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Molecular Profiling as a Cornerstone of Precision AML Therapy

Announcer:
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Dr. Ghayas Issa:
This is CME on ReachMD, and I'm Dr. Ghayas Issa. In this brief lecture, I'll review the molecular profiling of patients with acute myeloid leukemia and how to use this molecular testing to individualize treatment for our patients.

So as you all know, acute myeloid leukemia is a heterogenous disease with multiple genetic alterations that could cause acute myeloid leukemia. The most common genetic alteration is mutation of the NPM1 gene, followed by mutations in FLT3. There are other actionable mutations, in other words, targeted therapies that can be added to certain mutations in AML, such as IDH1, IDH2 mutations.

In addition, there are mutations that help decide on the prognosis of acute myeloid leukemia and decision whether to use a stem cell transplant in consolidation. For example, the mutation in the TP53 gene is associated with an adverse risk with an indication for transplant, whereas a mutation in the CEBPA, especially if it's bZIP, is a good prognosis mutations and may allow patients not to receive or may indicate that the patients may not benefit from the addition of a stem cell transplant in consolidation.

So this means that in standard practice, it is recommended that molecular profiling of AML is done even in the community setting, because it helps guide treatment decision. Not just standard therapies such as the addition of FLT3 inhibitors in frontline therapy or the addition IDH inhibitors in relapsed/refractory setting, or the addition of the IDH1 inhibitor, ivosidenib, for older patients.

It is also important to guide decision on a stem cell transplant in order to better risk stratify patients. So the best way to do that is by doing conventional cytogenetics. This allows you to pick up the core-binding factor leukemia, which is a leukemia that benefits from high-dose cytarabine and may not need a stem cell transplant, or identification of alterations that could guide treatment. For example, KMT2A-rearranged leukemias frequently have translocation involving the gene 11q23, and this can be picked up by cytogenetics. But this may not be sufficient for KMT2A-rearranged leukemias. In that case, additional testing should be done such as FISH or RNA-seq that allows picking up cryptic alterations. And this may matter, especially in the relapsed/refractory setting, where a targeted therapy is approved and could change the treatment or the management of patients with this leukemia.

So, in the relapsed or refractory setting, it is important to perform next-generation sequencing to pick up mutations because not all mutations in AML are stable. There are instances of acquired mutations, such as mutations in the gene FLT3, that would change management when a FLT3 inhibitor is indicated.

Or for example, use of next-generation sequencing can help guide whether leukemia is persistent. For example, in NPM1-mutant acute leukemia, where this is a founding event. And there are currently some MRD assays using next-generation sequencing that track NPM1 and allow us a dynamic monitoring of acute myeloid leukemia.

Ultimately, in the future, we are going to see new tests that allow comprehensive assessment of leukemia with less steps. For example, whole genome sequencing may be a future step that would allow us to pick up karyotype, cytogenetics, and the additional mutational information. So this would allow us a comprehensive profiling of AML, a good risk stratification, and identification of alterations that can be targeted with specific small molecules. All these results need to be integrated in clinical practice and are important so that the treatment decisions are done based on each patient.

Well, my time is up. I hope I've given you something to think about. Thank you for listening.

Announcer:
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