
Enasidenib in Newly Diagnosed and Relapsed/Refractory Mutant IDH2-positive AML

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Welcome to *Managing AML*, I'm Dr. Eytan Stein. I will be reviewing two abstracts on enasidenib and mutant IDH2-positive acute myeloid leukemia that were presented at the European Hematology Association's Annual Congress. The first abstract I'm going to be discussing is an abstract about enasidenib monotherapy in patients with newly diagnosed and untreated AML with an IDH2 mutation. The second abstract I'm going to be discussing is about continuing enasidenib in patients with stable disease, and what the outcomes of these patients are.

As everyone likely knows, mutations in isocitrate dehydrogenase-2 are seen in approximately 15% of patients with acute myeloid leukemia. What happens when you have a mutation in IDH2 is that instead of isocitrate being converted to alpha-ketoglutarate, alpha-ketoglutarate is converted to beta-hydroxyglutarate. When you have increased intracellular levels of beta-hydroxyglutarate, that causes a block in myeloid differentiation through a variety of biological mechanisms. If you can drug that mutation such that you lower the levels of intracellular beta-hydroxyglutarate, you can cause myeloid differentiation to again progress normally and, therefore, get rid of acute myeloid leukemia. Enasidenib has been already approved for the treatment of relapsed and refractory acute myeloid leukemia based on the results of a large phase 1/2 study which showed that the overall response rate of the drug as a single agent in the relapsed and refractory setting was approximately 40%; with about 20% of those patients achieving complete remission and a median overall survival in the range of eight and a half to nine months.¹ In this first abstract, what the authors were interested in looking at was what happens if you give this enasidenib IDH2 inhibitor to patients with newly diagnosed AML. This was part of the larger phase 1/2 study, but it was a separate cohort. In this study, there were 39 untreated patients with IDH2 mutant acute myeloid leukemia. These patients were ineligible for induction chemotherapy or other standard of care therapy; either de facto or what we normally do which is hypomethylating agents (that was decided by their local physician). Because of that, they were enrolled on the study where they would get single-agent enasidenib. The median age of these patients was quite old (77 years old), and the breakdown of the two subtypes of IDH2 mutations that we see, the R140 mutation versus the R172 mutation, was approximately 70% R140 mutants and 30% R172 mutants. The outcomes of these patients were quite good. The overall response rate was 31%, with 18% of the patients achieving a true complete remission. The median overall survival in this small study was 11.3 months. I think what this represents is actually a very low toxicity regimen that can be used in those patients where one might not feel comfortable giving them a drug that is

myelosuppressive; certainly like induction chemotherapy, but also a drug like azacitidine or decitabine. That group of patients that are so old or so infirm that really all they can tolerate is an oral medication which has minimal side effects. Based on these data, the NCCN has included in their guidelines that for newly diagnosed AML patients older than age 60 with an IDH2 mutation, enasidenib would be considered an acceptable alternative to what we currently do, which is low-dose cytarabine or hypomethylating agents.

The second abstract I want to discuss is about what happens to patients with relapsed and refractory AML who receive enasidenib, who have stable disease as their best response after three cycles of therapy. One of the things we know about enasidenib is that, like any differentiating agent, what happens when you take this drug is that it takes time for cells to differentiate. The median time to best response in the group of patients with relapsed and refractory AML is 3.7 months.¹ We ask ourselves, well, what if you have a patient that you are treating with enasidenib and they have gotten three cycles (90 days) of therapy, and you do a bone marrow biopsy and the bone marrow biopsy has not changed much? That is, they started at 60% blasts and they ended at 60% or 50% blasts, but they have certainly have not achieved a response yet. Should you continue giving patients enasidenib or should you call it a day and move on to something else? We looked at all of the patients on the study who had been on enasidenib for 90 days and whose best response after 90 days was stable disease, and we asked ourselves, what happens to these patients who are continued on enasidenib? The answer was that about a third of the patients will go on to achieve a complete remission or a response. It can also be something less than a complete remission, like a complete remission with incomplete count recovery. A third of the patients will maintain stable disease as their best response, and then a third of the patients will develop progressive disease. What you can legitimately tell your patients is that if they have stable disease for 90 days, there is about a 33% chance that with continued administration of enasidenib, they will have a response. By having a response, that translates into better overall survival, so if you compare the patients who have a response to the patients who don't have a response after 90 days (three cycles), the patients who don't have a response obviously don't live as long as the patients who do have a response.

The last thing which is important is that we are trying to figure out now whether we identify at day 90 who are that 33% of patients who are destined to respond? Can we identify them so that we don't put 66% of the patients on continued therapy when they are not going to benefit from it? There is some thought that it may have to do with the molecular alterations that are present in the myeloblasts in addition to IDH2, such that patients with FLT3 abnormalities are probably less likely to be in that group of patients who end up responding than patients who do not have FLT3 abnormalities, but that is information that is still being analyzed. Both of these abstracts show the power of differentiating therapy for acute myeloid leukemia, and the power of an oral agent that can be taken at home by patients with relapsed and refractory disease, and represents a new standard of care for IDH2 mutant patients with AML. Thank you very much for viewing this activity.

Abstracts

Pollyea DA, Tallman MS, de Botton S, et al. Enasidenib Monotherapy is Effective and Well-Tolerated in Patients with Previously Untreated Mutant-IDH2 (MIDH2) Acute Myeloid Leukemia (AML). EHA23: 2018. Abstract S1561.

https://learningcenter.ehaweb.org/eha/2018/stockholm/214480/daniel.a.pollyea.enasidenib.monotherapy.is.effective.and.well-tolerated.in.html?f=ce_id=1346*ot_id=19045*media=3

Stein EM, Stone RM, Pollyea DA, et al. Continuing Enasidenib Treatment for Patients with Mutant-IDH2 Relapsed/Refractory Acute Myeloid Leukemia (R/R AML) with Stable Disease May Result in Improved Responses and Survival Over Time. EHA23: 2018. Abstract PS980.

https://learningcenter.ehaweb.org/eha/2018/stockholm/215305/eytan.m.stein.continuing.enasidenib.treatment.for.patients.with.mutant-idh2.html?f=ce_id=1346*ot_id=19045*media=3

Reference

1. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant-IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017: blood-2017-04-779405.
<http://www.bloodjournal.org/content/early/2017/06/05/blood-2017-04-779405?sso-checked=true>