Enhanced Delivery of Oncolytic Adenovirus by Neural Stem Cells for Treatment of Metastatic Ovarian Cancer.

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Public Summary:
Oncolytic virotherapy is a promising approach for treating drug-resistant ovarian cancer, but clinical efficacy has been hindered because the immune system quickly recognizes and clears the therapeutic virus. To overcome this barrier, stem cells can be used to shield the virus from the immune system, thereby enabling improved viral delivery to tumors. However, obtaining an adequate, reproducible stem cell supply has been a significant challenge when implementing this viral delivery solution. Here, we demonstrate the ability of an "off-the-shelf" stem cell line line to protect oncolytic viral cargo from immune defenses present within patient ascites fluid. The stem cells also improve delivery to tumors within preclinical ovarian cancer models. The viral payload used in this study is an adenovirus, specifically engineered to infect only tumors. We found this viral agent was effective against cisplatin-resistant ovarian tumors and could be used as an adjunct treatment with cisplatin to decrease tumor burden without increasing toxicity. This report suggests NSC-delivered CRAd-S-pk7 virotherapy holds promise for improving clinical outcome, reducing toxicities, and improving quality of life for patients with advanced ovarian cancer.

Scientific Abstract:
Oncolytic virotherapy is a promising approach for treating recurrent and/or drug-resistant ovarian cancer. However, its successful application in the clinic has been hampered by rapid immune-mediated clearance or neutralization of the virus, which reduces viral access to tumor foci. To overcome this barrier, patient-derived mesenchymal stem cells have been used to deliver virus to tumors, but variability associated with autologous cell isolations prevents this approach from being broadly clinically applicable. Here, we demonstrate the ability of an allogeneic, clonal neural stem cell (NSC) line (HB1.F3.CD21) to protect oncolytic viral cargo from neutralizing antibodies within patient ascites fluid and to deliver it to tumors within preclinical peritoneal ovarian metastases models. The viral payload used is a conditionally replication-competent adenovirus driven by the survivin promoter (CRAd-S-pk7). Because the protein survivin is highly expressed in ovarian cancer, but not in normal differentiated cells, viral replication should occur selectively in ovarian tumor cells. We found this viral agent was effective against cisplatin-resistant ovarian tumors and could be used as an adjunct treatment with cisplatin to decrease tumor burden without increasing toxicity. Collectively, our data suggest NSC-delivered CRAd-S-pk7 virotherapy holds promise for improving clinical outcome, reducing toxicities, and improving quality of life for patients with advanced ovarian cancer.