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REVIEW

New Targets, New Agents, and Radiotherapy: Primary Brain Tumors

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SUMMARY

Primary brain tumors represent a heterogeneous and biologically complex group of neoplasms that require multidisciplinary management approaches. Following the publication of the 2021 World Health Organization classification of central nervous system tumors, the incorporation of molecular markers into histopathological diagnostics has markedly improved diagnostic precision and facilitated the development of individualized treatment strategies. The identification of actionable molecular targets, particularly in high-grade malignant tumors, has paved the way for novel therapeutic approaches. Integrating targeted therapies with conventional modalities—surgery, radiotherapy, and chemotherapy—holds considerable promise for optimizing treatment responses. Nonetheless, establishing the long-term efficacy, safety, and impact on overall survival of these innovative strategies will require large-scale, multicenter clinical trials.

Keywords: Molecular targets; multidisciplinary treatment; personalized oncology; primary brain tumors; targeted therapy.

INTRODUCTION

Although primary brain tumors account for only about 2% of all cancers, their annual incidence is approximately 22 per 100,000 population,[1–3] and they contribute to 3.1% of all cancer-related deaths. Among adults, gliomas comprise approximately 75% of these tumors.[1–3]

The fifth edition of the World Health Organization classification of central nervous system tumors, published in 2021, goes beyond the classic histological classification to define subgroups at the molecular level.[4] The integration of molecular profiling with histopathology not only enhances diagnostic precision but also provides valuable information for therapeutic decision-making. Conventional treatment of primary brain tumors has relied on surgery, radiotherapy, and cytotoxic chemotherapy. However, advances in the understanding of tumor molecular biology have led to a paradigm shift toward targeted therapies aimed at inhibiting angiogenesis, growth factor signaling, and intracellular pathways involved in tumor pathogenesis. The new agents commonly used are listed below:

ANTIANGIOGENIC TARGETED AGENTS

Vascular endothelial growth factor (VEGF) plays a central role in tumor angiogenesis. Inhibition of VEGF not only prevents the formation of new blood vessels within the tumor but also induces regression of existing microvasculature. This reduction in vascular permeability enhances the distribution and efficacy of chemotherapeutic agents throughout the tumor tissue.[5] Several antiangiogenic agents have been developed to target distinct stages of the VEGF signaling pathway.

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Bevacizumab

Bevacizumab, an anti-VEGF monoclonal antibody, was approved by the FDA in 2009 for the treatment of patients with recurrent glioblastoma.[6] In a randomized Phase II study of 167 patients receiving either bevacizumab alone or in combination with irinotecan, the 6-month progression-free survival (PFS) rates were 43% and 50%, respectively.[6] Two pivotal Phase III trials—AVAglio and RTOG 0825—evaluated the addition of bevacizumab to standard chemoradiotherapy in newly diagnosed glioblastoma patients. In these studies, patients were randomized post-surgery to receive either standard chemoradiotherapy with placebo, followed by temozolomide and placebo for 6 months, or standard chemoradiotherapy with bevacizumab, followed by temozolomide and bevacizumab. Both trials demonstrated a prolongation of PFS with the addition of bevacizumab; however, no overall survival (OS) benefit was observed.[5,7] Similarly, the EORTC Phase III trial in recurrent glioblastoma showed that though locally PFS was 2.7 months longer in the combination group, bevacizumab did not improve OS compared to lomustine alone.[8]

Nevertheless, bevacizumab remains the most commonly used antiangiogenic agent for recurrent glioblastoma, likely reflecting the tumor's highly vascular nature. The phase II RTOG 1205 trial evaluated concurrent bevacizumab with hypofractionated radiotherapy versus bevacizumab alone in recurrent glioblastoma. While no OS benefit was observed, the combination therapy significantly improved 6-month PFS.[9] Overall, studies indicate that no systemic therapy has consistently demonstrated an OS benefit in recurrent glioblastoma.[5,10] In a recent meta-analysis including 926 patients with recurrent glioblastoma, it was shown that patients receiving reirradiation combined with bevacizumab exhibited improved OS and reduced rates of radiation necrosis compared to reirradiation alone.[10] Nevertheless, further randomized prospective studies are required to optimize the timing, dose, and duration of bevacizumab in conjunction with reirradiation protocols. Common adverse events associated with bevacizumab include gastrointestinal perforation, bleeding, and arterial thromboembolism.[5–10]

Aflibercept

Aflibercept is a human recombinant fusion protein with anti-angiogenic properties. It exhibits a higher binding affinity for VEGF-A than bevacizumab. [5,11] and is theoretically expected to demonstrate greater efficacy by simultaneously inhibiting VEGF and placental growth factor (PlGF).[11] However, Phase II clinical trials in patients with recurrent malignant gliomas have shown no improvement in OS.[11] The most commonly reported adverse events include proteinuria, fatigue, injection site reactions, and hypertension.[5,11]

Ramucirumab

Ramucirumab is a human monoclonal antibody that exerts its effect by binding with high affinity to the extracellular domain of VEGFR-2, thereby blocking its interaction with natural ligands.[6] In a non-randomized Phase II clinical trial in patients with recurrent glioblastoma, ramucirumab was compared with a platelet-derived growth factor receptor (PDGFR) monoclonal antibody and demonstrated superior PFS and OS outcomes.[12] The most commonly reported adverse events include hypertension, venous thrombosis, diarrhea, and epistaxis.[6]

TYROSINE KINASE INHIBITORS (TKIS)

Sunitinib

Sunitinib, a multi-targeted tyrosine kinase inhibitor, showed initial promise in glioblastoma treatment; however, a phase II study demonstrated no improvement in PFS.[13] Similarly, the STELLAR study failed to show superiority of sunitinib over lomustine in recurrent glioblastoma.[14] In a prospective, multicenter, non-randomized Phase II study of sunitinib in patients with refractory atypical or malignant meningioma, the 6-month PFS was 42%, with a median PFS of 5.2 months and a median OS of 24.6 months.[15] These findings highlight the need for randomized trials to further assess efficacy. The most commonly observed adverse events associated with sunitinib include hypertension, left ventricular dysfunction, thyroid dysfunction, bone marrow suppression, hepatotoxicity, and osteonecrosis of the jaw.[15]

Sorafenib

Sorafenib is a small-molecule tyrosine kinase inhibitor that targets multiple signaling pathways, including VEGF, PDGFR, and RAS/RAF/MEK pathways. A Phase II study evaluated the efficacy of dual anti-angiogenic therapy with bevacizumab and sorafenib in patients with recurrent glioblastoma.[16] The combination did not improve outcomes compared to bevacizumab alone; however, the potential synergistic effects of dual anti-angiogenic therapy warrant fur-

ther investigation.[16] The most commonly reported adverse events of sorafenib include diarrhea, nausea, vomiting, fatigue, rash, and hypertension.[16]

Cediranib

Cediranib is an orally available agent that simultaneously targets angiogenic growth factor pathways. In a Phase III randomized controlled trial, cediranib, either as monotherapy or in combination with lomustine, did not improve progression-free survival (PFS) in patients with recurrent glioblastoma.[17] The most commonly reported adverse events included hypertension, dysphonia, fatigue, and diarrhea.[17]

Regorafenib

Regorafenib is an oral tyrosine kinase inhibitor that targets pathways involved in oncogenesis, tumor angiogenesis, and the tumor microenvironment.[18] Preclinical studies have demonstrated its antitumor activity in glioblastoma models.[5] The REGOMA Phase II trial evaluated the efficacy and safety of regorafenib in patients with recurrent glioblastoma, reporting a median overall survival (OS) of 7.4 months in the regorafenib arm versus 5.6 months in the lomustine arm.[18] These findings highlight the need for a robust Phase III trial. The most commonly observed adverse events associated with regorafenib included hand-foot skin reactions, elevated lipase, and increased bilirubin levels.[18]

INTEGRIN INHIBITORS

Integrins are cell surface adhesion proteins that play critical roles in angiogenesis, tumor proliferation, and metastasis.

Cilengitide

Cilengitide is a selective αvβ3 and αvβ5 integrin inhibitor. Early Phase I and II studies in glioblastoma suggested a potential OS benefit.[19–20] However, the Phase III tCENTRIC trial failed to demonstrate any OS or PFS advantage when cilengitide was added to temozolomide.[21] Despite these disappointing results, integrins continue to represent a promising target for further investigation in glioblastoma therapy.

PROTEASOME INHIBITORS

Proteasomes mediate the degradation of p53 and cyclin-dependent kinases, which are critical regulators of cell proliferation and apoptosis. Consequently, proteasome inhibitors enhance tumor cell death by modulating the cell cycle.[22]

Bortezomib

Laboratory data showed Bortezomid as an effective agent in glioma cell lines. In the phase II BRAIN study, patients with recurrent glioma were treated with a combination of bevacizumab+bortezomib. Although PFS was reported as 40.6% with the combination of a proteasome inhibitor and bevacizumab, there was no improvement with combination compared to bevacizumab monotherapy.[22]

Marizomib

Marizomib activates cell growth signaling pathways, including those regulating apoptosis and angiogenesis.[23] Unlike other proteasome inhibitors, it can cross the blood-brain barrier.[23] Results from a Phase I/II study evaluating marizomib, either as monotherapy or in combination with bevacizumab, in recurrent glioblastoma have been reported.[24] Neither marizomib alone nor the combination therapy demonstrated a meaningful clinical benefit. The most commonly observed adverse events included hypertension, confusion, headache, and fatigue.[24] As a relatively new therapeutic agent, further data from ongoing Phase II (NCT03463265) and Phase III MIRAGE (NCT03345095) trials are eagerly awaited.

These topics are comprehensively summarized in Table 1. Anti-Angiogenic and Vascular-Targeted Agents.

BRAF (B-RAF PROTO-ONCOGENE, SERIN/THEONINE KINASE) INHIBITORS

BRAF is a gene found on chromosome 7 that encodes a protein also called as BRAF. This protein plays a critical role in regulating the MAPK/ERK signaling pathway which controls several important cell functions as growth, division, cell migration and apoptosis. The BRAFV600E mutation is detected in approximately 4% of gliomas overall, but its prevalence is higher in specific subtypes: 50–60% of pleomorphic xanthoastrocytomas, 10% of pilocytic astrocytomas, 20% of gangliogliomas, and 10–15% of pediatric high-grade gliomas.[25] BRAF mutations are more frequently observed in pediatric gliomas, and targeted therapies against BRAF or combined BRAF/MEK inhibition can provide durable responses.[25]

In the Phase I PNOC002 study, dabrafenib, a BRAF inhibitör, combined with trametinib, a MEK inhibitör,

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Table 1 Anti-angiogenic & vascular-targeted agents

Agent	Mechanism	Efficacy	RT
Bevacizumab	Anti-VEGF	PFS↑, no OS benefit	Used with re-RT; reduces radionecrosis
Aflibercept	VEGF/PlGF trap	No OS benefit	Limited RT value
Ramucirumab	VEGFR-2 blockade	Small Phase II signal	RT synergy unclear
Sunitinib	Multi-TKI (VEGFR/PDGFR)	Negative in GBM	RT benefit not proven
Sorafenib	Multi-TKI	No added benefit	No meaningful RT synergy
Cediranib	VEGFR TKI	Phase III negative	Limited RT relevance
Regorafenib	Multi-TKI	REGOMA OS benefit	RT data limited
Cilengitide	Integrin inhibitor	Phase III failed	Concurrent RT showed no benefit

RT: Radiotheraphy; VEGF: Vascular endothelial growth factor; PFS: Progression-free survival; OS: Overall survival; PlGF: Placental growth factor; TKI: Tyrosine kinase inhibitor; PDGFR: Platelet-derived growth factor receptor; GBM: Glioblastome multiform

demonstrated longer progression-free survival (PFS) and lower toxicity compared to carboplatin plus vincristine in pediatric low-grade gliomas.[26] These findings underscore the importance of early molecular testing for BRAFV600E mutations. In a "basket" study of 24 patients with BRAFV600E-mutant gliomas across various histologies, vemurafenib, another BRAF inhibitor, treatment achieved an objective response rate of 25%, with responders maintaining a median treatment duration exceeding 1 year; in pilocytic xanthoastrocytoma, this duration exceeded 2 years.[27]

BRAF-KIAA fusions have shown responsiveness to MEK inhibitors. Notably, over 90% of craniopharyngioma cases harbor the BRAFV600E mutation, and a Phase II study investigating vemurafenib combined with cobimetinib (NCT03224767) is ongoing, reporting favorable preliminary results.[28] Common toxicities of BRAF inhibitors include fever, arthralgia, fatigue, headache, and palmar-plantar erythrodysesthesia.[26,28]

NTRK (NEUROTROPHIC TROPOMYOSIN KINASE RECEPTOR) INHIBITORS

The family of NTRK is am transmembrane tyrosine kinases responsible for neuronal development. Alterations of NTRK genes can induce carcinogenesis both in neurogenic and non-neurogenic cells. NTRK gene fusions are relatively rare in gliomas, with a prevalence of less than 5% in low-grade gliomas and approximately 1.7% in adult glioblastoma. The presence of NTRK1 gene fusion is associated with favourable outcome while the fusion of NTRK2 is with poor prognosis. Further studies are needed to determine the efficacy of agents such as larotrectinib and entrectinib in NTRK fusion–positive glioblastoma. Larotrectinib and entrectinib have demonstrated high response rates and durable responses in large "basket" studies for brain tumors harboring NTRK fusions. Larotrectinib, in particular, has shown rapid clinical responses in pediatric gliomas.[29] Several multicenter trials are ongoing, including the Phase I SCOUT study of larotrectinib (NCT02637687), the Phase I/II STARTRK-NG study of entrectinib (NCT02650401), and the Phase I/II CARE trial of repotrectinib (NCT05004116).[29] The most commonly reported toxicities of NTRK inhibitors are fatigue and mild dizziness, the latter attributed to the role of TRK proteins in balance regulation.

EGFR (EPIDERMAL GROWTH FACTOR RECEPTOR) INHIBITORS

Approximately one-third of adult high-grade gliomas exhibit EGFR amplification. Small-molecule EGFR inhibitors such as erlotinib, gefitinib, and lapatinib have been investigated alone or in combination with standard therapy in high-grade gliomas, showing modest effects when added to chemoradiotherapy but no significant survival benefit.[30] Similarly, the RTOG 0211 study, which evaluated concurrent gefitinib with radiotherapy, reported median survival comparable to historical controls treated with radiotherapy alone.[30] Irreversible EGFR inhibitors, including afatinib, administered alone or in combination with temozolomide, have not demonstrated efficacy in recurrent glioblastoma. A Phase II study of the second-generation EGFR inhibitor dacomitinib is ongoing (NCT01520870). Antibody-drug conjugates targeting EGFR, such as Depatux-m (Depatux-mafodotin), have been extensively evaluated in both recurrent and newly diagnosed glioblastoma. In patients

progressing after temozolomide, the combination of Depatux-m with temozolomide showed longer survival compared to Depatux-m alone or chemotherapy alone; however, definitive conclusions were limited by the small sample size (n=86).[31] Similarly, in a small randomized study (n=73), rindopepimut—a peptide vaccine targeting the EGFRvIII receptor—demonstrated a modest survival advantage when combined with bevacizumab. Two-year survival was 20% in the rindopepimut group versus 3% in the bevacizumab plus placebo group. However, a subsequent Phase III trial failed to confirm a survival benefit of monthly rindopepimut combined with temozolomide following concurrent radiotherapy.[30,31]

FGFR (FIBROBLAST GROWTH FACTOR RECEPTOR) INHIBITORS

Another pro-angiogenic growth factor frequently elevated in glioblastoma is basic fibroblast growth factor (bFGF).[32] FGFR expression in astrocytes can drive malignant transformation and glioblastoma progression through activation of mitogenic, migratory, and anti-apoptotic pathways. Although FGFR mutations and amplifications are relatively rare in glioblastoma (<2%), targeted therapy remains a strategy for selected patients. Dovitinib, a potent bFGF inhibitor, has been proposed as a potential anti-angiogenic therapy for recurrent glioblastoma; however, a Phase II clinical trial demonstrated no improvement in overall survival (OS).[32] The oral pan-FGFR kinase inhibitor erdafitinib has been employed in the treatment of FGFR3-TACC3-positive recurrent glioblastoma, with commonly reported adverse events including appendicitis, fatigue, and thrombocytopenia.[32]

IDH1/2 (ISOCITRATE DEHYDROGENASE 1/2) INHIBITORS

IDH is an essential enzyme involved in cellular respiration in tricarboxyclic acid cycle. Mutations in IDH1 or IDH2 genes are commonly found in tumors as glioma, chondrosarcoma, AML and cholangiocarcinoma. These mutations result in altered IDH1 and 2 proteins with a new function that connects the α-ketoglutaric acid (α-KG) to 2-hydroxyglutaric (2-HG) acid. The increased levels of 2HG inhibit the α-KG dependent enzymes that play crucial role in cell regulationand tissue homeostosis. The expression of mutant IDH also impairs cell differentiation.

Vorasidenib is a dual inhibitor of IDH1 and IDH2 mutations. In a phase III trial evaluating patients with residual or recurrent grade 2 IDH-mutant gliomas, vorasidenib significantly improved PFS compared to placebo; OS data are not yet available.[33] Ivosidenib, a selective IDH1 inhibitor, represents an alternative for patients who cannot tolerate vorasidenib. Vorasidenib demonstrates strong therapeutic potential in low-grade gliomas harboring IDH mutations.[33]

HISTONE DEACETYLASE INHIBITORS

Epigenetic alterations can contribute to malignant transformation. Histone acetylation plays a central role in regulating transcription and controlling gene expression, whereas deacetylation of histone proteins within nucleosomes results in a more condensed chromatin structure, inhibiting transcription. Disruption of the balance between these processes can lead to abnormal cell differentiation and proliferation.[34] Malignant gliomas, like many other cancers, exhibit such histone modifications, suggesting that histone deacetylase (HDAC) inhibitors, such as vorinostat, may have therapeutic potential. However, a Phase II study in recurrent glioblastoma demonstrated only limited efficacy of vorinostat when used as monotherapy.[34]

IMMUNOTHERAPY

Over the past decade, considerable research has focused on immunotherapeutic strategies for the treatment of primary brain tumors. However, the immunosuppressive tumor microenvironment of gliomas presents a major barrier to the success of such approaches. Nivolumab has been evaluated in three randomized Phase III trials involving over 1,600 patients with recurrent and newly diagnosed glioblastoma.[35] These studies demonstrated no improvement in outcomes when nivolumab was added to standard chemoradiotherapy or radiotherapy, or when compared with bevacizumab in recurrent or newly diagnosed disease.[34] A Phase I trial, however, highlighted the potential importance of combining pembrolizumab and bevacizumab with hypofractionated stereotactic reirradiation.[36]

COMBINATION THERAPIES

Primary brain tumors are equipped with multiple immune evasion mechanisms, highlighting the potential importance of combining RT with immunotherapeutic

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Table 2 Molecular, immune, and other targeted agents

Agent	Mechanism	Efficacy	RT
Bortezomib	Proteasome inhibitor	Limited clinical benefit	Radiosensitizing in vitro only
Marizomib	BBB-penetrant proteasome inhibitor	Limited benefit	RT combinations under study
BRAF inhibitors	BRAFV600E inhibition	High ORR	RT sequencing individualized
NTRK inhibitors	TRK fusion inhibition	High ORR, durable	RT may be deferred
EGFR inhibitors/ADCs	EGFR blockade / cytotoxic delivery	Mixed/negative	RT combinations ineffective
FGFR inhibitors	FGFR pathway inhibition	Variable	Very limited RT evidence
IDH inhibitors	Mutant IDH inhibition	PFS↑ in grade 2	RT–drug sequencing studied
HDAC inhibitors	Epigenetic modulation	Limited	Preclinical radiosensitization
Immune checkpoint inhibitors (ICI)	PD-1 blockade	Phase III negative	RT+ICI investigated

RT: Radiotheraphy; BBB: Blood brain barrier; ORR: Objective response rate; NTRK: Neurotrophic tropomyosin kinase receptor; TRK: Tropomyosin kinase receptor; EGFR: Epidermal growth factor receptor; ADCs: Antibody-drug conjugates; FGFR: Fibroblast growth factor receptor; IDH: Isocitrate Dehydrogenase; HDAC: Histone deacetylase

approaches. RT exerts significant immunomodulatory effects, including increased antigen expression, enhanced release of reactive oxygen species, and induction of proinflammatory cytokines. High-dose RT can counteract the immunosuppressive activity of T cells, while increasing endothelial permeability, thereby facilitating immune cell infiltration into the tumor microenvironment. Consequently, RT may alter the tumor microenvironment and induce an "abscopal" effect, triggering systemic immune responses at sites distant from the irradiated area.[37] Targeting a single molecular pathway can result in compensatory activation of others and contribute to treatment resistance; RT may help overcome resistance to PD-L1 inhibitors by promoting T lymphocyte infiltration. Combination strategies, including fractionated stereotactic radiotherapy or stereotactic radiosurgery with immunotherapy, are currently under investigation. Proton therapy is also hypothesized to enhance immunotherapeutic efficacy. An ongoing phase II trial (NCT02179086) is evaluating whether proton therapy is more effective than standard-dose RT combined with temozolomide in newly diagnosed glioblastoma.[38] These topics are comprehensively summarized in Table 2 (Molecular, Immune, and Other Targeted Agents.

CONCLUSION

The treatment of primary brain tumors is increasingly shifting toward personalized approaches, driven by the identification of molecular targets. Optimizing outcomes with targeted therapies will likely require combination strategies involving multiple agents, integration with conventional treatments such as radiotherapy and chemotherapy, or concomitant use with immunotherapies. Strategies that overcome the blood-brain barrier and favorably modulate the tumor microenvironment are particularly critical for achieving clinical benefit. Larger, multicenter studies are essential to rigorously evaluate the efficacy, safety, and long-term outcomes of these emerging targeted treatment strategies.

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