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EDITORIAL

Current challenges in the treatment of gliomas: The molecular era

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Abstract

Gliomas originate from glial cells in the central nervous system. Approximately 80%-85% of malignant brain tumors in adults are gliomas. The most common central nervous system tumor in children is low-grade pediatric glioma. Diagnosis was determined by histological features until 2016 when the World Health Organization classification integrated molecular data with anatomopathological information to achieve a more integral diagnosis. Molecular characterization has led to better diagnostic and prognostic staging, which in turn has increased the precision of treatment. Current efforts are focused on more effective therapies to prolong survival and improve the quality of life of adult and pediatric patients with glioma. However, improvements in survival have been modest. Currently, clinical guidelines, as well as the article by Mohamed *et al* accompanying this editorial piece, are adapting treatment recommendations (surgery, chemotherapy, and radiotherapy) according to diagnosis and prognosis guided by molecular biomarkers. Furthermore, this paves the way for the design of clinical trials with new therapies, which is especially important in pediatric gliomas.

Key Words: Gliomas; Chemotherapy; Radiotherapy; Isocitrate dehydrogenase-type mutant; Pediatric gliomas; Astrocytoma; Oligodendroglioma; 1p/19q-codeleted

Core Tip: The current trimodal approach including surgery, radiotherapy, and chemotherapy for the treatment of gliomas has benefited from the introduction of molecular diagnosis. However, new challenges have appeared. There is still debate on the best therapeutic option. In this editorial, we focused on the controversial areas in molecular classification and new treatment advances.

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INTRODUCTION

Gliomas are central nervous system (CNS) tumors that are histologically similar to normal glial cells (astrocytes, oligodendrocytes, and ependymal cells), occurring in both adults and children. Gliomas were traditionally categorized histologically as diffuse gliomas and nondiffuse gliomas. Beginning in 2016, however, the World Health Organization (WHO) categorization guidelines of CNS tumors introduced molecular features for the first time[1].

In 2021 the WHO released updated guidelines classifying gliomas according to histology, grade, and molecular data, focusing on molecular biomarkers as essential diagnostic criteria[1]. The most recent recommendations have further evolved following the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW)[2]. Diffuse gliomas are now categorized as pediatric-type and adult-type for the first time. The pediatric diffuse gliomas are further categorized as low-grade glioma (pLGG) and high-grade glioma (pHGG). pLGG is the most frequent pediatric CNS tumor (accounting for 30%-40% of reported diagnoses)[3]. Adult-type diffuse gliomas account for 80%-85% of malignant brain tumors in adults[4]. In this regard, the old concept of high- and low-grade status in adult patients has become obsolete.

pLGG

pLGG is further categorized into four subtypes, as follows: (1) Diffuse astrocytoma with MYB-altered or MYB1-altered, and diffuse LGG with MAPK pathway-altered; (2) Angiocentric glioma; (3) Polymorphous low-grade neuroepithelial tumor of the young; and (4) Diffuse LGG with MAPK pathway-altered. pLGG now reflects gliomas caused by alterations in the MAPK/ERK pathway or the mTOR pathway[5]. Some tumors previously classified as pLGG have been reclassified as circumscribed gliomas, glioneural, and neuronal tumors according to the WHO 2021 guidelines. These form a heterogeneous group of tumors affecting children, adolescents, and young adults, but also older patients occasionally. For example, pilocytic astrocytoma is no longer classified as pLGG, having become a subtype of astrocytic glioma.

pHGG

There are four pHGG subtypes, as follows: (1) Diffuse midline glioma with H3 K27-altered; (2) Diffuse hemispheric glioma with H3 G34-mutant; (3) Diffuse hemispheric glioma with H3-wild type (WT) and isocitrate dehydrogenase (IDH)-WT; and (4) Infant-type hemispheric glioma. Diffuse midline glioma with H3 K27-altered can also manifest in adults, but the location varies according to age. They are usually present in the brainstem, protuberance, and spinal cord in pediatric patients, whereas the thalamus and spinal cord are the most frequent location in adolescents and adults.

The *H3*-WT and *IDH*-WT subtype diagnosis requires molecular genotyping of the *H3* and *IDH* genes to confirm the WT genotype. This type of pHGG is further categorized based on molecular alterations in the receptor tyrosine kinase 1, *RTK2*, and *MYCN* genes[5]. Infant-type hemispheric glioma includes multiple subgroups, with most tumors presenting fusions of RTK involving the genes *NTRK*, *ROS1*, *ALK*, and *MET*[5].

It must be noted that adolescents and young adults (individuals between 15 years and 39 years of age) are in the intersection of pediatric and adult management, which is important to consider in the context of CNS tumors[6].

Adult-type diffuse gliomas

Adult-type diffuse gliomas, which were previously classified as 10 distinct tumors in the WHO 2016 guidelines, were consolidated into only 3 subtypes in the WHO 2021 guidelines. The criteria for diagnosis include histology, mutation of *IDH*, and other molecular alterations. The subtypes are *IDH*-mutant astrocytoma, oligodendroglioma, and *IDH*-WT glioblastoma (GB)[7,8].

IDH-mutant astrocytomas are assigned a grade (2, 3, or 4) according to histological features (nuclear atypia, mitosis, endothelial proliferation necrosis) and molecular alterations. *IDH1* and *IDH2* mutations confer a better prognosis. These gliomas typically also have inactivating mutations in *TP53* and *ATRX*. Grade 4 *IDH*-mutant astrocytomas are characterized by a deletion in the cyclin-dependent kinase inhibitor 2A/B even if they lack the typical histological features of this grade.

Grade 2 and 3 oligodendrogliomas are defined by a mutation in *IDH* and a codeletion in 1p19q. *ATRX*-WT in an *IDH*-mutant glioma indicates the need to test for the 1p19q codeletion to distinguish the tumor from an oligodendroglioma. The diagnosis of GB is driven by the lack of mutations in *IDH*, which allows for a precise diagnosis in the absence of classical histological characteristics (vascular proliferation and necrosis). Diagnosis of grade 4 *IDH*-WT GB can also be

determined molecularly by the gain in chromosome 7 and loss of chromosome 10, amplification of the epidermal growth factor receptor gene, and mutation in the telomerase reverse transcriptase gene despite the lack of necrosis, proliferation, or microvascularization[9].

Molecular testing is also necessary to diagnose glioma subtypes that are characterized by specific alterations, such as H3 K27-mutant diffuse midline glioma or H3 G34-mutant diffuse hemispheric glioma. The guidelines of the National Comprehensive Cancer Network added an independent algorithm for this category of HGGs[10]. These tumors are typically more aggressive than GB and tend to be less sensitive to temozolomide (TMZ).

Molecular biomarkers, clinical practice impact, and patient management

Molecular testing aids in the selection of the most adequate treatment. For example, the methylation status of the promoter of O-6-methylguanine-DNA methyltransferase is prognostic and predictive of the benefit of TMZ in the treatment of *IDH*-WT GB[11]. Consequently, a detailed molecular analysis must be conducted for the diagnosis of gliomas. The molecular analysis improves prognosis because patients receive an individualized postoperative treatment option. Molecular analysis also improves patient stratification for clinical trials testing new treatment approaches. Molecular analysis will likely encompass whole DNA sequencing or DNA methylation profiling to obtain an accurate molecular profile of each patient[8].

The article that accompanies this editorial piece summarized and updated the diverse treatment modalities for specific grade and molecular classifications of adult and pediatric gliomas that maximize survival and quality of life[11]. The current trimodal approach of surgery, radiotherapy (RT), and chemotherapy (CT) for the treatment of gliomas has benefited from molecular testing tools, although there is still debate and new challenges to overcome.

SURGICAL MANAGEMENT

Advances in surgery have focused on achieving the maximum resection while preserving safety. Generally, *IDH*-WT gliomas are treated to the maximum extent according to contrast-enhancing areas. However, according to the RANO resect group, supramaximal resection could offer an additional survival benefit in patients with *IDH*-WT GB[12]. Although resection does not offer a significant survival benefit in the elderly, the risk/benefit analysis favors an optimal tumor resection if a detailed geriatric evaluation is performed[13].

In *IDH*-mutant tumors, maximum resection is a critical first step. Supramaximal resections are associated with a better overall survival (OS). However, for oligodendroglioma cases with small residual tumors supramaximal resection does not result in better OS[14]. In short, all efforts must be focused on achieving the maximum resection as long as neurological function is preserved.

RT AND CT IN THE MOLECULAR ERA

GB represents 48.6% of all brain tumors, and it is extremely aggressive. The OS of GB is 15-20 months, and the 5-year survival is less than 10%. After surgical resection, standard therapy (according to the Stupp protocol) is RT with concomitant TMZ followed by maintenance TMZ for six cycles[15,16]. Clinical trials treating GB with novel agents (nivolumab, depatux-M, bevacizumab, marizomib, veliparib) have not shown an improvement in OS[9].

IDH-mutant gliomas represent 70%-80% of LGGs. They are usually diagnosed in patients less than 50 years of age and respond better to therapy than *IDH*-WT gliomas[4]. Grade 3 *IDH*-mutant astrocytomas are treated with RT and 12 months of adjuvant TMZ (CATNON trial). Grade 3 oligodendrogliomas are treated with RT and procarbazine + lomustine + vincristine (PCV) after two randomized clinical trials showed that the addition of PCV to RT almost doubled the OS (RTOG 9402: 7.3 *vs* 13.2 years; EORTC 26951: 9.3 *vs* 14.2 years). An ongoing clinical trial (CODEL) is testing the efficacy of TMZ after RT as compared to PCV after RT[15,16].

Although the definition of a low-risk glioma patient is controversial, LGGs are typically treated with surgical resection only. Before the updated WHO guidelines, trials were conducted to determine the characteristics of patients who do not require additional treatment. These patients included those with total macroscopic resection, good performance status, 1p19q codeletion positivity, and age younger than 40 years. RT is typically delayed in these patients to maintain cognition.

Vorasidenib is an oral inhibitor of IDH1 and IDH2 in the brain. It was evaluated in a phase III study (INDIGO) against [17] placebo in patients with *IDH*-mutant grade 2 gliomas that were residual or recurrent after surgery and who had not received prior RT or CT. That trial found improved progression-free survival and in time-to-next intervention without significant toxicity in this specific population considered appropriate candidates for a watch-and-wait approach. Another trial (RTOG 9802) demonstrated an improvement in progression-free survival and OS with the addition of adjuvant PCV after RT. RT with concurrent and/or adjuvant TMZ was also included in another randomized phase II trial (RTOG 0424) [17,18]. The addition of vorasidenib to standard therapy originates new questions about the optimal management of high-risk grade 2 gliomas.

RT for *IDH*-mutant grade 2 gliomas requires a dose of 45.0-54.0 Gy in daily fractions of 1.8 Gy. For grade 3-4 gliomas, 59.4-60.0 Gy in daily fractions of 1.8-2.0 Gy is recommended. Higher doses of 59.4-60.0 Gy should be considered for patients with either *IDH*-WT or cyclin-dependent kinase inhibitor 2A/B diffuse LGG. They tend to be treated like HGGs because they tend to be more aggressive[10]. Hypofractionated RT with higher doses per fraction and a lower total dose is

appropriate for elderly patients and those with a worse prognosis[15,16].

Modern RT techniques such as stereotactic RT or proton-beam therapy can improve precision and minimize long-term neurocognitive and endocrinological toxicities associated with brain radiation in children. In adults, the use of protons could also offer a reduced risk of cognitive decline, which is important for long-term survivors[11].

NEW MOLECULAR TARGETS

A potential new target for treating gliomas is a mutation in the *BRAF* gene. The BRAFV600 variant is present in 6% of GBs, 60%-80% of pleomorphic xanthoastrocytomas, 20%-70% of gangliomas, and 10% of pilocytic astrocytomas. Simultaneous *BRAF* and *IDH* mutations in gliomas have not been reported, but the importance of this observation is unclear currently. BRAF and mitogen-activated protein kinase inhibitors increase survival in patients with LGGs or HGGs with a *BRAF* mutation[18].

Gene fusions in the *NTRK* gene have been found in both adult and pediatric gliomas[16], including *IDH*-WT GB, LGGs, pilocytic astrocytomas, and gangliogliomas. Larotrectinib and entrectinib (NTRK inhibitors) have initially been found to be safe and efficacious for the treatment of these tumors[18].

Combination CT has shown promising results. The combination of dabrafenib + trametinib after recurrence of HGGs revealed an objective response rate of 33% (phase II ROAR trial)[16].

CHALLENGES IN PEDIATRIC GLIOMAS

pLGG is heterogeneous and represents a complex challenge in the treatment of these patients. Typically, total tumor resection will be curative depending on size and location. However, CT with vincristine + carboplatin or vinblastine is recommended for cases that are inoperable. Unfortunately, unresectable or partially resected pLGG tends to progress. Frequent follow-up and additional treatment are justified for these cases, although the optimal timing for CT and RT is controversial[11]. Recent advances due to the understanding of the molecular drivers of pediatric gliomas are facilitating the use of effective drugs against the RAS/MAPK pathway (BRAF, mitogen-activated protein kinase, and other tyrosine kinase inhibitors)[19]. These drugs also have less side effects than CT and RT.

Understanding the molecular mechanisms that promote tumor progression in pHGG and developing drugs than can surpass the blood-brain barrier will lead to the development of new treatment options for patients with pHGG. Currently, the most promising approach is based on the highly immunogenic characteristics of pHGG that can be exploited through the reactivation of ineffective or exhausted immune mechanisms or through other strategies such as chimeric antigen receptor T cells or vaccines[20].

CONCLUSION

Neuro-oncology has experienced considerable advances in the last decades. The understanding of molecular biology and pathology has translated into precise classifications and prognosis. Even though improvements in survival have been modest, there is an opportunity to design clinical trials with novel therapies for specific subtypes of glioma due to the molecular analysis of these tumors. Given that pediatric and adult gliomas are different, molecular and genetic analyses are essential to diagnose and treat gliomas in the pediatric population.

FOOTNOTES

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