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Role of the tumor board when prescribing mutant isocitrate dehydrogenase inhibitors to patients with isocitrate dehydrogenase-mutant glioma

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Abstract

Isocitrate dehydrogenase (IDH)-mutant gliomas, comprising both astrocytomas and oligodendrogliomas, represent a distinct group of tumors that pose an interdisciplinary challenge. Addressing the needs of affected patients requires close collaboration among various disciplines, including neuropathology, neuroradiology, neurosurgery, radiation oncology, neurology, medical oncology, and other relevant specialties when necessary. Interdisciplinary tumor boards are central in determining the ideal diagnostic and therapeutic strategies for these patients. The key tasks of a tumor board include the evaluation of imaging findings, selecting the appropriate surgical approach, discussing additional treatment options, and identification/determination of tumor recurrence and progression. In addition to established treatments such as radiotherapy and alkylating chemotherapy, patients with an isocitrate dehydrogenase (IDH)-mutant glioma for whom additional treatment is indicated may now also have the option of receiving treatment with an mutant isocitrate dehydrogenase inhibitor such as vorasidenib or ivosidenib. In this regard, the collaborative nature of tumor boards becomes even more crucial for evaluating comprehensively the needs of these patients. Through interdisciplinary discussions, tumor boards aim to develop personalized treatment strategies that maximize therapeutic efficacy while minimizing potential side effects and preserving patients' quality of life.

Key Points

- The management of patients with IDH-mutant gliomas needs collaboration across specialties.
- Tumor boards assess pathological and imaging findings as well as treatment plans.
- Some patients may now receive treatment with mIDH inhibitors like vorasidenib.

Composition and Tasks of Tumor Boards in Neuro-Oncology

Tumor boards serve as pivotal platforms where multidisciplinary expertise converges to navigate the complexities of cancer treatment. They represent a collaborative effort involving various medical disciplines, each contributing unique insights and specialized knowledge crucial for devising comprehensive treatment plans tailored to individual patients. Given the unique challenges posed by brain tumors, such as seizures and cognitive impairment, comprehensive evaluation in a neuro-oncological tumor board is typically helpful to allow for the best possible diagnostic and therapeutic recommendations.[1,2] Isocitrate dehydrogenase (IDH)-mutant gliomas represent a distinct group of tumors in the current World Health Organization (WHO) classification of central nervous system (CNS) tumors.[3]

Similar to other diffuse gliomas, they require multimodal management, including the expertise of neuropathologists and neuroradiologists, as well as neurosurgeons, radiation oncologists, neurologists, and medical oncologists.[4] Furthermore, palliative care medicine specialists should be involved early on to provide supportive care and enhance the quality of life for patients facing advanced disease stages, particularly since cure is generally not possible for diffuse gliomas. At present, treatment options comprise surgical resection, radiotherapy, and chemotherapy as well as targeted therapies or immunotherapy for selected patients.[5] Especially the timing of treatment initiation is controversial, acknowledging the balance between prolonging survival and the risk of long-term negative consequences for brain functions. With the recent emergence of mutant isocitrate dehydrogenase (mIDH) inhibitors such as vorasidenib and ivosidenib, the spectrum of available treatment options has further broadened, making it even more important to discuss the optimal treatment approach in an interdisciplinary setting.[6] Here, we provide an overview of diagnostic and therapeutic considerations that are important in managing patients with IDH-mutant gliomas. Moreover, we outline the contribution of the involved disciplines in the care of these patients.

Neuropathology

Diagnosing and characterizing IDH-mutant gliomas requires a multifaceted approach that integrates neuroimaging and histological features with data obtained from molecular analyses. Given the importance of precise diagnosis and classification in guiding treatment decisions and prognostication, an optimal and contemporary neuropathological approach includes histological evaluation, immunohistochemistry, chromosomal analysis for 1p/19q and CDKN2A status, DNA sequencing, and epigenetic profiling for selected cases. The most recent WHO classification of CNS tumors (WHO CNS5) serves as the basis for glioma classification, ensuring standardized and up-to-date categorization of these tumors. Typically, the histological diagnosis of a diffusely infiltrating glioma triggers further analyses with a particular focus on the IDH status of the tumor. Importantly, the presence of a mutation in the IDH1 or IDH2 gene is essential for classifying tumors as IDH-mutant astrocytoma or oligodendroglioma. The grading of these tumors still mainly relies on histologic features. The range of grades for IDH-mutant astrocytomas spans from 2 to 4, whereas oligodendrogliomas may be assigned a grade of 2 or 3. The fact that only grade 2 gliomas were included in the INDIGO (*Investigating Vorasidenib in Glioma*) trial for vorasidenib,[7] may pressure pathologists to assign a grade 2 instead of 3. However, neuropathologists should strictly adhere to WHO classification criteria to ensure accurate and unbiased grading. Of note, differentiating grade 2 from grade 3 astrocytomas is notoriously difficult since clear mitotic cutoffs have never been determined.[8,9] Immunohistochemistry often represents the first step in identifying IDH mutations in glioma tissue samples.[10] Immunohistochemical staining for mutant IDH protein expression allows for the indirect detection of IDH mutations. Antibodies directed at the IDH1 R132H mutated protein that constitutes around 90% of all IDH mutations in gliomas have been shown to be highly specific and sensitive.[11] Yet, they do not allow the identification of rare IDH1 and IDH2 mutations such as IDH1 R132C and IDH2 R172K. Importantly, the presence of non-canonical IDH1 mutations may be associated with prolonged survival.[12] The preferred molecular technique for tumors negative for IDH1 R132H immunohistochemistry is DNA sequencing. This includes targeted sequencing methods that focus specifically on the regions of the genome that contain the IDH1 and IDH2 mutational hotspots. Next-generation sequencing (NGS) technologies offer high-throughput and comprehensive sequencing capabilities, enabling the detection of IDH mutations alongside other relevant genetic alterations. In the routine setting, IDH immunohistochemistry should be done in all gliomas. If IDH1 R132H is negative, especially in patients under 60, NGS should be used to detect other IDH mutations. Supplementary molecular tests for markers like 1p/19q co-deletion and ATRX/TP53 mutations are also useful for comprehensive classification and treatment planning. For the differentiation between oligodendroglioma and astrocytoma, the determination of the 1p/19q status is the next diagnostic step in all IDH-mutant gliomas. Nuclear expression of alpha-thalassemia/mental retardation syndrome X-linked (ATRX) is a valuable surrogate for chromosomal analysis of 1p/19q assessment. Astrocytoma typically shows a loss of nuclear expression whereas ATRX is retained in oligodendroglioma and for cases with unequivocal immunohistochemical results, the additional molecular analyses can be omitted. Since non-neoplastic cells like endothelial cells should have retained nuclear ATRX, admixtures of such cells can serve as useful internal positive controls. Additional analysis of CDKN2A/B homozygous deletions is strongly advised in IDH-mutant diffuse astrocytomas as it contributes to a more aggressive biological phenotype, resulting in a WHO grade 4 classification irrespective of other morphological features and is associated with an increased risk for tumor progression.[13] Finally, an assessment of the MGMT promoter methylation status is often done; however, the predictive value of the MGMT promoter methylation status in IDH-mutant tumors for response to alkylating chemotherapy remains controversial.[14,15]

Molecular techniques for characterizing IDH-mutant gliomas extend beyond genetic analysis to include epigenetic profiling. DNA methylation profiling, in particular, has emerged as a powerful tool for subclassifying gliomas based on their methylation patterns, which can reflect underlying molecular alterations.[16] Integrating DNA methylation data with histopathological and genetic information enhances the accuracy of glioma classification and prognostication, facilitating personalized treatment strategies.[17]

Neuroradiology

Diagnosis

Alongside comprehensive clinical assessment, contrast-enhanced brain MRI serves as the primary diagnostic tool for assessing disease status, treatment response, and progression. There are several previously published criteria

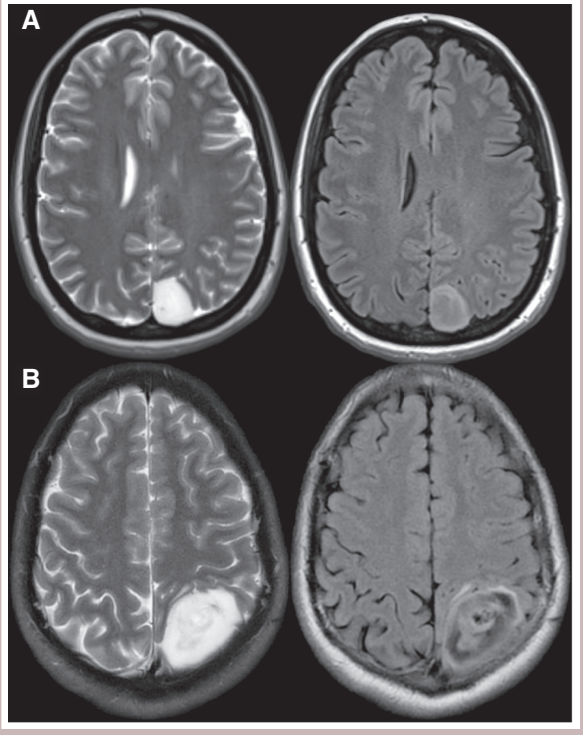

Figure 1. Two examples of the T2-FLAIR mismatch sign with axial T2-weighted imaging (left) and corresponding T2/FLAIR-weighted imaging (right). Example A was diagnosed as astrocytoma, IDH-mutant, WHO grade 2. Example B was diagnosed as astrocytoma, IDH-mutant, WHO grade 3. Cases courtesy of Dr. Evan Calabrese, Duke University Medical Center.

for MRI-based tumor response assessment, most notably the RANO criteria,[18] which are predominantly used for clinical trials, and the Brain Tumor Reporting and Data System (BT-RADS), which is aimed at more routine clinical use.[19] Despite these published guidelines, many routine clinical MRI response assessments are unstructured and subjective. IDH-mutant tumors frequently present as a T1 hypointense and T2/FLAIR hyperintense mass without contrast enhancement, though variable contrast enhancement may be present. It is not possible to definitively distinguish astrocytomas from oligodendrogliomas using imaging alone. Oligodendrogliomas are more likely to exhibit calcification, though this is variable. Some astrocytomas exhibit a relative hypointensity on T2-weighted FLAIR imaging compared to standard T2-weighted except for a thin peripheral rim, referred to as the "T2-FLAIR mismatch sign."[20,21] T2-FLAIR mismatch is not present in oligodendrogliomas and has been described as a highly specific imaging marker for astrocytoma rather than oligodendroglioma (Figure 1). Higher-grade tumors (grades 3–4) are more likely to exhibit contrast enhancement, reduced diffusivity on diffusion-weighted imaging, and elevated relative cerebral blood volume (rCBV), none of which are typically present in grade 2 tumors.[22,23] Differential diagnosis includes IDH wildtype gliomas such as glioblastoma, metastases, central nervous system lymphoma, and other circumscribed and/or lower-grade glioneuronal tumors. Common non-neoplastic mimics include infarction, hemorrhage, and a variety of inflammatory/infectious etiologies. One of the key diagnostic roles for neuroradiology is determining if a lesion represents a diffuse glioma, and importantly, ruling out tumor mimics and tumors with substantially different clinical management such as lymphoma. Particularly considering the genetic/molecular focus of the recent WHO CNS5, the role of neuroradiology for determining a specific diffuse glioma diagnosis is limited making tissue-based diagnostic classification essential. Imaging-based determination of IDH status has been extensively studied and has shown promise in several studies. Several imaging features of IDH-mutant diffuse gliomas have been reported including the T2-FLAIR mismatch sign, a prominent nonenhancing tumor component, and magnetic resonance spectroscopy (MRS) features such as elevated choline-creatinine ratio[24] and a detectable spectroscopic peak for D-2-hydroxyglutarate, a metabolic product of the mutant IDH enzyme.[25] Of note, MRS can only detect 2-hydroxyglutarate, and cannot differentiate between L- and D-enantiomers. Since L-2-hydroxyglutarate can be produced in IDH wildtype cells under acidic or hypoxic conditions,[26,27] MRS may not clearly differentiate between IDH wildtype and IDH-mutant gliomas. Still, the majority of patients with imaging findings that are suspicious of an IDH-mutant glioma will undergo a surgical procedure to allow for a histological diagnosis (see below).

Follow-up

The most important role of neuroradiology in the management of IDH-mutant gliomas is in MRI-based follow-up of patients during or after the completion of tumor-specific therapy. For most patients with IDH-mutant tumors, 2–4-month imaging intervals are typically recommended initially. It is crucial to compare with a baseline scan, as subtle growth is easily missed otherwise.[28,29] Longer intervals may be warranted for patients with sustained tumor control or less aggressive tumors, for example, grade 2 tumors. If disease progression is suspected, control MRI scans at a shortened interval may be helpful to confirm progression. Such situations should be discussed in the tumor board and evaluated using current RANO criteria[30] as well as clinical judgment with consideration of the specific patient situation, treatment modalities, and clinical exam. Pseudoprogression is common within the first few (typically 3) months after completion of radiotherapy and new imaging findings should be interpreted with caution in this period. MR scanning at shorter intervals may be helpful in distinguishing pseudoprogression from true progression. In addition, several advanced imaging techniques may be helpful for this determination, including diffusion, perfusion, and nuclear medicine techniques. Various different diffusion imaging techniques have been proposed as markers for tumor progression with varying specificity.[31] Perfusion imaging, and more specifically elevated rCBV derived from DSC perfusion imaging, has been extensively reported as a reliable marker for true progression.[32] Nuclear medicine imaging, including standard FDG PET and amino acid PET, where available, has also been explored to distinguish pseudoprogression from true progression and define the optimal biopsy target (ie,

"hotspot").[33] In addition, PET has been studied for the assessment of disease monitoring as well as for improving target delineation for radiotherapy in clinical trials. However, its implementation in routine care is still an ongoing process.[34,35]

MRI follow-up is particularly important for longitudinal monitoring of response to novel treatment modalities such as mIDH inhibitors. IDH-mutant tumors treated with these agents may reduce, halt, or even decrease their growth rate over time; however, these changes typically play out over several months and may not be readily apparent over 3-month intervals.[36] It is therefore critical for neuroradiologists to assess tumor growth over multiple prior MRI exams following initiation of therapy and convey this information to the tumor board to aid in treatment decisions. While tumor size change on standard MRI remains the primary method for assessing treatment response during mIDH inhibitor therapy, several other advanced imaging approaches have been proposed. For example, some prior studies have demonstrated that MRI spectroscopy can detect decreases in tumor 2-hydroxyglurate (2HG) levels, which are associated with treatment response to mIDH inhibitors.[25] Others have suggested a role for amino acid PET in identifying early treatment failure before tumor size changes manifest.[37] However, these techniques are currently only performed at specialized centers, and additional supporting data, expertise, reduced costs, and provider education will likely be needed before widespread adoption can occur.

Neurosurgery

Neurosurgery is fundamental in the management of patients with glioma. Given that treatment decisions for these patients largely rely on a tissue-based diagnosis, surgery is typically conducted with both diagnostic and therapeutic goals. A major goal of surgery is to provide access to tumor tissue that can be used for diagnostic purposes. In nonenhancing lesions like typical IDH-mutant low(er) grade glioma, advanced imaging can be considered for optimal sampling. Such techniques include amino acid PET (see above), MRS, perfusion, and diffusion-weighted imaging. Obtaining a definitive tissue-based diagnosis is crucial for informing patients and caregivers, even when further tumor-specific therapy is not recommended. To acquire a tissue sample is usually possible even in critical locations as stereotactic biopsy (frame-based or frameless) is associated with low morbidity, but an unfavorable risk-benefit ratio may sometimes justify a wait-and-scan strategy in small lesions where also the diagnostic yield of a biopsy may be lower. Otherwise, collecting a tissue sample is mandatory to allow for a definite diagnosis and subsequent treatment planning.

In most patients, the neurosurgical procedure also has a therapeutic goal.[38] The mainstay of treatment is to remove as much tumor tissue as possible while preserving neurological function. Various tools, such as surgical navigation systems, preoperative functional workup (navigated transcranial magnetic stimulation, functional MRI, and tractographies), intraoperative imaging with CT, MRI, and/or ultrasound, and intraoperative mapping and monitoring can assist in minimizing postoperative residual tumor volumes and/or reduce the risk of new neurological deficits. Permanent postoperative deficits can result in severe functional impairments, which contradict the goal of achieving extended life expectancy while preserving function and quality of life. Severe post-surgical complications may potentially also shorten survival if further oncological treatment is impeded. Therefore, preventing the occurrence of new permanent neurological deficits is prioritized over the extent of resection. Still, in many cases undergoing extensive resection temporary deficits are seen and most patients recover within 3 months. Unless contraindicated, the extent of resection is evaluated using early MRI, ideally within 72 hours. An approach with a scan at 3 months may be recommended for baseline evaluation, as images are easier to interpret and patients are allowed to recover from surgery and any surgically induced transient deficits. If reoperation is a *likely* option following tumor recurrence, this should be communicated by the neurosurgeons participating in multidisciplinary tumor boards, as this can influence the timing of other possible treatment options (see below).

Particularly in the context of glioblastoma surgery, the concept of supramaximal or supramarginal resection has emerged over the last year. This strategy aims to extend the benefits of maximal tumor removal. Currently, there is a lack of clarity in the literature regarding the precise definition of supramaximal resection. The situation is even less clear in IDH-mutant tumors, which frequently present with little or no contrast uptake. Still, supramaximal resection may have a role in IDH-mutant astrocytomas but appears less important in oligodendrogliomas.[39] However, the information for molecular-guided surgery is most often not available. The T2-FLAIR mismatch sign, when present, can provide important information (see above) and intraoperative molecular information may become increasingly available in the coming years.[40] Similar to classical surgical approaches, prioritizing the preservation of patients' quality of life by minimizing postoperative deficits is paramount also for the highly selected patients suitable for supramaximal resection. If the emergence of mIDH inhibitors changes the indications for supramaximal resection need to be evaluated in clinical trials. While supramaximal surgery is not curative, its main benefits include delaying the need for radio- and chemotherapy and postponing malignant transformation, thereby improving survival.[41] A similar benefit could potentially be achieved with mIDH inhibitors. Currently, in surgical candidates, there is no indication to treat late recurrences or recurrences in previously treated patients with mIDH inhibitors instead of surgery, except within clinical trials.

Radiation Oncology

Radiotherapy has been used for the treatment of patients with gliomas for several decades. Similar to other treatment modalities, no data from prospective trials enrolling exclusively patients with IDH-mutant glioma is currently available. However, several trials were performed for

patients with grade 2 or 3 gliomas, with a majority of these tumors harboring IDH mutations. Therefore, the challenge lies in translating the findings of these historical studies to contemporary patients who are diagnosed according to the current WHO classification.[42] Tumor board discussions should take these data into consideration and evaluate if the treatment strategies that have shown clinical benefit in these trials are still appropriate.

In the context of IDH-mutant grade 2 gliomas, radiotherapy is generally reserved for patients deemed at high risk of progression after surgery. Based on the results of the RTOG 9802 trial, contemporary guidelines will often recommend additional radiotherapy and chemotherapy for patients over 40 years old or those who underwent a biopsy only or had subtotal tumor resection. However, since the definition of "high risk" has varied in published trials, therapeutic decision-making should take additional prognostic factors into account. Although not prospectively validated, a tumor size of more than 6 cm, a tumor crossing the midline, histology of astrocytoma, and the presence of neurological deficits may trigger a decision towards adjuvant treatment.[43]

The non-randomized low-risk arm of the RTOG 9802 trial showed that patients younger than 40 years old with gross total resection had overall better outcomes after being initially observed than patients who had tumors that were assigned to the "high-risk" group.[44] It is important to note that the EORTC 22845 trial previously demonstrated that early post-surgical radiotherapy improved progression-free survival (PFS) but not overall survival (OS) for patients with low-grade glioma.[45] Thus, it is not always clear that even patients with high-risk features need to be treated right away, though it is important to note that the majority of patients initially observed will have progression that necessitates treatment later.

The introduction of mIDH inhibitors will change the indications for radiotherapy by providing an alternative; however, it is currently unclear to what extent. The INDIGO trial extended PFS compared to placebo for patients with residual or recurrent grade 2 IDH mutant glioma without previous radiotherapy or chemotherapy. Inclusion criteria included patients who underwent surgery between 1 and 5 years before and were appropriate for a "watch-and-wait" approach. Enrolled patients did not have clinically relevant functional or neurocognitive deficits caused by the tumor. Thus, INDIGO provides data supporting mIDH inhibitors in this lower-risk group. Additional data is needed before altering current recommended post-surgical radiotherapy indications for patients with higher risk features such as grade 3 histology, tumor symptoms, uncontrolled seizures, brainstem involvement, and nodular enhancement on imaging. Future studies may also include treatment paradigms incorporating both mIDH inhibitors and radiotherapy for these patients.

Radiation doses for grade 2 glioma are typically in a range of 50.4–54 Gy, administered in fractions of 1.8–2.0 Gy each. There is no data suggesting that higher irradiation doses result in prolonged PFS or OS. In patients with grade 3 and 4 gliomas, doses up to 60 Gy have been applied in trials. Given that IDH mutation rather than grade is more prognostic of outcome, this traditional paradigm based on grade has become controversial. It is common for doses ranging between 54 and 60 Gy to be administered. For adjuvant treatment after surgery, radiotherapy is typically administered in combination with alkylating chemotherapy as these combined treatment modality approaches have shown superior activity compared to radiotherapy alone (see below). Patients with IDH-mutant astrocytomas classified as grade 4 tumors may be treated using the treatment paradigms established for glioblastomas.[46]

Organs at risk during radiotherapy include, among others, the lens, optic nerve, optic chiasm, brainstem, spinal cord, hippocampi, cochlea, and pituitary gland. Radiation exposure to these structures should be minimized. As most patients with IDH-mutant glioma have a life expectancy of many years, it is of crucial importance to mitigate the risk of neurocognitive decline and other treatment-related sequelae as they may significantly impair the patient's quality of life.[47] More advanced radiation techniques such as intensity-modulated radiation therapy (IMRT) or proton beam therapy may be utilized to avoid excess doses to these organs at risk. While discussing detailed radiotherapy plans is beyond the scope of a regular tumor board, acceptable dose constraints must be considered to avoid therapy-related long-term toxicity.

Finally, radiation oncology participation in tumor boards can be helpful in interpreting imaging findings after radiotherapy. The probability of pseudoprogression and radiation necrosis is dependent on the radiation dose received by the affected area of the brain. An understanding of the radiation dose distribution map is helpful in distinguishing imaging changes after treatment from progressive tumors.

Management of Systemic Therapy and Role of the Neuro-Oncologist

In most countries and institutions, neuro-oncologists, typically neurologists or medical oncologist by training, have a coordinating function in the diagnostic and therapeutic management as well as long-term follow-up of patients with IDH-mutant glioma. Furthermore, at most expert centers, dedicated neuro-oncologists are responsible for the administration of systemic therapies. The latter has long been dominated by the use of alkylating agents.[48] However, the arsenal of therapeutic options is about to be broadened by the emergence of the mIDH inhibitor vorasidenib and possibly other drugs that interfere with the function of mutant IDH in the future. A careful evaluation of the therapeutic needs of the patient as well as the availability of different drugs, which may differ between countries, will be a crucial part of the discussion at an interdisciplinary tumor board.

All patients with a newly diagnosed glioma should be discussed in the tumor board to obtain an interdisciplinary consensus on the next therapeutic steps. Watch-and-wait strategies may be considered for asymptomatic younger patients (typically under 40–45 years) with grade 2 glioma presenting solely with seizures. These patients can be managed with clinical observation and regular radiographic imaging following a gross total resection. For patients with incomplete resection or those older than 40 years, involved-field radiotherapy in combination with PCV

(procarbazine, lomustine, and vincristine) chemotherapy should be considered. The RTOG 9802 trial demonstrated prolonged PFS and OS in patients with grade 2 gliomas by adding PCV chemotherapy to radiotherapy (54 Gy) compared to radiotherapy alone. Most importantly, additional treatment with PCV resulted in a significant improvement of the median OS compared to radiotherapy alone (13.3 vs. 7.8 years). Of note, not all patients in this trial had IDH-mutant tumors.[49] However, a post-hoc analysis suggests that the additional benefit conferred by PCV is restricted to the population of patients with IDH-mutant gliomas and most pronounced in patients with oligodendrogliomas.[50] Temozolomide can be considered as an alternative to PCV on an individual basis, especially if there are concerns about PCV-associated toxicity.

The role of upfront chemotherapy alone has not been fully clarified. It may be considered following interdisciplinary discussion in the tumor board when radiotherapy is not feasible, particularly in patients with large tumor lesions. However, data from a randomized trial suggest that PFS is short in patients receiving single-agent treatment with temozolomide compared to radiotherapy.[51] Therefore, in patients who require additional treatment after surgery, radiotherapy followed by PCV chemotherapy is considered the standard of care.[5,52]

Postsurgical treatment of patients with astrocytoma, IDH-mutant, grade 3 typically involves radiotherapy with 60 Gy in 1.8–2 Gy fractions, followed by up to 12 cycles of temozolomide chemotherapy.[53] No clear clinical benefit was observed for the administration of concomitant temozolomide during radiotherapy.[15]

In the context of oligodendrogliomas, adopting watch-and-wait strategies is justified for patients with grade 2 tumors who have undergone gross total resection. It may also be considered in young patients who had incomplete resection but did not experience neurological deficits beyond seizures. If post-surgical treatment is warranted, the standard of care involves radiotherapy followed by PCV.[49] The grading of oligodendrogliomas in grades 2 and 3 tumors remains controversial. Therefore, a watch-and-wait strategy might even be considered in patients with oligodendroglioma WHO grade 3 who underwent gross total resection. Data from 2 randomized clinical trials demonstrated that the combination of radiotherapy and PCV chemotherapy (given either before or after radiotherapy) prolongs PFS and OS in these patients.[54] Because a significant proportion of patients with oligodendroglioma live longer than 10 years, the role of the tumor board is to carefully explore if post-surgical therapy is warranted or can be deferred given the potential damage caused by any adjuvant therapy. Maintaining quality of life and cognitive function are important aspects that need to be taken into account for all treatment-related decisions. The ongoing CODEL trial, for patients with WHO grade 2 and 3 oligodendrogliomas is comparing PCV to temozolomide with radiotherapy in both arms (NCT00887146). The results of this study will inform about the possibility of replacing PCV with temozolomide without losing therapeutic activity but with better tolerability.

The emergence of drugs that interfere with the function of mutant IDH will change the treatment landscape. Early clinical trials evaluating the efficacy of mIDH inhibitors in patients with glioma have shown promising results, demonstrating their potential to improve outcomes. In contrast to alkylating agents, which act on DNA, resulting in its crosslinking and DNA strand breaks, mIDH inhibitors specifically target mutant IDH, which is considered a genetic aberration that drives tumor growth. Therefore, similar to other targeted drugs, these inhibitors represent a novel class of agents with a more precise and tailored mechanism of action. Ivosidenib, a drug that is approved by the FDA for the treatment of patients with relapsed or refractory acute myeloid leukemia with an IDH1 mutation, was also assessed in patients with IDH-mutant gliomas demonstrating a favorable safety profile and preliminary signs of efficacy.[55] More recently, vorasidenib, an inhibitor of mutant IDH1 and IDH2 was assessed in the double-blind, phase 3 INDIGO trial in patients with residual or recurrent grade 2 IDH-mutant glioma. In this study, vorasidenib significantly extended PFS compared to placebo (median 27.7 vs. 11.1 months). Vorasidenib also delayed the time to the next intervention, which was the key secondary endpoint of the trial. As patients were allowed to switch from placebo to vorasidenib upon confirmed disease progression, evaluation of OS will be difficult.[7] Treatment recommendations on the use of vorasidenib and possibly other mIDH inhibitors will be subject to constraints regarding the label that is approved by the FDA and other regulatory agencies. Patients who did not have any post-surgical therapy, as in the INDIGO trial, may be candidates for treatment with vorasidenib if further treatment is needed. The optimal sequence of mIDH inhibitor administration, radiotherapy, alkylating chemotherapy, or their combinations needs to be defined in future clinical trials. In some countries, off-label use may be possible and, following discussion in a tumor board could be considered as part of a patient-tailored therapeutic approach.

Treatment at progression remains a challenge as no standard of care has been established for patients with IDH-mutant gliomas. In this situation, the tumor board has a crucial role. The choice of the best treatment strategy requires interdisciplinary discussion, taking the patient's neurological status, radiographic patterns of progression, previous therapy, and the interval between the last treatment and tumor progression into account.[52,56] Typically, multiple treatment options are considered. These include re-resection, possibly renewed radiotherapy, or various forms of systemic therapy, including alkylating agents. As mentioned above, the role of mIDH inhibitors at recurrence following radiotherapy or chemotherapy remains to be determined as compelling data for these patients is currently lacking.

Summary and Outlook

Altogether, neuro-oncology tumor boards exemplify the synergy of diverse medical disciplines working in concert to confront the complexities of brain tumors, with the ultimate goal of improving patient outcomes and advancing the field of neuro-oncology. The management of patients with IDH-mutant glioma optimally includes a multidisciplinary approach to carefully evaluate diagnostic and therapeutic procedures. Because of the young age of many of the affected patients as well as their life

expectancy which often exceeds 10 years, the patient's quality of life, possible treatment-associated burden, and long-term sequelae of any applied therapy need to be considered. Many unresolved questions such as the role of repeated surgery or radiotherapy, the choice of the most appropriate alkylating chemotherapeutic regimen, as well as the place and ideal treatment window for mIDH inhibitors, require results from future clinical trials as well as real-world data.[57] As alkylating agents may induce additional mutations in tumor cells, more data are needed to understand if this limits or precludes the therapeutic activity of mIDH inhibitors.[58] Preliminary data available so far suggests that IDH inhibition may be less beneficial or inactive in patients with contrast-enhancing tumors, suggestive of a higher WHO grade. If this is due to a changed biological phenotype that is less dependent on the IDH mutation, remains another open question. Finally, it will be important to clarify if mIDH inhibitors may also contribute to seizure control.[59] As of now, treatment recommendations must be based on intense interdisciplinary discussion. As research in this field continues to evolve, further insights into the optimal use of vorasidenib and other mIDH inhibitors and their role in combination therapies are expected to emerge, paving the way for improved outcomes and better quality of life for patients with IDH-mutant glioma.

Keywords:

astrocytoma | IDH | oligodendroglioma | therapy | vorasidenib

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