The Evolving Role of Oncolytic Viruses in the Era of Cancer Immunotherapy

BACKGROUND

Oncolytic viruses (OVs) have emerged as a paradigm-changing cancer immunotherapy.[1] Talimogene laherparepvec (T-VEC) is currently the only FDA-approved oncolytic virus for the treatment of unresectable stage IIIB-IVM1c melanoma.[2] However, there are currently more than 90 ongoing clinical trials that are investigating novel OVs as single agents and/or in combination with other therapeutic modalities, such as immune checkpoint inhibitors.[3]

OVs can selectively kill cancer cells through multiple mechanisms.[4] The viruses can be designed to selectively replicate within tumor cells, leading to cancer cell lysis and death.[5] The mechanism of OV specificity to cancer cells varies depending on the type of cancer being targeted and the genetic modifications that are introduced into the DNA or RNA viruses.[4] Certain OVs can take advantage of the altered pro-tumorigenic signaling pathways in cancer cells, which promote more efficient viral replication compared with normal cells.[4] Additionally, OVs can be designed to express proteins that have anticancer and/or immune-stimulatory activity, which augment the efficacy through induction of an anticancer immune response.[5]

Induction of cancer cell lysis by OVs leads to the release of cancer cell antigens and immune-stimulatory molecules that consequently trigger a systemic anticancer immune response.[6] This led to the hypothesis that combining OVs with immune checkpoint inhibitors, another revolutionary class of anticancer immunotherapies, can result in a more effective therapeutic response.[7] There are currently several clinical trials that are investigating this strategy. The results of these trials will have an impact on the current clinical guidelines.

To keep pace with the rapid development of the role of OVs in cancer immunotherapy, medical oncologists and healthcare providers need educational programs that present the unique characteristics of the emerging OVs, their mechanisms of action, and efficacy and safety as monotherapy and in combination with immune checkpoint inhibitors.

Educational analysis

Gap #1: Physicians may be unaware of the potential applications of oncolytic viruses in cancer treatment.

Learning objective #1: Describe the mechanisms of action of oncolytic viruses in the treatment of cancer.

OVs induce selective cancer cell death through several mechanisms. These engineered DNA or RNA viruses can selectively infect cancer cells, but not normal cells.[8] This selectivity can be attributed to the altered mitogenic signaling pathways within cancer cells that promote efficient viral replication.[8] Additionally, the genome of the OVs can be modified to weaken their virulence and enhance their safety profiles.[8] The replication of OVs within cancer cells leads to cell lysis and death, which releases tumor antigens and damage associated molecular patterns (DAMPs).[9] These molecules can activate local and systemic anticancer immune responses that augment viral-mediated lytic cell death. Moreover, certain OVs are engineered to express proteins (eg, cytokines) that have anticancer and/or immune-stimulatory effects.[9]

Viral tumor specificity can also be enhanced through the genetic engineering of DNA and RNA viral particles that express certain binding motifs such as antibodies, polypeptides, or ligand-binding domains on the surface of the envelop or non-enveloped viral particles.[10] These strategies can enhance viral localization to cancerous lesions, reduce clearance, and limit systemic toxicity.[10]