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EDITORIAL – THORACIC ONCOLOGY

Can Surgeons Expand the Role of Oncolytic Viruses for Cancer Treatment? An Editorial Comment on "Fighting Fire with Fire: Oncolytic Virotherapy in Thoracic Malignancies"

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There has been extensive progress in the treatment of cancer over the past decade, most notably through molecularly targeted therapeutics and tumor immunotherapy. Despite the availability of these new drugs, only a subset of patients with advanced disease achieve complete responses and treatment is associated with both primary and acquired drug resistance, as well as significant toxicity, in some cases. Thus, early detection and complete surgical excision remains the most important initial therapeutic option for most patients with solid tumors.[1] Indeed, surgery has been recognized for centuries as an effective strategy for cancer treatment. While surgical doctrine in the 19th century explored more radical excisions as a way to improve patient outcomes, prospective randomized clinical trials in the 20th century, particularly in breast cancer, established that limited excision was superior to more extensive procedures and could often be supplemented with adjuvant therapy, such as radiation and chemotherapy.[1] These observations have important implications for the contemporary treatment of cancer. First, local approaches to solid tumors, in particular surgery, are a critical component of effective cancer care. Second, the identification of pathologic features and other biomarkers of individual patient tumors are needed to guide potential adjuvant therapy. Third, comprehensive care for cancer patients must include surgical evaluation and input. Given the advances seen with targeted therapy and immunotherapy, it is worth asking whether and how surgeons can best optimize modern cancer therapy.

Oncolytic viruses are a relatively new class of cancer therapeutics that mediate antitumor activity through selective killing of cancer cells and induction of host antitumor immunity. In essence, oncolytic viruses allow for in situ vaccination against personal tumor-associated antigens expressed by injected tumor cells in individual patients.[2] Talimogene laherparepvec (T-VEC) is an attenuated herpes simplex, type 1 virus encoding the cytokine granulocyte–macrophage colony-stimulating factor (GM-CSF) and was approved for the treatment of melanoma that recurs after primary surgical management.[3] T-VEC is associated with an objective response rate of 25–30% as monotherapy and is being actively studied in combination with other systemic treatments, most notably immune checkpoint blockade with promising early-phase clinical trial results.[4] Importantly, oncolytic virus treatment appears to be associated with a highly favorably safety profile, with most adverse events being low-grade constitutional symptoms and injection site reactions.[3] Thus, oncolytic viruses provide an opportunity for treating cancers with a directed local therapy that has limited toxicity and is ideally suited for exploring potential combination approaches. Predictive biomarker research is needed to help identify the best oncolytic viruses for specific cancer indications and to help promote more rational combination clinical studies. Nonetheless, there is growing enthusiasm around investigating oncolytic viruses beyond melanoma. In their review, Ekeke et al. report on the current status of multiple clinical strategies and results of oncolytic viruses in the treatment of a range of thoracic malignancies.[5] While the article nicely provides highlights of promising

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clinical studies, the review also touches on the barriers to effective development of oncolytic viruses for thoracic cancers, and, by extension, for other types of cancer as well.

Oncolytic viruses mediate antitumor activity through multiple mechanisms, and thus the potential benefit of different viruses may differ depending on the unique biologic features of specific tumors, the status of host immune responses, and the inclusion of differing payloads that can be expressed by the virus. In addition, because oncolytic viruses are usually delivered directly into the tumor and may be associated with initial progression before response, new clinical study designs and endpoints may be needed to more accurately define their clinical benefit.[4] Furthermore, oncolytic viruses may be best utilized in specific settings. For example, since they induce immunogenic cell death, they need to be delivered to established tumor cells and this is usually accomplished by direct injection into accessible, established tumors. However, the potential for using oncolytic viruses in the neoadjuvant setting is especially interesting as this may allow for better priming of tumor-specific immunity prior to surgery and may also promote a less extensive procedure if tumor regression occurs prior to planned operation. There is renewed interest in exploring immunotherapy in the neoadjuvant setting, including oncolytic viruses alone and in combination with systemic immunotherapy, and this may also allow better characterization of how oncolytic viruses work since resected tumor specimens can be used for molecular and cellular analyses.

While most oncolytic viruses are delivered by intratumoral injection, an increasing number of studies are exploring intravenous delivery. However, to date, clinical responses appear to be higher when the viruses are injected locally, likely due to better tumor bioavailability and avoiding premature clearance by circulating antibodies or serum proteins.[6] In general, direct injection is simple for cutaneous malignancies but is more complicated for visceral disease. As pointed out in the article by Ekeke et al., thoracic malignancies can be targeted for direct injection using interventional radiology or minimally invasive surgical approaches. Serial injection also allows for serial biopsy and can help foster kinetic studies that follow the impact of oncolytic viruses on the local tumor microenvironment during treatment. Such studies will help inform when and how to optimize viral delivery.

The further development of oncolytic viruses will depend on interdisciplinary studies between virologists and tumor immunologists to identify the best viruses for particular cancers and to determine the optimal payloads for improving anti-tumor immunity. In addition, clinicians with experience in local therapy are needed to better define patient eligibility and tumor indications, and to determine optimal dosing, schedule, and clinical endpoints, as well as combination opportunities for oncolytic viruses. In particular, clinicians with experience in accessing tumors, conducting serial tissue sampling, and considering the best timing for injections, as well as managing local injection sites, will be key to fully realizing the potential of oncolytic virus therapy for all types of cancer. Thus, I would conclude that surgeons will not only be helpful in expanding the role of oncolytic viruses in thoracic and other visceral solid tumors but they represent the most important stakeholder to the future of this field. Surgical oncologists, in particular, should serve as investigators in oncolytic virus clinical trials and should be the leaders in clinical implementation of oncolytic virus therapy.

DISCLOSURES Howard L. Kaufman is an employee of Immuneering Corporation.

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