Chapter 2: Safety and Efficacy of Enasidenib in Patients with Mutant-IDH2 Relapsed AML

Eytan M. Stein, MD
Assistant Professor
Leukemia Service
Memorial Sloan Kettering Cancer Center
New York, New York

Enasidenib Improved Durable Remissions in Patients with Mutant-IDH2 Relapsed AML (S471)

Welcome to *Managing AML.* My name is Dr. Eytan Stein and I am an Assistant Professor of Medicine at Memorial Sloan Kettering Cancer Center in New York City. Today, I will be reviewing two abstracts presented in acute myeloid leukemia this year at the annual meeting of the European Hematology Association. The first study I am going to cover are the results of a phase 1 dose escalation and expansion study reviewing enasidenib, formally known as AG-221, in mutant IDH2 relapsed or refractory acute myeloid leukemia. The background to this study is that approximately 10% to 15% of patients with acute myeloid leukemia will have a mutation in the gene called IDH2. The normal function of IDH2 and its wild-type state is to convert isocitrate to alpha-ketoglutarate to produce energy for the cell. When one has a mutation in IDH2, instead of isocitrate being converted to alpha-ketoglutarate, alpha-ketoglutarate gets reduced to beta-hydroxyglutarate. When you have increased levels of beta-hydroxyglutarate, that causes a histone hypermethylation and a block in cellular differentiation which, as you all know, is what the phenotype of acute myeloid leukemia is. The preclinical hypothesis was that if you could block the action of this mutant IDH2 enzyme, you could lower levels of beta-hydroxyglutarate intracellularly, reverse the histone hypermethylation, and restore myeloid differentiation, and thereby get rid of acute myeloid leukemia. In an effort to do this clinically, the preclinical hypothesis was proven correct in a number of elegant studies that were published in a variety of journals. In an effort to prove this clinically, a phase 1 study that had four expansion arms, and then a phase 2 portion that was tacked on, was conducted. This study started as a dose escalation study where doses between 50 mg and 650 mg of enasidenib were tested. This drug is an oral drug given once a day, and although no maximum tolerated dose is reached, the dose that was used for the expansion arms in the phase 2 trial was 100 mg once a day. What I am going to be presenting at this meeting are the results of the group of patients who had relapsed and refractory AML. So that is the group of patients in the dose escalation arm that had relapsed and refractory AML, the group of patients in the two expansion arms that included patients with relapsed and refractory AML, and finally the phase 2 component of the study that only had patients with relapsed and refractory AML. If you only look at the relapsed and refractory AML patients, that takes up about 250 patients in the study.

As in all phase 1 studies, the first thing we were interested in was looking at the safety of the drug. The thing we are very excited about is that the side effects that we thought were specifically related to enasidenib were quite few, and those side effects that were grade 3 to 4 in severity, the incidence of those were below 10%. The most common grade 3 to 4 drug-related adverse event is hyperbilirubinemia. Now, it is important to note that this is actually an indirect hyperbilirubinemia that has nothing to do with the function of the liver. The reason patients get this is because one of the off-target effects of enasidenib is to inhibit the enzyme that

conjugates bilirubin. What you will see clinically is that some patients, specifically those with underlying Gilbert disease, will actually develop a hyperbilirubinemia in the 2 to 3 range, but it really has no clinical sequelae. We noticed it is a laboratory abnormality, but we do not do much about it we just keep treating through it. Of note, there are no elevations in the transaminases, no elevation in alkaline phosphatase or any other parameters that one might associate with liver toxicity. I think the most important serious adverse event of note is a differentiation syndrome which occurs in approximately 10% of patients. As I said, we are very excited about the safety of the drug and when it came to the efficacy, we are also very excited. That is because the overall response rate in this group of relapsed and refractory AML patients, that really were highly pretreated, was 40%, 20% of those patients had a true complete remission, 20% of those patients had either a partial remission or a complete remission with incomplete count recovery of neutrophils or incomplete count recovery of platelets, or a morphologic leukemia-free state. The overall response rate is 40%. Interestingly, the time to first response is about 1.9 months. It takes time to get to your first response, and the time to best response, which is a complete remission obviously, is nearly 4 months. This is the kind of drug, kind of like hypomethylating agents, where one does not want to pull patients off the treatment right away. This is a kind of drug where you want keep patients on the drug for at least 4 cycles to see if they start responding. The thing that we also take away from this is we looked at the overall survival. The overall survival in the entire patient population with relapsed and refractory AML is 8.3 months. If you break that down into the group of patients with a complete remission, in those patients the median overall survival is approximately 2 years, 22.3 months. If you look at the patients who responded but had less than a complete remission, the overall survival is 15.8 months, and we find that extremely exciting in a group of patients with relapsed and refractory acute myeloid leukemia. By comparison, if you look at the overall survival statistics of large phase 3 studies in the control arm, those studies typically show in this kind of patient population, the median overall survival of approximately 3 months. As many of you may know, this agent is now being reviewed by the Food and Drug Administration for approval. The date of a decision about whether the drug will be approved or not is August 30, 2017, and we are very hopeful that these positive results will allow us to get this drug to our patients quite soon.

The way this may impact the treatment landscape is that, overall, I think we are really honing in and understanding the molecular genetics of acute myeloid leukemia. Acute myeloid leukemia, although it has the same phenotype block differentiation, is really a disease with multiple causes and those are multiple genetic and epigenetic abnormalities that occur both singly and in combination to produce this disease. I think where we are going with the treatment for acute myeloid leukemia is to hone in on these molecular abnormalities and to try to develop drugs for specific molecular abnormalities. An example of this is the drug midostaurin that was recently approved for the treatment of FLT3 positive AML in combination with induction chemotherapy. I am hoping that there are going to be other inhibitors that are able to do the same thing. I think what lies ahead for this drug are the following items. First of all, we are trying now that we see the great effect in relapsed and refractory disease is to get this drug to patients in an earlier line of therapy. To that end, there are ongoing phase 1 and phase 2 clinical trials combining enasidenib with induction chemotherapy. In addition, there is a phase 2 trial that is randomized in patients to get enasidenib with azacitidine versus azacitidine alone, with the primary outcome of that study being response rate. We are very excited to see the results of those studies because

with an agent that is so potent and has produced so durable remissions in the relapsed and refractory population, we are very hopeful that is going to extend into newly diagnosed population.

I think the things that are going to be challenges with this drug are the following: unfortunately, even patients who achieve a complete remission, even the majority of patients eventually relapse while on this drug. One of things we really need to do is understand, number one, why there are groups of patients who do not respond to the drug even though they have an IDH2 mutation, and number two, what is the mechanism of relapse? Why are our patients are relapsing? Is it that there are some other mutations or some other clone that grows and causes the relapse? That might give us insight into combination strategies with this drug.

Neither Complex Karyotype nor FLT3/ITD Predicts for Worsened Outcomes in Patients with AML Receiving 7+3 (P553)

The second study I will cover looked at patients with acute myeloid leukemia who have mutations in IDH1 or IDH2 and their response to induction chemotherapy was 7+3 despite the presence of a complex karyotype or a FLT3-ITD. This is the study we undertook in Memorial Sloan Kettering Cancer Center where we retrospectively looked at all of the patients who had either an IDH1 or IDH2 mutation, who received induction chemotherapy with 7+3 at Memorial Sloan Kettering. The reason we thought this was important is because there are a number of large studies that retrospectively look at the outcomes of patients who receive induction chemotherapy. To my knowledge, none of those studies look specifically at the group of the patients who receive only 7+3.This is important because, as I said earlier, one of the things we are doing now is we are combining enasidenib with induction chemotherapy. In order to understand how much better that combination might work, you need a baseline for understanding what is the outcome of patients, the complete remission rate, who receive induction chemotherapy with 7+3. The results of this study I thought were quite interesting, and the reason is because patients with IDH1 and IDH2 mutations really do have a quite good remission rate just with 7+3 alone, it is about 75% to 80%. Interestingly, when you look at the subsets of different IDH mutations that can occur, the only one that seems to predict for acquiring more than one induction cycle is having the mutation called an IDH2 R172K mutation. We saw that in those patients, they needed two induction cycles in order to achieve a complete remission rather than one induction cycle, and we thought that was very important. The other thing that we thought was important is that even if you had a complex karyotype or a FLT3 internal tandem duplication where you might not expect the remission rate to be as high, when you had an IDH1 or an IDH2 mutation, the remission rates were similar whether you had a complex karyotype or FLT3/ITD. That is having a complex karyotype or FLT3/ITD did not predict for worsened outcomes when it comes to overall complete remission. As I said earlier, I think the most important part of the study is using it to understand the combination strategy of 7+3 with induction chemotherapy and enasidenib.

Monitoring for and Managing Differentiation Syndrome in AML Patients Prescribed Enasidenib (P215)

I would like to talk a little bit about differentiation syndrome. The reason I would like to talk about this is because there are now agents being investigated in clinical trials, specifically inhibitors of

mutant IDH, where we seem to see what is termed a differentiation syndrome. What is a differentiation syndrome? Differentiation syndrome clinically manifests as a noncardiogenic pulmonary edema and fluid overloaded state. What happens is that we think that as immature myeloid cells and acute myeloid leukemia or acute promyelocytic leukemia start to mature, those cells release certain cytokines that cause capillary leak syndrome. As I said, clinically, this capillary leak syndrome can manifest as acute-onset shortness of breath in patients getting these inhibitors of mutant IDH. It can manifest sometimes as renal failure. It can manifest as pericardial effusions. It can manifest as having pleural effusions. When it comes to IDH inhibitors in a large clinical study, phase 1 and phase 2 clinical study that are using IDH inhibitors in patients with relapsed and refractory acute myeloid leukemia, approximately 10% of patients developed this differentiation syndrome, some of which were severe and required patients to be hospitalized. We have been looking very hard to understand what are the risk factors for developing a differentiation syndrome. To date, in this patient population, we have not been able to identify specific risk factors, specifically the white blood count when you start therapy does not seem to predict a differentiation syndrome nor does the degree of IDH mutation that the patient has. What is important to know about this is that the treatment for differentiation syndrome is actually quite simple if you recognize it early. The treatment is giving steroids, specifically dexamethasone 10 mg twice a day until the symptoms of the differentiation syndrome resolve. The reason that this is important is because, as you can imagine, having pulmonary infiltrates pleural or pericardial effusions, what can happen is that this can often mimic an infectious process. It is important to be quite aware that if you start antibiotics on your patients, those antibiotics do not seem to be working, if the pulmonary edema and pleural effusions are greater than you might expect in a patient with an infection, it is important to keep this syndrome in mind and start steroids at the earliest possible moment because the steroids are very effective in reducing the symptoms related to this disorder.