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Stratifying Risk to Guide Therapy in R/R AML

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Dr. Fathi:
This is CME on ReachMD, and I'm Dr. Amir Fathi. Today I'll provide a brief overview of risk stratification to guide treatment strategy for patients with relapsed or refractory acute myeloid leukemia.

Over the course of the last 10 to 15 years, we've learned a lot about the range of molecular aberrations and drivers of leukemogenesis in acute myeloid leukemia. Over time, we have found a large series of mutations or alterations underneath AML. And that is important because it tells us a lot about the pathophysiology of the disease, about how the disease emerges. It tells us about the diagnostic aspects of the disease, but also about prognosis, about how patients ultimately will do because certain alterations or mutations portend a better prognosis, while others portend a poorer prognosis.

And perhaps most relevant to the discussion today, certain alterations within AML cells place them within a vulnerable area of therapeutic impact. So a patient with a FLT3 mutation, for example, can be a target for FLT3-inhibitor therapy. Or one with an IDH mutation can be a candidate for IDH-inhibitor therapy. Similarly, in patients who have NPM1 alterations, or KMT2A alterations, the topic of discussion today, they may be candidates for a menin inhibitor

Since 1973 up until the year 2017, there were very few therapies that were approved for use in acute myeloid leukemia. So this is decades of time. But starting in 2017, less than a decade ago, there were a large series of small molecule inhibitors, again developed to target specific molecular subtypes of AML that were developed and studied in clinical trials and subsequently approved by regulatory agencies. These included the FLT3 inhibitors—midostaurin and gilteritinib—the IDH inhibitors—enasidenib, ivosidenib, and most recently, olutasidenib,—and revumenib, the most recent addition, is a menin inhibitor approved for use in KMT2A rearranged AML.

Here we have the 2022 International Consensus Classification, the ICC classification of AML. As you can see, molecular alterations and chromosomal changes are a big factor in its development, and gives you an idea of how important these alterations are in terms of diagnosis of AML. And diagnosis is important because it allows you to make a determination regarding, ultimately, of targeted therapies that a particular AML may be vulnerable to, allowing you to expand the armamentarium you have for therapeutic success.

It's not just diagnostic impact in terms of the new mutations that have been discovered, but also their impact on prognosis. So if you have certain alterations, such as core-binding factor alterations, NPM1 mutations, biallelic CEBPA alterations, these are considered more favorable alterations. If you have other alterations, like inversion 3, p53 mutations, certain MDS-defining alterations in AML, they

carry a much more adverse risk. So our knowledge of these mutational alterations, these chromosomal changes, has really changed the prognostic as well as the diagnostic landscape of AML.

The International Consensus Classification of AML allows a hierarchical approach to diagnosis based on the proportion of blasts in the marrow or blood, and thereafter, looking at specific mutations or alterations and making, ultimately, a diagnosis for the patient, and thereafter the choice of therapy.

These days, it is highly recommended that mutational testing and chromosomal testing be done at baseline, but also at the time of relapse, particularly for alterations that may be relevant to therapeutic targets. Important mutations would be FLT3 and IDH, but also NPM1 and KMT2A rearrangements and p53 alterations, because they impact the choice of therapy. In addition, core-binding factors are important for prognosis and choice of addition to induction therapy in the form of gemtuzumab ozogamicin.

So having this data earlier is important to make decisions regarding diagnosis, prognosis, and treatment.

Well, my time is up. I hope you found this overview useful. Thank you very much for listening.

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