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DIPG-21. PRECLINICAL ASSESSMENT OF A MULTIMODAL TREATMENT APPROACH WITH GIVINOSTAT, PAXALISIB, AND RADIOTHERAPY FOR DIFFUSE MIDLINE GLIOMA (DMG)
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BACKGROUND: Despite an extensive body of clinical research conducted, the prognosis for patients with Diffuse Midline Glioma (DMG) has remained stagnant for the past five decades. Years of investigations underscore the robust resistance of DMG tumors to treatment, rendering monotherapy an improbable route to a cure. Recognizing the need for a multimodal approach, this study evaluated a treatment strategy incorporating radiotherapy and two brain-penetrable compounds with potential immunomodulatory effects, Givinostat and Paxalisib. METHODS: We selected Givinostat, a pan-HDAC inhibitor undergoing clinical studies in children with Duchenne muscular dystrophy, by comprehensive screening of a panel of HDAC inhibitors for their efficacy in DMG neurosphere cultures, ability to penetrate the blood-brain barrier, and clinical utility; in addition, we selected the PI3K/mTOR inhibitor Paxalisib based on a phase II clinical trial currently undergoing in DMG patients (PNOC DMG Adaptive Combination Trial, PNOC022). The anti-tumor, radio-sensitizing, and immunomodulatory effects of both compounds were assessed in vitro and in immunocompetent mice, using various cytotoxicity and proteomic assays and (single-cell) sequencing techniques. RESULTS: Our investigations revealed that the combination of Givinostat and Paxalisib exerts a profound cytostatic and cytotoxic effect on DMG cells, by reducing cell viability, enhancing DNA damage, and inducing apoptosis. Moreover, this combination therapy sensitized DMG cells to ionizing radiation, potentially by diminishing DNA repair mechanisms and elevating oxidative stress. Additionally, the combination of Givinostat and Paxalisib considerably reduced tumor growth in vivo and transformed the immune-cold microenvironment of DMG tumors into a pro-inflammatory phenotype. CONCLUSIONS: This study positions Givinostat as a potential addition to the backbone of Paxalisib in forthcoming clinical trials, either as a radio/chemotherapy combination or as a foundation for immunotherapy.