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Practical management of patients with IDH-mutant glioma in the coming era of mIDH inhibitors: New drugs, new evidence, new guidelines, and new considerations

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With the World Health Organization (WHO) in 2016 and then in 2021 solidifying diagnostic guidelines for adult diffuse glioma around the presence or absence of mutations in the isocitrate dehydrogenase (IDH) gene, neuro-oncology providers can give cogent prognostication to glioma patients.[1,2] Generally, patients with mIDH gliomas have a better prognosis when compared to their counterparts who have IDH-wild-type gliomas. Traditionally, patients with gliomas, irrespective of IDH genotype status, were treated with the same tools: Surgery, radiation therapy, and cytotoxic chemotherapy. Knowledge of the IDH mutation and how the mutant enzyme was responsible for gliomagenesis via the production of oncometabolite 2-hydroxyglutatarate (2-HG) opened the possibility of targeted therapies. The success of targeted agents in other cancers that harbor mIDH provided the framework to bring this approach to patients with mIDH gliomas. Where other targeted therapeutics failed in gliomas, in particular glioblastoma, orally available mIDH inhibitors such as ivosidenib, vorasidenib, olutasenib, and safusidenib appeared promising in selected patients with mIDH glioma (Table 1). With the results from the pivotal phase III trial of vorasidenib versus placebo in patients with mIDH low-grade glioma (WHO grade 2), targeting mIDH has emerged as an opportunity beyond traditional treatments such as surgery, radiation therapy, and cytotoxic chemotherapy.[4] In August 2024, vorasidenib received FDA approval to treat patients with mIDH low grade glioma (WHO grade 2). Time will tell when vorasidenib will be approved and available in Europe and worldwide. We need to understand the practicalities of how, when, and on whom to use mIDH inhibitors. Given the implication that this type of therapy is presumed to be utilized in a long-term manner, how to manage this globally, financially, and holistically must be addressed.

Goals of This Supplement

The *Neuro-Oncology Practice* (*NOP*) editorial team invited two editors, one representing the Society of Neuro-Oncology (SNO) and European Association of Neuro-Oncology (EANO), to provide practical evidence, guidance, and reflection on the use of mIDH inhibitors in patients with mIDH glioma. Assigned supplement editors developed the topics and invited author leadership for each manuscript. Leaders for each manuscript were encouraged to enlist interprofessional, multidisciplinary teams from SNO and EANO to craft the following five manuscripts: *Who Will Benefit From Vorasidenib? Review of Data from the Literature and Open Questions, How Do I Prescribe and Manage mIDH Inhibitors in Patients with IDH-Mutant Glioma, Symptom Management in IDH-Mutant Glioma, Role of the Tumor Board When Prescribing mIDH Inhibitors to Patients with IDH-Mutant Glioma, and Financial Challenges of Being on Long-Term Medications.* Unique to this supplement is the development of a *Patient and Caregiver Information Sheet* for vorasidenib. It is key to note that the tone of this supplement, along with its associated manuscripts and accompanying patient and caregiver information sheet, aims to be practice-driven and patient-centric.

Summaries of Highlights of Invited Manuscripts and Patient and Caregiver Information Sheet

Targeting the Right Person, Right Time, and Right Scenario for Using mIDH Inhibitors

The first manuscript in this supplement, entitled "Who Will Benefit From Vorasidenib? Review of Data from the Literature and Open Questions," *led my Darlix and Taylor,* gives the reader an overview of the current evidence for the use of mIDH inhibitors for patients with mIDH glioma in the context of prior norms and guidelines in the treatment of these patients, in particularly low-grade glioma. Before the pivotal phase III study of vorasidenib versus placebo in patients with mIDH glioma

Table 1: Orally Available mIDH Inhibitors and Key Clinical Trials in mIDH Gliomas

Drug name	Target	Important clinical trials in mIDH glioma
Ivosidenib	Mutant IDH1	Ivosidenib in Isocitrate Dehydrogenase 1—Mutated Advanced Glioma[3] Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: a randomized, perioperative phase 1 trial[4]
Vorasidenib	Mutant IDH1 and IDH2	Vorasidenib, a Dual Inhibitor of Mutant IDH1/2, in Recurrent or Progressive Glioma; Results of a First-in-Human Phase I Trial[5] Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: a randomized, perioperative phase 1 trial[4] Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma[6]
Olutasidenib	Mutant IDH1	Olutasidenib (FT-2102) in patients with relapsed or refractory IDH1-mutant glioma: A multicenter, open-label, phase Ib/II trial[7]
Safusidenib	Mutant IDH1	The first-in-human phase I study of a brain-penetrant mutant IDH1 inhibitor DS-1001 in patients with recurrent or progressive IDH1-mutant gliomas[8]

(INDIGO), treatment paradigms for low-grade were informed by EORTC 22845, phase III study randomizing low-grade glioma patients to early versus delayed radiation therapy, RTOG 9802, phase lil study randomizing low-grade glioma patients to radiation therapy alone versus radiation therapy with procarbazine, lomustine, and vincristine (PCV),[9,10] or extrapolation of the results of the EORTC 26053 -22054 (CATNON) phase III study, randomizing patients with 1p/19q non-co-deleted anaplastic glioma 1:1:1:1 to radiotherapy alone, radiotherapy with concurrent temozolomide chemotherapy, radiotherapy with adjuvant temozolomide, or radiotherapy with both concurrent and adjuvant temozolomide. The first studies did not benefit from knowing the prognostic significance of IDH genotype status. With the results of INDIGO study and the prognostic power of the IDH genotype, there is an opportunity to reevaluate how glioma patients are treated. In this first manuscript, three questions are posited in this article.[4] They include (1) who may benefit from mIDH inhibition based on tumor grade, tumor biology, and/or radiographic appearance of disease (non-enhancing vs. enhancing), (2) when mIDH inhibitors should be considered during the patient journey, whether alone or in combination with other therapies such surgery, radiation therapy, and chemotherapy, and (3) how to manage these drugs in terms of duration of use and assessment of therapeutic response. These questions are likely on the minds of neuro-oncology providers, researchers, patients, and caregivers. Moreover, these questions will drive the next stage of research to give much-needed answers.

Practical Guidance on How to Prescribe These Medications: What Providers Need to Know

The audience for the second article entitled "*How Do I Prescribe and Manage mIDH Inhibitors in Patients with IDH-Mutant Glioma"* includes all neuro-oncology providers that are currently or will prescribe and manage patients receiving mIDH inhibitors. This manuscript led by Berghoff and Leung details dosing considerations for vorasidenib and ivosidenib, recommendations for monitoring adverse events/side effects, and contraindications before prescribing, and known drug–drug interactions. Because the median age of diagnosis for patients with low-grade glioma is roughly 43–46 years of age, questions about fertility and pregnancy are appropriate to posit.[11] Little is known about the impact that these mIDH inhibitors have on fertility (both male and female), fetal health/outcomes, or lactation, but it is critical to highlight these concerns with patients before they initiate therapy. Given the novelty of these agents, this manuscript promises to be a valuable resource to providers that manage mIDH glioma patients. Moreover, it will hopefully provoke further clinical exploration and future understanding of clinical outcomes in this unique patient population.

Practical Guidance on How to Take These Medications: What Patients and Caregivers Need to Know

For this supplement, we, the invited editors, believe that providing practical support to neuro-oncology providers and, more importantly, practical advice for patients and caregivers was critical. Led by Dr. Mallika P. Patel, a clinical pharmacist practitioner, a team of neuro-oncology providers, advocates, and patients, developed a "Patient and Caregiver Information Sheet" for vorasidenib based on the outcomes published from the INDIGO study.[4] This sheet, made available to neuro-oncology providers, can be given to patients and caregivers when considering and initiating vorasidenib. Components of the sheet are background information, medication diaries, advice on how to take the medication, handling the medication, side effects, and reproductive considerations. Given the patient-centric tenor of this supplement and the NOP journal, we hope this type of publication will be adopted when new medications come to market.

Tumor Board for IDH-Mutant Glioma Patients: Role Induction in Context of mIDH Inhibitors

Tumor boards are essential for managing patients with IDH-mutant gliomas due to their complex nature and varied treatment options and give multidisciplinary expertise to tailor comprehensive treatment plans for each

patient. In the article by Roth and colleagues entitled "Role of the Tumor Board When Prescribing mIDH Inhibitors to Patients with IDH-Mutant Gliomas," the multidisciplinary panel of authors integrates each of their subspeciality expertise in neuro-oncology, neurosurgery, neuropathology, radiation oncology, and neuroradiology in context of new clinical results with mIDH inhibitors. Moving forward, the opinions of each subspeciality will need to be considered not only in regard to mechanisms of treatment (eg, surgery, targeted therapies, radiation therapy, and chemotherapy) but also in the importance of determining IDH genotype status by neuropathology and by correct evaluation of imaging for progression by neuroradiology. This collaborative approach ensures that treatment plans are personalized, considering each patient's specific clinical picture, molecular profile, and goals of care. This multidisciplinary, interprofessional coordination is crucial in navigating the complexities of IDH-mutant glioma management and optimizing patient outcomes and quality of life.

Managing Symptoms in Patients Receiving mIDH Inhibitors

The manuscript was led by Drs. Koekkoek and Walbert entitled "Symptom Management in IDH Mutant Glioma" highlights caring for patients with mIDH glioma involves not only treating the "cancer" but also treating "the patient." Particular symptoms associated with mIDH glioma patients are seizures, cognitive dysfunction, mood disorders, and fatigue. The etiology of these symptoms is often attributable to underlying disease, commonly used concomitant medications such as corticosteroids and anti-seizure medications, and effects of treatments (surgery, radiation therapy, and chemotherapy). Now we have to consider these symptoms in the context of using mIDH inhibitors. While patients enrolled in the INDIGO study were required to have measurable disease radiographically (>1 cm non-enhancing disease on FLAIR/T2 imaging), eligibility requirements restricted enrollment of patients with a poor functional status, worsening neurologic symptoms, or uncontrolled seizures.[4] Therefore, while evaluation of quality of life, cognitive, and seizure activity was assessed in the INDIGO study, the only initial conclusions, because patients were highly functional and neurologically doing well, were that patients did not experience a decrement in quality of life, cognitive function, or seizure control regardless of randomization to placebo or vorasidenib.[12] Future studies and continued reports of symptom/quality of life outcomes need to be published and discussed as the utilization of mIDH inhibitors becomes more commonplace.

Financial Considerations of Long-Term Use of mIDH Inhibitors

The last manuscript "Financial Challenges on Being on Long-Term Medications" by senior author Budhu and colleagues, focuses on the intricacies of what it will mean for patients and the entire global healthcare system to support the financial long-term use of mIDH inhibitors in this patient population. This article first considers how medications are approved, priced, and paid for globally. Next, the authors explore what having a "cost-effective" medication means. The cost of implementing clinical trials across its many phases continues to grow, along with the cost of healthcare topping around $1.3 trillion globally.[13] Given the projected treatment duration pattern of mIDH inhibitors to be a long-term use medication, how will neuro-oncology providers, patients, and caregivers contend with these financial challenges? Time will tell what this financial impact will be for our patients and how the healthcare system, approval agencies, and insurance companies adapt to implementing these agents.

Conclusions

The addition of mIDH inhibitors to the treatment arsenal for patients with mIDH glioma is practice-changing for all neuro-oncology providers. This supplement hopes to provide the evidence and clinical guidelines as we embark on this journey with our patients and their caregivers. Moreover, as invited editors, we give some answers and practical guidance along with bringing forward future questions, future directions for research, and future considerations, both holistically and globally.

Keywords

glioma | inhibitor | isocitrate dehydrogenase | mutant

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