

Ivosidenib – Another Feather in the Hat of Treatment for Acute Myeloid Leukemia

Abstract

The treatment of acute myeloid leukemia has undergone a paradigm shift in the past few years. Multiple new targeted and nontargeted agents have been approved in the recent past. Isocitrate dehydrogenase (IDH) mutation is one such target that has been identified, and two new drugs, ivosidenib and enasidenib have been approved. The former is an IDH1 inhibitor, and the latter is an IDH2 inhibitor. The mechanism of action, key trials, adverse events, and monitoring of ivosidenib has been discussed in this article.

Keywords: Isocitrate dehydrogenase inhibitors, ivosidenib, new drugs in acute myeloid leukemia

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Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy. Until the recent past, the standard treatment of newly diagnosed AML in fit patients was induction (1–2 cycles) with cytarabine and daunorubicin followed by consolidation (2–3 cycles) with intermediate or high dose cytarabine. Allogeneic stem cell transplantation is done as consolidation in intermediate- and high-risk category patients. Despite all the above expensive treatments,^[1] the cure rates for AML were very modest.^[2] Moreover, in elderly patients who are not fit for such aggressive treatments, the treatment is aimed at just prolonging life and controlling symptoms with agents such as decitabine, azacytidine, and low-dose cytarabine.^[3]

Of late, there have been multiple new targeted drugs that have been approved for use in AML, especially in elderly patients. One such group of drugs is isocitrate dehydrogenase (IDH) inhibitors.^[4] There are two IDH inhibitors approved for use. Ivosidenib is an IDH1 inhibitor, and enasidenib is an IDH2 inhibitor. This is a review of ivosidenib.

Mechanism of Action and Pharmacokinetics

IDH1 gene is located on the 2p33.3 chromosome. It encodes for an enzyme

called IDH1, which is located in the cytoplasm and peroxisomes. This enzyme converts isocitrate to alpha-ketoglutarate, which produces nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is required for many cellular processes such as fat metabolism and scavenging of reactive oxygen species. Cytogenetically, normal AML patients harbor IDH1 mutations in about 6%–20%.^[4-6] The most common mutation in IDH1 gene is located in the arginine 132 (R132) residue. This mutation results in hypermethylation of DNA and histones, which in turn, causes an arrest in the differentiation of the myeloid series. Ivosidenib is an IDH1 inhibitor that inhibits the mutated IDH1 and causes a release of the differentiation arrest.

The metabolism of ivosidenib is by the CYP3A4 enzyme, and it is primarily excreted in feces, and the terminal half-life of ivosidenib is 93 h. There is a high risk of developing QT prolongation and arrhythmias when ivosidenib is coadministered with other drugs, which cause QT prolongation and CYP3A4 enzyme inhibitors. Ivosidenib itself induces the CYP3A4 enzyme. This may lead to a decrease in the efficacy of the azole group of the antifungal drug, which is commonly coadministered in AML. Caution must be taken in patients using oral contraceptives along with ivosidenib, as there may be a decrease in efficacy due to the induction of the CYP3A4 enzyme.

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Key Trials

Study AG120-C-001 (NCT 02074839)

This is an ongoing phase 1 single-arm, multicenter, dose escalation and expansion trial looking at safety, pharmacokinetics, pharmacodynamics, and clinical activity of single-agent oral ivosidenib (AG120) in advanced hematologic malignancies with IDH1 mutation.^[7] This trial included 179 relapsed/refractory AML patients. Complete response (CR) or complete response with partial hematologic recovery (CRh) was seen in 30.4%.^[8] This trial also included 28 previously untreated patients with therapy-related AML and AML with myelodysplasia, of which 12 patients (42.9%) achieved a CR or CRh.^[9] Two patients underwent allogeneic stem cell transplantation after CR with ivosidenib. Based on this trial, the Food and Drug Administration (FDA) has approved ivosidenib in newly diagnosed AML patients ≥ 75 years of age with IDH1 mutation and relapsed or refractory AML patients with IDH1 mutation.

Study AG120-C-009 (NCT 03173248)

This is an ongoing phase 3 multicenter randomized double-blinded trial looking at ivosidenib with azacytidine versus placebo with azacytidine in untreated AML patients of ≥ 18 years of age with IDH1 mutation. This trial has an estimated enrollment of 392 patients and expected to be completed by June 2022.^[10]

Maintenance therapy after allogeneic stem cell transplantation (NCT 03564821)

This is an ongoing phase 1 study evaluating the use of ivosidenib as maintenance after allogeneic stem cell transplantation in AML, myelodysplastic syndromes, and chronic myelomonocytic leukemia patients with IDH1 mutation. It has estimated to enroll 22 patients.^[11]

Diagnostic Test

The FDA has approved a companion diagnostic test for testing IDH1 mutation called Abbott Real Time TM IDH1 assay.

Dosage

Ivosidenib comes as a 250 mg tablet. The recommended dosage is 500 mg once daily until progression or unacceptable toxicity. The treatment should be continued for at least 6 months to show a clinical response.

Adverse Events and Special Caution

The common adverse events are diarrhea (53%), fatigue (47%), edema (26%), anemia (26%), leukocytosis (26%), dyspnea (24%), and hypomagnesemia (24%).^[9]

Differentiation syndrome (DS) is a unique adverse effect of this novel drug. It occurs in about 20% of the patients. DS is treated using standard drugs such as corticosteroids,

diuretics, and hydroxyurea (in case of leukocytosis). DS seldom requires permanent discontinuation of the therapy.^[12]

Caution must be taken if a patient develops QTc prolongation, as it may lead to dangerous arrhythmias. Dose reduction to 250 mg once daily is recommended for patients who develop QTc > 500 ms after normalization.

Guillain-Barre syndrome is a very rare, but dangerous adverse effect of ivosidenib, which was reported in $< 1\%$ of the patients in the trial. It requires permanent discontinuation of the drug.

If a strong CYP3A4 inhibitor is coadministered, the dose must be reduced to 250 mg once daily.

Monitoring

Blood counts and biochemical tests are to be done once weekly in the 1st month, once in 2 weeks in the 2nd month, and then once monthly. Creatinine phosphokinase should be monitored once weekly for the 1st month. ECG should be monitored once weekly in the 1st month and then once monthly.^[13]

Other Indications

Ivosidenib has also been indicated off label in IDH1 mutant gliomas. Ivosidenib has also shown to have activity in IDH1 mutant cholangiocarcinoma and chondrosarcoma.^[14]

Conclusion

Ivosidenib is a novel targeted drug that is a promising option for IDH1 mutant AML patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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