Molecular Therapy
Oncolytics
Editorial

Oncolytic adenovirus for treatment of malignant ascites

Formation of ascites, fluid in the peritoneal cavity, is a feature of many types of cancer when disseminated intra-abdominally or in the liver. Typically, this occurs at a late stage when the disease has become refractory to medical therapies. Thus, ascites formation indicates a difficult clinical situation for which effective treatments are usually lacking. Ascites formation is particularly prominent in patients with advanced ovarian, pancreatic, and gastrointestinal malignancies.[1,2]

Although only a few patients studied in Zhang et al. had ovarian cancer,[1] this is the tumor type where ascites formation is perhaps most frequent. Ovarian cancer is a common and deadly disease, and most patients are not cured with available therapies, as the majority of cases are detected when already disseminated. While chemotherapy is often effective initially, resistant disease eventually emerges, often accompanied by ascites.

Likewise, most cases of pancreatic and hepatobiliary cancer are detected in a situation where curative treatments are lacking. Chemotherapy can work initially, but refractory disease emerges rapidly and is usually fatal.[3,4] Many cases of colorectal cancer are detected early, but when metastases are present, treatments are typically non-curative.[5]

All of these tumor types can cause ascites formation when intraperitoneal or hepatic disease predominates. No curative treatments are available in these situations, meaning that new approaches are needed.

As studied by Zhang et al., one such approach is oncolytic immunotherapy, where tumor-selective viruses are used to lyse tumor cells[6] while simultaneously causing an immune reaction. The immunogenicity of oncolysis depends on the type of virus used, and adenovirus appears to be among the types of viruses most capable of inducing anti-tumor immunity.[7] Intriguingly, anti-viral immunity seems to contribute to anti-tumor immunity through a variety of mechanisms.[8] These include immune response against infected tumor cells, epitope spreading, and potent danger signaling in the tumor microenvironment.[9,10] Oncolysis is a form of immunogenic cell death, which releases danger-associated molecular patterns, which convert an immune-suppressive tumor microenvironment into an immunostimulatory one. In addition, pathogen-associated molecular pattern signaling is activated, again contributing to reversion of immunosuppression locally.[7]

Intraperitoneal disease offers the possibility of local treatment. This is an advantage, as most oncolytic immunotherapeutics available today have limited activity when given intravenously. This has necessitated intratumoral injection, which has its limitations when the tumor has spread. Although some virus types such as 5/3 chimeric adenoviruses are able to transduce tumors through the intravenous route and spread from tumor to tumor following intratumoral application,[11,12] convincing monotherapy efficacy following systemic administration has not yet been demonstrated for any oncolytic virus. Intraperitoneal dissemination, often accompanied by ascites formation, is therefore an opportunity for locoregional virus delivery. The presence of ascites, in fact, facilitates intraperitoneal virus delivery, as ascites can be easily seen in ultrasound imaging, allowing for direct injection or catheter placement. Using a catheter allows for convenient repeated administration (which was not regularly used in this study), but catheter complications such as infections are common. Ascites allows the virus to spread within the peritoneal cavity, presumably giving access to most parts of the intraperitoneal tumor burden.

The peritoneal cavity is a unique organ in the sense that it is immunologically quite active. It can be seen as a large inside-out lymph node, facilitating immunotherapy approaches.[13] Moreover, peritoneally disseminated disease tends to grow along the walls of the cavity, resulting in smaller tumor masses than what is seen in, e.g., liver and lung metastases. Large tumor masses are known for their immunosuppressiveness, meaning that their absence can facilitate immunotherapy.[14]

In Zhang et al., the oncolytic adenovirus H101 was given intraperitoneally to patients with intraperitoneal disease, as indicated by the presence of ascites and detection of tumor cells therein. The treatment was well tolerated, resulting in the usual adverse effects associated with intraperitoneal administration of oncolytic adenoviruses: mild to moderate fever, fatigue, chills, and abdominal pain.[1,15] As the investigators used a catheter for virus administration, there were some catheter complications. Efficacy was evaluated by measuring the volume of ascites 4 weeks later, and in many cases, it was decreased or even completely absent. Ascites control was achieved in 75% of cases. While it can be discussed whether ascites control at 4 weeks is a robust endpoint or whether longer follow up with, perhaps, repeated injections would be useful, probably the most interesting part of the study involved studying induction of anti-tumor immunity. Several different methods were used, and the data suggest generation of both T cell- and dendritic cell (DC)-mediated immunity. It is easy to agree with Zhang et al. that use of oncolytic adenovirus for treatment of malignant ascites is a promising approach, and it was satisfying to read that they have initiated a prospective trial to investigate it further.[1]

DECLARATION OF INTEREST

A.H. is a shareholder in Targovax ASA and an employee and shareholder in TILT Biotherapeutics Oy.

Akseli Hemminki[1,2,3] and Camilla Heiniö[1]

[1]Cancer Gene Therapy Group, Translational Immunology Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland; [2]TILT Biotherapeutics, Ltd., Helsinki, Finland; [3]Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland

Correspondence: Akseli Hemminki, Cancer Gene Therapy Group, Translational Immunology Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland.
E-mail: akseli.hemminki@helsinki.fi

Correspondence: Camilla Heiniö, Cancer Gene Therapy Group, Translational Immunology Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland.
E-mail: camilla.heinio@helsinki.fi

https://doi.org/10.1016/j.omto.2022.07.010

REFERENCES

1. Zhang, Y., Qian, L., Chen, K., Gu, S., Wang, J., Meng, Z., Li, Y., and Wang, P. (2022). Intraperitoneal oncolytic virotherapy for patients with malignant ascites: characterization of clinical efficacy and antitumor immune response. Mol. Ther. Oncolytics *25*, 31–42. https://doi.org/10.1016/j.omto.2022.03.003.

2. Zheng, L.N., Wen, F., Xu, P., and Zhang, S. (2019). Prognostic significance of malignant ascites in gastric cancer patients with peritoneal metastasis: a systemic review and meta-analysis. World J. Clin. Cases *7*, 3247–3258. https://doi.org/10.12998/wjcc.v7.i20.3247.

3. Walker, E.J., and Ko, A.H. (2014). Beyond first-line chemotherapy for advanced pancreatic cancer: an expanding array of therapeutic options? World J. Gastroenterol. *20*, 2224–2236. https://doi.org/10.3748/wjg.v20.i9.2224.

4. Anwanwan, D., Singh, S.K., Singh, S., Saikam, V., and Singh, R. (2020). Challenges in liver cancer and possible treatment approaches. Biochim. Biophys. Acta Rev. Cancer *1873*, 188314. https://doi.org/10.1016/j.bbcan.2019.188314.

5. Bell, P.D., and Pai, R.K. (2022). Immune response in colorectal carcinoma: a review of its significance as a predictive and prognostic biomarker. Histopathology. https://doi.org/10.1111/his.14713.

6. Morgan, R.A., Dudley, M.E., Wunderlich, J.R., Hughes, M.S., Yang, J.C., Sherry, R.M., Royal, R.E., Topalian, S.L., Kammula, U.S., Restifo, N.P., et al. (2006). Cancer regression in patients after transfer of genetically engineered lymphocytes. Science *314*, 126–129. https://doi.org/10.1126/science.1129003.

7. Cervera-Carrascon, V., Quixabeira, D.C.A., Havunen, R., Santos, J.M., Kutvonen, E., Clubb, J.H.A., Siurala, M., Heiniö, C., Zafar, S., Koivula, T., et al. (2020). Comparison of clinically relevant oncolytic virus platforms for enhancing T cell therapy of solid tumors. Mol. Ther. Oncolytics *17*, 47–60. https://doi.org/10.1016/j.omto.2020.03.003.

8. Kanerva, A., Nokisalmi, P., Diaconu, I., Koski, A., Cerullo, V., Liikanen, I., Tähtinen, S., Oksanen, M., Heiskanen, R., Pesonen, S., et al. (2013). Antiviral and antitumor T-cell immunity in patients treated with GM-CSF-coding oncolytic adenovirus. Clin. Cancer Res. *19*, 2734–2744. https://doi.org/10.1158/1078-0432.CCR-12-2546.

9. Hemminki, O., Dos Santos, J.M., and Hemminki, A. (2020). Oncolytic viruses for cancer immunotherapy. J. Hematol. Oncol. *13*, 84. https://doi.org/10.1186/s13045-020-00922-1.

10. Heiniö, C., Havunen, R., Santos, J., de Lint, K., Cervera-Carrascon, V., Kanerva, A., and Hemminki, A. (2020). TNFa and IL2 encoding oncolytic adenovirus activates pathogen and danger-associated immunological signaling. Cells *9*, 798. https://doi.org/10.3390/cells9040798.

11. Zafar, S., Quixabeira, D.C.A., Kudling, T.V., Cervera-Carrascon, V., Santos, J.M., Grönberg-Vähä-Koskela, S., Zhao, F., Aronen, P., Heiniö, C., Havunen, R., et al. (2020). Ad5/3 is able to avoid neutralization by binding to erythrocytes and lymphocytes. Cancer Gene Ther. *28*, 442–454. https://doi.org/10.1038/s41417-020-00226-z.

12. Havunen, R., Santos, J.M., Sorsa, S., Rantapero, T., Lumen, D., Siurala, M., Airaksinen, A.J., Cervera-Carrascon, V., Tähtinen, S., Kanerva, A., and Hemminki, A. (2018). Abscopal effect in non-injected tumors achieved with cytokine-armed oncolytic adenovirus. Mol. Ther. Oncolytics *11*, 109–121. https://doi.org/10.1016/j.omto.2018.10.005.

13. Kanerva, A., Koski, A., Liikanen, I., Oksanen, M., Joensuu, T., Hemminki, O., Palmgren, J., Hemminki, K., and Hemminki, A. (2015). Case-control estimation of the impact of oncolytic adenovirus on the survival of patients with refractory solid tumors. Mol. Ther. *23*, 321–329. https://doi.org/10.1038/mt.2014.218.

14. Taipale, K., Liikanen, I., Koski, A., Heiskanen, R., Kanerva, A., Hemminki, O., Oksanen, M., Grönberg-Vähä-Koskela, S., Hemminki, K., Joensuu, T., and Hemminki, A. (2016). Predictive and prognostic clinical variables in cancer patients treated with adenoviral oncolytic immunotherapy. Mol. Ther. *24*, 1323–1332. https://doi.org/10.1038/mt.2016.67.

15. Moreno, V., Barretina-Ginesta, M.P., García-Donas, J., Jayson, G.C., Roxburgh, P., Vázquez, R.M., Michael, A., Antón-Torres, A., Brown, R., Krige, D., et al. (2021). Safety and efficacy of the tumor-selective adenovirus enadenotucirev with or without paclitaxel in platinum-resistant ovarian cancer: a phase 1 clinical trial. J. Immunother. Cancer *9*, e003645. https://doi.org/10.1136/jitc-2021-003645.