Key Findings in AML: An Overview

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

Welcome to Managing AML, I'm Dr. Eytan Stein from Memorial Sloan Kettering Cancer Center. I'm happy to present highlights from the 2018 European Hematology Association Annual Congress, and to talk a little bit about where we are when it comes to the treatment of acute myeloid leukemia.

As you know, over the past year and a half or so, there has been huge amounts of excitement about the strides that we are making to treat acute myeloid leukemia. That excitement has come to fruition in a number of drug approvals, including: midostaurin in combination with chemotherapy for newly diagnosed patients with acute myeloid leukemia with a FLT3 internal tandem duplication or tyrosine kinase domain mutation; gemtuzumab ozogamicin in combination with chemotherapy for the treatment of “fit” newly diagnosed patients with acute myeloid leukemia; and gemtuzumab ozogamicin as a single agent for patients with relapsed and refractory acute myeloid leukemia, and for newly diagnosed patients not eligible for induction chemotherapy because of age or comorbid medical conditions. The drug CPX-351 (a liposomal formulation of daunorubicin and cytarabine) was approved for the treatment of AML with myelodysplasia-related changes. Finally, the IDH2 inhibitor enasidenib was approved for the treatment of relapsed and refractory AML for patients with mutations in IDH2.

What was going on at the European Hematology Association and is going on in the world of AML that is exciting right now? There have been a number of analyses of CPX-351 that were presented at the European Hematology Association that are helping us to delineate where is the best place to use CPX-351, how many cycles of CPX-351 need to be given, and what molecular subtypes of patients with AML (secondary AML or AML with myelodysplasia-related changes) will respond to CPX-351. That is very exciting, and I think in the future we will understand how to use CPX-351 better, and then think about combinations of CPX-351 with other agents.

In the world of FLT3, there is a huge amount of excitement and that is because there are two second-generation FLT3 inhibitors that have very advanced data that has been released. One of them is a drug called quizartinib, which is a second-generation FLT3 inhibitor. There is a randomized phase 3 study in the relapsed and refractory setting comparing quizartinib to re-induction chemotherapy, and the high-level message from this presentation at EHA was that the median overall survival with quizartinib was six and a half weeks longer (about a month and
a half) than with re-induction chemotherapy. That is very exciting because what it demonstrates for the first time is that in the relapsed and refractory setting for patients with FLT3 internal tandem duplications, there is a drug out there that may not be as toxic as chemotherapy and may be more effective than chemotherapy. That is very, very exciting. The other drug that I think everyone is extremely excited about is the drug called gilteritinib, another FLT3 inhibitor. It inhibits both the FLT3 internal tandem duplication and the tyrosine kinase domain mutation, as opposed to quizartinib which only inhibits the internal tandem duplication. That drug was part of a large randomized phase 3 study called the ADMIRAL study which compared gilteritinib in the relapsed and refractory setting with re-induction chemotherapy. The sponsor of that study (Astellas Pharmaceuticals) has now filed for approval with the FDA in the relapsed and refractory setting to try to get gilteritinib approved based on the results of an interim analysis of the ADMIRAL study. The final analysis is not going to be done for a little while, but the interim analysis is done, and our understanding is that the FDA will be making a decision about that application before the end of the year. What this means in terms of FLT3 therapy is that right now, the standard of care for patients with newly diagnosed AML with a FLT3 internal tandem duplication or tyrosine kinase domain mutation would be to get induction chemotherapy with midostaurin. Then in the relapsed and refractory setting, we may have two drugs before, hopefully, the middle of next year that are approved as single agents in the relapsed and refractory setting. There is another drug called crenolanib, another potent FLT3 inhibitor that also is in clinical trials, although I do not believe they have yet filed an application for approval with the Food and Drug Administration.

When it comes to IDH inhibition, I spoke about a second ago that enasidenib, the IDH2 inhibitor, was approved last year, but there are two IDH1 inhibitors that are in development. One of these is called ivosidenib. Ivosidenib is an IDH1 inhibitor that shows very, very exciting responses in the relapsed and refractory setting in patients with IDH1 mutant AML, where the overall response rate is in the range of about 41% to 42%. Nearly 30% of those patients have a complete remission or completion remission with incomplete hematological recovery. The median overall survival in those patients is robust, and it approaches nine months. That's data that was published recently in June of 2018 in the New England Journal of Medicine. That drug ivosidenib is under review by the FDA and we are expecting an answer from the FDA by mid-August to see if that drug will be approved as a single agent for relapsed and refractory AML.*

There are other IDH1 inhibitors in clinical development. The one that just had data presented both at ASCO and at EHA was a drug by a company called Forma Therapeutics called FT-2102. They have used the IDH1 inhibitor in a variety of different settings (as a single agent in the relapsed and refractory setting, for myelodysplastic syndromes, in combination with azacitidine). Their data overall looks similar to the data with ivosidenib, although we will have to take a good look and see if the safety profiles are similar or different, because there then may be differences if both drugs were approved and what one might want to use.
The drugs that everyone is really buzzing about is the combination of azacitidine with the BCL2 inhibitor venetoclax. There have been a number of presentations on this and some publications on this where in patients with AML that are older and not eligible for induction chemotherapy, the overall response rates have been in the range of 70% with many of those patients achieving an MRD-negative complete remission – and those remissions tend to occur relatively quickly. That is when one is getting single-agent 5-azacitidine, you don’t typically expect a response for four to six cycles. With the combination of azacitidine and venetoclax, you typically will see responses within one to two cycles. That is beneficial for the patient in that you have an answer whether the drug is working or not quickly, and if it is not working, you can then move on to something else. Similarly, there have been presentations of the combination of venetoclax with low-dose cytarabine that have shown similarly exciting results as the combination of venetoclax and azacitidine.

Finally, another drug that has just been filed with the FDA is the combination of a drug called glasdegib (a hedgehog inhibitor) with low-dose cytarabine in older patients with acute myeloid leukemia. Hedgehog inhibitors are thought to alter or target leukemic stem cells, and by targeting leukemic stem cells, if that is the mechanism of action, you are getting rid of the underlying roots of the disease. With the combination of glasdegib and low-dose Ara-C, a new drug application has been filed with the FDA, that new drug application was accepted, and the FDA is processing it under a priority review so that we should know, hopefully before the end of the year, whether that drug will be available on the market.

In summary, I think there are a variety of new drugs that may be available within the next year and a half: the FLT3 inhibitors (gilteritinib and quizartinib) for relapsed and refractory acute myeloid leukemia; for newly diagnosed acute myeloid leukemia, the combination of aza-venetoclax and perhaps the combination of low-dose Ara-C and venetoclax or low-dose Ara-C and the hedgehog inhibitor glasdegib; and finally, for IDH1 mutant AML in the relapsed and refractory setting, the IDH1 inhibitor ivosidenib. As you can imagine, now that a lot of these drugs are being approved in the relapsed and refractory setting, we are now seeing them being moved up to the newly diagnosed setting. For example, gilteritinib is being tested with chemotherapy in the newly diagnosed setting. Quizartinib is also being tested with chemotherapy in the newly diagnosed setting for FLT3-positive acute myeloid leukemia. There is a lot of excitement in the world of acute myeloid leukemia. If aza with venetoclax ends up being approved for newly diagnosed AML, we may be seeing triplets with clinical trials of aza and venetoclax plus something else. It is an exciting time to be an oncologist and an AML doctor, and you are going to be seeing a lot more at the annual meetings such ASH and EHA that we all attend. I want to thank you again for listening, and please enjoy these congress highlights.

*On July 20, 2018 the FDA granted approval to ivosidenib for the treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved companion diagnostic.*

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References


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