Transcript Details
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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Myeloid Mutations in ALL: Disease Risk and Prognostic Implications

Announcer:
You're listening to *Project Oncology* on ReachMD. On this episode, we'll hear from Dr. Caner Saygin, who's an Assistant Professor of Medicine at the University of Chicago Medicine. He'll be discussing acute lymphoblastic leukemia, or ALL for short, with myeloid mutations, which he spoke about at the 2026 Society of Hematologic Oncology Annual Meeting. Here's Dr. Saygin now.

Dr. Saygin:
There has been a knowledge gap in terms of understanding the drivers of adult ALL, particularly the ALL that we're seeing in older adults. So what our work has previously shown that's also been validated and expanded by others is that approximately a third of adults develop ALL from preexisting clonal hematopoiesis. This might be TP53-mutant clonal hematopoiesis or myeloid mutant clonal hematopoiesis. And these myeloid genes are those involving DNMT3A, RUNX1, and ASXL1. These are the genes that you would typically see mutated in myeloid leukemias, but you have these mutations as drivers in ALL in the adult.

So these patients who have myeloid mutations or TP3 mutations in their ALL tend to have worse prognosis. Their response to standard chemotherapy is inferior, and they may benefit from newer approaches, such as immune-based approaches. So it's really important to characterize and diagnose this upfront by doing a more comprehensive genetic analysis.

So we have learned a great deal now about this unique biology in adults with ALL. Individuals may harbor these myeloid mutations or TP53 mutations in a clonal hematopoietic state for many years before they develop the full-blown acute lymphoblastic leukemia. So we have a window of opportunity there for intervention and for prevention trials, particularly for individuals who are at high risk for developing ALL. These might be individuals with multiple myeloma who are getting lenalidomide therapy and also have TP53-mutant CHIP clones or myeloid-mutant clones that are at high percentage.

Similarly, other individuals getting genotoxic therapy for a solid tumor may be at risk for therapy-related ALL, especially if they have these mutations as a CHIP clone. It is important to pay attention to that. And what typically happens is individuals often have a mutation as CHIP and then as the years go and as this evolves, they acquire additional alterations that drive this lymphoid bias towards acute lymphoblastic leukemia.

For example, we see low hypodiploidy frequently co-occurring with TP53 mutations. Or we often see RUNX1 and ASXL1 mutations in Ph-positive ALL. We may also see myeloid mutations frequently in Ph-like ALL. So myeloid mutations may accompany higher-risk genomic abnormalities like Ph-like ALL or low hypodiploidy. But in other cases, they may be on their own. For example, in T-lineage acute lymphoblastic leukemia, myeloid mutations are more common, and in most cases, they would portend a poorer prognosis. But some of these mutations may have therapeutic implications. For example, IDH-mutant T-ALL may respond to IDH inhibitors.

So it's important to study this biology and to tailor our therapies towards more precision medicine in adults with ALL.

Announcer:
That was Dr. Caner Saygin talking about myeloid mutations in patients with ALL. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!