Systemic Efficacy with Oncolytic Virus Therapeutics: Clinical Proof-of-Concept and Future Directions

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Abstract

Oncolytic viruses that can destroy cancer cells have been engineered in a variety of ways with the aim of improving their selectivity and efficacy. Here, we review data from clinical investigations of these virotherapeutic agents, specifically those that have shown systemic efficacy: vaccinia, measles, mumps, viruses, Newcastle disease virus, and reovirus. Further directions for optimizing i.v. delivery and efficacy are discussed. [Cancer Res 2007;67(2):429–32]

Introduction

Targeted oncolytic viruses (virotherapeutics) replicate in and destroy cancer cells (oncolysis) selectively. This novel primary mechanism of action is complemented by secondary mechanisms including induction of tumor-specific immunity and antivascular effects. In addition, therapeutic viruses can be “armed” to express therapeutic protein “payloads” that kill adjacent cancer cells by complementary or synergistic mechanisms. Cancer-selective targeting can be inherent to specific virus species and/or genetically engineered into a virus. Many approaches to engineering cancer selectivity have been previously described.

The vast majority of clinical trials over the last decade have used local (e.g., i.t.) or regional (e.g., intracavitary or intra-arterial) administration. Safety and selective replication in tumors has been shown, and localized cancer necrosis has been reported with wild-type and genetically engineered viruses. Effective treatment of metastatic cancer requires systemic efficacy, however. The study of i.v. administration and systemic efficacy has grown steadily over the last 5 years. The aim of this review is to provide an integrated analysis of systemic efficacy and i.v. administration from case series and clinical trials with oncolytic viruses. We identify novel paradigms for the field and discuss future directions to optimize systemic efficacy.

Cancer Remissions Induced by Viral Infection or Vaccination

Systemic anticancer effects have been reported both after viral infections and after live virus vaccinations. In 1904, a patient with leukemia had a dramatic decrease in WBC during a “flu-like” illness. In the 1950s to 1980s, examples included varicella-induced remission of acute lymphoblastic leukemia (1) and measles-induced remissions of leukemias (2), Burkitt’s lymphoma (3), and Hodgkin’s lymphoma (ref. 4, Table 1). Similar responses occurred following vaccination of cancer patients, including a patient with chronic lymphocytic leukemia who underwent a durable complete response following systemic vaccinia virus dissemination from a dermal vaccination site (5). Measles vaccination caused responses in two patients with Hodgkin’s lymphoma (6, 7). In summary, viremia following infection or vaccination can result in tumor responses in patients with lymphoma or leukemia.

Cancer Treatment: Case Series with Nonengineered Viruses

Viruses have shown replication and subsequent blood-borne dissemination and tumor infection following localized administration to tumors (vaccinia) or even normal tissue (West Nile); systemic efficacy resulted against melanomas and lymphomas, respectively. West Nile virus i.m. injection (n = 46) led to systemic dissemination followed by a replication “spike” (a 1,000- to 1,000,000-fold increase in virus concentration from days 4 to 10; ref. 8). Virus was detectable in the tumor(s) of >80% of patients. Efficacy was noted in lymphoma patients (n = 3). I.t. vaccinia resulted in melanoma responses both in injected (57%) and in non-injected tumors (n = 55 patients total; refs. 9–11). Six patients were disease-free for ≥2 years. Viral spread to a non-injected, regressing metastasis was proven in one patient.

I.v. efficacy has been shown in case series with in vitro passaged strains of vaccinia, mumps, and Newcastle disease virus (NDV). In contrast, neither systemic dissemination nor efficacy was reported with human adenoviruses after i.t. or i.v. administration. I.v. vaccinia led to tumor responses in three patients (12, 13), including two with adenocarcinomas and one with myeloma. A tissue culture–attenuated mumps virus was injected i.v., plus other routes (n = 90 patients), and caused responses in breast and cervical cancer patients (14, 15); tumor histopathology showed virus-induced cytopathic effects. I.v. NDV caused responses in myelogenous leukemia (16) and in glioblastoma (strain MTH-68/H; ref. 17); although safety was clear, concomitant treatments made the interpretation of tumor responses difficult.

Modern-Era Clinical Trials with Nonengineered and Engineered Oncolytic Viruses: 1996 to 2006

Oncolytic viruses from at least six different species have entered clinical trials. These include genetically engineered vaccinia, herpes simplex virus (HSV), adenovirus, and measles; non-engineered viruses include NDV and reovirus (Table 1).

Systemic efficacy has been shown following i.t. injection with the granulocyte macrophage colony-stimulating factor (GM-CSF)–armed vaccinia virus JX-594 (JENNEREX Biotherapeutics, San Francisco, CA), in contrast to non-armed adenoviruses (e.g., Onyx-015/dl1520) and reovirus. In a phase I trial, JX-594 was administered one to two times per week i.t. to metastatic melanoma after an initial
revaccination (n = 7; ref. 18). GM-CSF mRNA expression and infectious virus was detected in the majority of tumor biopsy samples. Objective responses occurred at the injection site (71%), and four patients had regressions of non-injected dermal metastases. Two patients with complete tumor eradication were disease-free for at least 1.5 years. Distant regressing tumors were heavily infiltrated by T lymphocytes. This is the first virus to show reproducible distant antitumor effects after a local injection in humans.

In contrast, systemic efficacy was not reported after i.t. adenovirus Onyx-015/dl1520 (n > 100 patients) or reovirus

### Table 1. Systemic efficacy with oncolytic viruses as single agents

<table>
<thead>
<tr>
<th>Virus species</th>
<th>Agent</th>
<th>Genetic Δ backbone/therapeutic transgene</th>
<th>Systemic tumor response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infection/vaccination</td>
</tr>
<tr>
<td><strong>Oncolytic viruses with demonstrable systemic efficacy</strong></td>
<td></td>
<td></td>
<td>+ Vaccination (CLL)</td>
</tr>
<tr>
<td>Vaccinia</td>
<td>Vaccine strain</td>
<td>--/--</td>
<td></td>
</tr>
<tr>
<td>JX-594</td>
<td>+ (tk−)/+ (GM-CSF)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Measles</strong></td>
<td>Wild type/vaccine strain</td>
<td>--/--</td>
<td></td>
</tr>
<tr>
<td>MV-CEA</td>
<td>--/-- (CEA, monitoring)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Mumps</strong></td>
<td>Wild type/vaccine strain</td>
<td>--/--</td>
<td></td>
</tr>
<tr>
<td><strong>West Nile</strong></td>
<td>Wild type/vaccine strain</td>
<td>--/--</td>
<td></td>
</tr>
<tr>
<td><strong>NDV</strong></td>
<td>PV701 (mesogenic)</td>
<td>--/--</td>
<td></td>
</tr>
<tr>
<td><strong>Reovirus</strong></td>
<td>Reolysin</td>
<td>--/--</td>
<td></td>
</tr>
</tbody>
</table>

### Oncolytic viruses without demonstrable systemic efficacy to date

<table>
<thead>
<tr>
<th>Virus species</th>
<th>Agent</th>
<th>Genetic Δ backbone/therapeutic transgene</th>
<th>Systemic tumor response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infection/vaccination</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Wild type (Group C)</td>
<td>--/--</td>
<td></td>
</tr>
<tr>
<td>d11520 (Onyx-015)</td>
<td>+ (E1B-55K−, E3B−)/−</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>H101</td>
<td>+ (E1B-55K−, E3−)/−</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>CV706</td>
<td>+ (PSE-E1A, E3−)/−</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ad5-CD/TKrep</td>
<td>+ (E1B-55K−, E3−)/−</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>CG7870</td>
<td>+ (rat probasin-E1A, PSE-E1B)/−</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>HSV</strong></td>
<td>Wild type</td>
<td>--/--</td>
<td></td>
</tr>
<tr>
<td>1716</td>
<td>+ (ICP34.5−)/−</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>G207</td>
<td>+ (ICP6−, ICP34.5−)/−</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>OncoVexGM-CSF</td>
<td>+ (ICP6−, ICP34.5−) + (GM-CSF)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>NV1020</td>
<td>HSV-1 and -2 hybrid (one copy ICP34.5−)/−</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HAI, hepatic arterial infusion; tk, thymidine kinase; NSCLC, non–small cell lung cancer; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease (lymphoma); CRC, colorectal carcinoma; SCCHN, squamous cell carcinoma of the head and neck; NA, not applicable; PSA, prostate-specific antigen; GBM, glioblastoma multiforme.
Systemic Efficacy with Clinical Virotherapy

(Reolysin; \(n = 19\)). HSV G207 and 1716 have been used locally in glioblastoma patients in whom systemic efficacy cannot be assessed (19); 1716 injection in melanoma did not reportedly cause distant responses. NV1020 hepatic arterial infusion did not reportedly have systemic efficacy. The GM-CSF–armed HSV OncovexGm-CSF (Biovec, Cambridge, MA) was injected i.t. into cutaneous metastases in a phase I trial. Although multi-nodular tumors had necrosis in multiple nodules, no systemic efficacy was reported to date.

I.v. efficacy has also been shown with two different NDV strains and with reovirus. In contrast, serotype 5–derived adenoviruses, such as Onyx-015/dll520 and CG7870, have not shown i.v. responses to date. Data from i.v. trials with engineered vaccinia viruses (e.g., JX-594) are awaited.

Two reports on i.v. NDV PV701 (Wellstat Biologics, Gaithersburg, MD) clinical trials were published (20, 21). In the first trial, dose-limiting toxicities included dyspnea, diarrhea, and dehydration (20). When patients were desensitized with a lower initial dose, the maximum tolerated dose (MTD) was increased 10-fold. Two objective responses were reported, and six patients had stable disease for \(\geq 6\) months. Virus was shown in only one tumor biopsy, however. A subsequent two-step i.v. desensitization trial reported improved patient tolerance and a single lymph node metastases response (viral replication data not reported).

The NDV strain OV 001 (replication-defective, lentogenic) was administered i.v. to 11 glioblastoma patients using intra-patient dose escalation (22). Patients without tumor progression received biweekly maintenance therapy. Virus was recovered from blood, urine, and saliva samples, even after antibody induction; 9 of 10 blood samples had infectious virus detectable for up to 9 days. Infectious NDV was detectable in one of two tumors tested. A complete response lasting 3 months was reported. Replication-independent mechanisms may cause efficacy with this attenuated strain.

A phase I i.v. dose-escalation trial of Reovirus (Reolysin; Oncolytics Biotech, Calgary, Alberta, Canada) was reported \((n = 29)\). The MTD was not defined. Antitumor efficacy was suggested in patients with stable disease for 4 to 6 months, blood tumor marker decrease \(\geq 50\%\) and/or tumor necrosis \((n = 5\) total). Virus replication was shown in a cycle 2 tumor biopsy.

I.v. adenovirus Onyx-015 did not induce responses in phase I \((n = 10\); ref. 23) or phase II \((n = 16\), colorectal; ref. 24). Low-level virus was present in only one tumor biopsy. A single dose of i.v. CG7870 adenovirus (Cell Genesys, San Francisco, CA) was administered to antibody-negative patients \((n = 23)\); transient transaminitis and thrombocytopenia were reported (25). Approximately 50% of patients had detectable viremia consistent with replication. Transient prostate-specific antigen decreases of 25% to 40% were noted (25).

Conclusions and Future Directions

Case reports of cancer remissions following infection (measles) or vaccination (vaccinia, measles) showed the feasibility of systemic viral efficacy in lymphoma and leukemia patients; the immunosuppression induced by hematologic malignancies may facilitate systemic virus dissemination following relatively small virus inocula. These observations led to case series of treatment with attenuated wild-type virus strains. Lm. West Nile virus replicated, spread to tumors, and induced responses in lymphomas. I.t. vaccinia in melanoma patients replicated, disseminated systemically, and infected distant tumors resulting in tumor regressions. I.t. (group C) adenovirus did not cause distant responses. I.v. vaccinia, mumps, and NDV led to tumor responses in case series; of note, these responses were in carcinomas (not hematologic malignancies).

Therefore, before the genetically engineered oncolytic virus era, there was evidence supporting the feasibility of systemic efficacy. The first engineered oncolytic virus to be developed clinically was the adenovirus Onyx-015. A randomized phase III clinical trial of chemotherapy \(\pm\) i.t. Onyx-015 in head and neck cancer was initiated in the United States, and a similar virus (H101) obtained marketing approval in China with the same study design (26). However, systemic efficacy after i.t. injection was not shown, and no responses occurred in i.v. trials. The failure of this virus i.v. contributed to a mistaken belief that i.v. therapy was not feasible; a long history had been forgotten.

Recent clinical successes have reconfirmed the feasibility of systemic virotherapy. I.t. injection with the GM-CSF–armed vaccinia JX-594 resulted in reproducible systemic efficacy. I.v. efficacy was shown in treatment-refractory carcinoma patients with three virotherapy agents: two NDV strains (PV701 and OV001) and reovirus (Reolysin). I.t. virus was anecdotally shown after i.v. administration. I.v. therapy has been extremely well tolerated. Out of \(\sim 150\) patients treated with oncolytic viruses i.v. to date, only one possibly treatment-related death (in a terminal patient) was reported; this death was associated with rapid tumor lysis in the lungs by PV701. This compares favorably with safety on other phase I oncology studies. Slowing the rate of i.v. infusion and a desensitization protocol also reduced toxicity and increased the MTD of PV701. Toxicities varied between virus species. For example, i.v. NDV was associated with transient thrombocytopenia and diffuse vascular leak, whereas i.v. adenovirus was associated with low-grade disseminated intravascular coagulation and transaminitis.

Viruses species-specific characteristics are therefore coming to light. I.v. efficacy following infection, vaccination, i.t. injection, and/or i.v. infusion has clearly been shown with vaccinia, measles, NDV, and reovirus. In contrast, despite i.t. treatment of \(\sim 150\) patients with group C adenoviruses, systemic efficacy against distant tumors has never been reported. I.v. adenovirus dosing of \(\sim 50\) patients on trials was also negative for responses. Virus species, therefore, vary dramatically as "pharmacophores." Different viruses have evolved very different life cycles in their hosts. Poxviruses (e.g., vaccinia) have evolved to disseminate through the blood to the skin and form pox lesions as an avenue for transmission to new hosts. Vaccinia has evolved an extracellular enveloped form that is resistant to antibody- and complement-mediated neutralization for transport in the blood. Measles and vaccinia also travel systemically within lymphocytes and/or monocytes. In contrast, HSV and group C adenoviruses do not typically cause a viremia. The underlying biology of a given virus will therefore have a major effect on its clinical application. Systemic delivery might be most efficient with viruses that have evolved to disseminate in blood.

The clinical development of oncolytic virotherapeutics can be improved. Dosing regimens must be better defined, especially with i.v. administration. Optimal dosing regimens must be defined for

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\(^{1}\) J. de Bono, personal communication.
each virus, including variables such as infusion duration (bolus versus infusion), frequency, and duration. Data with NDV suggest that toxicity can be significantly modulated through altering the infusion rate.

The likelihood of approval and clinical benefit will be improved if predictive factors for efficacy are identified. Virotherapy efficacy might be predicted by histologic tumor type, cancer cell features (e.g., viral receptor levels), and patient immune status. Tumor expression profiling should be explored.

Combination therapy with existing treatment modalities shows promise. Previous trials have shown synergistic efficacy with virotherapy and chemotherapy in certain tumor types (19). Several mechanisms have been proposed for synergistic interactions. For example, adenoviral E1A has been shown to have “chemosensitization/radiosensitization” effects, whereas DNA repair induction by chemotherapy or radiotherapy can promote replication and efficacy with some HSV mutants. Further results from clinical trials are awaited. Of note, virotherapy agents take advantage of specific tumorigenic pathways; thus, it will be wise to determine whether molecular targeted therapies are antagonistic to viral replication (e.g., Gleevec with poxviruses).

Finally, the field will benefit greatly from an improved understanding of viral replication, localization, and kinetics in humans. Serial analysis of tumor biopsies and genome concentrations in blood is indicated. Mathematical models can be used to estimate virus replication based on viral genome concentrations in blood over time. In addition, engineering viruses for noninvasive imaging approaches (e.g., Na/I symporter with positron emission tomography) and soluble peptides (e.g., carcinoembryonic antigen) may help to monitor the location and activity of engineered viruses.

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References

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