Alisertib Enhances Oncolytic Seprehvir Virus Infection and Antitumor Efficacy in Preclinical MPNST and Neuroblastoma Xenograft Models

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abstract

The most common cancer and a leading cause of death in patients with neurofibromatosis type 1 is malignant peripheral nerve sheath tumor (MPNST), which is essentially not responsive to cytotoxic chemotherapy or radiation. In an effort to discover novel therapies for MPNST, we previously showed moderate susceptibility of MPNST cell lines and xenografts to oncolytic herpes simplex virus viruses (Currier et al., Ped Blood Can 46:745, 2006; Mahler et al., Can Res 68:1170, 2008). We now confirm these findings using an oncolytic HSV, Seprehvir (HSV1716), which is in clinical trials, but also sought to increase therapeutic efficacy. Because DNA viruses are highly dependent on normal nuclear machinery for DNA synthesis/replication and virus packaging/assembly, we postulated that increased transit time in muscle may be beneficial to an oncolytic DNA virus. We focused on a non-invasive kinase inhibitor, as we had previously found Alisertib (MLN8237) was tumoricidal in the MPNST xenograft model S462TY (Patel et al., Clin Cancer Res 18:5020, 2012). Whereas each agent alone only resulted in delayed tumor growth, we found a single intratumoral injection of Seprehvir on day 8 added to an oral gavage pulse regimen of Alisertib at its maximum tolerated dose (20 mg/kg twice daily days 1-5) markedly enhanced antitumor efficacy (4/8 partial responses (PR) and 3/8 complete responses (CR)). To better elucidate drug exposures achievable in human subjects, we found similar effects using a 75% reduced dose of Alisertib (10 mg/kg once daily, days 1-5) followed by a single intratumoral dose of Seprehvir (day 5), using repeated cycles (5/10 delayed progression, 1/10 stable disease, 2/10 L, 2/10 CR). Immunohistochemical staining for HSV antigens revealed a marked difference in the extent and spread of virus as early as 24 hrs after virus injection. In a preliminary study of virus entry using cells in culture, we detected increased numbers of viral genomes within the cell after Alisertib exposure, suggesting Alisertib influences early steps in virus pathogenesis. These data strongly support Alisertib pretreatment (“priming”) tumor cells, making them highly susceptible to virus infection and spread and greatly accelerating the virolytic effects. Our findings provide rationale for clinical testing of Alisertib combined with Seprehvir in patients with MPNST.

references


methods

results

conclusions

acknowledgements