given that the pleural space may isolate this therapy from shared antigens. In conclusion, the authors utilize a strategy that has the ability to significantly influence patient care as immunotherapy continues to advance.

References

1. Ekeke CN, Russell KL, Murthy P, Guo ZS, Soloff AC, Weber D, et al. Intrapleural IL-2 expressing oncolytic virotherapy enhances acute antitumor effects and T cell

receptor diversity in malignant pleural disease. *J Thorac Cardiovasc Surg*. 2022; 163:e313-28.

2. Rosenberg SA. IL-2: the first effective immunotherapy for human cancer. *J Immunol*. 2014;192:5451-8.
3. Morgan DA, Ruscetti FW, Gallo R. Selective in vitro growth of T lymphocytes from normal human bone marrows. *Science*. 1976;193:1007-8.
4. Lotze MT, Matory YL, Ettinghausen SE, Rayner AA, Sharrow SO, Seipp CA, et al. In vivo administration of purified human interleukin 2. II. Half life, immunologic effects, and expansion of peripheral lymphoid cells in vivo with recombinant IL 2. *J Immunol*. 1985;135:2865-75.

See Article page e313.

Commentary: Regional oncolytics for pleural malignancies

Alfredo Amador, PhD,^a Alexander J. Byun, MD,^a and Prasad S. Adusumilli, MD^{a,b}

Oncolytic viruses are genetically engineered, replication-competent viruses that preferentially infect, replicate within, and lyse cancer cells; released virions subsequently infect neighboring cancer cells, resulting in tumor regression.^{1,2} Two oncolytic viral therapies are currently in clinical use: H101, to treat head-and-neck squamous cell carcinomas in China,³ and talimogene laherparepvec, to treat late-stage melanoma in the United States.⁴ Expanded use of oncolytic viral therapy for other malignancies is constrained by the development of neutralizing antibodies following systemic administration of oncolytic viruses.² We and others have studied measures to expand the efficacy of oncolytic viruses by delivering them regionally¹ or by engineering them to express cytokines to modulate the tumor

Pleural tumor with infiltrating T cells (green) following oncolytic viral infection (red).

CENTRAL MESSAGE

Intrapleural oncolytic virotherapy is feasible, effective, and augments antitumor immune responses without systemic toxicity in a preclinical model of pleural malignancy.

From the ^aThoracic Service, Department of Surgery; and ^bCenter for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, NY.

Disclosures: P.S.A. has received research funding from ATARA Biotherapeutics and ACEA Biosciences; has served on the Scientific Advisory Board or as consultant to ATARA Biotherapeutics, Bayer, Carisma Therapeutics, Imugene, and Takeda Therapeutics; and has patents, royalties, and intellectual property on mesothelin-targeted CARs and other T-cell therapies, method for detection of cancer cells using virus, and pending patent applications on T-cell therapies. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Dec 1, 2020; revisions received Dec 1, 2020; accepted for publication Dec 2, 2020; available ahead of print Dec 8, 2020.

Address for reprints: Prasad S. Adusumilli, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (E-mail: adusumip@mskcc.org).

J Thorac Cardiovasc Surg 2022;163:e330-1

0022-5223/\$36.00

Copyright © 2020 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2020.12.015>

microenvironment and promote immune responses.^{5,6} We have translated the regional delivery of oncolytic vaccinia virus to patients with pleural malignancies (Figure 1).⁷ There has been renewed interest in oncolytic viral therapies following the discovery that checkpoint blockade immunotherapy can augment neoantigen responses generated by lysis of a subset of cancer cells by oncolytic viruses.⁸

In this issue, investigators from the University of Pittsburgh assess the safety, potency, and antitumor immune responses of an interleukin-2-expressing vaccinia virus (VV-IL-2)⁶ in a preclinical model of malignant pleural disease. The authors hypothesize that intrapleural delivery of VV-IL-2 will limit IL-2 expression to the cell surface of the infected cancer cells, boost intratumoral immune responses, and avoid toxicity known to be associated with

FIGURE 1. Multiplex immunofluorescence image of a pleural biopsy following intrapleural administration of oncolytic virus (clinical trial NCT01766739) shows tumor infiltration of T cells. Oncolytic virus–infected tumor cells (red), infiltrating CD3+ T cells (green), cancer antigen mesothelin–positive cells (cyan), and cell nuclear staining by DAPI (blue).

systemic administration of IL-2. They demonstrate that intrapleural delivery of VV-IL-2 results in superior tumor regression, tumor-infiltrating CD8+ T cells, and intratumoral T-cell clonal diversity, compared with saline control or intraperitoneal delivery of VV-IL-2; immune responses are augmented by administration of antiprogrammed death inhibitor-1 agent.⁹ The strength of the study lies in its investigation of a clinical-grade, next-generation oncolytic virus in an orthotopic pleural cancer model. The study observations can be reinforced by future investigations of the comparative efficacy of systemically administered VV-IL-2, the influence of immunosuppressive malignant pleural effusion on the efficacy of intrapleurally delivered VV-IL-2, and the efficacy at metastatic sites beyond the pleura.

Although there are limitations to the study conduct and interpretation, as noted in the Discussion section of the manuscript, the study provides a foundation to design a clinical trial of intrapleurally delivered VV-IL-2 for pleural

cancer. Pleural mesothelioma and metastatic lung and breast cancer to the pleural cavity pose a therapeutic challenge and can benefit from this approach. Resulting anti-tumor immune responses can be further potentiated by antiprogrammed death inhibitor-1 agents that are already in clinical use. With knowledge of the anatomy, biology, and pathophysiology of thoracic cancers, as well as clinical expertise in regional access and the management of immune responses in surgical patients, in their armamentarium, thoracic surgeons are poised to advance immunotherapies for thoracic cancers beyond the current limited use of checkpoint blockade agents. By using an oncolytic virus that targets tumor cells, alters the tumor immune environment, and promotes an antitumor immune response without systemic toxicity, the authors of the current manuscript have provided one such example.

References

1. Adusumilli PS, Stiles BM, Chan MK, Mullerad M, Eisenberg DP, Ben-Porat L, et al. Imaging and therapy of malignant pleural mesothelioma using replication-competent herpes simplex viruses. *J Gene Med.* 2006;8:603-15.
2. Woo Y, Adusumilli PS, Fong Y. Advances in oncolytic viral therapy. *Curr Opin Investig Drugs.* 2006;7:549-59.
3. Garber K. China approves world's first oncolytic virus therapy for cancer treatment. *J Natl Cancer Inst.* 2006;98:298-300.
4. Dolgin E. Oncolytic viruses get a boost with first FDA-approval recommendation [erratum in: *Nat Rev Drug Discov.* 2015;14:510]. *Nat Rev Drug Discov.* 2015;14:369-71.
5. Wong RJ, Chan MK, Yu Z, Ghossein RA, Ngai I, Adusumilli PS, et al. Angiogenesis inhibition by an oncolytic herpes virus expressing interleukin 12. *Clin Cancer Res.* 2004;10:4509-16.
6. Liu Z, Ge Y, Wang H, Ma C, Feist M, Ju S, et al. Modifying the cancer-immune set point using vaccinia virus expressing re-designed interleukin-2. *Nat Commun.* 2018;9:4682.
7. Krug LM, Zauderer MG, Adusumilli PS, McGee E, Sepkowitz K, Klang M, et al. Phase I study of intra-pleural administration of GL-ONC1, an oncolytic vaccinia virus, in patients with malignant pleural effusion. *J Clin Oncol.* 2015; 33(15_suppl):7559.
8. Zamarin D, Holmgaard RB, Subudhi SK, Park JS, Mansour M, Palese P, et al. Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy. *Sci Transl Med.* 2014;6:226ra32.
9. Ekeke CN, Russell KL, Murthy P, Guo ZS, Soloff AC, Weber D, et al. Intrapleural IL-2 expressing oncolytic virotherapy enhances acute antitumor effects and T cell receptor diversity in malignant pleural disease. *J Thorac Cardiovasc Surg.* 2022; 163:e313-28.