Acute myeloid leukemia - Section 2

Targeting mutant isocitrate dehydrogenase

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Mutations in the conserved enzymatic active sites of isocitrate dehydrogenase isoforms 1 and 2 (IDH1 and IDH2) lead to novel enzymatic activity that catalyzes the conversion of α-ketoglutarate to β-hydroxyglutarate (2-HG). Increased intracellular levels of 2-HG lead to defects in histone demethylation with a resulting block in cellular differentiation. In hematologic malignancies, mutations in IDH family members are found most commonly in acute myeloid leukemia (AML) and angioimmunoblastic T-cell lymphoma, but also occur in myelodysplastic syndromes and myeloproliferative neoplasms. Inhibitors of the mutant enzymes, including AG-221 and AG-120 (Agios/Celgene) and IDH305 (Novartis), both alone and in combination with standard induction chemotherapy and hypomethylating agents are in early and advanced clinical studies. Additional IDH inhibitors are expected to enter the clinic shortly.

In ongoing phase I/II clinical studies, the overall response rate of AG-120 and AG-221 as single agents in patients with relapsed and refractory AML is between 35% and 40%. Additional patients have hematologic improvement despite the lack of a decrease in myeloblasts. Some patients develop a differentiation syndrome characterized by weight gain, non-cardiogenic pulmonary edema and pleural/pericardial effusions when treated with IDH inhibitors, similar to, but not identical to that seen with all-trans retinoic acid and arsenic trioxide in acute promyelocytic leukemia. Primary resistance and relapse after response to IDH inhibitors may be mediated through the influence of competing clones and subclones. Rational combination strategies are needed to target other mutant proteins (FLT3, JAK2, RAS) in combination with IDH inhibitors.

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