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EDITORIAL – TRANSLATIONAL RESEARCH AND BIOMARKERS

Regional Delivery of Oncolytic Vaccinia Virus: It's Time for Clinical Trials

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Malignant peritoneal mesothelioma is both rare and deadly with very poor overall long-term survival. Historically, therapies have offered little survival benefit, but recent advances in surgical therapy—a combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)—have shown promise and demonstrate a role for regional, intraperitoneal treatment.[1] This regional delivery needs to be employed with other agents, including biologic therapies such as oncolytic viruses, to continue to improve survival for this disease.

In this month's issue, Acuna et al. describe the use of an oncolytic vaccinia virus (vvDD) for regional, intraperitoneal therapy in a murine model of peritoneal mesothelioma. The authors have been instrumental in the design, construction, and pre-clinical development of this exciting, tumor-selective mutated virus over the last 13 years, and in this manuscript they perform important translational studies to demonstrate the efficacy of this virus as a regional treatment for peritoneal mesothelioma. They establish the selective cytotoxic effects of double-deleted vaccinia virus (vvDD) against two different mesothelioma cell lines and demonstrate improved survival in two different orthotopic murine models of malignant peritoneal mesothelioma after regional (intraperitoneal) treatment with vvDD. The authors verify the remarkable selectivity of the virus, with replication only in the tumor and the ovary. In a model, believed by the authors to be a surrogate for cytoreductive surgery (removal of all macroscopic disease), mice with only microscopic disease achieved a significant survival benefit when treated with vvDD compared to controls. Fifty percent of the mice were cured after a single intraperitoneal injection of 1×10^9 plaque-forming units (pfu) of vvDD.

Oncolytic viral therapy has been studied as a local, regional, and systemic therapy in various human cancers. Adenovirus led the way, but was limited by its inefficiency in vivo and the clinical results were disappointing. Clinical trials using oncolytic herpes virus and measles virus have established viral replication in tumors, but the clinical results have been equally disappointing. The most encouraging results have been from the use of oncolytic vaccinia virus expressing granulocyte–macrophage colony-stimulating factor (GmCSF) in patients with hepatocellular cancer. Intralesional vaccinia-GMCSF therapy resulted in a 15 % response rate utilizing modified response evaluation criteria in solid tumors and a prolongation in survival (14.1 months versus 6.7 months; $p = 0.02$) comparing high dose (10^9 pfu) with low dose (10^8 pfu) intralesional treatment.[2] Several different oncolytic viruses including adenovirus, measles virus, and vaccinia virus have shown promise in treating human mesothelioma cell lines and in models of pleural mesothelioma.[3–5] Although no human trials have been reported to date, we know of three ongoing Phase I trials that are utilizing oncolytic vaccinia, measles, or herpes virus for pleural mesothelioma. vvDD is an efficient, tumor selective virus due to its deletion of both the thymidine kinase and vaccinia growth factor genes, and it has been shown to be both tumor selective and a potent oncolytic agent.[6] We have recently completed clinical trials of intralesional and intravenous delivery of vvDD (unpublished) and realize that poor delivery and premature immune clearance of the virus limits systemic efficacy. Other oncolytic viruses have been delivered intraperitoneally in clinical trials to enhance delivery and improve viral infection.[7–10] Regional delivery of vvDD into the peritoneal cavity leads to direct exposure of high concentration of virus to the tumor and productive infection of the malignant cells, avoiding the antibody and complement

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mediated clearance of the virus. Because peritoneal mesothelioma is superficially exposed within the peritoneal cavity, it is the perfect opportunity for this delivery approach.

The clinical implications of the study by Acuna et al. are potentially two-fold. First, similar to work that has been done using HIPEC for mesothelioma treatment, the authors validate the efficacy of regional therapy for what is typically a diffuse process that is difficult to completely eradicate surgically. Second, the authors' findings suggest that there may be a role for a combination of cytoreductive surgery and regional therapy with oncolytic viral treatment. Additionally, the authors note the possibility of combining oncolytic viral therapy with the expression of tumor antigens or with chemotherapy. However, other methods of immune modulation, such as expression of proinflammatory cytokines or chemokines, may also enhance viral efficacy, especially because vaccinia can be a potent immune stimulant, in addition to having oncolytic effects.

The lack of a suitable animal model for cytoreductive surgery is a major limitation of these experiments, which is addressed by the authors. Until a better model can be developed, it will be difficult to conclude that the combination of cytoreductive surgery and vvDD treatment improve survival compared with cytoreductive surgery or vvDD treatment alone. The model of "microscopic disease" is imperfect, as it represents an early tumor microenvironment instead of a mature microenvironment that has been surgically treated. In a sense, the authors are examining the role of vvDD treatment in preventing tumor progression, instead of treating a diffusely progressed disease with multimodal therapy. The issues of the optimal timing of virus delivery after cytoreduction and the possibility that surgical scarring prevents dissemination of vvDD in the peritoneal cavity have not been addressed. The complexity and safety of delivering a live virus in the immediate postoperative period when anastomoses need to heal and other inflammatory responses are being endured by the patient also needs to be addressed. Despite the imperfect model, the findings still demonstrate the efficacy of vvDD as regional therapy in the treatment of both microscopic and macroscopic malignant peritoneal mesothelioma representing a significant finding in a disease with such poor overall survival.

Malignant peritoneal mesothelioma is a lethal disease that presents a surgical challenge given its diffuse nature and the reality that microscopic disease is left behind after cytoreductive treatment. It has been shown that regional therapy, in the form of HIPEC, is beneficial to these patients. Acuna et al. are the first to demonstrate that in an orthotopic animal model of peritoneal mesothelioma, local oncolytic viral therapy with vvDD is effective for improving median and overall survival. These promising results should be confirmed in a clinical trial where vvDD may provide a significant survival benefit to patients in dire need of new therapies.

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