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Chapter 9 - Lessons learned from evolving frameworks in adult glioblastoma

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Abstract

Glioblastoma (GBM) is the most common and aggressive malignant adult brain tumor. Significant effort has been directed to achieve a molecular subtyping of GBM to impact treatment. The discovery of new unique molecular alterations has resulted in a more effective classification of tumors and has opened the door to subtype-specific therapeutic targets. Morphologically identical GBM may have different genetic, epigenetic, and transcriptomic alterations and therefore different progression trajectories and response to treatments. With a transition to molecularly guided diagnosis, there is now a potential to personalize and successfully manage this tumor type to improve outcomes. The steps to achieve subtype-specific molecular signatures can be extrapolated to other neuroproliferative as well as neurodegenerative disorders.

Introduction

Glioblastoma (GBM) has an annual incidence of ~3 cases per 100,000 individuals, GBM accounts for ~15% of all primary CNS tumors and ~57% of all gliomas (Ostrom et al., 2019). The risk of a GBM increases with age, peaking between 75 and 84 years of age, with males are approximately 1.6 times more likely to develop a GBM. Despite extensive efforts to improve treatment, the 5-year survival rate is only 6.8% (Ostrom et al., 2019). In contrast, the 5-year survival rate for all malignant CNS tumors following diagnosis is 35.8%. Such a dismal clinical outcome reflects in part the complex and highly heterogeneous biology of GBM and necessitates the development of personalized treatment strategies based on subtype-specific molecular signatures. This chapter summarizes the current knowledge of molecular alterations in GBM and reviews the ongoing efforts to improve treatment based in part on subtype-specific molecular signatures.

Section snippets

Medical Imaging of GBMs

Magnetic resonance imaging (MRI) is used extensively to diagnose and manage a patient's glioblastoma (Fig. 9.1). There have been significant efforts to advance MRI technology and integrate it into a multimodal platform with molecular diagnostics to provide detailed insight into the nature of glioblastoma and its characteristics in a patient. Multiple studies have identified associations between MRI features and survival in patients with high-grade gliomas by linking molecular and imaging…

Histopathology

Histopathology of GBM is complex and highly diverse, with significant inter- and intratumoral heterogeneity. Tumors are composed of pleomorphic astrocytes with active mitotic activity and nuclear atypia. Necrosis and microvascular proliferation are present. Histological variants of GBM include giant cell GBM, gliosarcoma, and epithelioid GBM. Macroscopic examination reveals yellowish central necrosis from myelin breakdown, grayish periphery with poorly defined margins, and variable areas of…

Diagnosis

The 2016 and 2021 WHO classifications and cIMPACT-NOW highlight biomarkers as relevant in the diagnostic workup of diffuse gliomas: *IDH* status, 1p/19q codeletion, histone H3 K27M mutation, *EGFR* gene amplification, *CDKN2A/B* homozygous deletion, *TERT* promoter status, and the +7/−10 signature (simultaneous gain of chromosome 7 and loss of chromosome 10) (Louis et al., 2016, Louis et al., 2020, Louis et al., 2021) (Fig. 9.2). Wild-type *IDH* and histone H3 status and the presence of necrosis and/or…

Clinical Trials and Future Perspectives

The standard treatment of GBM includes surgery combined with adjuvant radiotherapy and/or temozolomide. Despite decades of rigorous research and improvement, the achievements in terms of prolonging survival have been modest, at best: only 1 in 5 patients receiving treatment lives past 2 years after diagnosis, and only a fraction survives past the 5-year mark. There is an urgent need for more effective treatments, including those targeting personalized new molecular events and pathways....

Conclusions

Continuous research efforts and improvement of a diagnostic arsenal over the recent decades has significantly contributed to the understanding of molecular events leading to the development of GBM. The discovery of new unique molecular alterations has resulted in a more effective classification of tumors and presented new therapeutic targets within subtypes. Also, several groups of novel therapeutic agents, including PRMT5 and CDK5 inhibitors, are being rigorously investigated, and so are ways...

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