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Symptom management in isocitrate dehydrogenase mutant glioma

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Abstract

According to the 2021 World Health Organization classification of CNS tumors, gliomas harboring a mutation in isocitrate dehydrogenase (mIDH) are considered a distinct disease entity, typically presenting in adult patients before the age of 50 years. Given their multiyear survival, patients with mIDH glioma are affected by tumor and treatment-related symptoms that can have a large impact on the daily life of both patients and their caregivers for an extended period of time. Selective oral inhibitors of mIDH enzymes have recently joined existing anticancer treatments, including resection, radiotherapy, and chemotherapy, as an additional targeted treatment modality. With new treatments that improve progression-free and possibly overall survival, preventing and addressing daily symptoms becomes even more clinically relevant. In this review we discuss the management of the most prevalent symptoms, including tumor-related epilepsy, cognitive dysfunction, mood disorders, and fatigue, in patients with mIDH glioma, and issues regarding patient's health-related quality of life and caregiver needs in the era of mIDH inhibitors. We provide recommendations for practicing healthcare professionals caring for patients who are eligible for treatment with mIDH inhibitors.

Key Points

- The use of mIDH inhibitors in mIDH glioma enhances the need to address daily symptoms.
- Regular monitoring of neurocognitive and HRQoL outcomes is recommended.
- Caregivers require comprehensive support to manage increased distress levels.

Gliomas are the most common primary malignant brain tumors in adults and eventually recur despite multimodal treatment in most patients. Gliomas with a mutation in isocitrate dehydrogenase (IDH), an enzyme of the Krebs cycle, are considered a distinct disease entity according to the 2021 World Health Organization (WHO) classification of central nervous system tumors, and mainly present in patients between 20 and 50 years old.[1,2] IDH-mutant (mIDH) gliomas without an unbalanced translocation between chromosomes 1 and 19 are defined as astrocytomas, mIDH, and gliomas with both an IDH mutation and 1p/19q codeletion are defined as oligodendrogliomas, mIDH, 1p/19-codeleted. Compared to IDH wild type (wtIDH) gliomas, mIDH gliomas have a much better prognosis, ranging from 3 to 4 years in astrocytomas, mIDH, WHO grade 4, and up to >15 years in oligodendrogliomas, mIDH, WHO grade 2.[1,3,4]

Initial treatment of mIDH glioma consists of an early and maximally safe resection. Depending on the presence of risk factors such as age >50–60 years and residual tumor, a resection is followed by adjuvant treatment with radiotherapy and/or chemotherapy.[5,6] Radiation therapy is administered at a dose of 50–60 Gy in 1.8–2.0 daily fractions, where the highest total dose increases with tumor grade.[7] Radiotherapy is often followed by chemotherapy with either procarbazine, lomustine (CCNU), and vincristine (PCV), or temozolomide. The added value of adjuvant treatment with temozolomide

was demonstrated in the CATNON trial, which showed an improvement in progression-free and overall survival in anaplastic astrocytoma, but in clinical practice often is used to treat patients with astrocytoma mIDH grades 2–4.[5,8] In patients with a lower-grade glioma undergoing gross total resection or a partial resection without any other risk factors for early tumor progression (such as age >50–60, presence of (progressive) neurological deficits, or a largely contrast enhancing tumor) wait-and-scan after surgery is a viable option, in order to postpone potential long-term neurotoxicity from adjuvant treatment.[7]

The recent emergence of mIDH inhibitors has changed the landscape for patients with mIDH glioma following a "wait-and-scan" strategy after tumor resection. mIDH inhibitors, such as vorasidenib, ivosidenib, and olutasidenib, are orally available selective inhibitors of IDH-mutant enzymes that decrease D-2-hydroxyglutarate levels (D-2-HG), and are the most advanced targeted treatment strategy for mIDH glioma.[9–12] The phase 3 INDIGO clinical trial has demonstrated a significant improvement in progression-free survival and time to next intervention in patients with astrocytoma, mIDH grade 2 treated with vorasidenib, a pan mIDH1/2 inhibitor, compared to placebo.[10] Patients on vorasidenib had preserved health-related quality of life (HRQoL) and cognitive function over time, as well as seizure control, were similar compared to placebo assigned to placebo.[13] This is promising because patients with mIDH glioma currently have significant tumor and treatment-related symptoms that have a large impact on the daily life of patients and their caregivers, potentially worsening patient's HRQoL for an extended period of time.[14] In light of a treatment that increases progression-free and possibly overall survival in patients with mIDH glioma, preventing and addressing daily symptoms becomes even more clinically relevant. In this review, we focus on the management of the most common symptoms in patients with mIDH glioma, particularly in those patients that are eligible for treatment with mIDH inhibitors.

Tumor-Related Epilepsy

Seizures are a common symptom for patients with diffuse infiltrative gliomas, occurring in approximately 30%–75%.[15] Prior to the current molecular classification, tumor-related epilepsy (TRE) risk was driven by the WHO grade with low-grade gliomas more commonly associated with seizures. Current understanding reveals the IDH mutation as a driver for TRE. Different from wtIDH, mIDH1 and mIDH2 reduce α-ketoglutarate to D-2-HG, contributing to a 10-100-fold increase of D-2-HG concentration in mIDH gliomas compared to wtIDH gliomas. D-2-HG is exported out of mIDH glioma cells where it increases neuronal excitation, leading to epileptic seizures.[16] Compared to patients with wtIDH gliomas, patients with mIDH gliomas are more likely to have seizures both as part of their initial presentation and postoperatively[17–21] Interestingly, time to seizure recurrence after clinical intervention (surgery, chemotherapy, or radiation therapy), is the shortest in astrocytoma mIDH, followed by glioblastoma wtIDH, and longest in oligodendrogliomas.[16] This timing is likely due to the responsiveness of oligodendrogliomas to chemotherapy and/or radiotherapy after surgery.

There are few studies evaluating responses to specific antiseizure medications (ASM) in relation to IDH genotype status.[22] In TRE, levetiracetam is the most commonly used ASM due to favorable efficacy, good tolerability, rapid therapeutic titration, and minimal drug–drug interactions.[23–26] However, mood disturbances are relatively common and are more frequently noted in patients with frontal lobe tumors and a history of depression and/or anxiety.[27,28] Additional first-line agents include valproic acid, lacosamide, lamotrigine, and zonisamide.[29–31] Enzyme-inducing ASMs (eg, phenytoin, phenobarbital, carbamazepine, and cenobamate) are often avoided due to potential drug–drug interactions (eg, lomustine and dexamethasone) as well as increased potential for drug toxicity.[32,33] In practice, monotherapy with another ASM should be attempted if the first ASM does not reduce seizure frequency. As more patients receive treatment with mIDH inhibitors, it is important to consider potential interactions with ASMs. Avoiding ASMs with similar mechanisms of action can avoid additive side effects. Generally, it is best to avoid coadministration of the mIDH inhibitors (ie, ivosidenib and vorasidenib) with strong or moderate CYP3A4 inducers (eg, phenytoin, carbamazepine, phenobarbital, and cenobamate) as this will decrease the concentration of the mIDH inhibitor. Clobazam is a potential add-on ASM when other ASMs are ineffective; however, fatigue and cognitive slowing may limit the ability to titrate to higher doses when needed.[34] Seizure freedom after surgery and adjuvant treatment is associated with longer progression-free survival in patients with grade 2 or 3 mIDH glioma.[35] In patients with stable mIDH glioma and long-term seizure freedom discontinuation of ASM can be discussed with the patient on a case-by-case basis.[32,36,37] Importantly, if seizures recur after a period of seizure freedom, reevaluation with imaging is warranted as seizure recurrence may portend tumor progression or malignant transformation.[38]

There have been 5 trials evaluating the safety of mIDH inhibitors, but seizure control was not studied as an endpoint. In these trials, seizures were reported as an adverse effect which was likely a consequence of having an mIDH tumor versus the effect of the drug.[9,10,39–41] While the INDIGO trial sought to evaluate seizure control as an exploratory endpoint, eligibility criteria did not allow patients to be on study if seizures were uncontrolled as defined by persistent seizures interfering with activities of daily living and failed 3 lines of ASM.[13] Thus, it is challenging to ascertain from this study if vorasidenib provides improved seizure control for this patient population. During this study's first 13 cycles of treatment, there was no difference in seizure frequency or utilization of ASM for patients on vorasidenib versus placebo. As the study matures, providers will benefit from continued analysis of seizure control for this patient group, including the patients who started vorasidenib after crossing over after tumor progression.

In practical experience with off-label ivosidenib in patients with mIDH1 glioma, 21 out of 25 patients (84%) on ivosidenib with seizures at baseline had a stable or improved seizure frequency.[12] This aligns with previous observations that ivosidenib is associated with a clinically

meaningful reduction in seizure frequency.[42,43] However, due to their retrospective nature and lack of a control arm it is unclear whether these data reflect the actual effect of ivosidenib or the natural course of the disease.

There is an assumption that control of tumors, including decreasing tumor volumes, should benefit seizure control, but this needs to be prospectively analyzed. Future studies of mIDH inhibitors should evaluate seizure control as a primary or secondary endpoint.[32,44]

Long-term use of mIDH inhibitors may result in durable tumor control, but results are still being investigated. Moreover, the use of an mIDH inhibitor may limit the use of some ASMs due to drug–drug interactions. From the lens of TRE, upfront treatment with a gross total resection is beneficial for patients from both an oncologic and epilepsy standpoint.[45,46] Additional initial treatment considerations may include temozolomide and/or radiation therapy in the appropriate patient population as this may be beneficial for seizures.[47]

Cognitive Dysfunction

Existing evidence suggests better inherent preservation of neurocognitive function (NCF) in patients with mIDH gliomas when compared to wtIDH gliomas.[48,49] A retrospective study evaluating presurgical neuropsychological function in glioma patients showed better performance on measures of learning and memory, processing speed, language, executive functioning, and dexterity in patients with mIDH tumors compared to wtIDH tumors.[50,51] Higher diffuse brain network connectivity, and thereby efficiency, is presumed to underlie improved NCF performance in mIDH patients with wtIDH patients experiencing more widespread disruptions of the neural networks by their tumors.[49,52] In addition, the slower growth associated with mIDH tumors may provide more opportunity for successful neural reorganization allowing in fewer cognitive deficits.[53] Despite overall better preservation of NCF compared to wtIDH tumors, mIDH patients do suffer neurocognitive decline over the course of their disease likely related to the tumor and treatment, including surgery, radiotherapy, and chemotherapy.

There is a clear risk to NCF with surgery due to direct injury to the brain and its interconnecting network. Preoperative and intraoperative techniques such as neuropsychological assessment, functional magnetic resonance imaging, Wada testing, and intraoperative mapping can be employed to help minimize cognitive morbidity. While gross total resection has been shown to improve survival in mIDH gliomas and possibly cognitive function, (attention, memory, and language) as seen in the postoperative period, there is no clear evidence linking the extent of resection to cognitive outcome after surgery.[54–56] Awake surgery does seem to have a positive effect on neurocognitive functions.[57]

Currently, adjuvant treatment for mIDH gliomas after surgery may include radiation therapy followed by PCV chemotherapy per Radiation Therapy Oncology Group (RTOG) 9802[58] protocol or temozolomide per CATNON/European Organization for Research and Treatment of Cancer (EORTC) 26053-22054 protocol.[8] A study of low-grade glioma patients treated with and without focal radiation therapy did show worse neurocognitive function in the radiotherapy group at 6 and 12 years.[59,60] This longitudinal study showed the progressive decline in function over time even with lower fraction doses (ie, ≤2 Gy).[60] In contrast, the 5-year follow-up data for RTOG 9802 showed that both the radiotherapy followed by PCV group, compared with radiotherapy alone group, showed improvements in cognitive function at 5 years.[61] Of note, in this trial cognitive functioning was only assessed with the Mini Mental State Examination, which is known to have sensitivity issues.

There is no clear data showing the independent detrimental effect of chemotherapy on NCF in glioma populations. A small-scale study ($N = 6$) suggests that neoadjuvant chemotherapy followed by resection in mIDH gliomas does not lead to major acute cognitive impairment.[62] As noted above, low-grade glioma patients from RTOG 9802 treated with both radiotherapy and chemotherapy did not show any worsening of NCF compared to the radiotherapy arm alone.[61] EORTC 22033-26033 compared radiotherapy to temozolomide monotherapy in low-grade gliomas and found no discernable difference in memory at 12 months.[63] The authors do note that it may take at least 5 years before a difference in NCF may be detected.

Indeed, cognitive deficits have a delayed onset in low-grade gliomas,[59,64–67] with radiotherapy linked to poorer executive functioning, information processing, and attention outcomes.[60] Yet, the magnitude of risk associated with late cognitive effects of radiotherapy treatment is uncertain.[68] Long-term neurocognitive data from seminal trials such as RTOG 9802 and CATNON/EORTC 26053-22054 are pending, especially with details in regards to the mIDH patients. Fewer long-term survivorship studies have looked specifically at the potential late consequences of chemotherapy treatment, making it difficult to draw conclusions about its impact on cognitive functioning outcomes.[68,69] Until we have those data, it is not clear if there is an advantage between early or delayed treatment with regard to late cognitive effects.

Newer treatments such as proton beam radiotherapy and mIDH inhibitors have emerged as therapeutic modalities to try to alleviate cognitive morbidity. Pediatric data[70,71] as well as studies with adult populations[72–74] have reported generally stable neurocognitive outcomes with proton beam radiotherapy, although cerebral radiation necrosis is more frequently observed in patients treated with protons compared to photons.[75] Shorter-term results of the INDIGO trial reported preservation of cognitive functioning during the median treatment duration of 14.2 months.[13]

Group-level findings on cognitive functioning as assessed with set test batteries in trials, are informative to gauge the potential impact of molecular markers or treatment strategies. For longitudinal follow-up of cognitive impairments in mIDH glioma patients (ie, >1 year), the use of digit span backward, semantic fluency, Stroop interference test, TMT B, and finger tapping is recommended.[76] However, these say little about individual patients' cognitive deficit profiles and the subsequent impact on everyday life activities. Clinical neuropsychological assessment remains pivotal and can help direct appropriate

(cognitive) rehabilitation services. However, the assessment of neurocognition beyond screening tests such as the Montreal Cognitive Assessment (MoCA) is challenging given the time and resources required.

Currently, brain-tumor-specific evidence suggests the benefits of cognitive retraining and compensation strategies, although study limitations such as heterogeneity of outcome measures, patient samples, and attrition limit establishing clear conclusions.[77,78] Similarly, the role of pharmacological strategies, such as stimulants, in the management of cognitive impairment remains unclear.[78,79] Determining the acute and long-term impact of treatment on glioma patients' cognitive functioning, as well as the extent to which cognitive rehabilitation strategies and/or pharmacological treatment can mitigate or prevent late effects remains a top research priority.

Mood Disorders

Mood disorders are characterized by sustained and abnormal changes in emotional state. These disorders are not uncommon in cancer patients with a 12-month prevalence of 13% following cancer diagnosis, and a 24% lifetime prevalence.[80] The quintessential mood disorder—major depressive disorder ("depression")—is defined by low mood and/or anhedonia manifesting for most of the day, occurring almost every day, and lasting at least 2 weeks.[28] The 6-month prevalence of depression in newly diagnosed glioma is estimated at 21%,[81] with a median point prevalence of depressive symptoms (a broader umbrella term encompassing results from various patient-reported questionnaires) of 27%.[82] Only inconsistent associations have been observed between predictive clinical variables and depression. Most risk factors for depression in glioma therefore remain incompletely understood, beyond a known association with poorer functional status.[82–84] Furthermore, most studies of depression in glioma did not differentiate between mIDH and wtIDH glioma. A recent small study found no statistically significant difference in the frequency of depressive symptoms between the molecular subtypes.[85] Consequently, there is no good evidence that IDH mutation status is associated with depression, but the question has not been definitively investigated.[82–84]

With the evolution of our understanding of the pathophysiology of depression, there may be a link with mIDH glioma. Traditionally, the monoamine hypothesis assumes that the pathology in depression is due to low levels of monoamine neurotransmitters in the brain (eg, serotonin and noradrenalin). Recent studies have demonstrated the potential involvement of glutamate in the pathology of depression.[86] Esketamine, an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, has emerged as treatment for depression.[87] Zhao et al. (2021) assessed racemic ketamine as potential treatment for depressive symptoms in a mixed sample of brain tumor patients in a placebo-controlled, double-blind randomized controlled trial (RCT) and showed a beneficial effect of ketamine on depressive symptoms. At postoperative day 3, 41% (17/41) of patients had a response (ie, ≥50% reduction in depressive symptoms compared to baseline) in the racemic ketamine group compared to 16% (7/43) of patients in the placebo group (relative risk [RR] = 2.51 [95% CI = 1.18–5.50]).[88] IDH mutations result in the accumulation of D-2-HG, which has the ability to act as an NMDA receptor agonist and can lead to dysregulation of glutamate metabolism.[89,90] It has been suggested that D-2-HG is downregulated in patients with depression during remission.[91] Therefore, pharmacological agents affecting the glutamatergic system and/or D-2-HG such as (es)ketamine and mIDH inhibitors might be promising strategies in depressed mIDH glioma patients by restoring glutamate homeostasis.

Several studies have reported depressive outcomes in patients treated with mIDH inhibitors. Ivosidenib was approved by the US Food and Drug Administration in 2018 for adult patients with refractory or relapsed acute myeloid leukemia. An open-label, phase I, dose-escalation and expansion study was conducted in 66 mIDH1 glioma patients to evaluate the safety and efficacy of ivosidenib. Depression as an adverse event occurred in 7 (11%) patients, but in none as a serious adverse event (grade ≥3).[39] However, with no placebo control group these numbers are difficult to interpret, and phase 3 trials in other cancer populations did not report depression as an adverse event.[92,93] In a phase 1 RCT comparing ivosidenib ($n = 25$) with vorasidenib ($n = 24$) in mIDH glioma patients depression as an adverse event occurred more often in ivosidenib (3 patients [12%] vs 0 patients [0%]), though none were grade 3 or above. Compared to ivosidenib, vorasidenib showed improved brain penetrance with more consistent suppression of D-2-HG.[41] In the recent INDIGO trial depression was reported in less than 10% of patients and none of events were severe.[10] Enasidenib, an mIDH2-inhibitor for adult patients with refractory or relapsed acute myeloid leukemia showed similar findings and depression was rare (≤10%) and never severe.[94,95] Several different clinical trials assessing the safety and efficacy of mIDH inhibitors are currently ongoing.[96]

The clinical management of depression in mIDH glioma is similar to that in patients without glioma. The main treatment strategies consist of self-management (eg, doing physical exercise, manage sleep), psychotherapy (eg, cognitive behavioral therapy), and pharmacotherapy.[97,98] Unfortunately, no RCTs have been conducted assessing antidepressant treatment of depression in glioma.[99] High levels of distress are associated with maladaptive coping strategies in patients with mIDH glioma, which could be addressed by cognitive behavioral therapy.[100]

Fatigue

Fatigue is one of the most common symptoms reported by cancer patients, especially when receiving chemotherapy, radiation therapy, or treatment with biologic drugs.[101] In patients with low-grade glioma, fatigue is a burdensome symptom that contributes to worse HRQoL. A systematic review of fatigue in patients with low-grade glioma estimated a prevalence of 39%–77% with a preponderance of mild-to-moderate fatigue, rather than severe fatigue.[102]

Recent studies with mIDH inhibitors reported fatigue outcomes which were similar across studies. In a phase

I trial with ivosidenib, fatigue was reported in 15/66 patients treated and was the most common symptom of any grade tumor.[39] A phase I trial with vorasidenib in patients with recurrent or progressive glioma, reported fatigue in 33% of participants.[40] In the perioperative trial comparing ivosidenib and vorasidenib, fatigue was more common in the vorasidenib arm (29%) compared to the ivosidenib arm (12%).[41] In a phase Ib/II study in mIDH1 glioma patients, patients that received olutasidenib reported fatigue in 50%, but none were classified as grade 2 or above.[9] Lastly, in the double-blind, placebo controlled phase 3 INDIGO trial with vorasidenib, fatigue was reported by 32% of patients on active treatment. This frequency was similar to that observed in the placebo arm (32%).[10]

These studies indicate that fatigue is a commonly reported symptom in patients taking mIDH inhibitors, but it is not clear how much is related to treatment or disease. At this point, there are a lack of studies utilizing multidimensional or validated fatigue-specific instruments to explore the association fatigue and use of mIDH inhibitors in glioma.

Treatment of fatigue in mIDH patients is similar to current standards of treatment for other cancer-related fatigue. Fatigue should be assessed routinely using a validated instrument.[103,104] Treatable causes should be identified. These may include sleep disturbances, pain, mood disorder, anemia, nutritional deficit, physical deconditioning, use of concomitant medications such as ASMs, and adverse effects of anticancer treatments such as endocrine dysfunction or infection.[104] Addressing reversible factors is paramount to improve fatigue and related functioning and well-being.[105,106] A multidisciplinary approach to treatment will be beneficial. Referral to rehabilitation can help address impairments in daily functioning.[107] In a small pilot RCT, patients with low-grade or anaplastic glioma receiving a home-based, remotely coached, aerobic training session of 20–45 min had less fatigue compared to the control group.[108] Trials evaluating pharmacologic treatment with psychostimulants such as methylphenidate, armodafinil, and modafinil have shown mixed results in patients with brain tumors.[109–111]

While extensive experience is missing, there is currently no signal to suggest that mIDH inhibitors influence fatigue in one way or the other. Future studies will explore fatigue in greater detail including longer follow-up and the use of validated fatigue scales.

Health-Related Quality of Life

Health-related quality-of-life (HRQoL) is a multidimensional construct that embodies the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.[112] In order to determine the net clinical benefit of a treatment strategy, HRQoL outcomes can be evaluated in clinical trials together with traditional outcomes such as progression-free and overall survival. In clinical practice, information on core symptoms and functions in daily life can be retrieved through regular HRQoL assessments, thereby guiding clinical decision-making. Validated HRQoL outcome measures include the EORTC Quality of Life core Questionnaire (QLQ)-C30 (30 items), the Functional Assessment of Cancer Therapy- Brain (FACT-Br) subscale (50 items), and the Short-Form-36 (SF-36) questionnaire (36 items). Symptom focused assessments include the EORTC Brain Cancer Module (QLQ-BN20) (20 items) and the MD Anderson Symptom Inventory Brain-Tumor Module (MDASI-BT) (28 items).[113] Other tools used in brain-tumor follow-up include the National Institute of Health developed patient-reported outcomes measurement information system system.[114] To address respondent burden we recommend to collect only a core set of symptoms and functional constructs, as previously proposed for high-grade glioma by the Response Assessment in Neuro-Oncology Patient-Reported Outcome (RANO-PRO) Working Group.[115]

Global HRQoL is significantly worse in low-grade glioma compared to healthy controls, although generally better than in patients with high-grade glioma.[14,116] Longitudinal studies in patients with low-grade glioma suggest that patients experience sustained HRQoL impairments at stable but low levels for an extended period of time.[14,117] Compared with healthy controls, patients with clinically stable low-grade glioma showed lower physical role functioning and general health at long-term follow-up.[117] After tumor resection, patients with mIDH glioma perform better on several symptom and functioning scales, compared to glioblastoma wtIDH.[118] Patients with mainly WHO grades 2–3 mIDH glioma who undergo adjuvant treatment with radiation therapy and/or chemotherapy show significantly lower scores on physical and cognitive functioning from 3–12 months after surgery when compared to patients treated with only observation.[14,119] Patients with clinically stable astrocytoma, mIDH, grade 2/3, and oligodendroglioma, mIDH, 1p/19q codeleted, grade 2/3, who reported subjective neurocognitive complaints had lower total HRQoL scores after treatment with combined radiotherapy and chemotherapy compared to patients who underwent surgery only.[116]

In addition, seizures as well as ASMs, impact HRQoL for patients with low-grade gliomas. When compared to patients without seizures, patients with a higher epilepsy burden are noted to have significant reductions in multiple neurocognitive domains which could be, in part, due to antiseizure medications.[120] However, ongoing seizures rather than the use of ASMs has been shown to have a significant impact on HRQoL in this patient population.[120] Furthermore, a higher epilepsy burden has been associated with worse psychological well-being and worse social functioning.[14]

Although adverse effects, like fatigue, headache, diarrhea, and liver transaminase elevations, are reported in patients on mIDH inhibitors, these adverse effects are generally mild and reversable through adequate medication management.[10] Thus far, there are no clear reported negative effects of mIDH inhibitors on HRQoL in contrast to glioma patients treated with radiotherapy and/or chemotherapy. These patients show a transient worsening on several HRQoL symptom and function scales the first months after initiation of treatment. The INDIGO trial showed consistently high HRQoL scores up to one year in the vorasidenib and placebo arm, both in terms of the total HRQoL scores, and scores on the brain cancer subscale and functional well-being.[13]

Similar favorable results from mIDH inhibitors are found in patients with non-central nervous system cancer. In an RCT comparing ivosidenib to placebo in patients with advanced mIDH cholangiocarcinoma, HRQoL results tended to favor ivosidenib, with preservation of physical and emotional functioning compared to the placebo group.[93] Another trial compared enasidenib to conventional treatment in older patients with late-stage mIDH2 relapsed acute myeloid leukemia and showed worsening HRQoL in both treatment arms during the early cycles. However, these results should be interpreted with caution as HRQoL data were missing at baseline and/or follow-up in 50% of the patients in the conventional treatment arm, and in 25% in the enasidenib arm.[121] Another study of patients with newly diagnosed mIDH1 acute myeloid leukemia patients on ivosidenib combined with azacitidine showed better scores on all HRQoL symptom and functioning scales in the ivosidenib and azacitidine arm compared to patients on placebo plus azacitidine.[92]

Long-term survivorship becomes more meaningful to patients if there is preservation of functioning and well-being. By increasing progression-free survival, mIDH inhibitors may postpone the physical and global health deterioration, as measured by HRQoL scales, when the tumor progresses.[122,123] In addition, mIDH inhibitors may significantly prolong the time to deterioration in HRQoL, especially in regards to neurocognitive function, by delaying long-term neurotoxicity associated with radiotherapy. Although the first results of the efficacy and safety of mIDH inhibitors in patients with mIDH glioma point towards preservation of relatively high levels of HRQoL, the long-term effects of being on chronic mIDH inhibitors are still unknown. Coping with long-term medication use as well as polypharmacy is known to be burdensome for patients, particularly in terms of physical functioning.[124] To establish whether improved progression-free and overall survival is reflected in prolonged well-being on the long-term, it remains critical to consider other measures including HRQoL symptom and functioning subscales, both in clinical trials and clinical practice.[115,125]

Caregiver Needs

Family members or friends who provide physical and emotional support to glioma patients cope with the inherent difficult aspects of cancer (sudden diagnosis, aggressive treatment, and adverse effects) and the progressive neurological condition (eg, cognitive dysfunction, epilepsy, and changes in behavior). The dual burden of this disease is highlighted by worse HRQoL in caregivers of brain-tumor patients than those of patients with other systemic cancers.[126,127] Caregivers to glioma patients with or without mIDH can experience high levels of distress throughout the disease trajectory.[128] Higher levels of neuro-oncology caregiver distress have been linked to younger patient age,[129] worse functional status,[130] and poorer cognitive functioning.[131]

Caregiver and patient well-being are interdependent, with patients and caregivers influencing each other's mental and physical health.[132–134] In this light, support to caregivers is crucial not only to prevent caregiver strain and their eventual need for professional care, but also to allow them to support the patient even during long-term survivorship. Caregiver supportive care may improve coping and reduce psychological distress; both of which may benefit both patients and the caregiver. Support may include provision of information on patient treatment and disease-induced changes, adaptive strategies for social and work life, and psychological support.[135] Peer support groups, supportive educational interventions, including telemedicine interventions, can validate and support caregivers.[136] Unfortunately, the variability in reported outcomes amongst studies looking at effective supportive interventions for caregivers hampers widespread availability in clinical practice.[137–140] Furthermore, prospective high-quality intervention studies are needed.

As noted above, mIDH glioma patients also experience issues related to HRQoL and cognitive dysfunction. While the burden and distress reported in caregivers of patients with low-grade glioma are typically milder than in those caring for high-grade glioma patients, caregivers still report high levels of fatigue throughout low-grade glioma patient survivorship, even in the absence of impaired caregiver HRQoL.[127,141]

It is clear that the needs of caregivers of patients with mIDH gliomas need to be elucidated and defined. With mIDH inhibitors potentially delaying the need for other tumor-directed therapies such as radiotherapy and/or chemotherapy, it is pivotal to understand the downstream effects on long-term patient symptom burden and the translational effects on the caregiver. If mIDH inhibitors lead to for example, fewer late cognitive effects, and better seizure control compared to other anticancer treatments, we expect and hope that there will be a correlative improvement in caregiver well-being.

Conclusion

Advances in molecular research have resulted in an updated understanding of the underlying pathology and molecular drivers of brain-tumor development and progression.[142] The discovery of IDH mutation in glioma and its impact on tumor behavior, has not only changed how gliomas were re-classified in the 2021 WHO tumor classification for CNS tumors, but is also reshaping clinical care for this patient population. The clinical implications of these most recent findings are just emerging with the development of IDH targeted therapies. Clinically, patients with mIDH glioma tend to be younger (age below 50 years) and have a different disease trajectory defined by prolonged survival and symptom clusters that are distinctly different when compared to wtIDH glioma. Patients have a much higher frequency of tumor-related epilepsy and are more susceptible to cognitive impairment and fatigue induced by both tumor and treatment. Symptoms caused by tumor, surgery, radiation, and chemotherapy often cause deficits that affect patients' HRQoL and their ability to participate in society for years to come. The arrival of new medical therapies in form of mIDH inhibition might therefore have tremendous implications on symptom management. mIDH inhibitors not only promise increased progression-free survival but also raise the hope that patients will live longer and better by avoiding toxicities during the earlier stages

Table 1. Recommendations on General Symptom Management for Patients With mIDH Glioma, and Specifically for Glioma Patients Who Are Eligible for mIDH Inhibitors

Symptoms and issues	General recommendations	Specific recommendations for patients eligible for mIDH inhibitors
Tumor-related epilepsy	Levetiracetam is preferred and most commonly prescribed as first-line ASM, due to its efficacy and generally good tolerability. Additional first-line agents include lacosamide, lamotrigine, or zonisamide. Enzyme-inducing ASMs should be avoided, as well as ASM prophylaxis in patients without epilepsy.	Avoid coadministration of mIDH inhibitors with strong or moderate CYP3A4 inducers (eg, phenytoin, carbamazepine, phenobarbital, cenobamate as this will decrease the concentration of the mIDH inhibitor)
Cognitive dysfunction	Gross-total resection and awake surgery seem to have a positive effect on several neurocognitive domains. Patients may benefit from cognitive retraining and compensation strategies. There is inconclusive evidence for pharmacological interventions.	Despite preservation of cognitive functioning on the short-term in patients on mIDH inhibitors, routine clinical neuropsychological assessment is recommended and can help direct to appropriate cognitive rehabilitation services.
Mood disorders	No specific (non-)pharmacological interventions are recommended. Main treatment strategies consist of self-management (eg, doing physical exercise, manage sleep), psychotherapy (eg, cognitive behavioral therapy to reduce mental distress), and pharmacotherapy. Physicians should screen for endocrinopathies and medications that might provoke depressive symptoms (eg, corticosteroids, certain ASMs).	No specific additional recommendations.
Fatigue	Non-pharmacological interventions (eg, aerobic training sessions, cognitive behavioral interventions) might improve fatigue. There is inconclusive evidence for any specific pharmacological interventions.	No specific additional recommendations.
Health-related quality of life	Routine assessment of patient's HRQoL including symptom scales of the most common symptoms, as well as functioning scales, at least including physical and role functioning, is recommended.	No specific additional recommendations.
Caregiver needs	Caregivers can be supported by providing information on patient treatment and disease-induced changes, coping strategies for social and work life, and psychological support. Interventions may include the use of peer support groups, educational interventions or telemedicine interventions.	Caregivers may benefit from continuously active engagement by health care professionals, as the long-term implications for symptom burden in patients on mIDH inhibitors are currently unknown.

ASM, antiseizure medication; mIDH, isocitrate dehydrogenase mutant; HRQoL, health-related quality of life.

of the disease. In addition, by targeting the underlying molecular mechanism, new therapies might not only have direct impact on symptoms such as seizures but also might result indirectly in improved long-term effects on HRQoL. We provide recommendations for practicing healthcare professionals caring for patients with mIDH glioma, and specifically for patients who are eligble for mIDH inhibitors (Table 1). An important aspect that will require further investigation is the psychological and financial impact on patients' lives when possibly being on life-long drugs to prevent disease progression. Further long-term studies are needed to determine the full impact of this new class of therapies on patients' symptoms as well as their families' and caregivers' quality of life.

Keywords

epilepsy | glioma | IDH inhibitor | quality of life | symptom management

Conflict of interest statement

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