REVIEW ARTICLE

Unraveling Glioblastoma: An Integrative Review of Genomics, Immunology, and Clinical Approaches

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Abstract

Children are at a lower risk of developing glioblastoma compared to adults. Although it is uncommon, existing studies indicate that juvenile glioblastoma is markedly different from its adult counterpart. These variations are related to molecular genetics, the efficacy of supplementary treatments, and potentially the results following therapy. Recent advancements in translational research have provided a significant number of new insights into juvenile glioblastomas, presenting substantial opportunities for future therapeutic approaches. This chapter seeks to emphasize the main clinical characteristics of pediatric glioblastoma, incorporating recent advancements in clinical and laboratory research.

Key words: Astrocytoma's, hemorrhagic tumor, high grade gliomas, low grade gliomas, Pediatric glioblastoma, temozolomide

INTRODUCTION

Glioblastoma multiforme (GBM) is the most prevalent and aggressive type of primary brain tumor in adults; however, it occurs infrequently in the pediatric population, representing approximately 7–9% of all central nervous system (CNS) tumors.[1] These tumors encompass anaplastic astrocytomas, anaplastic oligodendrogliomas, and glioblastomas.[2] Research indicates that survival rates do not significantly differ based on factors such as gender, age, initial presentation with or without seizures, symptoms of increased intracranial pressure, or tumor location.[3] Clinically and morphologically, glioblastoma can be categorized into at least two subtypes: Primary glioblastoma, characterized by a short patient history of no more than three months and the absence of prior less aggressive tumors, and secondary glioblastoma, which develops over several years from lower-grade astrocytomas (World Health Organization [WHO] grade II or III). Rare histological variants include the giant cell subtype and gliosarcoma.[1] According to data from the European Union and the Central Brain Tumor Registry of the United States, glioblastoma accounts for <3% of all primary CNS tumors in children, with an incidence of approximately 1.4/1,000,000 individuals.[4] Pediatric patients with high-grade gliomas (HGGs) may experience symptoms such as headaches, seizures, visual impairments, and focal neurological deficits. In infants, signs can include irritability and changes in feeding behavior. The likelihood of developing GBM is higher in children with certain genetic disorders, including neurofibromatosis Type 1 (NF1), Turcot syndrome, and Li-Fraumeni syndrome.[4]

The WHO classification is the internationally accepted system for naming and diagnosing gliomas, assigning them Grades I through IV based on histopathological indicators of malignancy. Grade I gliomas generally have low proliferative activity and are often treatable with surgery. In contrast, Grades II to IV indicate increasing levels of malignancy and invasiveness. GBM, designated as a Grade IV tumor by the WHO,[5] represents the most aggressive and least differentiated form of glioma. Prognosis is generally better in younger children (under 5 years), who exhibit fewer

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mutations, whereas older children often present with H3F3A mutations at K27, which are associated with a poorer prognosis. H3 K27-mutant tumors are primarily located in midline brain structures, including the thalamus, pons, and upper spinal cord, whereas other genetic alterations are more commonly observed in the cerebral hemispheres.[6] As a crucial initial diagnostic tool, contrast-enhanced magnetic resonance imaging (MRI) reveals either rim or heterogeneous enhancement, with rim-enhanced tumors showing a more favorable prognosis. T1-native and contrast-enhanced MRI can identify a necrotic core within the tumor mass and areas with a compromised blood-brain barrier. T2-weighted imaging provides insights into disease progression to surrounding structures due to the higher water content in these tissues. Diffusion-weighted imaging aids in differentiating between brain abscesses and tumor-suspect lesions. In addition, magnetic resonance spectroscopy is valuable for more accurately classifying lesions, particularly in deep-seated tumors that are challenging to biopsy, since brain tumors often show reduced concentrations of N-acetyl aspartate and creatine, along with increased levels of choline.[7]

The primary treatment approach for juvenile GBM in children over 3 years old involves gross total resection (GTR) followed by radiation therapy, typically administered at doses of 50–60 Gy, along with temozolomide (TMZ), which currently provides the best overall survival rates. TMZ, a key component of adult GBM treatment alongside radiation, has shown lower toxicity compared to other treatment regimens with similar effectiveness, leading to its inclusion in standard care. However, juvenile GBM cells tend to have a markedly lower rate of methylguanine-DNA methyltransferase (MGMT) promoter methylation, leading to a reduced therapeutic response to TMZ compared to what is typically observed. For children under 3 years old, surgery and, when feasible, chemotherapy are the primary treatment modalities, as radiation is generally not recommended due to severe neurocognitive side effects and is often unnecessary initially, given that younger children tend to respond more favorably to chemotherapy than their older counterparts. Due to their young age, the long-term consequences can be severe, and most patients may still require radiation therapy in the event of a relapse.[7] In addition, while chemotherapy has not yet demonstrated a significant positive effect on tumors in adults, it has been shown to enhance the overall prognosis for several pediatric brain cancers, including medulloblastoma and supratentorial HGGs. In addition, to minimize the harmful impact of radiation on the developing nervous system, chemotherapy is increasingly employed to postpone or entirely eliminate the need for radiotherapy in young children with high-grade tumors or incompletely resected low-grade tumors. Finally, children generally have a more favorable prognosis than adults for cancers with similar histological characteristics.[8]

Over 40 years ago, field radiation therapy was established as the standard treatment for glioblastoma patients, potentially doubling survival rates and improving local control. Conventional radiation is delivered in doses ranging from 1.8 to 2 Gy, totaling 54 to 60 Gy. Research indicates that hypofractionated radiation therapy, a hypofractionated radiotherapy regimen, delivering a total dose of 40 Gy over 15 fractions at 2.67 Gy per session, has emerged as a viable and well-tolerated treatment option for elderly patients and individuals with poor performance status. This approach offers similar therapeutic benefits to standard fractionation while reducing overall treatment time and the burden on patients who may not tolerate prolonged therapy courses. In addition, the application of amino acid positron emission tomography is currently being explored to enhance the precision of radiation target volume delineation. However, there is no evidence that newer radiation delivery methods or the combination of radiotherapy with potential radiosensitizers surpass the effectiveness of traditional fractionated radiotherapy. In cases where tumors exhibit MGMT promoter methylation, radiation may be withheld from elderly patients or those with low performance status, with TMZ being the preferred treatment for these individuals.[9]

PATHOLOGY

Histological features

The WHO categorizes pediatric gliomas using a malignancy classification system that relies on histological criteria. The 5-year survival rates for gliomas classified as WHO grades I–IV show significant variation; for instance, gliomas of Grades I and II boast a 95% survival rate over 5 years, whereas Grade IV gliomas have survival rates that drop below 10% or even 1%. People diagnosed with Grade 3 and 3 gliomas are now living longer, with an average survival time of 2–3 years – about 30–40% longer than previously observed. It is important to note that survival rates can vary even among tumors of the same histological grade due to the presence of genetic markers and the impact of specific genes on histological grading.[10] Low-grade gliomas (LGG) encompass pilocytic astrocytomas, gangliogliomas, dysembryoplastic neuroepithelial tumors, and diffuse gliomas the category of HGGs encompasses more aggressive tumor types such as anaplastic astrocytomas and GBM, both associated with rapid progression and limited survival. Although histological grade is a key factor in determining management strategies, subtypes based on cell origin often exhibit a specific distribution of histological grades, even when the tumor's cell origin does not directly affect clinical outcomes and treatment. Consequently, GBM is consistently classified as Grade IV. Brainstem gliomas are typically classified as grade IV due to their aggressive nature, whereas optic nerve gliomas are generally assigned a lower histological grade. Ependymomas, on the other hand, are most often categorized up to Grade III and are rarely classified beyond this level.[10]

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Oncological pathways involved in GBM

The wide range of molecular and genetic changes associated with GBM results in the disruption of key signaling pathways, ultimately driving the initiation and progression of brain tumors [Figure 1a]. While it is clear that several established pathways contribute to glioma development, the development and progression of glioblastoma are influenced by a web of interconnected molecular mechanisms, including possible unknown contributors. Prominent among the disrupted pathways are those involving tumor suppressors and cell cycle regulators, such as TP53, MDM2, MDM4, and CDKN2A-p14ARF, as well as the RB/CDKN2A-p16INK4a axis. In addition, signaling triggered by growth factor receptors – especially the Ras pathway – is frequently altered.[11]

A) This illustration highlights the distinct alterations in signaling pathway interactions observed in primary (dark gray) and secondary (light gray) GBM. Genes that undergo inactivation are marked in green, while those that are abnormally activated are shown in red. The phosphatidylinositol 3-kinase (PI3K)/phosphatase and tensin homolog (PTEN)/Akt signaling cascade becomes active when PI3K is recruited to the plasma membrane through growth factor receptors. This event catalyzes the transformation of phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3), initiating downstream signaling through effectors such as AKT and mammalian target of rapamycin (mTOR), which promote cellular growth and block programmed cell death. PTEN counters this signal by dephosphorylating PIP3; however, its loss of function results in continuous AKT activation and enhanced tumor cell proliferation and survival. In addition, mutations in TP53, or increased TP53 degradation via upregulated mouse double minute 2 (MDM2) protein, impair the cell's ability to halt the cycle or undergo apoptosis in response to DNA damage. Cyclin-dependent kinases 4 and 6 (CDK4/6), in conjunction with cyclin D proteins, phosphorylate the retinoblastoma protein (RB), which leads to the release of E2F transcription factors that stimulate the expression of genes required for DNA replication. Loss of RB function results in unchecked E2F activity, thereby accelerating cell cycle progression and tumor growth.

B) The key molecular distinctions between primary and secondary GBM are outlined, highlighting the most frequent and clinically significant genetic alterations. In addition, the diagram includes standard abbreviations for relevant terms – such as chromosome (Chr), epidermal growth factor (EGF), EGF receptor (EGFR), extracellular signal-regulated kinase (ERK), hepatocyte growth factor, loss of heterozygosity, NF1, platelet-derived growth factor (PDGF), PDGF receptor, transforming growth factor (TGF), and vascular endothelial growth factor (VEGF) – as defined by the WHO classification.

GLIOMA GENESIS

The formation of gliomas is closely linked to disturbances in the mechanisms that govern the cell cycle. Normally, cells progress through a series of coordinated phases, including division, growth, and DNA replication. This process is tightly regulated by checkpoints that serve as surveillance systems to maintain genomic integrity. Specifically, the M phase checkpoint controls the transitions within mitosis, while the G1 checkpoint ensures proper progression from the G1 to the S phase of the cell cycle.[12]

In GBM, research has predominantly focused on disruptions in the G1 checkpoint. This checkpoint is largely controlled by cyclins and cyclin-dependent kinases (CDKs), which work together to regulate the timing of DNA synthesis. CDKs are inactive without their corresponding cyclins, and once activated, they phosphorylate downstream targets to promote DNA replication. A majority of GBM cases display alterations within the p16^INK4a^/CDK4/RB1 pathway.[13] Under normal conditions, cyclin D1 activates CDK4, which then phosphorylates the RB1 protein. This phosphorylation event inactivates RB1, releasing the E2F transcription factor that promotes the G1/S phase transition.[14] However, the RB1 function is impaired in approximately 78% of patients with GBM.[15]

The G1 checkpoint functions as a sophisticated quality control mechanism. Tumor suppressor protein p53 plays a key role in this system by detecting DNA damage and activating CDK inhibitors, thereby pausing the cell cycle to allow repair or triggering apoptosis if the damage is irreparable.[12] This checkpoint is frequently disrupted in GBM, with p53 mutations found in roughly 87% of cases.[15] These alterations compromise the cell's ability to respond effectively to genotoxic stress, leading to unchecked cell division and tumor progression.

In healthy cells, cell cycle checkpoints initiate DNA repair processes that prevent mutations from accumulating and evolving into cancer. Consequently, disruptions in DNA repair – either through genetic mutations or epigenetic changes – are a hallmark of malignancies like GBM.[17] Importantly, the relationship between defective DNA damage response (DDR) and glioma development is often tied to p53 mutations, which diminish the apoptotic response and enable malignant transformation.[18]

DDR refers to the complex network of cellular pathways responsible for identifying, signaling, and repairing DNA lesions caused by both endogenous factors (like oxidative stress) and exogenous sources (such as radiation or chemotherapy). Tumor cells rely heavily on their DDR systems to survive internal pressures from increased metabolic activity, rapid cell division, and oxygen deprivation, as well as external therapeutic interventions like radiotherapy and chemotherapy.

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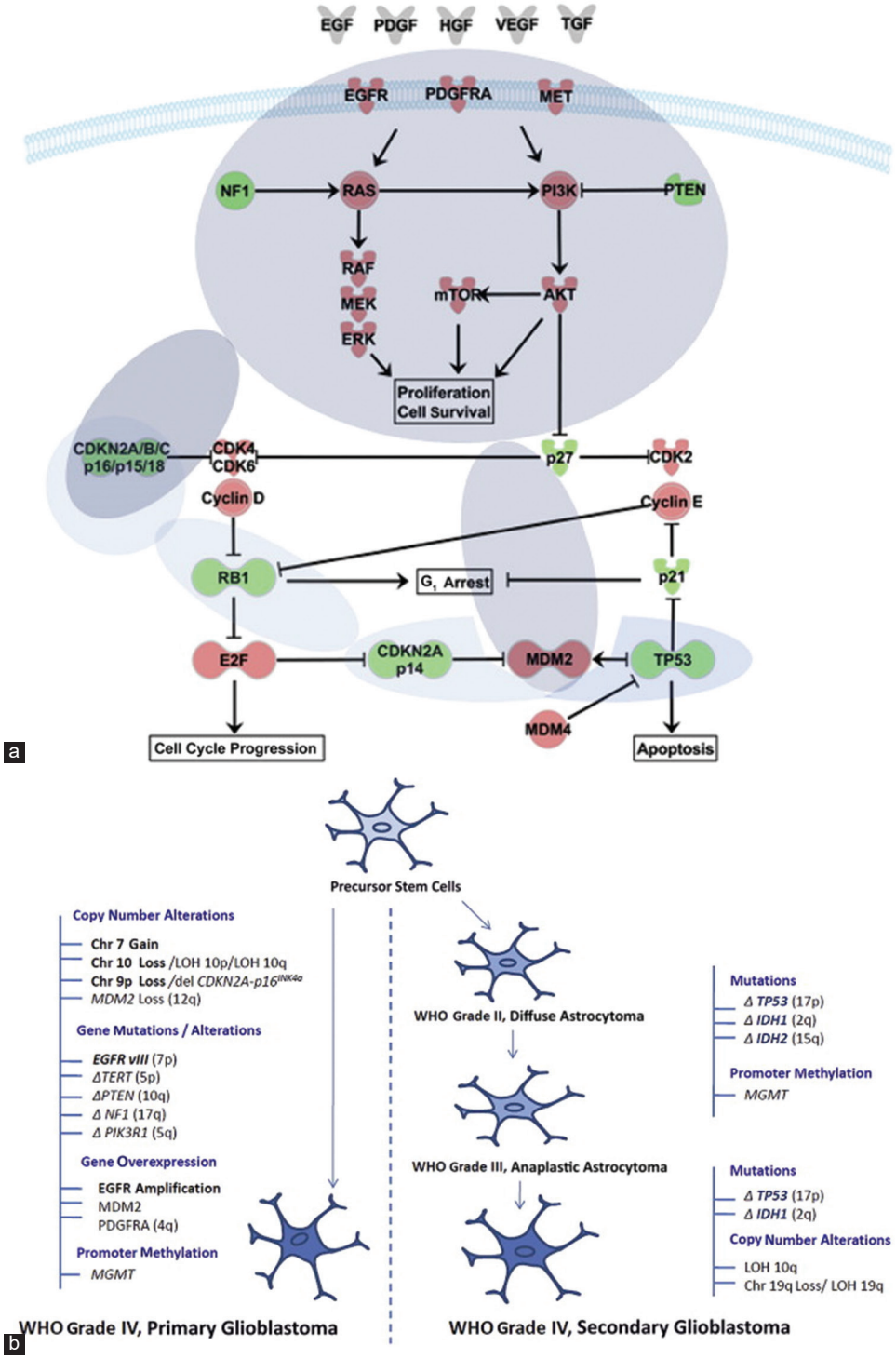

Figure 1: (a and b)A detailed diagram illustrating the interplay of multiple genetic mutations and core signaling pathways – such as TP53, RB, and RTK-Ras axes – that contribute to the initiation and progression of glioblastoma in humans

TMZ, a widely used alkylating agent in GBM therapy, introduces DNA lesions such as N7-methylguanine and N3-methyladenine. In contrast, ionizing radiation (IR) primarily results in double-strand breaks (DSBs), single-strand breaks (SSBs), and various forms of base damage.[19] The repair of these lesions involves both single-protein systems – such as O6-MGMT – and complex multi-protein pathways like homologous recombination (HR), non-homologous end joining (NHEJ), and base excision repair (BER).[20] Cancer cells often adapt by enhancing these repair mechanisms, contributing to treatment resistance and tumor relapse.

The patterns of mutations in GBM often reflect deficiencies in DNA repair, forming distinct mutational signatures that can be used to track the tumor's genetic history. These DNA damage repair deficiencies (DDRd) offer promising avenues

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for targeted therapies. One clinically significant marker is the methylation status of the MGMT promoter. Approximately 45% of GBM cases exhibit CpG methylation in the MGMT promoter region, which correlates with a reduced ability to repair TMZ-induced damage and is associated with improved therapeutic outcomes.[21]

Moreover, glioblastoma cells frequently overexpress certain growth factors and their receptors, establishing autocrine signaling loops that enhance their proliferative capacity. Among the most commonly implicated receptors are tyrosine kinase receptors (RTKs), including PDGF and EGFR.[22] These factors activate major growth-promoting pathways such as Ras/Raf/MAPK and PI3K/Akt/mTOR. Notably, there is evidence of a reciprocal inhibitory relationship between these two pathways, indicating a complex regulatory balance that supports tumor development and progression.[13]

The PI3K–Akt–mTOR signaling pathway

The PI3K–Akt–mTOR signaling cascade is integral to essential cellular functions, including cell proliferation, survival, apoptosis regulation, and cytoskeletal remodeling.[15] Activation of this pathway typically begins through receptor tyrosine kinases (RTKs), such as the EGFR, and is tightly modulated by PTEN, a tumor suppressor frequently altered in cancers, as shown in Figure 1. PTEN counteracts PI3K activity by dephosphorylating phosphoinositide substrates, thereby acting as a negative regulator of the RTK/PI3K/Akt axis.[16]

Central to this pathway are the serine/threonine kinases Akt (also known as protein kinase B) and mTOR, which orchestrate cell cycle progression and growth responses, depicted in Figure 2.[23] In GBM, dysregulation of this signaling network is highly prevalent – found in nearly 80% of cases – with around 40% involving loss-of-function alterations in PTEN, such as homozygous deletions or point mutations, which lead to continuous downstream signaling and uncontrolled cell survival.[15] In addition, PIK3CA, the gene encoding the catalytic subunit p110 of PI3K, harbors mutations in approximately 5–13% of primary GBMs, further contributing to aberrant activation of this growth-promoting pathway.[24]

The RAS–RAF–MAPK signaling cascade plays a central role in controlling cellular processes such as survival, growth, and differentiation. Upon activation, RAS proteins facilitate the recruitment of RAF kinases – including ARAF, BRAF, and CRAF1 – which are members of the serine/threonine kinase family. This interaction initiates a phosphorylation cascade, beginning with RAF-mediated activation of MEK (mitogen-activated protein kinase [MAPK]). Activated MEK subsequently phosphorylates mitogen-activated protein kinase, which then translocates to the nucleus and triggers the expression of genes essential for cell proliferation. Among the downstream transcription factors stimulated by

Figure 2: A schematic representation of the PI3K–Akt–mTOR signaling cascade, illustrating its role in promoting cell growth, proliferation, and survival through sequential activation of receptor tyrosine kinases, PI3K, Akt, and mTOR, and highlighting points of dysregulation commonly observed in glioblastoma

this pathway are c-myc, signal transducers and activators of transcription (STAT), and peroxisome proliferator-activated receptor gamma, all of which promote cell cycle progression and inhibit apoptosis.[25]

Although direct mutations in RAS genes are relatively uncommon in GBM, dysregulation of upstream modulators has drawn significant attention. One such regulator is neurofibromin 1 (NF1), a tumor suppressor that negatively controls RAS signaling. Alterations in NF1, including mutations or biallelic deletions, are identified in approximately 18% of GBM cases, with a notably higher incidence (around 37%) in the mesenchymal subtype of GBM.[15] These findings underscore the relevance of upstream control mechanisms in RAS pathway-mediated glioma progression.

Cellular dissemination and locomotion

The aggressive spread of glioblastoma (GBM) cells is driven by a complex interplay of cellular, molecular, and metabolic adaptations, which significantly complicates therapeutic intervention. These tumor cells demonstrate remarkable resilience, quickly adjusting to hostile conditions such as those induced by chemotherapy or radiotherapy. Despite

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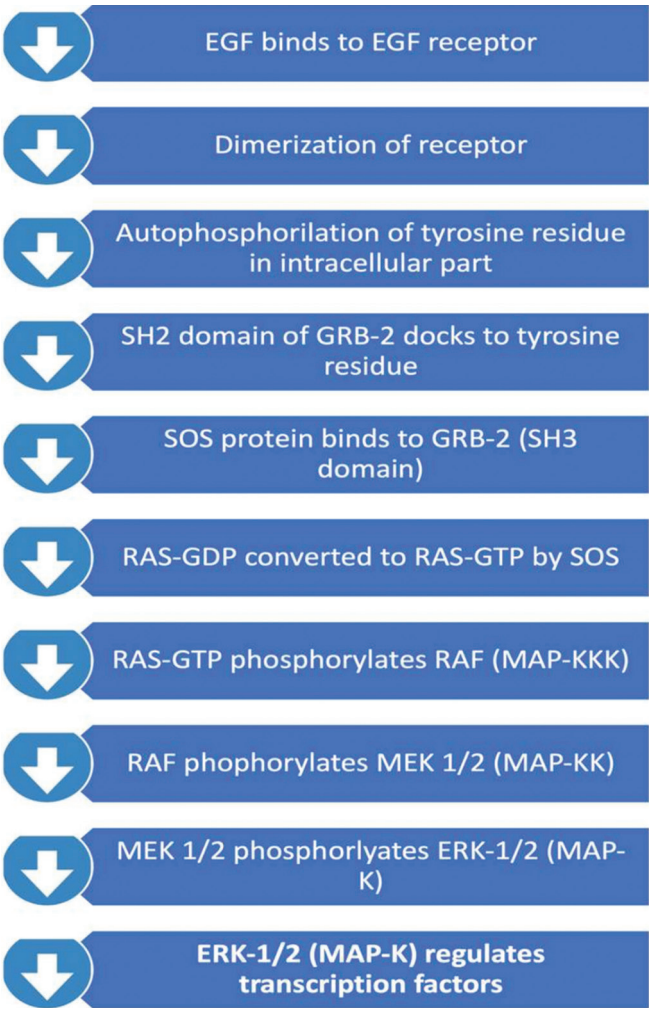

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Figure 3: Diagrammatic representation of the RAS–RAF–MAPK signaling cascade, highlighting its sequential activation of kinases that regulate cellular growth, division, and survival, and illustrating the role of transcription factors triggered by MAPK nuclear translocation in promoting oncogenic transformation

therapeutic pressure, they continue to proliferate, infiltrate adjacent brain tissues, and escape immune detection.

As GBM cells multiply rapidly, their demand for energy and nutrients rises, resulting in a stressed tumor microenvironment characterized by hypoxia and nutrient deprivation. To overcome these limitations, the tumor undergoes an angiogenic switch, wherein it increases the production of angiogenesis-promoting molecules, including cytokines, growth factors, and their corresponding receptors. This facilitates the development of new blood vessels to sustain tumor growth.[26] A key player in this process is VEGF, which is often overexpressed in GBM and strongly associated with enhanced angiogenesis.

In addition, GBM cells exhibit altered expression of numerous cell surface receptors, intracellular signaling molecules, and structural proteins of the cytoskeleton.[27] These changes support enhanced motility and invasiveness. Certain growth factors can trigger epithelial-to-mesenchymal transition (EMT) and activate downstream oncogenic cascades, such as the PI3K/Akt signaling pathway.[28] Through EMT, glioma cells acquire mesenchymal properties and increased migratory capacity, often marked by the upregulation of proteins like fibronectin and N-cadherin,[29,30] which aid in tissue invasion.

A subpopulation of GBM cells, referred to as glioma stem cells (GSCs), retains stem-like features that confer adaptability and long-term tumorigenic potential. These cells express markers typical of neural stem and progenitor cells, such as Nestin, CD133 (prominin-1), Musashi-1, and Bmi-1.[31] Transcriptional regulators involved in neural development, including Sonic Hedgehog (SHH) and Notch, are frequently dysregulated or overexpressed in GSCs, contributing to their capacity for self-renewal, pluripotency, and tumor initiation when implanted in animal models.[32]

Further complicating treatment, glioblastoma is associated with disruptions in immune-regulating pathways. One key pathway is interleukin (IL)-6/Janus kinase (JAK)/STAT3, which is critical for maintaining the undifferentiated state of neural stem cells. IL-6 activates JAK, leading to the phosphorylation of STAT3, a transcription factor involved in cell survival, proliferation, and immune evasion. Elevated STAT3 activity in GBM is correlated with higher tumor grade and poor prognosis.[33]

To avoid immune destruction, GBM cells deploy multiple immunosuppressive mechanisms. Tumor-associated endothelial cells form a protective barrier by manipulating immune checkpoint pathways. One such checkpoint molecule, CD200, is upregulated in GBM and suppresses proinflammatory cytokines like IL-2 and interferon-gamma, thereby inhibiting immune activation.[34] In addition, glioblastoma appears to impair the function of dendritic cells (DCs), which are pivotal in initiating adaptive immune responses. These antigen-presenting cells are crucial for capturing tumor antigens and activating T cells.[35] However, the tumor microenvironment in GBM is rich in immunosuppressive agents such as TGF-beta (TGF-β) and indoleamine 2,3-dioxygenase, both of which hinder DC activity and contribute to immune evasion.[36]

Through these multifaceted mechanisms – ranging from enhanced migration and vascularization to immune suppression and stem-like adaptability – glioblastoma maintains its aggressive phenotype and resistance to conventional treatments.

CLINICAL DIAGNOSIS

Undiagnosed pediatric tumors may remain untreated for extended periods. Young patients often struggle to articulate their symptoms, making it easy to miss common issues

like headaches that may not be particularly distinctive.[37] Although over 80% of LGGs present as seizure episodes, which assist in diagnosis, a significant number of patients may be asymptomatic, leading to delayed detection and further glioma progression. Therefore, there is a critical need to improve the diagnostic processes for pediatric gliomas. When evaluating young patients exhibiting neurological symptoms that suggest potential CNS dysfunction, healthcare providers must conduct thorough assessments. Symptoms may include papilledema, headaches, behavioral changes, double vision, vomiting, and nausea.[38] More specific neurological manifestations may include localized motor impairments resulting from pyramidal tract involvement, as well as conditions such as hemiplegia, involuntary movements like cholera, and coordination disturbances such as dysmetria. While seizures are a common presentation in LGG patients, they are considerably less frequent in HGG cases. Gliomas have a wide differential diagnosis that encompasses various pediatric demyelinating CNS disorders, including epilepsy and CNS infections like viral encephalitis.[39] A clinical examination alone is inadequate for diagnosing gliomas; while it may allow for speculation about lesion location, it cannot differentiate between various lesion types.[40]

IMAGING

It serves as the primary diagnostic tool for gliomas and tumors in general. CT is particularly useful for quickly identifying hemorrhagic tumor features and making initial diagnoses.[41] Although there is limited research linking novel imaging technologies to improved clinical outcomes, these methods offer enhanced insights into tumor type and structure, their relationship with surrounding critical structures, and improved diagnostic accuracy. The accuracy of imaging-based diagnoses is generally high, especially for LGGs, approaching 90%. More advanced techniques like PET scans and sophisticated MRI methods, including diffusion MRI and MRI spectroscopy, have shown even higher accuracy rates.[42] In pediatric cases, gliomas may respond notably to advanced imaging techniques. Given the longer life expectancy of children, even minor improvements in diagnostic precision or treatment efficacy can lead to significant survival benefits. Furthermore, studies indicate that enhanced imaging techniques can slightly improve surgical resection rates and patient survival.[43] Despite promising results, the existing body of evidence lacks the robustness and consistency needed to support the widespread adoption of advanced imaging techniques for routine glioma diagnosis. Consequently, any favorable outcomes reported so far should be approached with careful interpretation. There is a pressing need for further research, particularly through randomized clinical trials, to strengthen the current understanding. Given the limitations of imaging modalities, histopathological confirmation through biopsy remains the standard diagnostic approach in most glioma cases.[41]

TREATMENT OPTIONS

Chemotherapy

When evaluated on their own, chemotherapy seems to be a less effective treatment, offering minimal survival benefits. However, it is utilized because, when combined with other treatment strategies, it can significantly enhance survival rates – potentially tripling them.[42] Among the most potent chemotherapeutic agents identified in various clinical trials are vincristine and chloroethyl-cyclohexyl nitrosourea (CCNU). The combination therapy involving PCV has demonstrated potential in enhancing survival outcomes among children diagnosed with glioma. Conventional treatment with TMZ has been shown to increase median survival by around two months in adult patients; however, clinical trials in pediatric populations have not demonstrated a comparable improvement in survival outcomes.[41] A novel treatment avenue for HGG involves stem cell transplantation in conjunction with chemotherapy, though its efficacy compared to earlier methods remains unverified.[44]

Therapeutic irradiation

Radiation therapy remains a valuable therapeutic approach for managing gliomas, with particular effectiveness observed in cases of LGGs. When surgery is not feasible, it can serve as a standalone treatment or be administered both before and after surgery.[45] It is commonly combined with chemotherapy, which often increases toxicity levels. Recent studies indicate that using TMZ in combination results in lower toxicity compared to cisplatin-based regimens.[46] Furthermore, radio-sensitizing agents like gemcitabine may be administered in combination with radiation therapy to enhance therapeutic efficacy and potentially improve both clinical outcomes and the overall quality of life for patients.[47] Typically, radiotherapy is applied after tumor removal in glioma treatment, and it is also used in inoperable cases. Higher radiation doses do not seem to influence survival rates, with the standard dose being approximately 60 Gray (Gy) delivered in 30 fractions.[41]

Radiosurgery

There is an ongoing debate regarding the application of radiosurgery for treating juvenile gliomas. The main concerns include severe cerebral edema and damage to surrounding tissues, both of which can negatively impact prognosis and complicate future surgical interventions.[48] Gamma Knife radiosurgery has shown considerable efficacy in managing challenging glioma cases, including inoperable low-grade and high-grade tumors, as well as recurrent lesions. It has proven particularly effective in controlling tumor growth when targeting small residual masses.[49] Studies show that radiosurgery can decrease the volume of remaining tumors by as much as 70%, although gamma knife surgery is

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generally less effective for larger residual volumes. While specific volume thresholds for tumors have yet to be defined, evidence suggests that tumors measuring 2 cm^3 or less often respond favorably to radiosurgery, while those with volumes of 4 cm^3 or greater tend to have poor responses.[48] The standard radiation dose applied to the tumor margin is around 15 Gy.

Neurosurgical management

Historically, complete surgical excision has been regarded as the gold standard for glioma treatment, despite its significant technical difficulties. While some experts recommend a conservative approach with regular brain imaging for select low-grade glioma (LGG) patients, it is essential to operate on both LGG and HGG cases. Recent studies suggest that traditional postoperative care methods may offer greater advantages than merely monitoring LGG patients. Therefore, surgery should be the primary treatment for all glioma patients, except for specific types with unique characteristics, such as diffuse intrinsic pontine glioma (DIPG). In all glioma cases, neurosurgical intervention must be thorough and assertive. Evidence shows that GTR significantly improves survival rates compared to subtotal resection, which can increase mortality by 50-100% for patients, similar to the mortality rates associated with infratentorial tumor locations. The survival difference between GTR and subtotal resection can be as much as 35 months. The literature emphasizes that GTR is a critical component of glioma treatment, highlighting the vital role of the neurosurgeon in this process. It is important to recognize that the disparity in survival rates is significantly less pronounced in adults – approximately 30% – largely because children typically have a longer life expectancy, which influences overall survival outcomes.[52] However, achieving GTR remains challenging, with only 35–45% of pediatric patients attaining GTR, as indicated by studies.[51] This underscores the necessity for advanced technology to enhance surgical precision, yet there are limited publications showing increased GTR rates with these newer technologies, such as intraoperative MRI. At present, there is insufficient data to draw definitive conclusions, although some studies suggest that intraoperative imaging techniques, including MRI or fluorescence, may improve GTR rates.[53] The location of superficial tumors is the most common factor affecting GTR rates, with significantly lower rates observed for deep-seated brain tumors, while surface lesions appear more amenable to successful resection.[51] Nevertheless, the application of radiation therapy has enhanced the survival of those who do not achieve GTR.[54] When complete surgical removal (GTR) is not feasible, the use of radiotherapy and chemotherapy has been associated with extended survival. However, the lack of significant improvement in survival outcomes over recent decades highlights the urgent need to increase GTR success in pediatric glioma cases, as it remains the most consistent indicator of favorable prognosis.[55]

Palliative treatment

Given that many glioma patients face incurable conditions due to complications or relapses, palliative and end-of-life care becomes essential. Often, palliative care is the sole option available to physicians. This type of care includes family counseling and minor interventions aimed at slightly enhancing the quality of life during the final months. The outlook for incurable cases, such as DIPG, is generally grim, with an average life expectancy.[56] Despite this limited timeframe, patients and their families require both medical and psychological support during this challenging period. Palliative care involves a holistic approach that includes family-centered counseling, psychological support, symptom management therapies, and minor medical procedures – such as the insertion of external ventricular drains – to relieve complications like hydrocephalus.[57] The psychological support offered to patients and their families is a critical component of pediatric palliative care and is a particularly sensitive issue.[58] Studies show that anxiety and physical functioning are among the most adversely affected aspects of quality of life throughout the DIPG treatment process.[59] Typically, surgeons and oncologists manage treatment independently, and many healthcare providers unfortunately neglect vital elements of palliative care, particularly psychological support. Recent cohort studies have identified the most frequently utilized palliative treatments.[60]

CONCLUSION

Glioblastoma continues to pose a formidable challenge in neuro-oncology due to its highly aggressive nature and resistance to standard treatments. This resistance is largely driven by extensive genetic variability, mechanisms that allow immune system evasion, and its diffuse infiltration into surrounding brain tissue. The current review has explored the intricate relationships among molecular signaling pathways, the tumor microenvironment, and the shortcomings of existing diagnostic and therapeutic strategies. Progress in genomic technologies has enabled more refined tumor classification and holds promise for developing individualized treatment protocols. Concurrently, advances in immunotherapy – though still facing significant hurdles – represent a promising direction for future intervention.

The integration of molecularly targeted drugs, radiosensitizing agents, and comprehensive supportive care, including palliative options, highlights the value of a multidisciplinary approach in managing glioblastoma. Nonetheless, the lack of substantial improvement in survival rates, especially among children, signals the pressing need for innovative clinical research, early biomarkers, and translational studies to drive forward more effective and timely interventions.

Gaining deeper insights into the genetic and immune-related underpinnings of glioblastoma is essential for moving

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beyond one-size-fits-all treatments toward truly personalized medicine in the era of precision oncology.

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