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Topic Discussion

An Update on H3K27M-altered Diffuse Midline Glioma: Diagnostic and Therapeutic Challenges in Clinical Practice

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Abstract

H3K27-altered diffuse midline glioma (DMG H3K27-altered) is a relatively newly-designated WHO entity which primarily affects the midline structures of the central nervous system (CNS), including the brainstem (predominantly pontine region), thalamus, midbrain, or spinal cord, and primarily affects children and young adults. Despite the proximity of these tumors to eloquent areas in the CNS, novel stereotactic approaches have facilitated the ability to obtain tissue diagnoses without significant morbidity, providing molecular diagnostic information in more than half of patients. Conventionally fractionated radiation therapy to a total dose of 54-60 Gy in 27-30 fractions and 24 Gy in 12 fractions play a crucial role in the definitive treatment of these tumors in the primary and salvage settings, respectively. Hypofractionated regimens may allow for accelerated treatment courses in selected patients without jeopardizing disease control or survival. The decision to add concurrent or adjuvant systemic therapy mainly relies on the physicians' experience without solid evidence in the literature in favor of any particular regimen. Recently, novel agents, such as ONC201 have demonstrated promising oncologic outcomes in progressive/recurrent tumors and are currently under investigation in ongoing randomized trials. Given the scarcity of data and well-established guidelines due to the rare nature of the disease, we provide a contemporary overview on the molecular underpinnings of this disease entity, describe the role of radiotherapy and systemic therapy, and present practice management principles based on the published literature.

Introduction

H3K27-altered diffuse midline glioma (DMG H3K27-altered) is a relatively newly designated World Health Organization (WHO) entity. This highly aggressive brain tumor is usually localized in the midline, often in the brain stem (predominantly pontine region), thalamus, midbrain, or spinal cord, and primarily affects children

and young adults.[1] H3K27-alterations have also been observed in other nonglial brain tumors and do not carry the same negative prognostic connotations as their glial counterparts.[2] The incidence of DMG H3K27-altered is only 0.06 per 100,000 people, with a median age at diagnosis of 15 years (interquartile age: 7-33), according to the most recent *Central Brain Tumor Registry of the United States* report.[3] The WHO 2016 classification recognized a more specific tumor subcategory, DMG H3K27M-mutant, which was subsequently reclassified as H3K27M-altered in the updated 2021 report due to the discovery and integration of other subgroups with molecular alterations in histone H3F3A (H3.3) and HIST1H3B (H3.1) genes.[1] From the molecular perspective, a somatic gain-of-function missense mutation results in a deficit (ie, a loss-of-function phenotype) in the posttranslational modification of histone H3 (ie, trimethylation) via substitution of lysine (27) by methionine (K27M), facilitating chromatin accessibility for DNA transcription and promoting tumorigenesis.[4] Before the WHO 2016 update, diffuse intrinsic pontine glioma (DIPG) was considered as the archetypical tumor belonging to this entity, often diagnosed by imaging and location features alone, due to the difficulty in obtaining tissue samples and lack of clear data regarding molecular histopathologic classification. However, in addition to 80% of DIPGs being classified as DMG H3K27M-altered tumors, approximately 50% of thalamic and 60% of spinal cord high-grade gliomas (HGGs) exhibit these histone mutations.[2,5,6] Despite conflicting results regarding the prognosis based on tumor location, overall survival (OS) for patients who receive diagnoses of H3K27M-altered tumors is universally poor with a median OS of 10 to 15 months.7, 8, 9 However, patients older than ten years and younger than 3 years of age have a marginally better prognosis.7, 8, 9, 10 The failure to achieve a cure in these tumors, attributed to a combination of inoperability, lack of effective systemic therapy options, and inherent resistance to radiation therapy, has prompted efforts to better understand the molecular underpinnings of this disease, thereby encouraging the search for novel drugs and various combinations with radiation therapy. This expert opinion provides an overview of diagnostic and management paradigms for patients with DMG H3K27-altered tumors based on the published literature and reviews our current clinical practice.

Section snippets

Diagnosis

Recent collective efforts from more efficient biopsy techniques (ie, stereotactic biopsy) to immunohistochemistry and DNA sequencing tests, as well as the use of blood and CSF-based testing (still a developmental arena), have augmented our understanding of this rare entity. Because of the anatomically unfavorable locations from where these tumors arise and the often nearby critical neuronal networks controlling vital physiological functions, many clinicians avoid performing a biopsy, opting…

Practical Management Summary

At our institution, we always attempt interrogation for the presence of an H3K27M mutation via tissue diagnosis (surgery, if possible) in patients with midline tumors with MRI characteristics of HGGs, regardless of patient age. For treatment-eligible patients, reflexive NGS testing has also detected H3K27M in the rare patients with nonmidline gliomas.[81] Because of the dismal prognosis with standard therapies, patients are evaluated for clinical trials according to mutational status and other…

Disclosures

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