Biomarker-driven Treatments: Ivosidenib, Enasidenib, and Sy-1425

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

Welcome to *Managing AML.* I am Dr. Eytan Stein, and I am live at the ASH Annual Meeting in Atlanta, Georgia. Today I will review the results of two phase 1 trials with ivosidenib and enasidenib, and the early results of a phase 2 biomarker-directed trial of SY-1425 in AML and MDS.

First, let me briefly discuss the results and impact from ivosidenib (also known as AG-120) in mutant IDH1 AML and advanced hematologic malignancies, and the results of a phase 1 dose escalation and expansion study.

As many of you know, approximately 5% to 10% of patients with acute myeloid leukemia will have a mutation in IDH1. Mutations in IDH1 lead to the accumulation of the oncometabolite beta-hydroxyglutarate intracellularly, and a block in myeloid differentiation, which is what acute myeloid leukemia is. Therefore ivosidenib, formerly known as AG-120, blocks the mutant enzyme and lowers the levels of intracellular beta-hydroxyglutarate, leading to the restoration of myeloid differentiation and the eradication of acute myeloid leukemia. These were the results of a phase 1 trial with a large expansion phase primarily looking at the number of patients with relapsed and refractory AML with an IDH1 mutation who benefited from this oral drug. The results of this study are quite encouraging. First, the toxicity of the oral agent is quite low, with the main toxicities being the kinds of things you would see in a patient population with acute myeloid leukemia in general. There was a slightly increased incidence of QT prolongation, but that did not result in any clinical sequelae. Approximately 10% of patients will have what is called an IDH inhibitor differentiation syndrome, such as when those mutant cells start to turn into normal healthy cells. The mutant cells release cytokines that can lead to a noncardiogenic pulmonary edema. This is easily treated with steroids. The results of this study are encouraging with an overall response rate in the range of 40% and a complete remission rate in the range of 20%. The complete remission and complete remission with hematologic recovery rate is in the range of 30%. I find these results extremely encouraging.

The company has said they are going to be filling ivosidenib for approval before January 2018, and I am hoping that this drug gets approval for IDH1 relapsed and refractory mutant AML, just like the IDH2 inhibitor enasidenib also got approval in August of 2017 for IDH2 mutant AML that is relapsed and/or refractory.

My second abstract is going to focus on the phase 1 trial that assesses the safety and preliminary efficacy of combining ivosidenib or enasidenib with standard induction chemotherapy in patients with newly diagnosed AML with an IDH1 or IDH2 mutation.

The purpose of this study is to move these IDH1 and IDH2 inhibitors into earlier lines of therapy in combination with induction chemotherapy to hopefully get better responses. This trial enrolled two separate cohorts. It enrolled cohorts with mutations in IDH1 where and IDH1 inhibitor gets combined either with cytarabine and idarubicin, or cytarabine and daunorubicin. The same thing happens with patients with mutations in IDH2, where the IDH2 inhibitor enasidenib gets combined with Ara-C and daunorubicin, or Ara-C and idarubicin. The drug starts on day 1 of induction chemotherapy, and patients who achieve a complete remission can go on and get consolidation chemotherapy with either inhibitor, depending on what mutation they have. Patients who do not go on to an allogeneic bone marrow transplant can then go on and receive maintenance therapy. Patients who do get an allogeneic bone marrow transplant are not candidates for the maintenance therapy. The results of this trial, again, have been quite encouraging. We have not seen any toxicity in either of the groups, either the ivosidenib- or enasidenib-treated group, that would make us think that there is any increased toxicity by combining IDH inhibitors with induction chemotherapy. In the enasidenib-treated group, there was a group of patients with secondary acute myeloid leukemia who did have a slightly increased time to platelet count recovery. We do not think that is a big deal because with these patients we would expect to have a prolonged time to platelet count recovery anyway, given that they have secondary AML. The remission rates in this study are consistent with what one would see with 7 + 3 alone, maybe a little bit better. Based on these results, we are excited that this combination will now be moving on to a randomized placebo-controlled phase 3 study, where induction chemotherapy will be combined with ivosidenib or enasidenib, compared to induction chemotherapy being combined with placebo.

The final abstract I want to discuss is an abstract discussing a biomarker-directed phase 2 trial of SY-1425 in AML and MDS that demonstrated DHRS3 induction and myeloid differentiation following SY-1425 treatment.

This study is a little bit earlier on than those studies that I have talked about before, but it is really quite interesting. The pharmaceutical company Syros has discovered that patients with a certain biomarker – an RARA super-enhancer – may be sensitive to treatment with the differentiation agent SY-1425. SY-1425 is actually a drug called tamibarotene that has been approved for the treatment of acute promyelocytic leukemia in Japan, but is not used in the United States. It is more potent than all-trans-retinoic acid (ATRA) and that is the rationale for using it in this biomarker selected cohort. Approximately 30% of patients with AML will have this biomarker, this RARA super-enhancer. The purpose of this study is not only to give this drug to patients with relapsed or refractory AML, but to see whether that 30% group of patients can be identified. The results of this study showed that, just like the preclinical data would suggest, approximately 30% of patients with relapsed or refractory AML will have this PML-RARA

super-enhancer biomarker, and that if you take patient samples, you can show that there is myeloid differentiation in vitro and in vivo. The results of this study are going to be discussed in future presentations, but we are very excited in giving this drug that we now may have a way to select out these patients which will respond to this differentiation agent therapy.

Thank you very much for viewing this activity.

References:

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