rather than normal cells have been characterized, and several variants of replication deficient HSV-1 mutants have been created and studied. They follow a common theme in that their replication is significantly attenuated in normal cells, while activated in cancer cells. Studies have been performed in various strains including those known as G207, NV1020, talimogene laherparepvec (T-VEC, formerly known as OncoVEX^{GM-CSF}), and rRp450. Each of these mutants is attenuated relative to wild-type HSV-1 (→Table 1).

Construction of the Viral Vector

HSV is a neurotropic member of the human herpesvirus family. It is composed of two segments, a unique long (U_L) and unique short (U_S) segments with surrounding regulatory genes and elements.⁵ During a natural infection, the virus replicates in human skin or mucosa cells causing lysis of these cells. The released virions travel in neurons and continue along two main pathways of a replication cycle. They may continue to replicate in a lytic form or enter a latent state. The virus consists of a capsid and envelope with an intervening protein matrix. Replication-defective vectors are engineered by deleting one or more of the necessary HSV gene products. Several variants of replication deficient HSV-1 mutants have been created and studied. These follow a similar theme in their construction in which the natural infection and replication of HSV-1 is attenuated in normal cells relative to cancer cells.

In the case of rRp450, a genetically engineered HSV-1 mutant of laboratory strain KOS created by Chase et al,¹ the viral gene (U_L39) encoding infected cell protein 6 (ICP6) has

Structure of RR⁻ Mutant (rRp450)

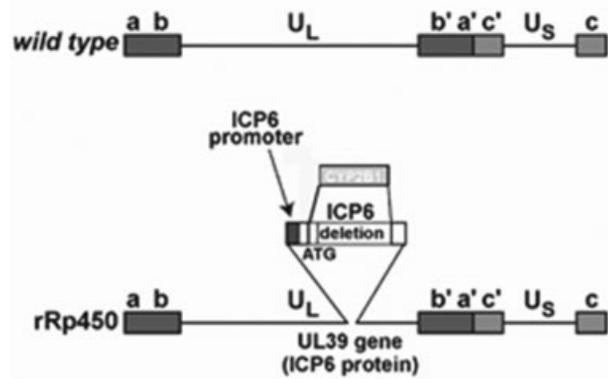


Fig. 1 Genomic structure of rRp450. The native HSV-1 repeats are shown as boxes (labeled a–c). The U_L39 gene encoding the large subunit of the viral ribonucleotide reductase (ICP6) contains an internal deletion into which is cloned the rat cytochrome P450 (CYP2B1) gene under the control of the U_L39 (ICP6) promoter for ICP6. Several HSV-1 oncolytic viral vectors follow similar approaches in attenuating native viral replication. HSV-1, Herpes simplex virus 1; ICP6, infected cell protein 6.

been removed and substituted with the coding sequence of another gene, rat *CYP2B1* cytochrome p450 gene (→Fig. 1). rRp450 is, therefore, defective in expression of ICP6 (large subunit of viral ribonucleotide reductase), markedly attenuating its replication in normal cells. Its replication in cancer cells is significantly more robust, as these transformed cells provide nucleotide precursors to complement the absence of viral ribonucleotide reductase.

By virtue of the *CYP2B1* transgene incorporated in rRp450, cells infected with rRp450 can also bioactivate the prodrug cyclophosphamide, leading to chemotherapeutic toxicity in addition to cytotoxicity caused by viral replication. This raises the potential of administering rRp450 together with cyclophosphamide for enhanced effect.

G207 is an HSV-1 mutant in which both copies of the γ 34.5 gene, implicated in viral replication have been deleted. *lacZ* is also inserted in the U_L39 gene to inactivate viral ribonucleotide reductase. T-VEC makes use of similar pathway which renders the virus incapable of replicating in normal cells.

Table 1 List of HSV-1–based oncolytic viruses in ongoing clinical evaluation

Vector name	Clinical stage and indication	Method of delivery
G207	Phase I for glioblastoma and other brain tumors	Stereotactic injection into tumor
NV1020	Phases I and II for metastatic colorectal cancer to liver	Intravascular delivery to liver
T-VEC (formerly known as OncoVex ^{GM-CSF})	FDA approval in the United States for melanoma	Direct injection into tumor
rRp450	Phase I for primary and metastatic tumors to liver	Intravascular delivery to liver

Abbreviations: FDA, Food and Drug Administration; T-VEC, talimogene laherparepvec.

The common theme is that interruption of essential gene products in virus replication results in HSV mutants incapable of replicating in normal cells. Cancer cells, however, in the process of transforming into malignant cells, have acquired deficiencies in antiviral mechanisms allowing these same viral mutants to retain the ability to replicate with resultant cellular lysis.

Current State of Viral Oncolytic Therapy

G207 is an HSV-1 mutant under development by MediGene in which both copies of the $\gamma 134.5$ gene, implicated in viral replication have been deleted, and the U_L39 gene is inactivated. In a phase I trial establishing safety in subjects with brain tumors, no toxicity or serious adverse events were attributed to G207.⁶ In addition, there was no difference in side effects between patients who had previously been exposed to HSV-1 versus those not previously exposed. In a phase I trial from the University of Alabama, published in May 2014,⁷ G207 was administered stereotactically into glioblastoma tumors in conjunction with radiation. Six of the nine patients in the trial demonstrated stable disease or partial response for at least one of the time points in the study with three demonstrating marked radiographic response.

NV1020 is an HSV-1 mutant in which the internal repeat is deleted and replaced by a fragment of the HSV-2 genome. In a study of interest to the interventional radiology community, a phase I, open-label, dose-escalating trial in patients with metastatic colorectal carcinoma of the liver has been performed. Subjects received a single 10-minute hepatic arterial infusion of NV1020.⁸ Adverse events were either mild or moderate in severity and self-limiting. Only three serious adverse events (one transient rise in serum γ -glutamyltransferase, one diarrhea, and one leukocytosis) experienced by three patients were considered to be possibly or probably related to NV1020. There was no evidence of disseminated herpes infection.

A multicenter phase I/II study published in September 2010² evaluated 32 patients with advanced metastatic colorectal cancer of the liver. Patients received 4 weekly intra-arterial NV1020 doses, followed by two or more cycles of conventional chemotherapy. An optimum biological dose of 10^8 plaque forming units per dose was established. Of the 22 patients receiving this dose, 11 (50%) initially showed stable disease.

T-VEC is an HSV-1 mutant expressing granulocyte macrophage colony-stimulating factor. In a phase II study, T-VEC was injected intratumorally into patients with stage IIIC or IV melanoma.⁹ Patients received an initial injection into 1 to 10 accessible tumors followed by a 3-week interval, then continued with injections every two weeks for a total of up to 24 injections. Both patients previously exposed and not previously exposed to HSV-1 were included in the study. Response rates were similar in these two groups. The overall response rate by RECIST (Response Evaluation Criteria In Solid Tumors) was 26% (eight with complete response and five with partial response). Overall survival was 58% at 1 year and 52% at 24 months.

T-VEC is currently being commercialized by Amgen, Inc. under the trade name Imlygic. As of October 2015, the U.S. Food and Drug Administration officially approved T-VEC for use in melanoma patients with injectable but nonresectable lesions in the skin and lymph nodes making it the first oncolytic virus approved for cancer therapy in the United States.

In separate studies, rRp450 is under investigation for viral oncolysis. Preclinical studies demonstrated that following administration into portal venous system, viral replication occurs preferentially in liver tumor cells versus normal liver.¹⁰ The cytotoxicity associated with the viral replication results in a marked reduction in tumor burden and prolongation of animal survival. Importantly, rRp450 retains its thymidine kinase gene, thereby rendering the virus susceptible to treatment with acyclovir and its analogs to terminate any unwanted viral replication.

A phase-I clinical trial to determine the safety of rRp450 and the highest dose of this agent that can be given safely is currently underway. This involves intra-arterial injection of rRp450 for treatment of primary liver tumors as well as metastatic tumors to the liver. Additional study goals include how the agent is absorbed by the liver cancers, how quickly it is eliminated, and evaluation of tumor response.

Conclusion

Viral oncolysis is an exciting area of research with applications to tumors throughout the body. Understanding viral oncolytic therapy background and development is important for future applications. For the interventional radiology community, intra-arterial viral oncolysis holds promise as a new treatment for primary and metastatic liver cancer and may soon become a relevant therapy in interventional oncology.

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