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Therapeutic Targets in Acute Myeloid Leukemia

ReachMD Announcer:

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Dr. Erba:

I am Dr. Harry Erba, director of the Leukemia Program and Medical Director of the Hematologic Malignancies Inpatient Unit at Duke University in Durham, North Carolina.

For several decades, therapy for AML was rather straightforward based on the determination of whether a patient was fit or unfit for intensive chemotherapy, and then subsequent selection from among limited treatment options. Recently, a deeper understanding of the pathogenesis of AML has led to the identification of potential therapeutic targets that give us options in addition to our standard cytotoxic chemotherapy.

From the Cancer Genome Atlas study, 23 recurrently mutated genes in AML were identified and categorized, with each mutation representing a potential target for drug development in AML. Among these genes, signaling and kinase pathway genes are common, including fms-like tyrosine kinase 3, or FLT3, which is often associated with gain-of-function mutations. Activating FLT3 mutations contribute to constitutive activation of the receptor and subsequent constant transduction of proliferation signals to downstream pathways.

The tumor suppressor gene TP53 is important for the regulation of apoptosis and cell cycle integrity. Mutated TP53 contributes to uncontrolled cellular proliferation and the promotion of neoplasia.

Mutations in the isocitrate dehydrogenase (IDH) family, including IDH1 and IDH2, are often seen in older patients and in patients with intermediate-risk disease. Mutated IDH enzymes catalyze the reduction of α -ketoglutarate to the oncometabolite, 2-hydroxyglutarate, which is associated with DNA and histone hypermethylation, altered gene expression, and blocked differentiation of hematopoietic cells. IDH inhibitors drive clinical efficacy via the induction of myeloblast differentiation.

The B-cell lymphoma-2, or BCL-2, family includes 12 or more proteins that either inhibit or promote apoptosis. The balance between the pro- and anti-apoptotic BCL-2 proteins determines whether a cell lives or dies. Pro-apoptotic proteins antagonize anti-apoptotic proteins, including BCL-2, by binding of the BH3 domain to the hydrophobic pocket of anti-apoptotic proteins. Molecules have been developed that mimic the BH3 domain to antagonize the effect of anti-apoptotic proteins.

In the past few years, the US Food and Drug Administration has approved eight therapies for patients with AML, targeting activating mutations of FLT3 and IDH, as well as expression of BCL-2, Smoothed in the Hedgehog Pathway, and the cell surface molecule CD33. Furthermore, synergistic activity between chemotherapy and these targeted agents has allowed for the development of additional regimens in AML that older and more infirm patients may be able to tolerate.

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