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Opinion Article

Omipalisib's Anti-Leukemia Properties in Acute Myeloid Leukemia

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DESCRIPTION

The hematological malignancy known as Acute Myeloid Leukemia (AML) is diverse and is characterized by clonal proliferation and poor cell differentiation. The dysregulated survival and proliferation of leukemic cells depends on chromosomal changes and mutations. The development of targeted therapeutics has significantly advanced recently as a result of a better understanding of the molecular landscape of AML obtained through extensive genomic analysis. Although the FDA has approved some new medications for the treatment of certain subgroups of AML, such as FLT3 inhibitors (midostaurin and gilteritinib), IDH1/2 inhibitors (enasidenib and ivosidenib), and BCL2 inhibitors (venetoclax), the development of efficient and long-lasting therapeutic approaches for other subgroups of AML remains unmet. When it comes to cell growth, differentiation, and survival, the phosphatidylinositol-3-kinase/AKT and mammalian target of rapamycin pathway is essential. PI3K/AKT/mTOR signaling is hyper activated in more than 50% of AML patients, who also have poor prognoses and treatment resistance. The dysregulated and constitutive activation of PI3K/AKT/mTOR signaling is linked to a number of somatic alterations, including mutations in receptor tyrosine kinases and GTPases.

Targeting the major proteins involved in PI3K/AKT/mTOR signaling has emerged as a crucial therapeutic approach given the significance of this pathway in leukemogenesis. Novel small-molecule medications have been reported to target PI3K or mTOR in AML, including the *in vitro* and *in vivo* mTOR inhibitors temsirolimus (CCI-779) and everolimus (RAD001), as well as the PI3K inhibitors duvelisib, alpelisib, idelalisib (CAL-101), and pan-class I PI3K inhibitor buparlisib. Dactolisib (BEZ-235) and gedatolisib (PF-05212384), dual PI3K/mTOR inhibitors, have been found to decrease AML proliferation and reverse multidrug resistance *in vitro* but have not been successfully used in AML clinical trials. Another effective dual PI3K/mTOR inhibitor, omepalisib has been demonstrated to specifically limit the proliferation of different tumor cells. The study shows that omipalisib has a strong *in vitro* and *in vivo* anti-leukemic impact. Its effects on other cancers have been researched, but its influence on leukemia has not. According to our findings, omipalisib effectively suppresses the PI3K/AKT/mTOR signaling pathway in AML cells, causing cell cycle arrest and controlling metabolic pathways.

The study includes integrate transcriptome, metabolome, and functional assays to examine the anti-malignant efficacy of omipalisib and its precise mechanisms in AML. A family of transcriptional coactivators known as PPAR gamma coactivator 1 increases mitochondrial biogenesis, oxidative phosphorylation, and fatty acid oxidation in a variety of malignancies. *PGC1* (*PPARGC1A*) or *PGC1* (*PPARGC1B*) abnormal expression has been linked to carcinogenesis in a number of malignancies. The survival of OCI-AML3 cells required the expression of *PPARGC1B* according to a DepMap study. Higher *PPARGC1B* expression was found in both cohorts after analysis of the The Cancer Genome Atlas (TCGA) Acute Myeloid Leukemia (AML) transcriptome databases, and high *PPARGC1B* expression was linked to a worse overall survival in AML patients. Omipalisib may target PGC1 however further research is needed to support this claim. The omipalisib markedly slowed down mitochondrial respiration, lowered membrane potential, and elevated ROS levels. Omipalisib also markedly reduced mitochondrial DNA (mtDNA), mitochondrial mass, the expression of numerous genes involved in mitochondrial biogenesis, and the amounts of these genes' proteins.

AML progression necessitates greater oxidative phosphorylation and mitochondrial biogenesis because AML cells have higher mitochondrial biogenesis than typical hematological cells. As a result, the biogenesis and mitochondrial metabolism of AML are prospective therapeutic targets. Omipalisib has recently been shown to have adequate tolerability in patients with idiopathic pulmonary fibrosis in a randomized, placebo-controlled study. The maximum observed concentration of participants receiving 2.0 mg omipalisib twice daily was 170 nM, which is significantly higher than the effective dose utilized in this investigation. Omipalisib has been shown to be an effective therapeutic approach for the treatment of several cancer types when combined with CDK4/6 and autophagy inhibitors. The benefit of omapalisib is that it makes cancer cells more susceptible to chemotherapy and radiation. Omipalisib combination treatment method is a successful future protocol for AML.

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