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Bench-to-bedside investigations of H3 K27-altered diffuse midline glioma: drug targets and potential pharmacotherapies

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Abstract

Introduction: H3 K27-altered diffuse midline glioma (DMG) is the most common malignant brainstem tumor in the pediatric population. Despite enormous preclinical and clinical efforts, the prognosis remains dismal, with fewer than 10% of patients surviving for two years after diagnosis. Fractionated radiation remains the only standard treatment options for DMG. Developing novel treatments and therapeutic delivery methods is critical to improving outcomes in this devastating disease.

Areas covered: This review addresses recent advances in molecularly targeted pharmacotherapy and immunotherapy in DMG. The clinical presentation, diagnostic workup, unique pathological challenges, and current clinical trials are highlighted throughout.

Expert opinion: Promising pharmacotherapies targeting various components of DMG pathology and the application of immunotherapies have the potential to improve patient outcomes. However, novel approaches are needed to truly revolutionize treatment for this tumor. First, combinational therapy should be employed, as DMG can develop resistance to single-agent approaches and many therapies are susceptible to rapid clearance from the brain. Second, drug-tumor residence time, i.e. the time for which a therapeutic is present at efficacious concentrations within the tumor, must be maximized to facilitate a durable treatment response. Engineering extended drug delivery methods with minimal off-tumor toxicity should be a focus of future studies.

Keywords: Diffuse midline glioma; H3 K27-altered; H3 K27M; ONC201; blood-brain barrier; convection-enhanced delivery; diffuse intrinsic pontine glioma; immunotherapy.