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How do I prescribe and manage mIDH inhibitors in patients with IDH-mutant glioma?

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Abstract

Recent interest has been in using mIDH inhibitors in patients with IDH-mutant gliomas. This review paper summarizes the indications, side effects, recommended dosing, and management for patients on ivosidenib and vorasidenib.

Key Points

- Summarizes indications for use and side effects of ivosidenib and vorasidenib in glioma.
- Recommendations for dosing and monitoring.

Background

Targeted therapy with mIDH (mutant isocitrate dehydrogenase) inhibitors is currently under investigation for use in patients with IDH-mutant gliomas. Ivosidenib, an oral inhibitor of mIDH1, is currently approved in the United States by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of adults with IDH1-mutant acute myeloid leukemia, myelodysplastic syndrome, and bile duct cancer.[1–3] Orphan status of ivosidenib for patients with mIDH1 glioma was designated in the United States starting May 2018 and has been adopted in off-label use in the United States.[4] Vorasidenib was recently investigated in a phase III trial in IDH-mutant grade 2 gliomas,[5] and, in part, based on significant improvement in progression-free survival (PFS) and favorable side effect profile, was granted accelerated assessment for approval in this patient population by both the FDA and the EMA.[6] It has now been approved by the FDA for patients "12 years and older with grade 2 astrocytoma or oligodendroglioma with susceptible IDH1 or IDH2 mutation following surgery including biopsy, sub-total resection, or gross total resection."[7]

What to Consider When Starting and Managing an IDH Inhibitor

Ivosidenib

There are no absolute contraindications for ivosidenib. The FDA and EMA recommended dose of ivosidenib for AML and biliary tract cancer is 500 mg daily.[3,8]

Ivosidenib should not be crushed, split, or chewed, so caution is recommended in patients who struggle with swallowing. Ivosidenib should also not be taken with a high-fat meal, as this has been shown to alter pharmacokinetics.[8,9]

Adverse Events

Two phase 1 studies evaluated the safety of ivosidenib in glioma patients.[10,11] The most common observed adverse effects of ivosidenib in these studies were diarrhea (17%–28%), headache (36%–40%), nausea (23%–24%), vomiting (20%), elevated creatine kinase (34%), fatigue (12%–23%), hyperglycemia (15%–20%), hypophosphatemia (11%), paresthesia

(11%–12%), seizures (18%) and prolonged QTc (12%–17%). Most treatment-related AEs were grade 1 or 2. Grade ≥3 events included headache (5%), seizures (3%), hyperglycemia (2%), and decreased phosphate levels (3%).[10,11] Seventeen percent of patients in a retrospective cohort study required dose reduction to 250 mg ivosidenib daily (Table 1).[4] Notably, patients enrolled in this study had recurrent mIDH glioma and based on these phase 1 findings, it was determined that ivosidenib was very well tolerated without unexpected neurological toxicity. Similar grade I adverse effects for diarrhea (26.7%), elevated creatine kinase (33.3%), and prolonged QTc (16.7%) were reported in real-world, off-label use in patients with IDHm gliomas grades 2–4.[4]

Additional toxicities occurred in patients with non-glioma cancer types. In lymphoma and AML, further side effects included anemia (12%–60%), hyperbilirubinemia (4%), jaundice, pleural effusion (3%–13%), neuropathy/Guillian-Barré Syndrome (11%–14%), myalgia (18%–25%), arthralgia (6%–36%), rash (2%–26%) and insomnia (7%).[8,12,13] A dreaded complication of AML patients receiving ivosidenib is differentiation syndrome which may occur in 11%–25% (grade ≥3 events in 5%–13 %).[13,14] It is important to note that differentiation syndrome has not been noted in glioma patients treated with ivosidenib.

Data from patients with locally advanced or metastatic cholangiocarcinoma revealed a similar toxicity profile with adverse effects of fatigue, nausea, diarrhea, abdominal pain, cough, anemia, and peripheral neuropathy. Laboratory abnormalities include aspartate aminotransferase, increased bilirubin, and anemia. Serious adverse reactions occurred in 34% of patients receiving ivosidenib, including more than 2% who experienced pneumonia, ascites, hyperbilirubinemia, and jaundice.[2,12]

Monitoring and Managing Adverse Events

Vomiting and diarrhea are typically not intolerable, but it is important to ensure patients can maintain adequate nutrition, hydration, body weight, and mobility, particularly in the elderly or frail populations or those with neurologic deficits.

It is also important to obtain a baseline complete blood count, chemistries, and electrocardiogram (ECG) prior to starting ivosidenib. Providers should obtain an ECG weekly for the first 3 weeks of treatment and then monthly thereafter (Table 2) and routinely throughout treatment. Blood work should also be monitored at least weekly during the first month of therapy, once every other week during the second month, and monthly thereafter. Monitoring electrolytes and ECGs for QTc prolongation is recommended, and decreasing or withholding doses if interval prolongation occurs.[8] Although rare, if Guillain-Barre syndrome occurs, treatment should be discontinued permanently.

Dosing should be decreased in patients taking other CYP3A4 inhibitors such as clarithromycin, diltiazem, ketoconazole, ritonavir, verapamil, and grapefruit. Ivosidenib should not be used in those taking strong CYP3A4 inducers such as phenobarbital, phenytoin, rifampicin, and glucocorticoids or sensitive CYP3A4 substrates such as acetaminophen, codeine, ciclosporin, diazepam, erythromycin, and chloroquine. Due to the risk of QTc prolongation, caution should be taken when prescribing ivosidenib concomitantly with other interval-prolonging drugs.[8] While there are no known absolute contraindications for ivosidenib, those with pre-existing arrhythmias, congestive heart failure, electrolyte abnormalities, or those taking medications known to prolong QTc interval or affect CYP3A4 enzymes should be more closely monitored.[8]

Table 1. Management of Adverse Events From Ivosidenib[3,4,8]

	Recommended action	Recommended monitoring
Prolonged QTc > 480 msec	Hold ivosidenib. Monitor and supplement electrolyte levels as clinically indicated. Review and adjust concomitant medications with known QTc interval-prolonging effects. Resume ivosidenib at 500 mg once daily after the QTc interval returns to ≤480 msec.	Monitor ECG at least weekly for 2 weeks following resolution of QTc prolongation.
Prolonged QTC > 500 msec	Hold ivosidenib. Monitor and supplement electrolyte levels as clinically indicated. Review and adjust concomitant medications with known QTc interval-prolonging effects. Resume ivosidenib at a reduced dose of 250 mg daily when the QTc interval returns to within 30 msec of baseline or ≤480 msec. Following the resolution of QTc prolongation, consider re-escalating the dose of ivosidenib to 500 mg daily if an alternative etiology for QTc prolongation can be identified.	Monitor ECG at least weekly for 2 weeks or until resolution.
QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue ivosidenib.	Monitor ECG at least weekly until resolution.
Guillain-Barré syndrome	Permanently discontinue ivosidenib.	

ECG, electrocardiogram.

Table 2. Recommended Interval Monitoring While on Ivosidenib[4,8]

Parameters to follow	Interval
Low-grade glioma follow-up	
MRI of the brain with and without contrast	Every 3 months for 3 years then every 6 months
Minimum required follow-up for adverse events in patients with mIDH low-grade glioma	
White blood cell count	Weekly for month 1, every other week during month 2, and monthly thereafter
Creatine kinase	Weekly for month 1, every other week during month 2, and monthly thereafter
ECG	Weekly for the first 3 weeks, then monthly

ECG, electrocardiogram; mIDH, mutant isocitrate dehydrogenase.

Pregnancy and Lactation

Preclinical data indicate that ivosidenib may cause birth defects or infertility; However, human data is lacking.[8] Its transmission in breast milk has not been well studied, but the manufacturer does not recommend breastfeeding while on treatment with ivosidenib, and for at least 1 month after discontinuation as its half-life is 93 hours and there is the potential for accumulation in the breastfeeding infant.[15]

Vorasidenib

This medication has been of considerable interest to patients with IDH-mutant gliomas even prior to its recent FDA approval. Although not explicitly mentioned in the prescribing information, it is still important to note that a phase I trial showed that it may be more helpful in non-enhancing tumors.[11]

Similarly to ivosidenib, there are no known absolute contraindications for vorasidenib. The recommended dose of vorasidenib in glioma patients is 40 mg daily, and this was the dose used in the phase III INDIGO trial.[5] Doses of more than 100 mg led to the dose-limiting toxicity of elevated liver transaminases, which resolved or improved to a lower grade by dose reduction. Thus, a favorable tolerable dose was felt to be less than 100 mg daily.

Adverse Events

The most common adverse effects with dosages of 10 to 400 mg daily in early glioma trials included headache (41%–46%), fatigue (29%–33%), insomnia (21%), diarrhea (15%–29%), nausea (33%–41%), vomiting (19%), dizziness (17%), seizure (29%), neutropenia (13%–17%), cough (15%), anemia (17%), hyperglycemia (13%–19%), hypoglycemia (11%–13%), abdominal pain (17%), memory impairment (17%), tinnitus (13%), upper respiratory tract infection (11%–13%), weight loss (13%), aura (13%), aphasia (12%), constipation (17%–21%), hypocalcemia (13%), hypophosphatemia (13%), and liver enzyme increases (17%–44%).[11,16]

Approximately 17%–19% of glioma patients and 46% of patients with non-glial tumors experienced grade ≥3 adverse events, which most frequently involved liver damage and seizures.[11,16] Approximately 4%–9% of patients taking vorasidenib in trials had to discontinue due to intolerable side effects (Table 3).[16] In the INDIGO trial, 29.9% of patients in the vorasidenib arm had to interrupt their treatment for transient side effects, 10.8% had a dose reduction of vorasidenib and 3.6% had to discontinue vorasidenib treatment because of these.[5]

Monitoring and Managing Adverse Events

Providers should obtain liver function tests every other week for the first 2 months and monthly thereafter for interval monitoring.[5] A contrasted MRI brain every 3 months for the first 3 years, then every 6 months thereafter is also recommended for follow-up of patients with low-grade glioma (Table 4). There is minimal data available about the long-term use of vorasidenib in glioma patients or other tumor types. In the INDIGO trial, treatment was continued until disease progression or unmanageable adverse events.

Patients taking vorasidenib should avoid concomitant use of other medications that strongly or moderately inhibit or induce enzyme CYP1A2.[7] Some common examples of these medications include phenytoin, rifampin, ciprofloxacin, vemurafenib, and fluvoxamine.[17] Note that smoking tobacco is a moderate CYP1A2 inducer and should also be avoided. Caution is advised with concomitant use of medications that are CYP3A substrates if steady concentrations are necessary for clinical efficacy. It is also possible that hormonal contraception may be less effective while on vorasidenib because of moderate CYP1A2 inhibition.[7]

Pregnancy and Lactation

Data are lacking for vorasidenib in pregnancy or lactation. Studies cited in the Voranigo package insert indicated that there was fetal harm in animal models.[7] Given the paucity of published data, it is advised that female patients should not get pregnant nor breastfeed during treatment with vorasidenib. Additionally, male patients

Table 3. Management of Adverse Events From Vorasidenib[5]

	Recommended action	Recommended monitoring
Elevated ALT or AST without elevated bilirubin		
Grade 1 (>ULN-3.0× ULN) if the baseline was normal/1.5–3.0× baseline if the baseline was abnormal	Continue vorasidenib. Investigate for alternate causes.	Monitor LFT weekly until stabilized.
Grade 2 (>3.0–5.0× ULN) if the baseline was normal/>3.0–5.0 baseline if the baseline was abnormal	First occurrence: Hold vorasidenib. Investigate for alternative causes. Second occurrence: If grade 2 elevation recurs and no alternative cause has been Identified, hold vorasidenib until resolution to baseline or grade ≤1, and reduce vorasidenib to 20 mg daily (50%). Third occurrence: If grade 2 elevation recurs despite dose reduction and no alternative cause has been identified, hold vorasidenib until resolution to baseline or grade ≤1, then reduce vorasidenib to 10 mg daily. Fourth occurrence: If elevation persists, discontinue vorasidenib.	Monitor LFT per institutional guidance until resolution, or according to the following parameters: Repeat LFT (ALT; AST; total, direct, and indirect bilirubin; alkaline phosphatase; GGT) within 3 days of initial elevation and at least 2 times weekly until stabilization.
Grade 3 (>5.0–20.0× ULN if baseline was normal; >5.0–20.0× baseline if baseline was abnormal)	First occurrence: Hold vorasidenib. Investigate for alternate causes. Resume vorasidenib at 20 mg daily when resolution to baseline or grade ≤1. Second occurrence: In the absence of an alternative cause, discontinue vorasidenib.	Monitor LFT per institutional guidance until resolution, or according to the following parameters: Repeat LFT (ALT; AST; total, direct, and indirect bilirubin; alkaline phosphatase; GGT) within 3 days of initial elevation and at least 2 times weekly until stabilization.
Elevated ALT or AST with elevated bilirubin		
Grade 2 or 3 (>3.0–20.0× ULN if baseline was normal; >5.0–20.0× baseline if the baseline was abnormal) ALT or AST with elevated total bilirubin ≥2 × ULN	First occurrence: Hold vorasidenib. Investigate for alternate causes. If an alternate cause is identified, treated, and ALT, AST, bilirubin levels resolve to grade ≤1, consider rechallenge at 20 mg daily (50%). Permanently discontinue vorasidenib if no alternative cause can be identified or if there is a second occurrence after rechallenge.	Monitor LFT per institutional guidance until resolution, or according to the following parameters: Repeat LFT (ALT; AST; total, direct, and indirect bilirubin; alkaline phosphatase; GGT) within 3 days of initial elevation and at least 2 times weekly until stabilization.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; LFT, liver function test; ULN, upper limit of normal.

Table 4. Recommended Interval Monitoring While on Vorasidenib[5]

Parameters to follow	Interval
Low-grade glioma follow-up	
MRI of the brain with and without contrast	Every 3 months for 3 years then every 6 months
Minimum required follow-up for adverse events in patients with mIDH low-grade glioma	
LFT (ALT, AST, GGT, alkaline phosphatase, total, and direct bilirubin)	Every other week for the first 2 months, then monthly for the first 2 years, and as indicated clinically

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; LFT, liver function test; mIDH, mutant isocitrate dehydrogenase.

should not impregnate their partners while on vorasidenib. Providers should counsel patients about these pregnancy-related issues before initiating treatment with vorasidenib. Additionally, as noted above, vorasidenib may alter the efficacy of some hormonal contraception, so this should also be explicitly discussed with patients, and women of childbearing age are recommended to use non-hormonal contraceptives throughout therapy.[7]

Other mIDH Inhibitors

Olutasidenib

Olutasidenib is approved for use in AML in the United States and has orphan drug status for AML in the European Union.[18,19] This drug is also being studied in patients with refractory IDH1-mutant gliomas, with a phase Ib/II trial demonstrating no dose-limiting toxicities at 150 mg twice daily.[20]

Safusidenib

Ongoing trials are in progress for the safety and efficacy of safusidenib in glioma patients (NCT05303519).[21]

Combination Therapy

Treatment is given continuously on a 28-day cycle. Off-label use of mIDH inhibitors includes use in patients with grade 4 IDHm astrocytomas. Current clinical trials are evaluating the use of mIDH inhibitors combined with immunotherapy in the recurrent setting (NCT05484622).[22] Although the combination with other chemotherapies has not been studied, limited institutional experience at the University of Florida has found mIDH inhibitors to be well tolerated when combined with temozolomide, bevacizumab, and/or pembrolizumab.[23] However, further research is needed to establish best practices for combinatorial approaches.

Summary

The recent scientific interest in mIDH inhibitors is encouraging for our glioma patients whose tumors have IDH mutations. Both ivosidenib and vorasidenib are generally well-tolerated medications (Figure 1,Table 5), but they do require significant monitoring and potential dose reduction.

Vorasidenib has been of particular interest because of the recently published results of the phase III clinical trial discussed above. It is not known if vorasidenib should be

Table 5. Summary of Adverse Events (%) for Vorasidenib and Ivosidenib in Patients With mIDH Glioma

Event	Vorasidenib		Ivosidenib	
	All grade	Grade ≥ 3	All grade	Grade ≥ 3
Increased ALT[5,11,16]	21–44	4–10		
Increased AST[5,11,16]	17–40	4	12	
Increased GGT[5]	16	3		
Fatigue[5,10,11,16]	29–33	0.6–2	12–23	
Headache[5,10,11,16]	27–46		36–40	5
Diarrhea[4,5,10,11,16]	25–29	0.6	17–28	
Nausea[5,10,11,16]	22–42	2	23–24	
Vomiting[16]	19	2	20	
Constipation[5,11,16]	13–21		16	
Dizziness[5,16]	15–17			
Seizure[5,10,16]	14–29	4–8	18	3
Cough[11,16]	15		24	
Upper respiratory infection[11,16]	12–13		16	
Hyperglycemia[10,11,16]	13–19	4	15–20	2
Hypoglycemia[16]	12			
Potassium decreased[11]			24	
Calcium decreased[11]	13		28	
Sodium decreased[11]			12	4
Phosphate decreased[10,11]	13	4	11	3
White blood cell count decreased[11,16]	14		16	
Neutropenia[10,16]	17	2	12	
Anemia[11,13]	17	4	36	
QTc prolongation[4,11]			12–17	
Elevated creatine kinase[4,11]			34	
Paresthesia[10,11]			11–12	
Insomnia[11]	21			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; mIDH, mutant isocitrate dehydrogenase.

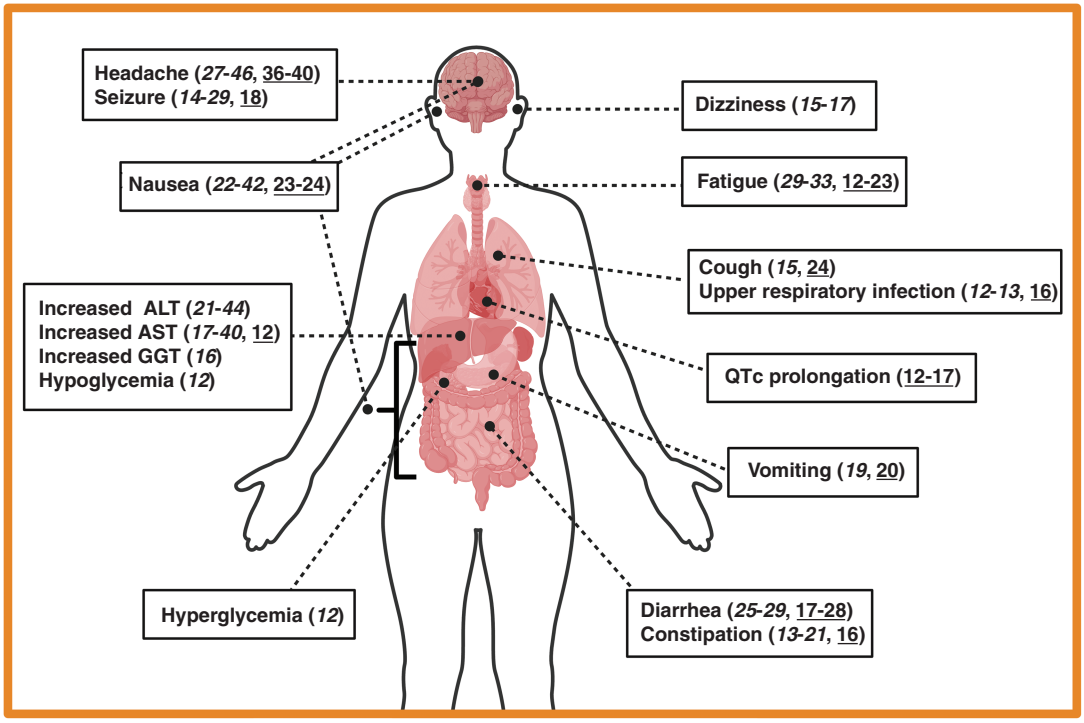

Figure 1. Common side effects of vorasidenib and ivosidenib. Italics = vorasidenib % occurrence. Underlined = ivosidenib % occurrence.

offered to patients who do not fit the narrow criteria of the clinical trial. Further studies are expected.

The use and safety of either mIDH inhibitor in pregnant or lactating patients is largely unknown at this time so care should be taken to adequately monitor for changes in pregnancy status and restrict use in these populations until more data is obtained.

There is not yet longer-term data to guide the duration of treatment, possible rebound growth, or change in tumor behavior after treatment discontinuation. The implications of long-term treatment and reproductive risk are also not known. This is of particular importance because the majority of these patients are young.

Keywords:

glioma | IDH inhibitor | ivosidenib | prescribing | vorasidenib

Conflict of interest statement

A.P.G. serves on the Advisory Board of Alexion Pharmaceuticals, Servier, and ONO Pharma, USA, as a consultant for Neosoma, Monteris Medical, Aptitude Health, and Guidepoint Global, as an investor in Neosoma, and held personal stock for Viatris Inc. from 2022 to 2023. D.L. serves on the Advisory Board of Servier. A.F.H. has served on Advisory Boards for Novocure, Servier, and Bayer (compensations paid to the institution).

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