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Two investigational antitumor agents work better together against MPNST and neuroblastoma

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Two investigational agents, Aurora A kinase inhibitor (alisertib) and HSV1716, a virus derived from HSV-1 and attenuated by the deletion of RL1, have shown some antitumor efficacy in early clinical trials as monotherapies. A new study published last week in *Oncotarget*, however, demonstrates that the combined usage of the agents results in significantly increased antitumor efficacy in models of malignant peripheral nerve sheath tumor (MPNST) and neuroblastoma."We chose to investigate this combination in MPNST and neuroblastoma because these are two difficult-to-treat sarcomas that have shown susceptibility to these agents individually," explains Timothy Cripe, MD, PhD, division chief of Hematology/Oncology & BMT at Nationwide Children's Hospital and senior author on the study. "MPNST is a rare pediatric cancer, but for patients with neurofibromatosis 1, a genetic cancer predisposition disorder, it is the leading cause of death. More importantly, MPNST is resistant to chemotherapy."

According to Dr. Cripe, who is also a principal investigator in the Center for Childhood Cancer and Blood Diseases in The Research Institute at Nationwide Children's, many mechanisms likely worked synergistically to increase the antitumor effect in this study. Particularly, HSV1716 increased the sensitivity of uninfected cells to alisertib cytotoxicity. Second, alisertib increased peak virus production and slowed virus clearance from tumors. The team also found that alisertib inhibited virus-induced accumulation of intratumoral myeloid derived suppressor cells.

"Our study shows that alisertib helps the infection phase of HSV1716 because innate immunity is impacted," says Dr. Cripe, also professor of Pediatrics at The Ohio State University College of Medicine. "It's possible that it could inhibit the second phase, the downstream immunotherapeutic effects of the virotherapy, but based on data from other studies, we don't think that is the case."

Moving forward, Dr. Cripe says that confirming the sustained immunotherapeutic benefits of HSV1716 in the presence of alisertib and building a clinical trial are important next steps in understanding how these agents work together and how they could impact care for patients.

"Our results, in the context of early trials of both substances individually that have shown safety and efficacy, support the testing of this combination in children and young adults with neuroblastoma and MPNST," says Dr. Cripe. "As these agents continue to move through the development and approval processes, we look forward to studying them further."

More information: Mark A. Currier et al, Aurora A kinase inhibition enhances oncolytic herpes virotherapy through cytotoxic synergy and innate cellular immune modulation, *Oncotarget* (2017). DOI: 10.18632/oncotarget.14885

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