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# ONCOLYTIC VIRAL THERAPY – AN IMMINENT CANCER CURE

**KEY WORDS:** Oncolytic Viral, Therapy

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**ABSTRACT**

Oncolytic virus therapy is the use of oncolytic viruses to kill cancer cells. Numerous clinical trials are under way using this approach. The use of viruses for cancer treatment is not new. Throughout the 20th century, case studies and small trials of various viruses in cancer therapy were reported. These trials used wild-type and crudely prepared viral isolates. It was in the 1990s that the era of genetic engineering of viruses to enhance their oncolytic potential began.

The main focus was to identify viruses or their engineered variants with tumor-selective replication. However, it has always been appreciated that an immune component is important and may be critical for the therapeutic efficacy of this approach.

Therapeutic efficacy of oncolytic virus therapy is achieved by a combination of selective tumor cell killing and establishment of anti-tumor immunity. Immune stimulation is caused by release of cell debris and viral antigens in the tumor microenvironment. Much research is required before the use of oncolytic viral therapy in clinics.

Oncolytic virus therapy is the use of oncolytic viruses to kill cancer cells. Numerous clinical trials are under way using this approach. In 2015, in a milestone for the field, talimogene laherparepvec became the first oncolytic virus to gain FDA approval.[1] The use of viruses for cancer treatment is not new. Throughout the 20th century, case studies and small trials of various viruses in cancer therapy were reported. These trials used wild-type and crudely prepared viral isolates. It was in the 1990s that the era of genetic engineering of viruses to enhance their oncolytic potential began. The first reported genetically engineered oncolytic virus was based on herpes simplex virus type 1 (HSV1).[2]

The main focus was to identify viruses or their engineered variants with tumor-selective replication. However, it has always been appreciated that an immune component is important and may be critical for the therapeutic efficacy of this approach. Indeed, oncolytic viruses are now broadly considered as immunotherapy agents for which effectiveness in patients depends on activation of host anti-tumor immune responses.[3,4]

Viruses provide a unique platform for the treatment of cancer. Viral infection has intrinsic cytopathic effects, inducing cell death and mediating cellular dysfunction. The viral genome can easily accommodate modifications that increase viral tropism to neoplastic cells, enhance selective viral replication and lytic capacity, alter viral pathogenicity, and induce host anti-tumor immunity. This forms the foundation for the use of viruses in cancer therapeutics. The ability to generate virions rapidly and genetically engineer additional genes that promote antitumor immunity, increase tumor cell susceptibility to ionizing radiation or cytotoxic chemotherapy.[5]

Therapeutic efficacy of oncolytic virus therapy is achieved by a combination of selective tumor cell killing and establishment of anti-tumor immunity. Immune stimulation is caused by release of cell debris and viral antigens in the tumor microenvironment. Tumor selectivity in oncolytic virus therapy is driven by several factors[6]:

- The entry of the virus in the cell via virus-specific, receptor-mediated mechanisms. A specific viral entry receptor is often highly expressed on tumor cells.
- Rapid cell division in tumor cells with high metabolic and replicative activity may support increased viral replication compared with normal quiescent cells.
- Tumor cells are deficient in antiviral type I interferon signaling, and thus, support selective virus replication.
- Viral replication within the tumor microenvironment leads to innate and adaptive immune activation.
- This activation limits virus spread; however, the presence of virus together with cell lysis, with release of tumor antigens and danger-associated molecular patterns, may overcome immunosuppression in the tumor microenvironment and promote antitumor immunity.

Oncolytic viruses range in size and complexity from large, double-stranded DNA viruses such as vaccinia (190 kilobase [kb]) and HSV1 (152 kb) to the tiny parvovirus H1 (5-kb linear, single-stranded DNA). Oncolytic viruses cause cell lysis by various means during their life cycle, with the exception of retrovirus, which can be rendered lytic by toxic transgene expression. Viruses under study for cancer therapeutics are reovirus (a human virus with low pathogenicity), coxsackievirus, newcastle disease virus (avian), parvovirus H1 (rat), vesicular stomatitis virus (VSV) (insects, horses, cows, and pigs), oncolytic vaccinia and measles.

**Clinical Applications Of Oncolytic Viruses:**

- Herpes Simplex Virus: Engineered HSV1 has been tested widely in patients. A major focus of the field is now talimogene laherparepvec, an immuno-stimulatory oncolytic virus that expresses granulocyte-macrophage colony-stimulating factor (GM-CSF). Intra-tumoral injection of talimogene laherparepvec led to significant improvement in durable response rate (DRR) in patients with melanoma (16.3%) compared with controls (2.1%). Effects were most pronounced in patients with stage IIIB, IIIC, IVM1a, or treatment-naive disease. The reason for the success of this agent is a combination of the choice of tutor as melanoma (an immunogenic tumor) and immuno-stimulation via GM-CSF as well as the use of a clinical HSV1 strain backbone, which may allow improved replication in patients compared with other oHSVs built on a laboratory HSV1 strain background.[7]

- Adenovirus: A genetically engineered [E1A/E1B-deleted virus (ONYX015)] oncolytic virus has been extensively tested and approved for treatment of head and neck cancer in China under the name H101. An integrin-binding re-targeted adenovirus, 24RGD (DNX2401), has

been examined in clinical trials in which the maximum tolerated dose (MTD) was not reached and some responses were observed.[8,9]

- Vaccinia Virus: Genetically engineered oncolytic virus, JX-594 (Pexa-Vec) is being tested in multiple tumor types. Pexa-Vec is based on the Wyeth vaccinia vaccine strain engineered to express human GM-CSF and has been tested in more than 300 patients. It is well tolerated and increased survival in patients with liver cancer after intravenous injection. Prostvac, a prime-boost regimen targeting prostate-specific antigen in prostate cancer, uses engineered vaccinia as a primary immunotherapy, followed by boosters using fowlpox virus. Both vectors express prostate-specific antigen and a panel of co-stimulatory molecules: ICAM-1 (intercellular adhesion molecule 1), B7.1, and LFA3. Subcutaneous injection of Prostvac initiates an anti-tumor immune response, is well tolerated, and significantly increased overall survival in phase 2 trials. This dual virus approach overcomes the rapid appearance of neutralizing antibodies against vaccinia. A phase 1 dose-escalation trial of Prostvac in combination with ipilimumab showed no additional toxic effects and some promising responses (MTD was not reached).[10,11]

- Measles Virus: A measles virus expressing the human sodium/iodide symporter SLC5A5 (MV-NIS) is currently in a range of clinical trials. MV-NIS allows imaging of infected cells and monitoring of treatment progression as well as radiovirotherapy with Iodine 131–labeled sodium iodide. Clinical data have confirmed safety and demonstrated imaging of virus infection and tumor regression with this approach.[12,13]

- Coxsackievirus: Coxsackievirus has oncolytic properties in cancer cell lines and leads to a robust immune response. Wild-type coxsackievirus A21 is in clinical trials under the name Cavatak. Numerous trials are ongoing and are built on favorable 2015 phase 2 data in stage IIIC and stage IV melanoma. A study reported a preliminary DRR of 21% with regression of distant non-injected lesions.[14,15]

- Polio Virus: Polio virus has demonstrated oncolytic properties in preclinical studies in brain tumors. These studies were performed using PVS-RIPO, which has been engineered to abolish the neuro-virulence of the native virus. PVS-RIPO is a cytotoxic and immuno-stimulatory virus with preliminary reports of durable radiographic and clinical responses in glioblastoma.[16,17]

- Retrovirus: Retroviruses are potentially useful agents because they readily infect mitotic cells and rapidly spread, although without necessarily causing cell lysis. Toca511 is based on murine leukemia virus engineered to express the yeast enzyme cytosine deaminase, which converts 5-fluorocytosine to the toxic metabolite 5-fluorouracil. In studies of mice with implanted gliomas, Toca511 therapy resulted in long-term survival and systemic anti-tumor immunity mediated by memory T cells. Toca511 is currently in a phase 2/3 clinical trial for malignant glioma and has shown promising interim results.[18,19]

- Reovirus: Reovirus usually produces mild symptoms in humans and can readily enter human cells and activate innate and adaptive immune system. Oncolytic reovirus is marketed as Reolysin and has been examined in clinical trials alone and in combinations in a range of cancers. Reolysin was given orphan drug status for the treatment of malignant glioma by the FDA in 2015.[20,21]

Various measures for safety, adverse effects, dose and viral pharmacokinetics and pharmacodynamics have to be taken into consideration for oncolytic virus clinical trials. Despite engineering for tumor cell specificity, there is the possibility of off-target effects, and genetic manipulation may result in unexpected toxic effects. Other concerns include virus mutation, evolution and recombination; cytotoxic gene products; and viral transmissibility. Immunocompromised patients or those with active viral infections should not be included in the trials. Local delivery of oncolytic viruses is generally well tolerated. The most common adverse effects reported are mild flu-like symptoms, which may be more severe after systemic administration, and local reaction at the injection site. These reactions can be reduced by acetaminophen administration before treatment. In contrast to results in conventional drug clinical trials, many oncolytic viruses do not reach a maximum tolerated dose owing to the concentration of virus stock that is possible to achieve or very high tolerance for the virus. Maximum tolerated dose may need to be re-established for trials using novel therapeutic combinations. Effectiveness of oncolytic virus therapy is monitored by standard approaches, including imaging and tumor-specific biomarkers. Viral pharmacokinetics and pharmacodynamics (shedding, viremia, replication, genomes, and viral load) are frequently included in oncolytic virus trials. These approaches allow tracking of viral fate in patients.

The major resistance mechanisms in oncolytic virus therapy result from to the ability of the host to rapidly shut down viral replication. Host antiviral mechanisms include the presence of neutralizing antibodies and the rapid mobilization of innate immune cells in response to oncolytic viruses. This has led to the idea that inhibition of immune responses early in treatment may be beneficial, and immunosuppressants such as cyclophosphamide promote viral replication.

Therapeutic delivery of oncolytic viruses is dependent on virus and tumor type. Most often, oncolytic viruses are injected directly into the tumor site. For example, tumors of the brain are treated using local delivery by multiple injections at a single time point (during surgery). Other, more accessible tumors can be treated with multiple doses and multiple injection sites over time. Intravenous injection is also commonly used and allows systemic administration to multiple tumor sites. Cellular carriers may also be used, which may protect the virus from recognition by the host immune system before reaching the tumor.

Much research is required before the use of oncolytic viral therapy in clinics.

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