REVIEW

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Overview of treatment of grade 2 astrocytomas

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Summary

Grade 2 astrocytomas are slow-growing brain tumors, most common in young patients and often presenting with seizures. In 2016, the World Health Organization (WHO) updated its classification to include molecular features to better assess tumor behavior. After gross tumor resection, based on a risk-adapted approach, a watch-and-wait strategy, radiotherapy followed by chemotherapy, or IDH-targeted therapy may be applied.

For adjuvant treatment, radiotherapy remains a key component, followed by chemotherapy regimens such as PCV or temozolomide, depending on patient tolerance. Advances in pharmacotherapy, including IDH inhibitors, show promise in delaying disease progression with favorable safety profiles, though their impact on overall survival and long-term toxicity remains uncertain. Immunotherapy and vaccine-based approaches are under investigation but are limited by the blood-brain barrier.

Long-term MRI monitoring is essential during and after adjuvant therapy. Future treatment strategies are expected to incorporate molecular-targeted agents and more advanced radiotherapy and surgical techniques to improve outcomes and preserve quality of life.

This paper reviews current and emerging treatments for grade 2 astrocytomas to support clinical decision-making. With the recent European Medicines Agency approval of IDH inhibitors, major therapeutic changes are anticipated, supported by ongoing evaluation of efficacy and safety in practice.

KEYWORDS: *Grade 2 astrocytoma, IDH therapy, vorasidenib, radiotherapy, toxicities*

INTRODUCTION

Low-grade gliomas are solid tumours arising from malignantly transformed cells of the brain or spinal cord. In most patients, these tumors are localized and grow slowly, but presentation varies depending on the location and size of the tumor(1). Their incidence is highest in patients in their 3rd and 4th decades of life, and seizure is the most common presenting symptom, although headache and focal neurological deficits are also frequently seen. There is no known causes of the tumor development, but tumor suppressor protein 53 (p53), phosphatase and tensin homolog (PTEN), and epidermal growth factor receptor (EGFR) are involved in the pathogenesis of these tumors(2). In 2016, the World Health Organization (WHO) published an updated version of the classification of CNS tumors with significant changes, and molecular features were included in addition to the previously described histopathological features(3).

Grade 2 gliomas are diagnosed by magnetic resonance imaging (MRI) as T1-hypointense and T2/FLAIR- hyperintense lesions, typically without contrast enhancement, which helps differentiate them from more aggressive tumors. Functional MRI, diffusion MRI, perfusion MRI, MR spectroscopy, and positron emission tomography (PET) are not routinely performed, but they can help

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identify changes in the tumor and surrounding microenvironment to monitor response to treatment and disease progression during the surveillance phase(4). The discovery of mutations in the isocitrate dehydrogenase (IDH) genes, which encode enzymes in the Krebs cycle, has been a significant breakthrough. The most common mutations are in the IDH1 (R132H) and, less commonly, in IDH2 gene, which results in altered enzyme function, and ultimately leads to the production of oncometabolite 2-hydroxyglutarate, which has a broad range of effects on gene expression. The mutation has an impact on overall survival (OS) so the mutation status of the IDH gene is mandatory in the pathology report(1,5).

Maximal safe tumor resection is performed at the time of initial diagnosis, even in asymptomatic, incidentally discovered tumors. Completeness of initial resection is an independent predictor of both progression-free survival (PFS) and overall survival. In a prospective series of 111 patients with low-grade glioma who underwent a gross tumor resection, the overall survival rates at two and five years were 99 and 93%, respectively. Approximately 50% of patients remained progression free after 5 years. Even limited residual disease on postoperative MRI may be associated with a negative impact on overall survival when compared to complete resection(6,7).

POSTOPERATIVE TREATMENT

After surgery, additional therapy is required in high-risk patients. High-risk features include any of the following: subtotal resection, age ≥40, tumor size ≥4-6 cm, tumor crosses midline, refractory seizures, or presurgical neurologic symptoms from a tumor(8). Also, subventricular zone involvement was a negative prognostic marker for malignant progression and overall survival on uni- and multivariate analysis(9).

There are three options for postoperative management: watchful waiting, radiotherapy (RT) plus chemotherapy, and IDH-targeted therapy. Watchful waiting after complete resection has traditionally preferred for most patients with grade 2 astrocytoma with an IDH mutation, as they have a low risk of early clinical progression and may not require further therapy for many years. It involves contrast MRI every 3 to 4 months. IDH-targeted therapy like vorasidenib may be an option to prolong PFS based on the INDIGO trial(10,11). Postoperative radiotherapy remains the standard of care for patients who need further treatment, and strategies to omit radiotherapy have resulted in suboptimal outcomes. EORTC 22845 compared immediate adjuvant RT versus salvage RT at progression in patients with grade 2 glioma. Although adjuvant RT demonstrated improvements in PFS (5.3 *vs*. 3.4 years) and 1-year seizure rate (25% *vs*. 41%), there was no improvement in OS (7.4 *vs*. 7.2 years) compared with salvage RT(12). Several clinical trials have failed to show a clear dose-response relationship. Therefore, 50.4 Gy in 28 fractions, as used in the EORTC 22033 trial, is recommended according to ESTRO-EANO guidelines(13). Common acute toxicities include hair loss, fatigue, and loss of appetite. Increased cerebral edema during radiation may cause headaches and aggravation of neurologic symptoms such as seizures or weakness. Certain potential late effects are specific to the location of treatment, for example, hearing loss, hypopituitarism, or progressive delayed neurocognitive impairment(14).

The RTOG 9802 study demonstrated improved survival with the use of chemoradiotherapy over radiotherapy alone for WHO grade 2 gliomas. The most significant finding is that adding PCV (procarbazine, lomustine, and vincristine) to RT more than doubled the median PFS (10.4 vs. 4.3 years) and nearly doubled the median OS (11.4 vs. 7.8 years) compared to RT alone(15). Although the use of PCV chemotherapy protocol is recommended, owing to its proven efficacy and manageable toxicity, temozolomide is a reasonable alternative in patients who do not tolerate PCV. There are no trials that have compared these two regimens head-to-head(12,16).

PROGRESSION

Re-resection, if feasible, is the best option, and if pathology confirms a grade 2 tumor, a watch-and-wait strategy can again be considered. Over time, greater than 70% of these tumors can transform into a higher grade or become more aggressive. For patients with a relatively low volume of recurrent, nonenhancing tumor or those who will not undergo further surgery, chemoradio-

therapy or vorasidenib are the next-line option. Still, there is no consensus on the size of residual tumor as a criterion for determining the next line of therapy(10). In the INDIGO trial, patients with recurrent or residual disease were randomly assigned to receive either vorasidenib or a placebo. Median age of participants was approximately 40 years, and more than 80% of patients had residual disease >2 cm in diameter. With a median follow-up of 14.2 months, patients in the vorasidenib group had significantly improved PFS compared with the placebo group (27.7 *vs*. 11.1 months)(10). Vorasidenib was well tolerated overall, with a low incidence of serious adverse events (<2%). The most common significant adverse event was elevated alanine aminotransferase (9.6%). Rates of treatment discontinuation due to treatment were <4%(17).

The phase 2 ROAR basket trial evaluated the combination of dabrafenib and trametinib in adult patients with recurrent or progressive BRAFV600E-mutant high-grade and low-grade gliomas. The treatment demonstrated clinically meaningful activity, with objective response rates of 69% in low-grade gliomas after a median follow-up of 32.2 months(18).

MONITORING

Since early progression after radiotherapy is uncommon, the first MRI can be safely delayed until 3–4 months post-treatment to avoid misinterpreting pseudoprogression. National Comprehensive Cancer Network (NCCN) guidelines advocate follow-up MRI every 3–6 months for 5 years then at least every 6–12 months or as clinically indicated(11). During vorasidenib therapy it is recommended to obtain brain MRI at baseline and then every 3 months for the first 3 years of therapy. For patients who remain stable, scan intervals may be lengthened to every 6 months in the absence of new symptoms(17).

NEW THERAPIES

Proton beam radiotherapy

Proton beam therapy offers a precise radiation delivery method, minimizing damage to healthy brain tissue compared to conventional radiotherapy(19). Tanja Eichkorn et al. analyzed 194 adult patients, including 131 with WHO grade 2 gliomas with IDH mutation. Patients underwent proton beam radiotherapy and were treated with a dose of 50.4–54 Gy in 1.8–2.0 Gy per fraction. They demonstrated the effectiveness of 5 year survival rate of 85%, indicating that there is no differences between proton and photon radiotherapy(2).

Immunotherapy and vaccines

In general, tumor infiltration by immune cells has been shown to play a role in tumor progression and has been used for cancer prognosis. Low grade gliomas have been shown to have reduced T-cell infiltration and decreased infiltration of myeloid cells with the potential for antigen presentation(20). Vaccine-reactive T-cell responses were detected in the post-vaccine LGG tumor tissue, but homing of immune cells through the intact BBB remains challenging. Penetration of immune effectors could be achieved with novel technologies, such as low-intensity focused ultrasound combined with microbubbles, allowing targeted transient opening of the BBB in the tumor. Beyond that, locoregional delivery such as intraventricular, intracavitary, or intratumor immunotherapy application has to be investigated in the context of IDH-mutant low-grade glioma in the future, as it has been demonstrated in several human phase I HGG trials to be a potential alternative to overcome the natural barriers(21).

DISCUSSION

Surgery alone is not curative in patients with grade 2 glioma, and additional anticancer therapy is ultimately required but its optimal timing is less certain, and the decision to proceed with immediate versus delayed postoperative therapy should be individualized. The treatment landscape has evolved significantly in recent years. Traditionally, postoperative radiotherapy and PCV or temozolomide chemotherapy are used, but questions remain regarding the ideal delivery and whether molecular classification can tailor treatment (e.g., timing, dose, protons vs. photons). However, the emergence of targeted therapies, particularly the IDH1/2 inhibitor vorasidenib, has introduced a novel therapeutic avenue that challenges the conventional approach. Vorasidenib could become an adequate alternative although patients without

measurable disease were not included in the INDIGO trial, and safety data for very long-term treatment with vorasidenib are only available for a limited number of patients treated on phase 1 trials. Data on seizure control, quality of life, and overall survival are not yet available so this is an area of uncertainty, and decisions should be individualized. Moreover, while vorasidenib significantly prolongs PFS, data on OS impact is still maturing, and head-to-head comparisons with chemoradiation are lacking.

CONCLUSION

Radiotherapy and chemotherapy with PCV or temozolomide still remain a standard of care for postoperative treatment of grade 2 gliomas, if watch and wait strategy is not applicable. However, it can be associated with long-term neurologic complications such as cognitive dysfunction, brain volume loss, leukoencephalopathy, and neurovascular complications that require ongoing monitoring and management. Vorasidenib could be considered in some patients but the long-term effects of IDH inhibition remain unknown, and while it delays progression, it is not curative. There is no consensus on size of residual tumor as a criterion for determining next line of therapy, and clinicians must use judgement in selecting patients for vorasidenib who are felt to be candidates for safe postponement of chemoradiotherapy.

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Sažetak

Pregled liječenja astrocitoma gradusa 2

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Astrocitomi gradusa 2 su sporo rastući tumori mozga, česti u mlađih bolesnika, a koji se manifestiraju epileptičkim napadima. Godine 2016. Svjetska zdravstvena organizacija ažurirala je klasifikaciju tumora uključivanjem molekularnih obilježja radi boljeg opisa biologije tumora. Nakon kirurške resekcije, ovisno o riziku, može se primijeniti strategija bliskog praćenja, radioterapija praćena kemoterapijom ili IDH-ciljana terapija.

Radioterapija ostaje temelj adjuvantnog liječenja, nakon koje slijede kemoterapijski protokoli poput PCV-a ili temozolomida, ovisno o podnošljivosti. Napredak u farmakoterapiji, uključujući IDH inhibitore, pokazuje obećavajuće rezultate u usporavanju napredovanja bolesti uz dobar sigurnosni profil, iako njihov učinak na ukupno preživljenje i dugoročnu toksičnost još nije do kraja utvrđen. Imunoterapija i pristupi temeljeni na cjepivima još su u istraživanju, ali njihovu učinkovitost ograničava krvno-moždana barijera.

Dugoročno praćenje MRI-om ključno je tijekom i nakon terapije. Očekuje se da će buduće strategije uključivati lijekove usmjerene na molekularne mete te naprednije metode radioterapije i kirurgije radi boljih ishoda i očuvanja kvalitete života.

Ovaj rad prikazuje sadašnje i nove mogućnosti liječenja astrocitoma gradusa 2 radi lakšeg donošenja kliničkih odluka. S nedavnim odobrenjem inhibitora IDH od strane EMA-e očekuju se terapijske promjene i daljnja procjena njihove učinkovitosti i sigurnosti u praksi.

KLJUČNE RIJEČI: *astrocitom gradusa 2, IDH terapija, vorasidenib, radioterapija, toksičnost*