Clinical trials

The sensitizing side of Onyx-015

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New clinical trial data on the use of the ONYX-015 adenovirus as a chemosensitizing agent indicate that further study of this approach to the treatment of advanced soft-tissue sarcomas is warranted and provide some encouragement to those interested in the use of viral agents for oncolysis. The concept of using viruses as oncolytic agents has a long history, but the restriction viral replication and lysis to tumor cells and the use of viruses to deliver genes are relatively new developments.^{1,2} Owing to safety concerns, initial efforts have used viruses that are prevalent in the human population but have low pathogenicity. Most of these fall into one of two basic categories: nonengineered wild-type viruses or recombinant forms with genetic manipulations.

Adenoviruses are one group of low pathogenicity viruses that have commonly been used as agents of oncolysis. In humans, adenoviruses normally cause acute mucous-membrane infections of the upper respiratory tract, eyes and regional lymph nodes, resembling the common cold. To replicate efficiently, adenoviruses promote S phase entry of the infected cell.³ One of the cellular responses to this infection is p53-induced apoptosis (ie, programmed cell death) to curb viral replication and limit viral propagation through infected tissues.

In 1996, Bischoff and co-workers^{4,5} suggested that a mutant of an adenovirus might be used as a 'magic bullet' that could selectively lyse tumor cells without harm to normal tissue. The adenoviral E1B gene encodes a 55 kDa polypeptide that inactivates p53 action, and so the virus counteracts the cell's apoptotic response.^{6,7} A mutant adenovirus with an inactive form of the gene E1B-55kDa, named *dl1520*⁸ but also referred to as ONYX-015, cannot inactivate the p53 response, and thus

allows the cell to self-destruct, as envisioned by Bischoff *et al.* However, a number of reports indicate that the interaction of the E1B-55KDa protein and p53 is more complex than originally assumed and that the ability of *dl1520* to productively replicate does not correlate with the p53 genotype of the host cell.^{9–19}

ONYX-015, which does not express a therapeutic or a fail-safe gene, has been administered to over 250 cancer patients in roughly 15 clinical trials in a variety of tumor types involving intratumoral, intravenous, intraperitoneal and hepatic arterial administration.²⁰ Controlled clinical trials using the mutant as an oncolytic agent have led to important insights into the use of this virus as an anticancer strategy.^{20–24} Firstly, ONYX-015 as a single-agent treatment has disappointing efficacy, but in combination with chemotherapy shows encouraging antineoplastic activity. However, it has not been established how the host's p53 genotype might affect the efficacy of this strategy, and neutralizing antibody titers before or after treatment with *dl1520* have not been predictive of antitumor activity. Current data from trials suggest that this approach is safe, but there is a difference in efficacy between *in vivo* animal models and human use. Although there is clear evidence of some efficacy, the available clinical data suggest that even with multiple intratumoral injections, there is room to improve the efficacy of these treatments for a larger proportion of patients. Lastly, to improve the potency of oncolytic viruses, the dynamics between virus replication, release and spread on one side and immune-mediated viral clearance on the other have to be better understood.

The article by Galanis *et al* 'Phase I-II Trial of ONYX-015 in Combination with Chemotherapy in Patients with Advanced Sarcomas' in this

issue of *Gene Therapy* reports of six patients with advanced soft tissue sarcomas (STS) of various histologic types (including two patients with gastrointestinal stromal tumors). STS are a group of histologically and genetically diverse cancers that predominantly arise from mesenchymal cells. STS account for approximately 1% of all adult malignancies with an annual incidence in the United States of approximately 8000 cases,²⁵ and more than 50 subtypes of STS have been identified.²⁶ At time of diagnosis, 10–25% of patients have metastatic disease. Prognosis and preferred treatment depend on histological grade and tumor stage. While low-grade tumors are usually curable by surgery alone, high-grade sarcomas are associated with higher local treatment failure rates and increased metastatic potential. For patients with stage III disease, chemotherapy produces an overall response rate of 15–30% with a 5-year survival of ~35%.²⁷ GIST can often be treated successfully with the tyrosinase kinase inhibitor imatinib.²⁸

Galanis' patients received intratumoral ONYX-015 on days 1–5 as well as chemotherapy (MAP-scheme: Mitomycin, Doxorubicin, Cisplatin, day 1 q28d). Dose escalation was performed to determine the maximum tolerated dose, but the maximum was not reached; the treatment regimen was well tolerated. *In vivo* viral replication was evaluated by *in situ* hybridization of tumor biopsy and qPCR of peripheral blood. Furthermore, the authors observed viral replication in some patients. However, it is unclear whether the chemotherapy regimen inhibited viral DNA replication. One patient achieved a partial response of the virus-inoculated lesion and other metastasis. However, it remains unclear whether this patient's response is due to chemotherapy (five out of six patients were naïve to chemotherapy), synergistic effects or immunological xenogenization of tumor cells by viral proteins.

Further evaluation of this treatment modality is warranted, but establishing another antitumor agent for this tumor type will be most welcome, as in noncurable neoplasms therapeutic agents are often used sequentially to halt progression of the tumor and to achieve the best possible quality of life for patients. ■

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