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Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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IDH Inhibitors in Acute Myeloid Leukemia and Myelodysplastic Syndrome

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H&O How common are isocitrate dehydrogenase (*IDH*) mutations in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)?

ES At diagnosis, approximately 20% to 25% of patients with AML have an *IDH1* or *IDH2* mutation. *IDH2* mutations are more common than *IDH1* mutations, occurring in approximately 15% to 20% of patients. In MDS, these mutations are less common; *IDH2* mutations occur in approximately 3% to 5% of patients, and *IDH1* mutations are found in approximately 3%.

The prognostic impact of these mutations tends to be related to the co-occurring mutations that arise. For example, patients with an *IDH* mutation and a nucleophosmin (*NPM1*) mutation usually do well. Patients with mutations in *IDH* and FMS-like tyrosine kinase 3 (FLT3) do less well. The patient's *IDH* status is important to know because these mutations predict response to specific *IDH1* and *IDH2* inhibitors in the relapsed and refractory setting. The presence of an *IDH* mutation is therefore not only prognostic, but also predictive of response to certain kinds of therapy.

H&O Which IDH inhibitors are currently approved for the treatment of AML?

ES Only 2 IDH inhibitors are approved by the US Food and Drug Administration (FDA). Enasidenib (Idhifa, Bristol Myers Squibb/Agios/Celgene) is approved for the treatment of patients with relapsed or refractory AML who have an *IDH2* mutation. Ivosidenib (Tibsovo, Servier) is approved for AML patients with the *IDH1* mutation who have relapsed/refractory disease, as well as for newly diagnosed patients ages 75 years and older or who have comorbidities that preclude the use of intensive induction chemotherapy. These drugs differ primarily in their side effect profiles, although most patients will not develop any adverse events. With ivosidenib, there is a small risk of prolongation of the QT interval. Enasidenib can be associated with indirect hyperbilirubinemia, which is of no clinical consequence. Laboratory testing might show that levels of indirect bilirubin are slightly elevated.

Ivosidenib and enasidenib work by causing myeloid differentiation. Both agents lead to differentiation syndrome in approximately 10% to 15% of patients. As the leukemic cells—the myeloid blasts—start to mature and differentiate, patients can develop pulmonary edema, plural effusions, and other manifestations of capillary leak syndrome. If not addressed immediately, differentiation syndrome can lead to serious consequences. Treatment consists of corticosteroids, which shut down the differentiation syndrome immediately in almost all cases.

H&O What clinical trial data led to the approval of these drugs?

ES The approval of enasidenib was based on the results

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of a single-arm phase 1/2 study in patients with relapsed or refractory AML who had an *IDH2* mutation. The rate of complete remission (CR) and CR with partial hematologic recovery was approximately 21%. The overall response rate, which included CR, CR with incomplete hematologic recovery, CR with incomplete platelet recovery, partial remission, or morphologic leukemia-free state, was approximately 40%. An important aspect of enasidenib is that it can lead to transfusion independence. The FDA deemed that transfusion independence was evidence of clinical benefit. Enasidenib was therefore granted full approval, rather than accelerated approval, based on the response rate, the duration of response (which was approximately 6 months), and the clinical benefit rate, which was the rate of transfusion independence.

Outcomes with the *IDH1* inhibitor ivosidenib were similar. The overall response rate in relapsed/refractory AML was approximately 40%. The rate of CR plus CR with partial hematologic recovery was approximately 30%. The duration of response was 6 months. Ivosidenib was also associated with the clinical benefit of transfusion independence. The FDA approval in this setting was based on the response rate, the duration of response, and the rate of transfusion independence.

The approval of ivosidenib for newly diagnosed patients with AML and the *IDH1* mutation was based on a small study of less than 30 patients with newly diagnosed AML. The overall response rate in this population was good, at approximately 50%. The CR rate was lower.

Enasidenib has also been studied in patients with relapsed/refractory MDS who harbor the *IDH2* mutation. These very small studies showed an overall response rate of approximately 50%.

H&O Are there any promising IDH inhibitors in development for AML or MDS?

ES Data from early clinical trials of the novel *IDH1* inhibitor olutasidenib have been presented at international hematology meetings. The outcomes were similar to those seen with ivosidenib.

LY3410738 is another *IDH1* inhibitor in early-phase and phase 1 clinical studies. An interesting aspect of this drug is that it appears to have activity against some of the resistant mutations that arise when patients are treated with ivosidenib. Physicians are excited about this drug because it would be beneficial in the long-term to have a second-generation agent that can target the mutations that arise during treatment with ivosidenib.

H&O Has anything been learned about the IDH inhibitors as they have moved from trials to use in the clinic?

ES The association with differentiation syndrome is more widely recognized now than it was when enasidenib and ivosidenib were in clinical trials.

H&O Are there any other promising areas of research?

ES My colleagues and I performed a phase 1 study in which IDH1 and IDH2 inhibitors were combined with intensive induction chemotherapy in patients with newly diagnosed *IDH1*- or *IDH2*-mutated AML. The study showed that IDH inhibitors and chemotherapy can be administered together safely, and the efficacy was good. The remission rate was approximately 70% with ivosidenib or enasidenib, and the rate of overall survival at 1 year was impressive, at 65% to 70%. This trial is important because it set the stage for a randomized phase 3 study comparing IDH inhibitors plus chemotherapy vs placebo plus chemotherapy. The results of this phase 3 study will indicate whether the use of IDH inhibitors in combination with chemotherapy is better than chemotherapy alone.

Disclosure

Dr Stein has received consulting fees from Agios Pharmaceuticals and Bristol Myers Squibb.

Suggested Readings

ClinicalTrials.gov. A study of ivosidenib or enasidenib in combination with induction therapy and consolidation therapy, followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia or myedysplastic syndrome EB2, with an *IDH1* or *IDH2* mutation, respectively, eligible for intensive chemotherapy (HOVON150AML). https://clinicaltrials.gov/ct2/show/NCT03839771. Identifier: NCT03839771. Accessed May 27, 2021.

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